

streptomycin, others to sulfonamides, aureomycin, or "Chloromycetin." The cost of the different drugs has to be considered at times, since there are very wide differences. The nature of the illness may also affect the choice of agent; for example, an orally administered drug may be unsatisfactory in a patient who is vomiting. In critically ill patients it is sometimes wise to give a combination of drugs until cultural and sensitivity studies reveal which is specifically indicated. In such cases cultures should always be taken before initiation of therapy. If an individual has previously shown hypersensitivity to a drug, or develops it during treatment, a different agent should be used if possible. Table 88 indicates the approximate order of preference of different drugs for some of the important pathogenic microorganisms.

Effect of Chemotherapy on Bacterial Flora of the Body. During the chemotherapy of infections there may be pronounced alterations in the normal bacterial flora of the body, especially in the mouth, pharynx, and gastrointestinal tract. When penicillin is being given, Gram-negative bacilli become predominant in the oral cavity, largely supplanting the alpha-hemolytic streptococci which are ordinarily the most numerous. Oral administration of "Sulfasuxidine," streptomycin, or aureomycin causes a marked reduction in bacterial population of the intestinal tract. These disturbances in bacterial equilibrium of the body may occasionally give rise to secondary infections. For example, patients being treated with penicillin have developed Friedländer pneumonia or influenzal meningitis, whereas children being treated with streptomycin have contracted severe staphylococcal infections. Superinfections of this type are not recognized frequently, but the possibility of their occurrence should be borne in mind.

SULFONAMIDES AND SULFONES

Discovery of the antibacterial properties of the sulfonamide drugs was of tremendous importance in the field of chemotherapy, since they were the first potent agents which did not act simply as protoplasmic poisons. In the period between 1937 and 1945 they were given extremely wide clinical usage. The later discovery of a series of potent antibiotic substances has, however, reduced very substantially the therapeutic indications for the sulfonamides.

Thousands of sulfonamide compounds have been synthesized and tested, but only a few, shown in figure 142, have been employed extensively in clinical practice. All of them possess an aromatic amino group; this must be free for the

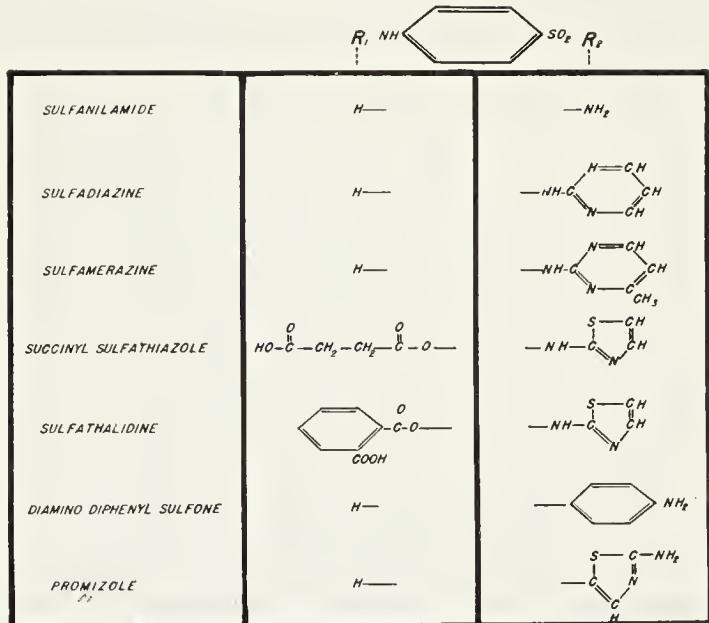


FIG. 142. Structural formulas of some commonly used sulfonamide preparations.

drug to have an antibacterial action. Succinyl-sulfathiazole, "Sulfathalidine," and various preparations of diaminodiphenylsulfone are themselves inactive, but are hydrolysed in the animal body, to form active derivatives.

Para-aminobenzoic acid will inhibit the antibacterial action of sulfonamides, and it seems probable that the sulfonamides act, in part at least, by competing with para-aminobenzoic acid, to prevent the formation of some essential substance, possibly pteroylglutamic acid.

Most of the sulfonamide compounds are readily absorbed from the gastrointestinal tract and widely distributed in the body. Exceptions are succinylsulfathiazole and "Sulfathalidinc," which are poorly absorbed and largely excreted in the feces. After absorption, the major metabolic alteration is acetylation of the primary amino group. Sulfonamides are excreted by the kidney, chiefly by means of glomerular filtration.

The quantity of sulfonamide in the blood or other body fluid can be determined accurately by colorimetric methods. The distribution of these compounds in the body depends upon the extent to which each becomes adsorbed to plasma and tissue proteins. Derivatives which are not firmly bound tend to be distributed evenly in total

body water and thus reach high concentrations in tissue cells, whereas those with a tendency to binding are concentrated in the plasma and extracellular fluids.

The principal toxic effects of sulfonamides are hypersensitivity reactions and injury of the kidneys. *Hypersensitivity* may be manifested by fever, rash, or granulopenia, similar to those produced by thiouracil compounds and barbiturates. The onset of these symptoms may take place any time after the first week of therapy, or even earlier in patients who have received the drugs previously. Sensitization to one compound usually, but not always, confers sensitivity to others. *Kidney damage* is the result of precipitation of the sulfonamide, especially its acetylated form, in the tubules of the kidney. It is most likely to occur when the reaction of the urine is acid, since the solubility of both acetylated and free forms is considerably greater in neutral or alkaline medium. Obvious methods of avoiding renal injury are to maintain copious urine output—at least 1200 ml. per day—or to administer sufficient alkali to render the urine neutral or alkaline. This can usually be accomplished by giving 6 to 20 Gm. of sodium bicarbonate per day. Another method of preventing precipitation in the urinary tract is to administer two or three different sulfonamide drugs concomitantly, since the solubility of each is independent of the presence of the others. The last measure has the disadvantage of increased likelihood of hypersensitivity reactions. A rare but serious manifestation of sulfonamide toxicity is development of *acute hemolytic anemia*. This may take place within the first 48 hours of therapy, and is manifested by rapid fall in erythrocyte content of the blood, icterus, hemoglobinuria, and high fever. Drug administration should be discontinued at once, and blood transfusion given.

Sulfadiazine and **sulfamerazine** are the compounds most commonly used in treating systemic infections. Sulfamerazine is excreted more slowly and, as a result, adequate plasma levels are maintained for a somewhat longer period of time than with sulfadiazine. For most types of systemic infection sulfadiazine is administered in a dose of 4 to 6 Gm. per day and sulfamerazine is given in a dose of 3 to 4 Gm. per day. Sulfadiazine is given at four- or six-hour intervals, and sulfamerazine at six- or eight-hour intervals. The

desirable blood level is between 5 and 15 mg. per 100 ml. To attain this initially a "loading" dose of 4 Gm. is advisable. If a patient cannot take oral medication, the more soluble sodium salts of these compounds can be injected subcutaneously or intravenously, in 0.5 per cent concentration. The subcutaneous route is preferable because it is less likely to result in unduly high blood levels, lessening the danger of renal injury. Intravenous administration to a dehydrated patient with acid urine is dangerous.

Succinylsulfathiazole and "**Sulfathalidine**" are of value only in suppressing bacterial growth in the gastrointestinal tract. They may be employed in preparing a patient for intestinal surgery, or in treatment of bacillary dysentery. They are ordinarily administered in doses of 3 Gm. four times daily. Therapy with these agents is less often complicated by renal damage because of the small quantity absorbed, but sensitivity reactions may occur.

Diaminodiphenylsulfone and **promizole** are potent antibacterial agents but have the disadvantage of a tendency to cause hemolytic anemia. Their use has been restricted largely to tuberculosis and leprosy, and is discussed in the chapters on those diseases.

PENICILLIN

The term *penicillin* was applied by Fleming to a substance produced by *Penicillium notatum* which exhibited an inhibitory effect on the growth of certain pathogenic bacteria. Subsequent investigation disclosed that the mold produces several penicillins, closely related chemically and in biologic activity. At the present time only one of these is used extensively in clinical medicine. It is called penicillin-G or benzyl penicillin or penicillin-II, and its structure

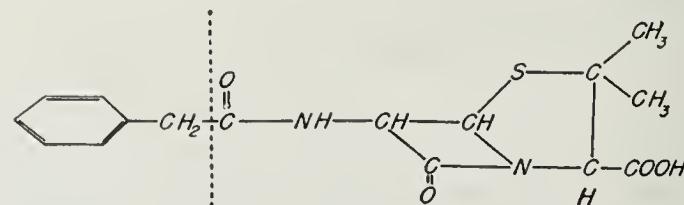


FIG. 143. Penicillin-G or benzyl penicillin.

is illustrated in figure 143. The other penicillins have been discarded because of difficulty in manufacture or because they are less effective. Penicillin-G has been prepared synthetically, but the process is very complex; consequently the en-

tire supply is still produced by fermentation methods.

Now that the drug is available in the form of a pure crystalline material, it would seem preferable to express dosage in terms of weight, but because of established clinical usage it will be difficult to break away from the original arbitrary unit system, based upon bio-assay. Actually, 1000 units is equal to 0.6 mg. of penicillin-G. The drug is supplied in the form of a sodium salt, there being approximately 0.1 Gm. of sodium in 1,000,000 units, a factor to be kept in mind when dealing with patients whose sodium intake should be restricted.

The most important clinical uses of penicillin are in treatment of infections caused by Gram-positive pathogens (*staphylococcus*, *streptococcus*, and *pneumococcus*), and in syphilis. For further indications, see table 88.

Following oral administration, only about 20 per cent of a dose of penicillin is absorbed into the blood stream, the remainder being destroyed by gastric acidity and by penicillinase in the lumen of the intestines. As a consequence, much larger doses are needed for oral than for parenteral therapy. Administration of alkali with the penicillin does not increase appreciably the amount absorbed.

When injected subcutaneously or intramuscularly, penicillin causes little or no local irritation, and it is very rapidly taken into the blood stream, whence it is either excreted by the kidneys or distributed evenly in the plasma and extracellular fluid. Normally, only minute amounts penetrate into the cerebrospinal fluid, but in the presence of meningeal inflammation appreciable levels may be obtained.

Penicillin is excreted by the kidneys with great rapidity, mainly by tubular excretion. The renal clearance approximates the total renal blood flow. This renders penicillin therapy a very wasteful procedure—the majority of a parenteral dose being excreted into the urine within the first hour. Attempts have been made to delay renal excretion of penicillin by concurrent administration of substances which would compete for available tubular excretory structures. "Diodrast" and para-aminohippuric acid have some ability to retard penicillin excretion, but their use is hardly practical, since large quantities would have to be administered by continuous intravenous injection. Carinamide (4-carboxy-

phenylmethanesulfonanilide) will also retard penicillin excretion by virtue of an action on the tubular excretory function; it has been used clinically with some success, being capable of elevating the plasma penicillin level two- to five-fold. It is given orally, the dose being 2 to 3 Gm. every three hours. Excretion of sodium by the kidney is increased during carinamide therapy; this is occasionally a matter of clinical significance.

Penicillin is almost devoid of toxicity in the human being. Its only untoward effects are in the nature of hypersensitivity reactions, consisting of urticaria, edema, arthralgia, and fever. These usually appear after seven or more days of therapy. The suggestion has been made that persons with fungous infections of the skin, such as epidermophytosis, are especially subject to penicillin reactions. Therapy consists in discontinuation of penicillin, and administration of antihistamine drugs, epinephrine injections, sedatives, and salicylates. It is undesirable to give penicillin to an individual who has suffered a severe reaction of this type within the past few months. Another antibacterial agent should be used whenever possible.

Although there is considerable doubt as to the necessity of maintaining continuous levels of penicillin in the plasma for effective therapy, a number of methods have been developed in an attempt to delay its absorption following subcutaneous or intramuscular injection. Various insoluble salts have been investigated. The most effective of these is the procaine salt, which can be administered in either an aqueous or an oily suspension. Whereas the soluble form of penicillin is excreted in two to three hours, the same dose of procaine penicillin will yield measurable plasma and urine concentrations for as long as 24 hours. Addition of aluminum monostearate to procaine penicillin preparations delays absorption even more, so that plasma concentration may be maintained for as long as 96 hours following a single injection. These preparations are excellent for treatment in the home or on an outpatient basis. The presence of the procaine has the additional advantage of lessening the pain of the injection. Penicillin is easily administered by inhalation, either in the form of a solution or in the form of a fine powder. By this means, high concentrations are attained in the upper respiratory passages, and a considerable portion is ab-

sorbed to become available for treatment of systemic infection. Occasionally there is blackening of the mucous membranes of the mouth and upper respiratory tract. Penicillin can be given orally in the form of tablets; these are useful in pediatric practice to avoid the distress of injections, but the dose must be three to five times as much as would be given parenterally. This route of administration should not be relied on in treatment of severe infections.

STREPTOMYCIN

Streptomycin is an antibiotic isolated from *Streptomyces griseus*. It is a basic substance having the structure indicated in figure 144, and is

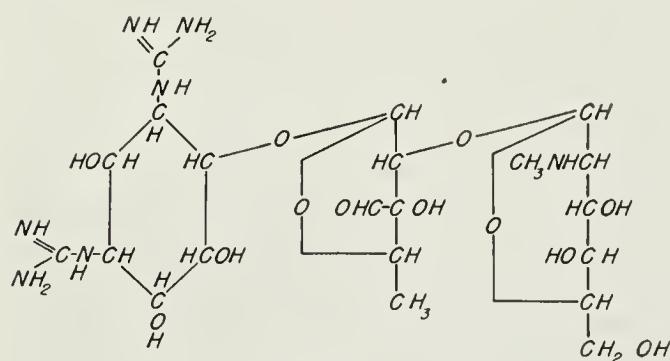


FIG. 144. Streptomycin.

usually prepared in the form of the hydrochloride, which is readily soluble in water. The carbonyl group may be hydrogenated to form *dihydrostreptomycin*, which has about the same antibacterial activity as the material isolated from fermentation broth.

Although readily soluble in water, streptomycin is poorly absorbed from the gastrointestinal tract. After oral administration, most of it passes through in the feces; only traces are demonstrable in blood and urine. Consequently, parenteral administration is required for the treatment of systemic infections, oral therapy being employed only for treatment of some enteric infections. When injected parenterally, streptomycin is distributed evenly in extracellular body fluids, but almost none of it penetrates the blood-spinal fluid barrier. After a single intramuscular injection, approximately 80 per cent appears in the urine over a period of 24 hours. Renal excretion appears to be largely by filtration; consequently the rate is much slower than that for penicillin.

The chief toxic manifestation from administration of streptomycin is damage to the eighth

cranial nerve. Evidence of this is nearly always demonstrable after the drug has been given in large dosage for a prolonged period of time—e.g., 2 Gm. or more per day for three weeks or longer. There may be vertigo, tinnitus, or impairment of hearing. Upon discontinuing therapy there may be some slow improvement, but complete recovery does not always occur. Early clinical trials suggested that dihydrostreptomycin was less likely to produce toxicity, but wider experience indicates that there is no great difference in the incidence and severity of toxic reactions to the two forms of streptomycin. Other side reactions which have been observed are headache, nausea and vomiting, and allergic reactions such as dermatitis and arthralgia. Hypersensitive skin reactions may follow repeated local application of streptomycin; these may be troublesome to nurses who prepare streptomycin solution for injection.

As has been pointed out previously in the present chapter, the frequency with which microorganisms acquire resistance to streptomycin seriously limits its value as a therapeutic agent. The chief clinical applications have been in therapy of tuberculosis and urinary tract infections. The drug is also highly effective in tularemia. Some strains of staphylococcus are inhibited by streptomycin, but penicillin and aureomycin are usually preferable in that type of infection. In combination with sulfadiazine, streptomycin has proved effective in acute brucellosis. As an adjunct to penicillin it is of value in therapy of bacterial endocarditis due to *Streptococcus faecalis*.

In the treatment of enteric infection, such as bacillary dysentery, streptomycin can be administered by mouth, in a dose of 0.25 to 0.5 Gm. every six hours. For other types of infection it is injected intramuscularly at 6- or 12-hour intervals. For acute infections where treatment is required for only a few days, 3 or 4 Gm. may be given per day; but in a chronic illness such as tuberculosis, 2 Gm. daily is the maximum recommended dose, and more commonly only 0.5 or 1.0 Gm. is given, in order to minimize eighth nerve damage. The drug should be made up in a solution containing not more than 0.5 Gm. per ml., since higher concentrations often produce considerable pain upon injection. Intrathecal administration may be advisable in treating cases of meningitis; the dose is 25 to 50 mg. in 5 ml. of

saline solution, given at intervals of one, two, or three days.

AUREOMYCIN

This antibiotic is a product of *Streptomyces aureofaciens*. It is a remarkable antibacterial agent because of its wide range of activity, encompassing not only many Gram-positive and Gram-negative bacteria, but also the Rickettsiae and some viruses. As indicated in table 88, it is of value in a great variety of infectious diseases. There is little tendency for microorganisms to develop resistance to aureomycin. It is a basic substance, but is usually prepared in the form of a hydrochloride, which is strongly acid in reaction. The dry salt is stable, but in solution the drug deteriorates rapidly, especially at pH above 6.0.

Aureomycin is so unstable in the presence of body fluids and bacteriologic mediums that definitive studies on its absorption, fate, and excretion have been difficult to obtain. Absorption from the gastrointestinal tract is rapid but inefficient, as a result of destruction of the drug by intestinal contents. After a single oral dose it can be detected in the urine within 15 minutes, and for as long as 24 hours. Concentration in the plasma falls rapidly below a detectable level, suggesting the possibility of localization and gradual release from some tissue or body fluid. Only a small proportion of the quantity injected parenterally can be demonstrated in the urine. Some aureomycin diffuses into the spinal fluid, but in lower concentration than that found in the plasma.

Concentrations of more than 0.2 per cent are very irritating because of the acidity, and can cause marked local inflammatory changes with necrosis. Subcutaneous and intramuscular injections, therefore, are not practical. Intravenous administration of buffered solutions is possible, but there is some risk of phlebitis at the site of injection. When the drug is given by mouth, nausea and vomiting occur occasionally. These symptoms presumably are due to the local irritating effect, since they do not occur when the drug is given intravenously, and they can be alleviated after oral administration by ingestion of food or alkali. Mild diarrhea, associated with loose, bulky stools, occasionally results from aureomycin therapy, presumably caused by local irritation and alteration in bacterial flora of the

intestinal tract. Aside from these minor difficulties due to its local irritating effect, aureomycin has shown no tendency to produce serious toxic reactions in the host.

The drug is available in capsules, for oral use. The dose range is from 1 to 6 Gm. per day; this can be given in divided doses at six- or eight-hour intervals. A leucine buffer solution is also available, to be used in dissolving the dry powder for intravenous injection. The dose for intravenous administration is one third to one fifth as large as that required for oral administration.

"CHLOROMYCETIN"

"Chloromycetin" was obtained originally from cultures of *Streptomyces venezuelae*. Later it was isolated in pure crystalline form, and the structure is shown in figure 145. The presence of the

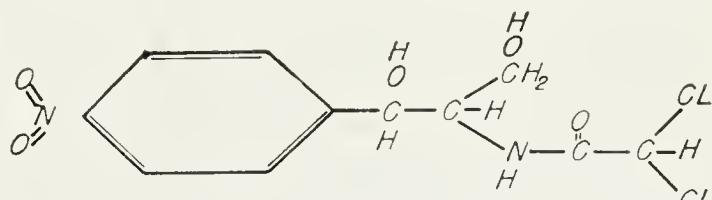


FIG. 145. "Chloromycetin."

NO₂ group makes possible a colorimetric method of assay similar to that used for the sulfonamides. The compound can be synthesized, and the synthetic product has been given the name *chloramphenicol*.

"Chloromycetin" is administered orally, in gelatin capsules. It is rapidly absorbed from the gastrointestinal tract, appearing in the blood within a few minutes. The maximum concentration occurs at the end of two hours, but some may still be found after 16 to 24 hours. About 80 per cent of the quantity administered orally can be demonstrated in the urine, by the colorimetric method of assay; however, only about 15 per cent is still active according to bio-assay. Inactivation appears to be due to conjugation with glucuronic acid.

Initial clinical experience with "Chloromycetin" has not revealed evidence of toxicity, such as fever, gastric irritation, skin eruption, hemopoietic disorder, or kidney injury.

The biologic activity of "Chloromycetin" is exerted principally against the Rickettsiae and the Gram-negative bacteria. There is little tendency for microorganisms to become resistant to the drug. Some strains of *Proteus* and of *Pseu-*

domonas are naturally resistant, however. The principal clinical uses are in the treatment of typhoid fever, brucellosis, urinary tract infections due to Gram-negative bacilli, and rickettsial diseases. The dose range is from 1 to 6 Gm. per day. This can be divided and given at 6-, 8-, or 12-hour intervals.

POLYMYXIN

Polymyxin is a polypeptide antibiotic, obtained from *Bacillus polymyxa*. The principal effect is upon Gram-negative bacilli, and it is one of the most potent chemotherapeutic agents for that group of pathogens, with the exception of organisms of the *Proteus* group which are resistant to it. It can be administered intramuscularly at intervals of 8 or 12 hours, the total daily dose being 0.2 to 0.5 Gm. A serious defect is its toxicity for the kidney, an effect which becomes evident at about the fourth or fifth day of treatment in a significant proportion of patients. There may be only proteinuria, or there may also be oliguria and nitrogen retention. Because of this, polymyxin should be employed only when other chemotherapeutic agents are ineffective, and when the patient's life is in jeopardy.

BACITRACIN

Bacitracin is a polypeptide antibiotic, produced by a strain of *Bacillus subtilis*. Its spectrum of

antibacterial activity is very similar to that of penicillin, being greatest against the Gram-positive pathogens. Its principal therapeutic use has been in treatment of superficial infections, such as ulcers, boils, carbuncles, infected wounds, chronic osteomyelitis, etc. The drug has also been administered systemically, but severe renal injury has resulted in some cases; consequently, its use will be restricted largely to topical application. It will probably never achieve wide usage because of its similarity to penicillin in the range of activity; there may, however, be a place for it in treatment of superficial infections due to penicillin-resistant organisms, or in persons who have shown evidence of hypersensitivity to penicillin.

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Pneumococcal Infections

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Etiology
Epidemiology
Pathogenesis
Pneumococcal Pneumonia
Pneumococcal Meningitis
Pneumococcal Endocarditis
Pneumococcal Peritonitis

Etiology. The pneumococcus is a Gram-positive, encapsulated, alpha-hemolytic organism which usually grows in pairs or chains. In the diplococcal form the adjacent edges of the cocci are flattened and the opposite ends pointed. The pneumococcus can be distinguished from alpha-hemolytic streptococcus by its solubility in bile, by its virulence for mice, and by capsular swelling with type-specific antiserum. The capsular substance, a polysaccharide, is responsible for type specificity and virulence; approximately 75 different serologic types have been identified, all of them pathogenic. Those encountered most frequently in clinical practice are 1, 2, 3, 5, 7, and 8. Their relative frequency varies considerably from year to year and from place to place, but type 1 usually accounts for 20 to 25 per cent of all pneumococcal infections. Type 14 is a common cause of pneumonia in infants, but is comparatively rare in older persons.

The mechanism by which pneumococcus damages tissues is obscure, since the cell itself has not been shown to contain or to elaborate toxic materials. Possibly, however, it does elaborate toxic substances when multiplying in the animal body. Or, possibly, by virtue of its rapid growth, it interferes with essential metabolic processes in the host.

Epidemiology. The pneumococcus is a normal inhabitant of the nasopharynx, various surveys having shown an incidence of 5 to 60 per cent in throat cultures of healthy persons. Transfer from one individual to another is probably accomplished by way of airborne droplets. Epidemics of pneumococcal infection have been observed in families and dormitory groups, but are com-

paratively rare. In most general hospitals patients with pneumococcal infections are cared for on open wards without isolation precautions. This practice seems justified by experience, and in view of the high carrier rate in the general population.

Pneumococcal infections are most frequent in the winter months, when common respiratory disease is prevalent. Both sexes and all age groups are susceptible.

Pathogenesis. Although a common inhabitant of the throat, the pneumococcus rarely if ever produces pharyngitis. When introduced into various other tissues, however, it can incite an acute, rapidly spreading inflammation, with production of an exudate rich in fibrin and polymorphonuclear leukocytes.

It is now believed that the pathway of infection in pneumococcal *pneumonia* is via the air passages. Ordinarily the lungs are protected from the pneumococci which may be harbored in the nasopharynx by natural body defenses. These include the mucus in the respiratory passages, ciliary action, and the directions and velocities of air currents. The effectiveness of these barriers seems to be impaired by common respiratory disease, fatigue, chilling, intoxication with alcohol, anesthesia, and depression of the cough reflex.

Pneumococci probably are carried into the lungs in droplets of saliva or mucus. Because of gravity and the direction of the major air pathways, infection usually begins in the lower portions of the lungs: the right lower and middle lobes and the left lower lobe. Once established in the pulmonary alveoli, pneumococci excite an acute inflammation with outpouring of edema fluid containing large numbers of pneumococci, which spreads rapidly, flowing into new areas by way of the bronchioles and small bronchi. The infection also spreads directly to adjacent alveoli or

through septums of the lung. As the margin of the infection advances, polymorphonuclear leukocytes and macrophages migrate into the infected alveoli and begin to ingest the bacteria. In areas where the process is oldest, bacteria are no longer present, the alveoli being distended with a fibrinous exudate containing many phagocytic cells. If the infection is not brought under control it continues to invade new areas of pulmonary tissue, and may spread into the opposite lung, or extend directly to the pleural or pericardial surfaces. The outcome of a pneumococcal infection of the lung depends on the rate at which the bacteria in the advancing edematous zone can multiply and spread into new areas, as compared with the ability of the host to immobilize and destroy them.

Bacteremia is likely to be present when pneumococcal infection is spreading rapidly, as in the early stages of pneumonia, or later if the local defense mechanisms do not keep pace with the multiplication of the bacteria.

Host resistance is greatly augmented by the presence of specific antibody; this enhances phagocytosis and also seems to retard the migration of the organisms in the tissues. Specific antibody is not essential for survival, however, since it is not invariably demonstrable in the blood of patients who recover from pneumococcal infection, with or without chemotherapy. Nevertheless, the dramatic recovery by crisis, which was commonly seen before the availability of chemotherapy, usually coincided with the appearance of free antibody in the blood.

When the progress of pneumococcal pneumonia is arrested, the pathologic process in the lung resolves rapidly. The alveolar exudate undergoes liquefaction, and is apparently removed principally by the lymphatics, since little sputum is produced. Restoration of the lung to its normal state usually takes place within a few days.

In addition to infecting the lungs, pneumococci may, by direct extension from the nasopharynx, produce infections of the *paranasal sinuses* or of the *middle ear* and *mastoid cells*. Pneumococcal bacteremia may give rise to infections in other parts of the body such as *meningitis*, *peritonitis*, *endocarditis*, and *arthritis*.

PNEUMOCOCCAL PNEUMONIA

In general there is little variation in the severity of manifestations of the pneumococcal

pneumonias caused by the different serologic types. Indeed, it should be pointed out that this disease is remarkable for its uniformity, in contrast with other infections such as typhoid fever, brucellosis, tularemia, and tuberculosis. The prognosis of type 3 pneumococcal pneumonia is often considered especially grave, but this is related in part to the fact that, for reasons as yet obscure, type 3 infections often occur in persons debilitated by other illness such as diabetes mellitus, carcinoma, and congestive heart failure.

Pneumococcal pneumonia has frequently been classified as lobar or bronchopneumonia, according to its anatomic distribution. The term *lobar pneumonia* designates a process which uniformly involves one or more large segments or lobes of the lungs. The term *bronchopneumonia* is applied to those cases in which there is a patchy involvement, usually of both lungs. The distinction between lobar and bronchopneumonia is not always definite, and has little clinical importance, since treatment is the same, and prognosis is dependent on other factors. Clinically the important consideration in classification of pneumonia is the etiological agent, not the anatomic distribution.

Typical Course of Disease. For present purposes, it is desirable to describe the progress of pneumococcal pneumonia as it evolves naturally, although the natural course of the disease is now rarely observed since it is altered so remarkably by effective therapy.

In the majority of instances pneumonia is preceded for a few days by some form of common respiratory disease. The onset of the actual pneumonic illness is abrupt, usually with a hard, shaking chill, a rapid rise in temperature, and a corresponding increase in pulse rate. Within a few hours the subject begins to have severe pleuritic pain in one side of the chest; occasionally this is referred to the upper abdomen or shoulder. He develops a cough which is painful because of the pleurisy, and is productive of small amounts of pink or rust-colored clear mucoid sputum. The patient appears tense and acutely ill, and frequently lies on the affected side to minimize respiratory motion. His breathing is rapid, shallow, and painful, with dilatation of the alae nasa on inspiration and a grunt on expiration. Some cyanosis is usually present. The patient may complain of headache, but pleuritic pain is usually the dominant symptom.

Physical examination of the chest reveals the

signs of pneumonia. There is restricted motion of the affected side of the chest. The percussion note is impaired or flat over the area of consolidated lung, and tactile fremitus is increased in this area. Auscultation at first reveals diminished breath sounds, but later they become bronchial in quality, and whispered pectoriloquy and increased voice transmission are noted. Fine and medium moist crackling rales are heard.

During the first week of illness, the clinical picture remains about the same. The fever is sustained, varying between 102.5° and 104.5° F. Herpetic lesions are likely to appear on the lips. With spread of the pneumonia the location of the pleuritic pain may shift. Gaseous distention of the abdomen may develop, causing further respiratory embarrassment. There may be slight jaundice.

At the end of 7 to 10 days the "crisis" occurs. As already mentioned, this phenomenon seems to be associated with the production of an excess of antibody. The body temperature falls to normal in a period of 6 to 12 hours, accompanied by profuse sweating. Dramatic improvement in all manifestations follows.

In cases which terminate fatally, there is usually extensive pulmonary involvement, with marked cyanosis, dyspnea, tachycardia, and a clinical appearance of "forward" circulatory failure. In a few patients death is associated with suppurative complications such as empyema and pericarditis.

Effect of Specific Chemotherapy. In contrast with the picture just described, pneumococcal pneumonia usually terminates quickly in response to appropriate chemotherapy. Following administration of penicillin, pleuritic pain subsides within a few hours, and the temperature, pulse, and respiratory rate fall to normal in 12 to 36 hours. The spread of the inflammatory process ceases, in many instances even before there is complete involvement of a single lobe. Abdominal distention subsides, and the patient can eat a regular diet. Resolution of the pulmonary consolidation takes place within a few days.

Complications: 1. **IN THE LUNG.** Atelectasis involving all or part of a lobe may occur during the active stage of pneumonia or even after specific treatment has been instituted. When the atelectatic area is large, the patient may complain of sudden pleuritic pain and show signs of distress, with an anxious appearance and rapid respira-

tory rate. Small areas of atelectasis are sometimes detected by x-ray in the absence of symptoms. These processes usually clear with coughing and deep breathing, but bronchoscopic aspiration is occasionally necessary. If atelectasis is allowed to persist, the affected area becomes fibrotic and functionless. Delayed Resolution: The removal of exudate from the lung following pneumococcal infection is usually complete within a few days, but occasionally, especially in elderly individuals, consolidation persists for longer periods. Sometimes the involved area never become re-aerated, and fibrosis results. Lung abscess is a rare sequel to pneumococcal infection. It is manifested clinically by continued fever and profuse expectoration of purulent sputum. X-ray shows one or more cavities. This complication is exceedingly rare in patients who receive penicillin therapy.

2. **IN ADJACENT STRUCTURES: PLEURAL EFFUSION** may be noted in about 5 per cent of patients with pneumococcal pneumonia, even with specific therapy. The amount of fluid is usually not sufficient to cause obvious displacement of mediastinal structures. If it does not become infected —i.e., if empyema does not develop—it is spontaneously reabsorbed within a week or two.

EMPYEMA. Prior to the introduction of effective chemotherapy, pneumococcal infection of the pleura with empyema occurred in 5 to 8 per cent of patients with pneumococcal pneumonia; it is now observed in less than 1 per cent of all cases. It is manifested by persistent fever or pleuritic pain, together with signs of pleural effusion. In the early stages the gross appearance of infected fluid may not differ from that of a sterile pleural effusion; later, however, there is profuse outpouring of polymorphonuclear leukocytes and fibrin, resulting in an exudate of thick, greenish pus containing large plaques of fibrin. The quantity of exudate may become large enough to compress the lung and displace mediastinal structures. In neglected cases this leads to extensive pleural scarring, with limitation of chest movement. Rupture and drainage through the chest wall (empyema necessitatis) can occur. Metastatic brain abscess is an occasional complication of chronic pleural empyema; the origin of this appears to be septic thrombi passing through the intercostal and vertebral veins.

PERICARDITIS. A particularly serious complication is spread of infection to the pericardial sac. This may be manifested by pain in the precordial

region, and a friction rub synchronous with the heart beat, although neither of these is always present. The possibility of coexisting purulent pericarditis should be considered whenever there is pleural empyema, especially when the patient appears gravely ill.

3. METASTATIC INFECTIONS: ARTHRITIS occurs more often in infants than in adults. The affected joint is swollen, red, and painful, with a purulent effusion. It subsides promptly with topical and systemic administration of penicillin.

ACUTE BACTERIAL ENDOCARDITIS complicates pneumococcal pneumonia in less than 1 per cent of cases. Its manifestations and treatment will be discussed later in this section.

MENINGITIS, another rare complication of pneumococcal pneumonia, will also be discussed subsequently.

Laboratory Findings. *X-ray* of the chest reveals a homogeneous density in the affected area of lung. In well-established cases the density may occupy one or more entire lobes, whereas in early cases only a portion of one lung may be involved. The white blood count usually shows a polymorphonuclear *leukocytosis* ranging from 12,000 to 25,000 per cu. mm. Normal leukocyte count or leukopenia is sometimes observed in old people, or in those with overwhelming infection and bacteremia. The *blood culture* is positive for pneumococci during the first three or four days of illness in 20 to 25 per cent of cases. The *sputum*, when stained by Gram's method, shows polymorphonuclear leukocytes and moderate numbers of Gram-positive cocci, singly and in pairs. Typing of these can be accomplished directly, by the Neufeld capsular swelling technic, but this procedure is not essential for present methods of therapy.

Differential Diagnosis: **"PRIMARY ATYPICAL PNEUMONIA"** differs from pneumococcal pneumonia as follows: The onset is more insidious, and the fever is not so high. Pleuritic pain is not a prominent complaint, but soreness of the chest may be caused by the cough. The sputum is seldom rusty or blood-tinged, and is scanty or absent in the early stages. Physical signs are surprisingly slight in comparison with the roentgenologic findings. The leukocyte count is usually within normal limits. Blood cultures are negative and sputum culture yields only normal throat flora. There is no response to penicillin, but improvement may follow treatment with

aureomycin. Cold agglutinins can be demonstrated in about half of the cases after the tenth day of illness.

FRIEGLÄNDER BACILLUS PNEUMONIA may produce a similar clinical picture. It should be suspected in males past middle age, especially if the sputum is dark red, thick, and tenacious. A presumptive diagnosis can be made if there are large numbers of Gram-negative bacilli in the sputum.

STAPHYLOCOCCAL PNEUMONIA is likely to be encountered during or after an epidemic of influenza. The clinical picture is less uniform than that of pneumococcal pneumonia, varying from bronchitis with few constitutional symptoms to a fulminating infection. There is a tendency to early formation of lung abscesses, empyema, and pyopneumothorax. The sputum may be frankly bloody. Diagnosis is established by culture of the sputum and blood.

HEMOLYTIC STREPTOCOCCAL PNEUMONIA may also occur in association with influenza, and the clinical picture may closely simulate that of pneumococcal pneumonia. There may be associated acute streptococcal pharyngitis. Diagnosis is established by blood and sputum culture.

TULAREMIC PNEUMONIA should be considered if the patient has handled wild rabbits or squirrels. The clinical picture is more like that of primary atypical pneumonia than pneumococcal pneumonia. There may be a paucity of physical signs, although the patient is extremely ill. Agglutinins for *Pasteurella tularensis* may not appear until late in the second week of illness. There is a good therapeutic response to streptomycin or aureomycin, but none to penicillin or sulfonamides.

PSITTACOSIS resembles primary atypical pneumonia; usually there is the additional history of contact with parrots, parakeets, pigeons, chickens, domestic ducks, or other birds. Diagnosis is established by isolation of the virus or by finding of complement-fixing antibodies in rising titer.

Q FEVER resembles primary atypical pneumonia, except that headache may be prominent and symptoms referable to the respiratory tract may be minimal. Physical findings in the affected lung are few. There may be a history of contact with cattle (dairy farmer, stockyard worker). The course is not affected by penicillin, but a good response may follow treatment with aureomycin or "Chloromycetin."

ACUTE TUBERCULOUS PNEUMONIA may be difficult to differentiate, since, in the early stages, tubercle bacilli may not be demonstrable in the sputum. Fever is likely to be remittent or intermittent rather than sustained. There is no response to penicillin or aureomycin, but there may be improvement with streptomycin.

PRIMARY PLEURAL EFFUSION DUE TO TUBERCULOSIS seldom has the abrupt onset of pneumococcal pneumonia, and the fever is usually remittent or intermittent. The leukocyte count is in the normal range. The physical and roentgenologic signs are those of effusion rather than consolidation. The natural course is prolonged. There is no response to penicillin or aureomycin, but fever may subside promptly following streptomycin therapy.

PULMONARY INFARCTION occurs especially in individuals with congestive heart failure or in persons confined to bed by other illness or surgical operation. There may be sudden onset of pleuritic pain, with anxiety and labored breathing; the physical and roentgenologic signs may resemble those of pneumonia. There is rarely a chill, and the temperature elevation is usually less than that in pneumococcal pneumonia. The sputum may be frankly bloody rather than rust-colored or pink. Signs of phlebothrombosis in the lower extremities may be detected. In persons with chronic passive congestion of the liver a moderate jaundice is likely to supervene.

ATELECTASIS may occur in persons confined to bed, particularly when respiratory motion is limited or when the cough reflex is depressed by sedation or organic disease (cerebrovascular accident or uremia). There may be pleuritic pain, and physical findings may suggest consolidation. The trachea and the mediastinal structures are often shifted toward the affected side. Bronchoscopy may reveal a mucous plug in a bronchus supplying the affected area.

PNEUMONITIS ASSOCIATED WITH BRONCHIECTASIS may be due to pneumococcus or to a mixture of bacteria. The clinical picture and roentgenologic findings may be similar to those of pneumococcal pneumonia. The underlying pathology will be suspected from the history of chronic productive cough.

LUNG ABSCESS may produce a clinical picture resembling that of pneumococcal pneumonia with abrupt onset, chill, and pleuritic pain. There may be a history of alcoholic intoxication or of

operation such as tonsillectomy or tooth extraction. The sputum is likely to be purulent and profuse. The temperature may be remittent or intermittent. Diagnosis is established by roentgenologic demonstration of cavity.

Treatment: GENERAL. The patient should be kept in bed in the position which is most comfortable. He may prefer to lie supine or on one side or in a semi-sitting position. He may be allowed to turn or sit erect for examination, or for any other necessary procedure. During the first few hours following treatment he may have little appetite and need not be urged to eat. Usually, however, within 12 to 18 hours after the beginning of specific therapy the patient will accept a soft or regular diet. The former emphasis on measures to avoid abdominal distention—i.e., diets, laxatives, enemas, stupes, etc.—seems unnecessary now that effective therapy is available. Oxygen therapy may be employed if there is intense cyanosis or notable tachycardia, but it is rarely, if ever, an essential factor in the treatment of pneumococcal pneumonia.

PLEURITIC PAIN. If mild, this may be controlled with codeine, 30 mg. every few hours. Adhesive strapping of the affected side may diminish pain, but may also increase the likelihood of atelectasis and interferes with subsequent examinations. The best means of relieving severe pleuritic pain is intercostal nerve block, injecting 2 ml. of 1 per cent procaine beneath the rib margins in the affected area proximal to the site of the pain. This procedure is not technically difficult or dangerous, and may be of enormous benefit in relieving pain. Transient relief of pleuritic pain can sometimes be obtained by injection of 10 ml. of 10 per cent calcium gluconate intravenously; this may be of assistance in obtaining a sputum specimen for examination, and may facilitate physical examination.

PENICILLIN is the drug of choice in the treatment of pneumococcal pneumonia. The borderline effective dose is very small—in the neighborhood of 60,000 units per day—and a total dose of 300,000 units daily provides a good margin of safety. This may be given in the form of procaine penicillin, once daily, or as aqueous solution of crystalline penicillin at three- or four-hour intervals. Treatment should be continued until the patient has been afebrile two or three days. A single injection of procaine penicillin with aluminum monostearate containing 300,000 units of

penicillin may actually be sufficient for the entire illness, but is not advised as a routine practice.

AUREOMYCIN has been shown to exert a curative effect in some cases of pneumococcal pneumonia, but it is probably not the agent of first choice. The dosage range is 1.5 to 6 Gm. per day.

SULFONAMIDES are effective in pneumococcal pneumonia, though not so dramatic as penicillin. The dose of sulfadiazine is 6 Gm. daily for adults.

SERUM THERAPY, though effective, has been abandoned because it is expensive, difficult to administer, and carries the risk of anaphylactic reactions and serum sickness.

Treatment of Complications: PLEURAL EMPYEMA. This should be watched for and treated as early as possible. When effusion is detected, the fluid should be examined for pneumococci. If these are found, 200,000 units of aqueous penicillin should be injected into the pleural space. The volume of penicillin solution injected into the cavity should be approximately one-fourth the volume of the exudate just withdrawn. This procedure should be repeated daily until cultures have been negative for several days or until no more fluid can be obtained. Fluoroscopic guidance may be required for the aspiration of small empyema pockets. When the exudate is especially thick and fibrinous, instillation of streptococcal fibrinolysin (streptokinase) may facilitate its withdrawal. In rare instances where aspiration and instillation of penicillin is technically difficult or when the empyema is of some weeks' standing, surgical drainage may be necessary, but cases of this type are now unusual.

ATELECTASIS should be treated by having the patient take deep breathing exercises, and by use of measures for relief of any associated pleuritic pain. These may serve to loosen a mucous plug which can then be expelled by coughing. If not, bronchoscopic aspiration should be employed without undue delay.

Prognosis. The fatality rate in pneumococcal pneumonia averaged 25 to 30 per cent before effective therapy was available. With penicillin therapy, the gross fatality rate is now less than 5 per cent. Deaths occur principally among individuals who are already debilitated by other serious illness such as carcinoma, alcoholism, or malnutrition, or among those who develop such complications as pneumococcal pericarditis, endocarditis, and meningitis.

PNEUMOCOCCAL MENINGITIS

Infection of the meninges may develop without preceding signs of infection elsewhere, or as a complication of pneumococcal pneumonia, otitis, sinusitis, or mastoiditis. It may follow a head injury in which skull fracture creates an opening into the nasal cavity or one of the paranasal sinuses. Rarely, it develops as a complication of pneumococcal endocarditis. The clinical manifestations are those of any acute pyogenic meningitis—fever, chills, headache, stiffness of the neck, positive Kernig and Brudzinski signs, and cranial nerve palsies. The spinal fluid is usually cloudy and may have a dirty greenish appearance. Stained smears often demonstrate myriads of bacteria and relatively few polymorphonuclear leukocytes. The dextrose content is reduced.

Treatment. The problem is one of obtaining adequate concentrations of penicillin in the affected tissues and in the spinal fluid. Clinical experience indicates that this can be achieved best by intramuscular injection of large doses of penicillin—i.e., 12,000,000 units daily. The only objection to this form of treatment is the expense. Almost as good results can be obtained by injecting smaller quantities of penicillin intramuscularly—i.e., 300,000 units daily—and 10,000 units of penicillin in 10 ml. of physiological salt solution intrathecally once daily. An objection to the second form of treatment is the necessity for numerous spinal punctures and the slight possibility of irritative changes in the leptomeninges caused by penicillin. Local irritating effects of penicillin can, however, be minimized by limiting the quantity injected to 10,000 units and by diluting this in 10 ml. of physiological salt solution.

Course and Prognosis. Most cases of pneumococcal meningitis appear to respond initially to penicillin therapy. Signs of meningeal irritation subside, the temperature falls toward normal, and bacteria disappear from the spinal fluid. Often, however, relapse occurs after several days or even weeks of therapy; this is accompanied by exacerbation of clinical manifestations and re-appearance of bacteria in the spinal fluid. Initial treatment should be continued for at least two weeks in order to minimize the chance of relapse, and in the event of a relapse it should be continued for at least 10 additional days. Cure of the meningitis can be achieved in 70 to 80 per cent of

cases. Failure may be due to a massive portal of entry such as infection in the cranial bones, or to the development of localized pockets of infection in the meninges into which penicillin does not diffuse adequately.

PNEUMOCOCCAL ENDOCARDITIS

The clinical picture is that of acute bacterial endocarditis, with remittent fever, splenomegaly, petechial hemorrhages in the conjunctivas, and secondary pneumococcal infections in the lungs, meninges, and joints. The valve on which the infection is localized may have been previously undamaged, therefore heart murmur is not always present. The blood culture is consistently positive for the pneumococcus, yet at the same time specific antibodies for the infecting organism can usually be demonstrated in the blood. This combination of findings is seldom observed except in endocarditis.

Penicillin is the treatment of choice. Despite the fact that pneumococcus is quite sensitive, large doses seem advisable (i.e., 6,000,000 or more units daily), since cases ending fatally often show an abscess in the adjacent myocardium even though healing had begun to take place on the valve leaflet. It seems logical to suppose that effective therapy of such a myocardial abscess would require a high concentration of penicillin in the blood.

PNEUMOCOCCAL PERITONITIS

Primary pneumococcal infection of the peritoneum occasionally occurs in young girls. The symptoms are fever, pain, distention of the abdomen, and vomiting. Purulent fluid accumulates rapidly in the abdominal cavity. A positive diagnosis can be made by examination of this fluid. The blood culture may also be positive.

Penicillin therapy is usually rapidly curative, the clinical manifestations subsiding within 24 to 48 hours, on a dose of 300,000 units per day.

Pneumococcal peritonitis is a frequent complication in the nephrotic syndrome, particularly in young children with "lipoid nephrosis." These patients may suffer repeated episodes of pneumococcal peritonitis. Here also the response to penicillin therapy is excellent.

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Staphylococcal Infections

Paul B. Beeson

Etiology

Pathogenesis

Infections of Skin and Subcutaneous Tissues

Infections of Respiratory Tract

Infections of Bone

Food Poisoning

Miscellaneous Staphylococcal Infections

Treatment

Etiology. The staphylococci are Gram-positive cocci which tend to group in clusters. They grow luxuriantly on infusion mediums in the presence of air, and are relatively resistant to heat, antisepsics, and diminished oxygen tension. On the basis of pigment production three varieties are recognized: *Staphylococcus aureus*, which produces a golden pigment; *Staphylococcus citreus*, which produces a lemon yellow pigment, and *Staphylococcus albus*, which does not produce pigment. Many strains of *S. aureus* can cause infections, whereas the other types are less frequently and only feebly pathogenic. The capacity to produce hemolysis on blood agar and to coagulate citrated plasma (coagulase test) are two properties usually associated with pathogenicity. Attempts at serologic classification of staphylococci have not proved of much value in clinical practice.

Staphylococci are widely distributed in nature, and can often be cultivated from soil, air, and water. They are always present on human skin and are often found in the anterior nasal cavity. Most of those on the skin seem to be harmless varieties of *S. albus*. Not uncommonly, however, potentially pathogenic strains are found in the nose, and nasal carriers may be important sources of staphylococcal infections.

Pathogenesis. Staphylococci can penetrate the hair follicles and infect normal skin. Sweating and friction in hairy areas predispose to such infection, as indicated by frequent involvement of the axilla, perineum, and back of the neck. Coccii discharged from one lesion are apparently able to penetrate adjacent hair follicles, sometimes resulting in chronic furunculosis. Staphylococci also infect injured skin in the region of cuts, abrasions, ulcers, and surgical wounds, espe-

cially in the presence of a foreign body such as a suture (stitch abscess). Organisms from the nose can invade other parts of the respiratory tract, causing sinusitis, otitis, mastoiditis, bronchitis, and pneumonia.

The characteristic lesion caused by the staphylococcus is a localized abscess filled with bacteria, polymorphonuclear leukocytes, and tissue debris. The surrounding tissue is often compressed into a false membrane, and there is thrombosis of neighboring lymphatics and small blood vessels. Bacteremia and metastatic infection may occur by dissemination of infected thrombi.

A few strains of *S. aureus* produce an erythrogenic toxin similar to that of the hemolytic streptococci, and in rare instances staphylococcal infection causes a rash identical with that of scarlet fever.

Infections of Skin and Subcutaneous Tissues. The commonest staphylococcal infections are *pustules*, *furuncles* (boils), and *carbuncles*. Pustules are small indolent abscesses located in the epidermis. They are usually caused by *S. albus* and rarely lead to systemic infection. Furuncles and carbuncles, however, are usually due to *S. aureus* and produce acute inflammatory changes with redness and pain. The carbuncle is more deeply situated, involving the subcutaneous tissue and draining to the skin surface through multiple openings. Furuncles and carbuncles may give rise to metastatic infection in distant parts of the body.

Occasionally staphylococci produce indolent granulomatous lesions in man similar to the condition called *botryomycosis* in cattle. Such processes are usually located in the subcutaneous tissues, and, resembling "cold abscesses," they may show great chronicity with none of the typical signs of acute staphylococcal infection.

Infections of Respiratory Tract. *S. aureus* is occasionally the etiologic agent in sinusitis and otitis media, and may rarely produce *acute pharyngitis* or *tonsillitis*. Infections of the tra-

cheobronchial tree and lung vary from mild *tracheitis* or *bronchitis* to overwhelming, rapidly fatal *pneumonia*. Epidemics of staphylococcal pneumonia sometimes occur in the wake of influenza. The clinical picture and radiographic findings may be indistinguishable from those of other acute bacterial pneumonias, except that subsidence by crisis is unusual and the incidence of lung abscess and empyema is high. Staphylococcal pneumonia is likely to be particularly severe in young children, with early invasion of the pleural cavity and frequent development of bronchopleural fistula leading to pyopneumothorax.

Infections of Bone. Acute hematogenous osteomyelitis, a disease of children and adolescents, is nearly always caused by *S. aureus*. The infection is usually located at the end of a long bone, beginning on the diaphyseal side of the epiphyseal line. It extends either into the marrow cavity or outward to the surface of the bone, where it spreads between the periosteum and cortex. Separation of the periosteum may interfere with the blood supply of the bone and result in necrosis and sequestration.

The clinical picture is characterized by rapid development of throbbing pain in the extremity, accompanied by fever and leukocytosis. On examination there is soft tissue swelling and exquisite tenderness to deep pressure over the affected bone. Occasionally there is effusion into a nearby joint, movement of which may be painful. The infection is likely to be accompanied by thrombophlebitis and bacteremia. Splenomegaly is common and metastatic infections may develop. Roentgenographic examination during the first few days may show only soft tissue swelling with no abnormality in the bone. Later, bone destruction becomes evident, followed by proliferative changes. Formerly the fatality rate during the first few weeks of the disease was about 20 per cent, and many surviving patients were incapacitated by chronic osteomyelitis with draining sinuses and recurrent flare-ups associated with sequestration of bone fragments. Since the introduction of penicillin therapy, however, the fatality rate during the acute stage is less than 5 per cent, and the incidence of chronic disability has been greatly reduced. Therapy is considered at the end of this chapter.

Food Poisoning. Staphylococci can multiply in foods at environmental temperatures considerably below that of the body. Under such condi-

tions some strains, usually *S. aureus*, can elaborate a toxin which, when ingested, produces gastrointestinal symptoms (enterotoxin). This is probably the commonest cause of epidemic food poisoning. The toxin can withstand boiling and is therefore not affected by ordinary cooking. Foods which provide good mediums for enterotoxin production and which have frequently been incriminated in food poisoning outbreaks include: pastries containing cream filling such as eclairs and cream puffs, custards, whipped cream, cottage cheese, milk, butter, cold meat, gravy, and salad dressing.

After a short incubation period, usually two to four hours, cramping epigastric pain, nausea, vomiting, and diarrhea suddenly appear. There is little or no fever, which helps to differentiate such attacks from acute bacillary dysentery. Abdominal tenderness may be present, but is not localized to one area. Involuntary rigidity and rebound tenderness are absent. Diarrhea may be severe for a few hours but seldom lasts more than a day, and the patient is commonly symptom-free by the end of 24 hours. A sharp attack may leave considerable weakness which is overcome gradually in two or three days. Treatment consists of bed rest and the withholding of food and liquids by mouth, while fluids and electrolytes are replaced parenterally. Paregoric (camphorated opium tincture) may be given for relief of diarrhea and cramping, provided the possibility of acute appendicitis has been ruled out.

Miscellaneous Staphylococcal Infections. *Acute bacterial endocarditis* may be caused by *S. aureus*, and was invariably fatal before the advent of penicillin. There is an irregular fever, often with chills followed by high peaks. Petechial hemorrhages appear in the skin and conjunctivas, and staphylococcal abscesses develop in various parts of the body, especially in the lungs, kidneys, and brain. Heart murmur may be present or absent. *Acute pyelonephritis* is often caused by *S. aureus*. The clinical picture resembles that of pyelonephritis due to Gram-negative bacilli. *Spinal epidural abscess* may occur as a complication of staphylococcal infection elsewhere. This is characterized by root pain, signs of compression of the spinal cord, fever, leukocytosis, and increase in the cells and protein of the spinal fluid. *Meningitis* may result from head trauma or extension from infection in the ears, paranasal sinuses, or mastoids, or from

bacteremia. The clinical manifestations are those of an acute purulent meningitis. *Acute puerperal mastitis* is usually caused by hemolytic *S. aureus*. *Septicemia* is occasionally the first evidence of staphylococcal infection, manifested by fever, splenomegaly, multiple abscesses in lungs, kidney, brain and bone, there being no clue as to the site of the primary focus. Infants and young children with staphylococcal bacteremia may develop hemorrhagic skin lesions which rapidly undergo necrosis. Before effective agents became available this condition was fatal in about 80 per cent of cases.

Treatment. Penicillin is the chemotherapeutic agent of choice and is highly effective in treating staphylococcal infections caused by sensitive strains. Unfortunately some strains are resistant to penicillin; these are being encountered more and more frequently. Even among sensitive strains there is a rather wide variation in tolerance to the drug. Consequently, in any potentially serious infection, the responsible organism should be isolated and tested for penicillin sensitivity. This permits proper adjustment of penicillin dosage and early recognition of resistant strains which require extraordinary measures. An adequate dose of penicillin may range from 200,000 units to many millions of units per day. In some localized infections, such as those of the joints and serous cavities, penicillin can be injected locally, and this should be done whenever practical.

Sulfonamides (sulfadiazine, sulfathiazole, sulfamerazine) have some bacteriostatic effect on the staphylococcus, and may be employed as adjuvants to penicillin therapy or in cases where the organism is penicillin-resistant. Some strains of staphylococcus are inhibited by streptomycin

at therapeutic levels; occasionally this agent is useful. Superficial staphylococcal infections may be treated by application of bacitracin or tyrothricin.

Aureomycin is bacteriostatic against most strains of staphylococcus, and may be used in cases when penicillin is ineffective, in a dose of 4 or 6 Gm. per day.

There is some controversy regarding the advisability of surgical treatment in acute hematogenous osteomyelitis. If the infection is due to a penicillin-sensitive organism, chemotherapy alone appears to be the method of choice. Some surgeons advocate combined antibiotic and surgical treatment of all cases. They recommend that drainage be instituted as early as possible, either by opening the periosteum or by making a series of burr holes in the marrow cavity.

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Hemolytic Streptococcal Infections

Charles H. Rammelkamp

History
Bacteriology
Acute Streptococcal Infections

Epidemiology

Pathogenesis

Clinical Manifestations

Treatment

Prevention

Late Nonsuppurative Complications of Beta Streptococcal Infections
Etiology and Pathogenesis
Epidemiology of Rheumatic Fever
Pathology of Rheumatic Fever
Clinical Manifestations
Laboratory Findings
Diagnosis
Course and Prognosis
Treatment
Prevention

Advances in our knowledge of streptococcal infections in the past few decades have made it increasingly clear that aerobic streptococci, as a group, are probably among the most important bacterial pathogens for man. These bacteria may invade any tissue or organ and, depending on the site of invasion and the parasite-host relationship, produce different clinical syndromes. Streptococcal infections may be divided conveniently into two large groups. The acute and often dramatic illnesses, such as sore throat, scarlet fever, erysipelas, puerperal fever, and lymphangitis, are included in the first group. These infections occur frequently and are characterized by certain toxic, septic, or suppurative features. The second group of diseases have been called the late, nonsuppurative complications of streptococcal infections. These illnesses, which include acute rheumatic fever and acute glomerulonephritis, commonly become manifest two or more weeks after an acute streptococcal infection. These diseases assume major importance because they may be followed by chronic valvular heart disease or chronic nephritis.

History. The number of scientists who have contributed significant data concerning streptococci and the diseases they produce is legion. In the late nineteenth century several investigators saw the streptococcus in exudates, and Pasteur in 1879 observed a chain of streptococci in blood from a woman with puerperal sep-

sis. Among others, Schottmüller, Mandelbaum, Brown, Griffith, and Lancefield made significant contributions toward the classification of these organisms. The various substances produced by streptococci which probably play an important role in the disease process have been described and studied by Weld, Todd, the Dicks, Tillett, and Duran-Reynals.

Mallory and Keefer and others have been especially interested in the pathologic features of the acute phase of streptococcal infections. Extensive studies of rheumatic fever have demonstrated that the Aschoff body, described in 1904, is characteristic of this late nonsuppurative sequela of streptococcal disease.

Since the recognition of scarlet fever by Sydenham in 1676, the various clinical manifestations of streptococcal infections have received the attention of many investigators. In this country the Dicks, Dochez, Swift, Blake, Birkhaug, Keefer, and Francis have attempted to relate the various diseases to the streptococcus and the substances elaborated by these organisms. Coburn, Jones, Longcope, Paul, and Rantz have been especially interested in the role of streptococci in rheumatic fever.

Bacteriology. There are certain characteristics of the streptococcus that are important. These cocci are Gram-positive and tend to form chains. On the basis of the colonial reaction when grown on an agar plate containing blood, it is possible to divide the streptococci into three fundamental classes. The alpha colonies show a zone of incomplete lysis and greening or methemoglobin formation of the red blood corpuscles in the medium surrounding the colony; beta streptococci exhibit a clear zone of complete hemolysis of varying extent; and, finally, gamma streptococci exhibit no reaction. Such a simple procedure as streaking a culture on a blood agar plate is sufficient to indicate the important pathogenic streptococci because those exhibiting beta-hemolysis are responsible for the majority of infections in man. Occasionally beta-hemolysis is not apparent

when the organisms are streaked on the surface of the plate, but becomes obvious only in a poured blood agar plate.

Although knowledge of the reactions of streptococci on blood agar plates is useful to the clinician as an indication of the possible pathogenicity of an organism, it was not until Griffith and Lancefield devised a serologic classification that the epidemiologic and immunologic features of streptococcal infections were established. A polysaccharide, termed "C substance," is present in the streptococcal cell and reacts in a precipitin test with specific antiserum. On the basis of this reaction it has been possible to divide streptococci into the 12 groups, A, B, C, D, E, F, G, H, K, L, M, and N.

Numerous investigators have shown that most respiratory tract infections in man are caused by Lancefield's group A streptococci. Groups C and G only rarely cause such infections. Group D streptococci, previously included in the classification as *Streptococcus faecalis* or enterococci, commonly inhabit the gastrointestinal tract and are responsible for infections of the abdominal cavity and the urinary tract. At times any of the Lancefield groups may cause infections in man.

Originally it was thought that the Lancefield groups included only beta streptococci. It is now known that there are some alpha and gamma streptococci in most of the groups, but such organisms are rarely found to belong to group A. Group D includes many nonhemolytic streptococci.

Not only may the streptococci be classified by grouping, but also most groups contain several different types which may be determined by serologic tests. Group A, of primary interest to the clinician, comprises at least 40 specific types. Typing is based either on an agglutinin reaction by the Griffith technic or on the precipitin test as described by Swift, Wilson, and Lancefield. The type-specific antigen detected in the streptococcus is the *T* substance in the former method, the *M* substance in the latter. Extensive study has shown the *M* substance to be a protein.

By grouping and typing streptococci, considerable information has been accumulated concerning streptococcal infections from both a theoretic and a practical standpoint. The carbohydrate responsible for the group characteristics is nontoxic and unassociated with virulence or immunity. In contrast, the *M* protein, which

tags the organism as the polysaccharide tags the pneumococcus, is identified by typing, is antigenic, and is probably responsible in part for the virulence of the organism as well as for type-specific immunity. Glossy forms of group A streptococci which contain no *M* substance are avirulent, whereas virulent organisms always contain this specific protein. The *T* substance is not related to virulence.

There are several substances produced during the growth of beta streptococci which serve to differentiate these organisms from other streptococci as well as to explain, in part, their pathogenic effects. The type of hemolysis has been used, as described above, for a rough classification of these bacteria. Of the various hemolysins produced by streptococci, at least two types have been recognized and termed "streptolysin O" and "streptolysin S." Streptolysin O is oxygen-labile. Streptolysin S is insensitive to oxidation or reduction but is destroyed rapidly by heat. These two forms of hemolysins are produced only by streptococci of Lancefield groups A, C, and G, the three organisms which cause the majority of human infections. These substances, when injected into animals, produce intravascular hemolysis and death. The role of these hemolysins in infections in man is not definitely known, but they may be responsible for the anemia observed during the course of certain streptococcal diseases. In man, infections due to streptococci of groups A, C, and G result in the production of antistreptolysins to the O and S types. Approximately 85 per cent of patients develop antistreptolysin O during the second to third week of convalescence. It is apparent, then, that the determination of the antistreptolysin titers of acute and convalescent serums may establish the diagnosis, since an increase in titer occurs only following a streptococcal infection.

Another filtrable toxin produced by group A streptococci is the erythrogenic or *scarlatinal toxin*. It is so named because it causes a scarlatiniform rash when injected into man, and, if sufficient quantities are given, there may be fever and nausea. That this toxin is responsible for the rash and toxic features of scarlet fever is now well established. Trask and Blake were able to demonstrate a toxin in the circulating blood of patients with scarlet fever and showed that it was neutralized by specific antitoxin. Using the

erythrogenic toxin as an antigen, a skin test for susceptibility to scarlet fever was developed by the Dicks. When one skin test dose is injected intradermally, subjects susceptible to the erythrogenic toxin respond with an area of erythema which reaches its maximum within 24 hours. Subjects exhibiting this skin reaction are susceptible to scarlatiniform rashes when infected by streptococci which produce erythrogenic toxin. It should be emphasized that individuals exhibiting a negative Dick skin test, although generally immune to scarlet fever, are not immune to infection by group A streptococci. The occasional occurrence of second attacks of scarlet fever may be explained by the fact that there are at least two types of immunologically distinct erythrogenic toxins.

From the standpoint of prevention and treatment of scarlet fever, the discovery of the erythrogenic toxin led to the use of prophylactic immunization as well as convalescent serum and specific antitoxin in treating severe cases.

In 1933, it was observed that hemolytic streptococci rapidly liquefied normal human fibrin. The extracellular substance responsible for this action was termed *fibrinolysin*. It is now known that fibrinolysin does not lyse the fibrin directly but, rather, activates a serum enzyme, *lytic factor*, which in turn lyses the clot. For this reason the term *streptokinase* has been suggested for the substance produced by the streptococcus. Streptokinase is produced by strains of Lancefield groups A, C, and G, and only occasionally in small amounts by groups B and F. Recently it has been shown that the various types of group A streptococci vary in their ability to produce streptokinase.

The exact role of streptokinase in the infectious process is not known. The spreading nature of streptococcal infections has been thought to be due to streptokinase which breaks down the fibrin barrier.

Following infection in man by a strain of group A streptococcus which produces large amounts of streptokinase, antibody usually develops which specifically prevents the lysis of fibrin. Thus, the measurement of antifibrinolysin or antistreptokinase may aid in diagnosis. This serologic test is not so useful a diagnostic tool as the antistreptolysin test because not all group A streptococci produce sufficient streptokinase to stimulate antibody formation.

Other substances which may play a role in the pathogenesis of streptococcal infections are leukocidin and hyaluronidase. Leukocidin, which is probably identical with streptolysin O, is able to inhibit phagocytosis in vitro. Whether it is absorbed in sufficient quantities in patients with streptococcal infections to inhibit phagocytosis in vivo has not been determined. The enzyme hyaluronidase, or spreading factor, undoubtedly facilitates the spread of bacteria by increasing tissue permeability. It is produced in large quantities by types 4 and 22 of group A streptococci.

ACUTE STREPTOCOCCAL INFECTIONS

EPIDEMIOLOGY

Aerobic streptococcal infections are found in all races, in both sexes, and at all ages. Furthermore, they occur during any season of the year throughout the world. It is true, however, that the *incidence* and the *clinical manifestations* are altered by certain of the above factors. Thus streptococcal respiratory infections, especially scarlet fever, are encountered during the colder months of the year in the Temperate Zones. Scarlet fever is said to be rare in the tropics. Age plays an important role in the type of infection acquired. Under the age of three months, streptococcal infections are rare and, when they occur, are associated with a high mortality. Between the ages of 6 months and 10 years, scarlet fever is prominent. Tonsillitis and pharyngitis are especially prevalent throughout childhood and early adult life. In the female during the child-bearing period, puerperal infections caused by streptococci are occasionally observed. Finally, erysipelas, which may occur at any age, appears to be more prevalent in infants and the older age groups.

Soon after birth, alpha streptococci appear in the upper respiratory tract and may be isolated therefrom throughout life. There is little evidence that they cause primary infections of the throat. Streptococci of Lancefield groups C and G and, more rarely, organisms of groups other than A may be isolated from the oropharynx of 5 or more per cent of the normal population. These organisms infrequently are responsible for a primary infection of the throat. Occasionally group C and G streptococci cause tonsillitis with or without a cutaneous rash.

The group A flora of the oropharynx of any population group is made up of many different specific types, but usually several types predominate. In general, at least 5 per cent of the people of any community harbor group A streptococci. The prevalence varies and depends upon the cultural methods used as well as upon environmental, host, and bacterial factors.

Variations in the carrier rate of beta streptococci are due primarily to variations in incidence of group A streptococci. Such streptococci are isolated more frequently in the winter months than during summer. Persons under 20 years of age, especially if the tonsils are present, are more likely to harbor group A streptococci than adults. Some individuals may harbor more than one type of streptococci.

Studies of carriers of group A streptococci suggest that many are convalescent carriers; that is, they recently suffered either an apparent or an inapparent infection. This appears to be especially likely if large numbers of streptococci are isolated from the oropharynx. Such individuals frequently give a history of a recent illness and the antistreptolysin titer of their serums is high. These data suggest that streptococci of group A rarely occur in the throat in large numbers except immediately before, during, or after an infection.

Group A streptococci are spread from one individual to another by means of direct contact, by infected droplets and droplet nuclei, and through intermediary objects such as food, dust, dishes, and blankets. Although direct contact undoubtedly accounts for some infections, it seems likely that droplets or droplet nuclei account for most infections. Droplet nuclei remain suspended in the air for some hours, especially in buildings where ventilation is poor.

Recent studies have emphasized the importance of the nasal carrier of group A streptococci in the spread of streptococcal infections. It has been demonstrated that nasal carriers contaminate their immediate environment to a high degree and give rise to secondary cases of streptococcal infections. Individuals harboring only a few streptococci in the oropharynx cannot disseminate the organisms widely, and are, therefore, believed to be an unimportant source of infection.

Outbreaks of streptococcal infection occasionally occur following the contamination of food. Such outbreaks are dramatic in that a large num-

ber of persons are affected almost simultaneously. Formerly this type of infection was termed "septic sore throat"; aside from the fact that the infection is caused by a single type of streptococcus, it varies clinically in no way from other streptococcal epidemics.

The spread of streptococci in any population group must also be related to the degree of exposure. Thus, during the winter months when people are confined to enclosed areas and under crowded conditions, dissemination of bacteria is especially likely to occur. Illness may or may not result from the spread of group A streptococci. Apparently strains of group A streptococci vary in their ability to produce disease and perhaps also in their ability to disseminate. There is no method to quantitate these attributes of the organisms, nor is there any proof that the disease-producing ability is related to the Lancefield type.

Epidemics of streptococcal infection do not occur unless the number of susceptible persons in a population reaches a certain critical level. This is dependent primarily on specific antibacterial immunity and, in the case of scarlet fever, on specific antitoxic immunity. Little is known about bacterial immunity to streptococcal infections other than that it is type-specific. Clinical studies have demonstrated that reinfection may occur by a second type of group A streptococcus in a patient recovering from streptococcal pharyngitis and tonsillitis.

Primary infection of the upper respiratory tract is undoubtedly the most common form of streptococcal infection in man. It is doubtful whether anyone in the United States escapes one or more of these infections. The disease occurs especially in individuals between the ages of 1 and 20 years, but it may develop at any age. It is especially prevalent in the Temperate Zones during the winter and early spring seasons. In most areas the disease is endemic, but occasionally it occurs in epidemic proportions. Epidemics are usually due to one or, at the most, several types of group A streptococci, whereas many different types are responsible for cases of pharyngitis and tonsillitis occurring sporadically.

Tonsillitis and *pharyngitis* due to the beta streptococcus are characterized by an acute sore throat which may or may not be accompanied by a cutaneous rash. If a rash is observed, a diagnosis of *scarlet fever* is made. The occurrence

of a rash is related to antitoxic immunity which may be measured by the Dick test. In this test 0.1 ml. of erythrogenic toxin containing one skin test dose is injected intradermally into the forearm. The results are read at 24 hours. A test is considered positive if there is an area of erythema greater than 10 mm. in diameter.

Studies of the Dick reaction in various population groups have shown that at birth and up to three months of age the test is usually negative. By the age of one to two years, 85 per cent of the reactions are positive. There is a rapid decline in the positive reactors to a level of approximately 15 per cent at the age of 10. During the rest of life the decline is gradual. These results would indicate that children under the age of 10 are most susceptible to scarlet fever, and this is the age period when most scarlet fever occurs. In general, Dick-negative persons do not develop a cutaneous rash when infected by a toxin-producing strain of streptococcus. Following an attack of scarlet fever the Dick reaction usually becomes negative. It is to be emphasized, however, that these relationships are not observed constantly. The discrepancies may be due to false reactions in the skin as well as to different immunologic reacting toxins.

The incidence of scarlet fever has not changed significantly in the past 30 years, but there has been a spectacular decline in mortality. Top reports a fatality rate in Detroit of 2.7 in 1920, 1.3 in 1930, and 0.3 in 1940. The reason for the apparent decreasing severity of scarlet fever is not entirely clear.

The epidemiology of scarlet fever is the same as that of tonsillitis or pharyngitis, with the exception that the erythrogenic toxin-antitoxin relationships must be considered. Organisms which produce erythrogenic toxin may cause tonsillitis or pharyngitis without rash in Dick-negative individuals. The same organisms in a Dick-positive individual may produce tonsillitis and an erythematous rash. There is some evidence that certain types of group A streptococci are more likely to produce a skin rash in susceptible subjects than are other types. In England, over a period of years, Griffith types 1, 3, 4, and 24 have been the common cause of scarlet fever. It should be emphasized again that any type may produce this infection.

Infections of the *paranasal sinuses* usually develop following infection of the tonsils or pharynx.

Not only may they occur as a complication of streptococcal sore throat, but they are also commonly seen following measles, influenza, pertussis, and other respiratory infections. When caused by streptococci, the organisms usually belong to group A. Patients with acute streptococcal infections of the throat may develop the above complications either early or late in convalescence. The early suppurative infections are caused by the same organisms responsible for the initial disease, whereas complications beginning after the second or third week frequently are due to a different type and, therefore, may be considered a cross infection.

Group D streptococci account for about 10 per cent of the milder *ear infections*. These infections, especially otitis media and mastoiditis, occur predominantly in children.

Bacterial pneumonia caused by aerobic streptococci accounts for less than 5 per cent of all cases of pneumonia. The disease is almost invariably caused by group A streptococci and may arise secondarily to an infection of the upper respiratory tract. Epidemics have been observed following influenza and measles. It also is likely to occur in those individuals with chronic lung disease, including asthma and bronchiectasis. Infection of the lungs is observed at any age but is commoner in infants than in older children and adults. Streptococcal empyema, a complication of pneumonia in most instances, is observed most frequently in patients under 30 years of age.

Formerly it was thought that *erysipelas* was caused by a specific strain of beta-hemolytic streptococcus, but it is now known that group A, C, or G streptococci may be isolated from the skin lesions. Group A organisms are responsible for the majority of infections, and the organism may belong to any of the various types in this group. Although there are examples where several people have contracted erysipelas following contact with a case, in most instances it has been impossible to trace the infection to such contact. Usually there is a history of preceding respiratory infection, and streptococci of the same group and type may be isolated from both the skin and the oropharynx. Erysipelas tends to occur in the older age groups, especially in those individuals with chronic disabling diseases. Immunity does not develop; in fact, individuals who have suffered from one attack are more susceptible than the normal population. In some of the recur-

rences, however, the organisms cannot be isolated from the skin lesions but may be found in the oropharynx. It is suggested that in such instances the disease is due to absorption of some toxic product of the streptococcus which, in turn, causes, the local inflammatory lesion in the skin that is altered in its reactivity.

Wounds may be infected by contamination at the time of dressing, either by droplets or droplet nuclei from the patient or the attending physician. Another source of infection is dust. *Lymphangitis* may arise from a minute abrasion.

Numerous studies have indicated that either aerobic or anaerobic streptococci cause *puerperal sepsis*. Approximately 70 per cent of fatal cases are due to beta-hemolytic streptococci. Most of the infections are caused by group A, although an occasional case is due to streptococci belonging to group B, C, D, or G. Since the group A streptococcus is rarely isolated from the genital tract either before or after labor, it is assumed that infection is extrinsic. Careful study of the patient and all persons coming in contact with her has shown that similar types of group A streptococci can be isolated from 75 per cent of cultures obtained from the oropharynx of such a patient or those attending her. It appears from these studies that infection is usually contracted from an outside source and occasionally from the respiratory tract of the patient herself. The transmission is either airborne or by contamination of the examiner's hands.

Aerobic streptococci are responsible for most instances of *bacterial endocarditis*. Streptococci of Lancefield group A are associated with acute endocarditis. Subacute endocarditis is almost invariably due to alpha or gamma streptococci, including members of Lancefield group D. The disease occurs primarily in those persons with rheumatic heart disease (80 per cent) and congenital heart disease (5 per cent); the remainder occurs in persons with apparently normal hearts. As a result of transient bacteremia, which is known to occur after oral operations such as tooth extraction, organisms become engrafted on the heart valves. The peak of deaths from subacute endocarditis occurs during the third decade of life.

PATHOGENESIS

Streptococci gain entrance to the body primarily through the upper respiratory tract. The

organisms, lodging on the mucous membranes or on other tissues, probably remain viable for relatively short periods unless they actually invade the tissues. In the nose and throat there is ample opportunity for invasion. The organisms usually gain entrance through the lymphoid tissues of the throat, especially the tonsils, whose crypts apparently offer an ideal locus. Occasionally the primary infection may be in the paranasal sinuses.

The factors which determine whether an infection follows exposure to the organism are multiple. Both the bacterium and the host must be considered in any discussion of the pathogenesis of infection.

The dosage or number of streptococci is apparently a decisive factor. Infection usually results when there is exposure to large numbers of group A streptococci, as occurs in food-borne outbreaks. Under natural conditions of spread, the number of organisms acquired is dependent in part on the duration and intimacy of exposure to the organism. Thus, an individual exposed for 10 hours in a small, poorly ventilated room to a person expelling large numbers of streptococci is more likely to develop disease than the individual exposed for 10 minutes in a large room to a person expelling few streptococci in the environment.

The second factor in relation to the organism is *virulence*. In general, little is known concerning this important feature. Streptococci of groups other than A may be considered relatively avirulent when implanted in the lymphoid tissues of the throat. The virulence of the group A organism may be related to their *M* antigenic component. Whether there is variation in the virulence of the group A streptococci according to the specific type is not definitely known, nor is there much evidence that rapid passage of a given type from man to man increases the virulence of the organisms, although this is a common belief.

Perhaps as important as the organism itself is the susceptibility of the host. It is stated that a recent or simultaneous infection with one of the common respiratory viruses renders the host more susceptible to bacterial invasion. Experience during World War I would seem to indicate that influenza does indeed make one more susceptible to bacterial infections. Whether the common cold or acute respiratory disease acts in a similar fashion is not known.

Whether the group A streptococcus gains a foothold in the tissues is also governed by the immune status of the host, both specific and non-specific. If the cellular clearing mechanism is efficient, the organisms may be removed before the signs of an infection appear. The presence of type-specific antibodies undoubtedly protects the individual against invasion by the streptococcus. No protective role against invasion has been ascribed to the antibodies of erythrogenic toxin, streptokinase, or streptolysin.

When the bacteria begin to multiply in the infected tissues, they produce certain toxic substances which account for the clinical manifestations of disease. Thus some of the constitutional symptoms observed in patients with scarlet fever are believed to be due to the erythrogenic toxin, for administration of antitoxin or convalescent serum is followed by a rather dramatic clinical response. Locally the organisms incite a cellular response, the tissue being invaded by inflammatory cells. Usually the mucous membrane is denuded and covered by a thin yellow, white, or gray exudate. There is edema and hyperemia of the lymphoid tissues. The lymphatics are dilated. The regional cervical lymph nodes are enlarged as a result of hyperplasia.

The organisms may invade the blood vessels if the local defense mechanism is not functioning adequately, and cause either metastatic infections such as meningitis, brain abscess, and endocarditis, or a generalized infection which without treatment almost invariably results in death. Mallory and Keefer have studied the cellular changes in such patients as well as the pathology of patients dying during the acute phase of streptococcal infections without bacteremia. In fulminating streptococcal infections the streptococci may be seen in blood vessels throughout the body as well as in the endothelial cells of the endocardium and in the perivascular areas. There is little cellular reaction around the organisms, but their distribution is similar to the distribution of those lesions observed in patients dying several days after onset of the infection. In the latter cases, foci of lymphocytes, plasma cells, and histiocytes are commonly found in the heart, especially just under the surface endothelium and endocardium. Such collections occur also in the perivascular connective tissues, myocardium, and pericardium. Occasionally some of the foci show polymorphonuclear leukocytes. In the kid-

neys interstitial nephritis is observed with focal areas of round cell infiltration in the tissue surrounding the tubules, glomeruli, and blood vessels. Similar infiltrative lesions may be observed in other organs, including the lung, portal areas of the liver, and pancreas. These widespread pathologic changes may explain the variations in the clinical features of the acute phase of streptococcal infection. Thus, during acute streptococcal infections, acute nephritis may be encountered with or without evidence of heart failure or other signs of cardiac involvement.

Most streptococcal infections are of short duration, the acute phase ending within five to seven days. The exact mechanism for recovery at this time has not been defined but, as in other bacterial infections, it is assumed that antibodies develop which aid in the destruction of the organism. Perhaps the most important of these are the antibacterial substances which have been studied by Kuttner and Rothbard. Techniques for measuring these antibodies are difficult, but it is apparent that following infection there is an increase in the bactericidal power of whole blood. Such bactericidal action is type-specific; the patient is protected only against the infecting type of group A streptococci and not against other types of this group of organisms. The duration of such antibacterial immunity is not known. In addition to the antibacterial antibodies, an increase in the antistreptolysin and antifibrinolysin titers of the blood begins to occur after five days of illness. So far as is known, however, these substances play little or no role in the bacterial-clearing mechanism. Antibodies to the erythrogenic toxin develop and, as a result, the skin rash, if present, disappears along with other toxic symptoms caused by this toxin. At the same time there is a reversal of the Dick test from positive to negative.

CLINICAL MANIFESTATIONS

ACUTE TONSILLITIS, PHARYNGITIS, AND SCARLET FEVER

The terminology used to classify streptococcal infections of the upper respiratory tract has been in use for many years and was introduced prior to the time that it was realized that *scarlet fever*, *septic sore throat*, *acute tonsillitis*, and *pharyngitis* with or without exudate were all caused by any of the numerous types of group A streptococci.

In these diseases the organism establishes itself in the lymphoid tissue; thus *streptococcal lymphoiditis* might well be substituted for the above names. Since there is no evidence that scarlet fever is more infectious than the other streptococcal diseases of the upper respiratory tract, there is little object in considering it as a separate illness. So far as is known, the course of the illness, complications, and sequelae are similar in scarlet fever, septic sore throat, and streptococcal tonsillitis.

Symptoms. The incubation period varies from 1 to 10 days, but is usually 3 to 5 days. The illness begins abruptly in most cases with symptoms of feverishness, chilliness, headache, and sore throat. Nausea and vomiting are especially common in children. Within a period of 24 to 48 hours the disease reaches its maximum intensity, and the temperature varies between 101° and 104° F. Chilliness is a constant symptom, but true rigors are rarely observed. Approximately 75 per cent or more of the patients complain of such constitutional symptoms as headache, malaise, and loss of appetite. The headache is usually generalized and not severe. Frontal headaches may occur.

The symptom which is very annoying and almost constantly present within 24 hours of onset is sore throat. The soreness is aggravated by swallowing and may be referred to the neck, so that even turning of the head is accompanied by pain. Nasal obstruction and discharge are minor complaints but occur in 60 per cent of patients. Occasionally the discharge is profuse. About half of the patients develop mild symptoms referable to the lower respiratory tract, including cough and hoarseness. The cough is not productive and is rarely associated with chest pain. Loss of voice due to laryngitis does not occur. Earache is common and may last a few hours to several days. Occasionally epistaxis is observed.

During the period of maximum temperature there may be a diffuse blush of the skin. In some cases it becomes more pronounced and a diagnosis of *scarlet fever* is made. The rash may appear from one to five days after onset of illness and is first noticed over the neck and upper chest. It spreads rapidly to include the skin over the abdomen and upper and lower extremities. The face appears flushed and a circumoral pallor is prominent in many cases. Itching occasionally occurs but is rarely severe.

Physical Signs. The severity of illness varies but the majority of patients appear mildly or moderately ill. The temperature is usually elevated to 102° to 104° F.; occasionally it may be as high as 106° F. A few patients experience no temperature rise. In children the pulse rate is between 140 and 160, in adults 120 to 140 per minute. Usually the respirations are not greatly increased.

The distinctive physical signs are due to the local inflammatory reaction and, in the case of cutaneous rashes, to the erythrogenic toxin. Various degrees of diffuse redness of the mucous membranes of the posterior pharynx, faucial tonsils, and soft palate are invariably present. The uvula is frequently edematous, as are the tonsils and pharynx, but to a lesser degree. There is lymphoid hyperplasia and edema which gives the posterior pharynx a cobblestone appearance. Characteristically there is discrete to confluent exudate on the tonsils, and variable numbers of pinhead-size areas of exudate appear on the pharynx. In severely ill patients the latter are seldom seen, probably because of the nasal secretions which cover the posterior wall. The exudate is often yellow in color, sometimes gray or white, and is relatively easily removed by swabbing. In about 20 per cent of adults, and more frequently in infants, exudative lesions on the mucous membranes do not develop. Occasionally, and especially if sinusitis and rhinitis are coexistent, there is a thick mucopurulent nasal discharge which may be tinged with blood. In children the nares may be excoriated. The cervical lymph nodes are enlarged and frequently tender. The lymph nodes just behind the angle of the jaw are the first to become enlarged and rarely may attain such size that the head is thrown back. Marked degrees of enlargement are not infrequently followed by suppuration. There is likely to be involvement, but to a lesser degree, of the anterior and posterior cervical chain of lymphatic glands.

In those patients with *scarlet fever* the signs include both an enanthema and an exanthema. The appearance of the throat is similar to that seen in tonsillitis and pharyngitis without rash, except that diffuse redness is more intense and has been described as "boiled lobster" red. There may be punctate redness of the soft and hard palates. The buccal mucous membranes appear red and swollen, as do the lips. About the second to fifth day, small, milk-white patches

may be seen on the buccal mucous membranes. These are easily peeled off and represent desquamation of the epithelium.

Early in the course of the infection the tongue is heavily coated and grayish in color. Soon the tip and edges become an angry red. Fungiform papillae become swollen and red and emerge through the gray surface of the tongue. By the fourth to fifth day there is complete lingual desquamation which leaves a red, raw-looking tongue with multiple papillary elevations, the so-called "strawberry tongue."

The color of the exanthema varies and has been described as scarlet, bright red, rose-colored, or dull dusky red. The color tends to be brighter in individuals with fair skin than in those with swarthy skin. At a distance there appears to be a uniform blush, but upon close inspection innumerable small reddish points or puncta are seen. The skin sometimes feels rough, especially over the extremities. This is caused by small pinpoint elevations at the site of the hair follicles. This sign is of special importance in races where the skin is heavily pigmented. A gooseflesh appearance is seen on the chest and abdomen. When the eruption is intense, there may be many small miliary vesicles over the chest and abdomen. The face may be free of rash, but ordinarily the temples and cheeks are deep red, leaving an area of pallor around the mouth and nose. The rash is due to hyperemia, and pressure causes it to fade. In some areas there may be punctate hemorrhages which do not fade; these are commonly seen in the creases at the elbow flexure (Pastia's sign), groin, and axillary folds.

Course of Illness (Fig. 146). The majority of upper respiratory illnesses caused by group A streptococci are self-limited. In adults the temperature usually returns to normal by the third to fourth day, whereas in children fever may persist for five to nine days. The temperature curve is not characteristic, although there is usually a slight morning remission. In patients with scarlet fever the temperature remains elevated until the rash has reached its maximum intensity. Fever may last for several weeks, but in such instances it is well to search for some suppurative complications. The constitutional symptoms, as well as the localizing symptom of sore throat, usually disappear at the time or shortly after the fever subsides.

The edema, redness, and exudate disappear

rapidly and, except for a few small isolated spots of exudate and a slight degree of redness, the throat appears essentially normal by the time the fever subsides. If such patients are observed for several weeks, the lymphoid tissues of the pos-

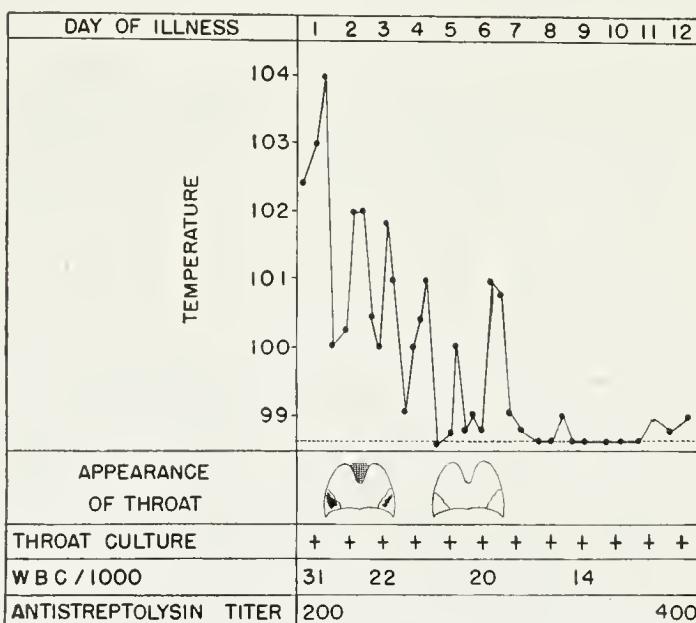


FIG. 146. The natural course of group A streptococcal tonsillitis.

terior pharynx as well as the tonsils decrease in size and by the third to sixth week appear to be normal. The lymph nodes follow a similar pattern; the tenderness disappears within a week but the nodes may not return to normal size for six weeks.

When rash does occur, it usually makes its appearance on the second day, reaches its maximum intensity shortly thereafter, and then begins to fade. The exfoliation of the epithelium begins during the decline of the eruption and is seen first in those areas where the rash originally appeared. By the sixth to seventh day it is more or less generalized. On the hands and feet the skin sheds in flakes, or, more rarely, an entire cast of the hand or foot may be observed. The skin in these areas becomes dry, hard, and wrinkled. The most typical form of desquamation is seen beneath the free edge of the fingernails and less commonly beneath the toenails. A fissure appears under the edge of the nail and then widens, revealing the soft, pinkish underlying skin. The duration of desquamation is variable.

Before the introduction of specific chemotherapeutic agents, the mortality rate was in the neighborhood of 3 per cent; it is now less than 0.5

per cent. This may be due to treatment or to the fact that few severe forms of scarlet fever are seen today. Streptococcal infections are likely to be fatal in the extremes of life and in those individuals with severe suppurative complications. The coexistence of other chronic diseases alters the prognosis unfavorably.

Laboratory Findings. The total leukocyte count is almost invariably increased and, during the first two days of illness, averages about 16,000. The percentage of polymorphonuclear leukocytes is likewise increased and may be over 80 per cent. As the illness progresses the leukocyte count as well as the percentage of segmented cells returns to normal. Usually by the fifth or sixth day normal values are obtained; in those cases where this does not occur, evidence of continuing infection may be found. During the first few days of illness eosinophils are rarely seen, but convalescence is usually associated with a temporary increase of these cells. Not infrequently a trace of albumin may be found in the urine during the acute phase of the illness. Rarely such specimens show a few red cells or casts. Proteinuria occurring during the first 10 days of illness is transient and is not attended by serious sequelae.

Cultures made on blood agar plates from a swab rubbed over the tonsils and oropharynx usually show a predominant growth of beta-hemolytic streptococci. Occasionally only a few colonies are observed. Rarely, no streptococci are isolated. In the latter instance, repeated cultures should be obtained. The organisms are usually found to belong to Lancefield group A and, more rarely, to groups C or G. The convalescent carrier state may continue for several months.

Diagnosis. Important features in the diagnosis of streptococcal pharyngitis and tonsillitis are the history of an acute onset of soreness on swallowing, associated with feverishness and other constitutional symptoms. The physical signs of diffuse redness and edema of the mucous membranes of the oropharynx, tonsils, and soft palate, the presence of discrete to confluent exudate, and enlargement and tenderness of the lymph nodes at the angle of the jaw are especially helpful. These findings, together with a leukocyte count of at least 12,000 suggest a beta-streptococcal infection. If the culture of the local lesion shows a predominant growth of beta-streptococci, the diagnosis is almost certainly

established. When only a few colonies grow on the blood agar plate, it is impossible to ascertain whether the patient is a carrier or actually has an infection due to the streptococcus. In such cases it is of considerable help to obtain acute and convalescent blood specimens for determination of the antistreptolysin or antifibrinolysin titer of the serums. An increase of titer of either of these antibodies occurs only after infection by Lancefield groups A, C, or G, the organisms which cause 98 per cent of all these infections.

When a rash is associated with the above clinical and laboratory findings, the diagnosis is scarlet fever. Confirmation is obtained if later the skin desquamates. Occasionally, however, the diagnosis is doubtful, and in such cases the *Schultz-Charlton test* may be of considerable aid. In this test 0.1 ml. of scarlet fever antitoxin or 0.2 to 0.5 ml. of scarlet fever convalescent serum is injected subcutaneously into the area of the skin where the heaviest rash appears. If the rash is due to the erythrogenic toxin, blanching is observed within two to eight hours. The test should be employed soon after the eruption appears because blanching may not occur after the second day of rash. In the presence of a rash a positive *Rumpel-Leede phenomenon* is usually obtained. In this test a tourniquet is applied to the upper extremity for 15 minutes and, in cases of scarlet fever, multiple petechiae will appear distally. The Dick test may also be of some use in establishing the diagnosis; early in the disease it is positive, whereas during convalescence it usually becomes negative.

Nonbacterial exudative tonsillitis and pharyngitis must be differentiated from streptococcal infections of the oropharynx. The cause of this disease is not known, but presumably it is of nonbacterial origin. In this infection the onset of illness is not rapid, soreness of the throat is seldom marked, and constitutional symptoms are mild. Hoarseness and cough are likely to occur several days after the onset. The exudate is usually pinhead to discrete in size and rarely confluent. Diffuse redness and edema of all the mucous membranes are rare. The lymph nodes may be slightly enlarged but they are not remarkably tender.

The leukocyte count is usually normal, although in a few cases it may be slightly elevated. Cultures of the throat fail to show beta-hemolytic streptococci. Occasionally a few strepto-

cocci are recovered, but these organisms usually belong to groups other than A and occur only in small numbers. No increase in the antistreptolysin or antifibrinolysin titers during the convalescent period can be demonstrated.

Infectious mononucleosis is most frequently observed in young adults and, because of the local reaction in the throat, is likely to be confused with streptococcal pharyngitis. The onset may be insidious and malaise is a prominent feature. Sore throat with exudative lesions of the tonsils is observed in over half of the cases. The exudate is usually white and pasty and persists for one to three weeks. The temperature tends to be very irregular and fever continues for a longer period than is common for streptococcal infections. Lymph node enlargement is more generalized but suppuration is not observed. The spleen may be palpable. In 10 to 15 per cent of cases a fleeting skin rash occurs which may be identical with that seen in scarlet fever. In such cases a negative *Schultz-Charlton test* may be helpful. The blood changes are characteristic, with a tendency for leukocytosis, and predominance of mononuclear cells. Abnormal mononuclear cells are also observed. A positive heterophil antibody test is usually obtained.

Vincent's angina is not easily confused with streptococcal infections. The disease is characterized by an insidious onset without constitutional symptoms. Fever is rare. The area surrounding the exudate shows little inflammatory reaction, and only one tonsil is involved. The cervical adenopathy is usually unilateral.

In contrast to streptococcal pharyngitis, the onset of *diphtheria* is rarely sudden and the symptoms are not severe. Sore throat is not a constant feature of the disease. The exudate is smooth and cream-colored and appears to be incorporated in the mucous membranes. The membrane is removed with difficulty, leaving a bleeding bed. Cutaneous rashes are absent. Cultures show *Corynebacterium diphtheriae*.

In those subjects with a rash, the disease must be differentiated from *German measles* and *measles*. In German measles the posterior cervical lymph node enlargement is helpful, as well as the fact that the rash tends to be macular and discrete. The tongue never peels. In measles there are prodromal respiratory symptoms and the maculopapular rash occurs chiefly on the face and neck. There is no blanching of the skin

following a *Schultz-Charlton test*. The presence of Koplik's spots aids in establishing the diagnosis.

Streptococcal infections without exudate or a cutaneous rash must be differentiated from influenza virus infections and common respiratory diseases. In general, such differentiations cannot be made on clinical evidence alone, so that the leukocyte count, culture studies, and serologic tests must be employed.

Herpes simplex infections of the throat are easily differentiated from streptococcal infections if vesicles are observed.

SINUSITIS, OTITIS MEDIA, AND MASTOIDITIS

Some degree of sinusitis probably occurs in every patient with streptococcal infection of the throat. Aside from a purulent rhinitis which persists for a few days, there are usually few symptoms or signs of involvement of the paranasal sinuses. When the nasal discharge persists, it is usually indicative of sinus infection. Such individuals may expel tremendous numbers of streptococci into their environment and thereby give rise to numerous secondary infections.

The symptoms of acute streptococcal sinusitis, other than purulent discharge, are fever, headache, and pain. The headache may be suboccipital when the sphenoid is involved, or temporal and supraorbital when the ethmoid is involved. Fever continuing after the fourth or fifth day of acute pharyngitis should suggest sinusitis. There may be edema and redness over the maxillary or frontal sinuses, and tenderness over those areas is elicited by slight pressure. The diagnosis is established by culture of the discharge, direct visualization of the nasal cavity, where pus may be seen emerging from the sinal ostiums, and, finally, by transillumination and roentgenograms.

A very common suppurative complication of streptococcal infections of the upper respiratory tract is involvement of the middle ear. Otitis media may be unilateral or bilateral. The two cardinal symptoms are fever and pain in the ear. In a few adults, and especially in children, these symptoms may be absent. Fever may develop suddenly and in the young is apt to be associated with nausea, vomiting, loss of appetite, and irritability. The temperature tends to be irregular, ranging between 102° and 103° F. Usually, feverishness is the first symptom and is followed

several hours later by pain. In older children and adults severe pain is almost invariably present. Infants, who cannot complain of pain, may refuse to lie on the affected side or may pull the ear. Drainage appears and the pain subsides when rupture occurs. With involvement of the mastoid cells, pain is intense and the fever is high.

The physical signs of middle ear infection include tenderness around the ear, inflammatory changes in the tympanic membrane, and discharge. The tenderness may be elicited either in front of or behind the ear. The auricle itself sometimes is tender. Examination shows a normal external auditory canal unless the drum membrane has ruptured, in which case pus is easily seen. Early in the infection the tympanic membrane is injected and red; later it may bulge, at which time the landmarks become obliterated. Finally, if the process does not resolve, rupture occurs.

Mastoiditis usually arises in patients with otitis media, but occasionally it may develop without an apparent infection of the middle ear. The skin overlying the mastoid cells becomes red and swollen and the posterior wall of the external auditory canal may be involved. The swelling may be so extensive that the auricle is pushed forward. Early roentgenograms show no abnormalities, but as the disease progresses there is cloudiness and destruction of the mastoid cells. The continuation of fever in patients with a draining ear suggests mastoiditis. Paralysis of the sixth cranial nerve and deep orbital pain indicates spread to the petrous cells. Chills and septic fever suggest invasion of the blood stream, thrombosis of the lateral sinus, or meningitis.

PERITONSILLAR ABSCESS

Complications of streptococcal sore throat are cellulitis and abscess formation around the tonsils. In young children these lesions appear in the retropharyngeal areas. Although these complications not infrequently follow a Lancefield group A infection, similar abscesses may be caused by other organisms. Characteristically, the patient recovers from the acute throat infection only to complain a few days later of soreness on swallowing and difficulty in opening the mouth. Trismus is caused by edema and spasm of the pterygoid muscles. Fever may recur, but in some instances it is absent. Examination early in the course of illness shows diffuse redness and edema of the

anterior pillar, the tonsillar fossa, and the soft palate on the involved side. As the disease progresses, abscess formation may become apparent and an area of fluctuation may be felt at the superior pole of the tonsil. At this time the pain is intense. Spontaneous rupture or surgical drainage is followed by rapid relief of symptoms.

PNEUMONIA AND EMPYEMA

The natural course of pneumonia caused by Lancefield group A streptococci is extremely variable, probably because in many instances it is secondary to such infections as influenza, tonsillitis, measles, and erysipelas. It may be associated with pneumococcal infections of the lung or may arise as a metastatic complication of streptococcal bacteremia. Although it is not a common complication of streptococcal sore throat, about 25 per cent follow this infection (Fig. 147).

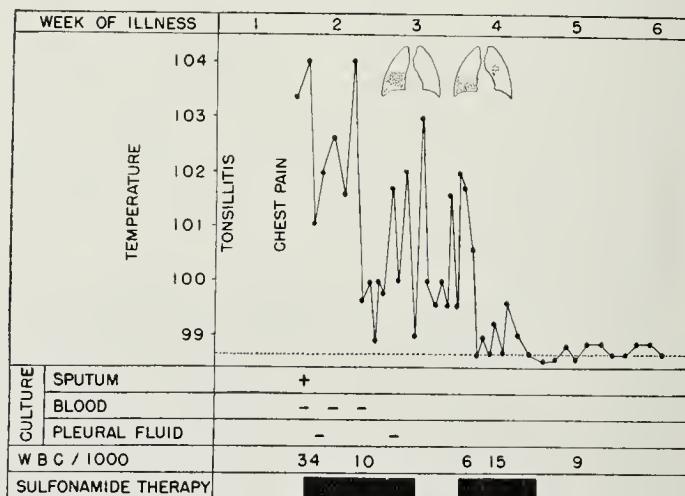


FIG. 147. Streptococcal pneumonia with a sterile pleural effusion developing after an attack of acute tonsillitis.

Characteristically, this organism produces an interstitial or confluent pneumonia. The reported mortality rate varies from 15 to 60 per cent.

The onset of pneumonia may be abrupt, with such constitutional symptoms as chills, feverishness, anorexia, and vomiting. In those instances where it arises secondarily to some other disease, the time of onset is difficult to determine. Symptoms which are especially frequent include cough, expectoration of purulent sputum, and chest pain. The pulse and respiratory rates are increased and cyanosis may be prominent. The temperature tends to be high (104° F.) and septic in type. Examination reveals local signs of pneumonia with scattered fine rales and occasional areas of dullness. Frank signs of lobar consolidation are rare.

The leukocyte count is almost invariably elevated to 20,000 to 30,000, and the sputum is found to contain large numbers of group A organisms. Usually the blood cultures are sterile, but when bacteremia does occur the prognosis is poor.

The disease, if untreated by the various chemotherapeutic agents, runs a variable course. In most instances recovery is delayed for several weeks, and lung abscess and bronchiectasis are not uncommon complications. In fatal cases mediastinitis and pericarditis may occur. The most frequent complication is empyema, which occurs in 20 per cent of the cases.

Streptococcal empyema is usually secondary to pneumonia caused by the same organism, but occasionally it arises following other infections of the lung, infarcts, or lung tumors. It is most likely to occur under the age of 30 years and the mortality rate in untreated cases is high.

When empyema develops after pneumonia, there is usually an afebrile period followed by fever and chest pain. In some cases there may be no intermission between pneumonia and empyema. Irregular fever, chest pain, dyspnea, rapid pulse, anemia, loss of weight, and leukocytosis suggest empyema. If the physical signs indicate the presence of fluid, a thoracentesis should be performed and the fluid cultured. Early in the disease the pleural fluid may be hemorrhagic. It becomes thick and purulent slowly, in contrast to the exudate seen in pneumococcal empyema.

PERICARDITIS, ARTHRITIS, PERITONITIS, AND MENINGITIS

Streptococcal infections of the various body cavities result from bacteremia or from extension from a local lesion. *Pericarditis*, a rare complication, is especially likely to occur during the course of pneumonia or empyema. The diagnosis is difficult, since the symptoms arising from pericarditis are overshadowed by the primary disease. The first sign may be a sudden increase in pulse rate and the development of an audible pericardial friction rub. Pericardial pain or discomfort develops and cyanosis and dyspnea may be extreme. The heart sounds become muffled. The apex impulse is diffuse and, if the pericardial effusion is great, signs of compression of the heart may be elicited. Roentgenograms are of great aid in establishing the diagnosis. Once the diagnosis

is suspected, aspiration and culture of the fluid are indicated.

Suppurative arthritis is secondary to bacteremia or to extension of a local cellulitis. It is a rare complication of streptococcal sore throat. Pain is the most common symptom and usually only one joint is involved. The pain is first noticed on motion, but within a short period redness, swelling, and tenderness develop and the pain becomes intense. Examination shows signs of fluid and aspiration reveals a fluid containing polymorphonuclear leukocytes and streptococci.

Infection of the peritoneum with the hemolytic streptococcus is rare but is especially apt to be associated with such local infections as erysipelas and tonsillitis. In these cases the organism belongs to Lancefield group A. Symptoms develop rapidly and, in addition to fever and other constitutional symptoms, prostration, abdominal pain, and vomiting are prominent. The pulse is rapid and weak. The abdomen is distended, tender, and rigid to palpation. Signs of fluid may be present and aspiration and culture establish the diagnosis.

A frequent form of peritonitis is associated with streptococci of groups other than A. Both alpha and gamma streptococci are found in cultures of the peritoneum from patients with peritonitis following rupture of an abdominal viscous or after various surgical procedures. These organisms are usually not obtained in a pure culture but are associated with other enteric bacteria. That they may play an important role in the outcome of such infections is suggested by the fact that penicillin exhibits a favorable influence on the course of the illness.

Streptococcal meningitis is usually caused by group A organisms, but occasionally members of other groups may be isolated from the spinal fluid. In most instances the meningitis arises by extension and invasion of the blood stream from an otitis media, mastoiditis, or petrositis, which are especially likely to develop following infection of the respiratory tract and are most frequently seen in the young age groups. Prior to the introduction of sulfonamide therapy these infections were always fatal. The symptoms of streptococcal meningitis are not distinguishable from other types of bacterial meningitis. It should be emphasized that all patients, especially infants, with infection of the middle ear should be watched for signs of meningeal irrita-

tion. Once such signs develop, lumbar puncture and culture of the spinal fluid establish the diagnosis.

WOUND INFECTIONS, LYMPHANGITIS, PUERPERAL FEVER, AND ERYSIPelas

As indicated earlier, *wound infections* are usually the result of contamination either at the time of an accident or surgical procedure, or later at the time of examination. Group A streptococci are most often involved, although members of other Lancefield groups are occasionally isolated.

Hemolytic streptococci are responsible for the majority of cases of the familiar form of *lymphangitis*. The disease is characterized by the rapid development of one or more fine red streaks extending upward from the hand or foot. Usually the process continues up to the axilla or groin, and the lymph nodes in these areas become enlarged and tender. Associated with the spread of the infection in the lymphatics, such symptoms as rigor, fever, malaise, headache, and vomiting occur. Occasionally the blood stream becomes invaded and metastatic abscesses develop. The original site of infection in these cases of lymphangitis may be inapparent. Although these infections may be serious, the course of the illness is usually short and suppuration seldom occurs along the course of the lymphatics or in the regional lymph nodes.

Puerperal infections caused by hemolytic streptococci are always serious. Following abortion or delivery, the streptococci invade the endometrium and lymphatics. The infection may spread to the surrounding structures, producing cellulitis, phlebitis, abscess, peritonitis, or bacteremia. The patient develops a high irregular fever associated with rigors. The pulse is rapid. The diagnosis is based on local signs of infection as well as on such laboratory findings as leukocytosis and isolation of streptococci from the blood stream or from the cervical discharge.

Erysipelas is an acute streptococcal infection of the skin and, to a lesser extent, of the mucous membranes. The onset is usually abrupt, beginning after an incubation period of approximately one to four days. In some patients a history of preceding respiratory infection is obtained. The initial symptoms are constitutional and include chilliness, feverishness, headache, malaise, anorexia, and vomiting. The first symptom may be a true rigor followed by rapid development of

fever. At the onset the local cutaneous lesion may not be apparent, although there may be slight redness in those instances where it arises in conjunction with an abrasion of the skin. The skin may itch and feel sore around the point of entry of the organisms. Within a few hours, and usually by 24 hours, the cutaneous lesion becomes obvious.

The skin of the face is most commonly involved, but any area of the body may be infected. The point of entry around the face may be just anterior to the ear, at the inner canthus of the eye, around the lips and nose, or over the cheeks. From these points the lesion spreads rapidly, reaching its maximum extent within three to six days. On the face, erysipelas frequently involves the butterfly area—i.e., the cheeks and nose. The lesion consists of an advancing border which is raised from the surrounding normal skin and may be purple in color. Within this border the skin is tense and usually a dark, dull red. If the infection occurs in areas where the skin is lax, such as around the eyes, edema is pronounced. The eyelids frequently become so swollen that they cannot be opened. Blebs or even necrotic areas may appear as the disease progresses.

At the height of the infection the temperature is usually high (104° to 105° F.), although occasionally the febrile response is slight. The blood stream is not uncommonly invaded during this period. The disease lasts for a variable length of time, but in most instances recovery is apparent by the sixth to seventh day. The local lesion begins to fade in the center and is usually accompanied by some desquamation and pigmentation. No scarring results unless abscesses develop.

Before the introduction of chemotherapy, the fatality rate was about 15 per cent. During the first 6 months of life approximately 65 per cent succumb, whereas in children and young adults the death rate is low. The presence of chronic debilitating disease alters the prognosis. In those patients with fatal infections the lesion is likely to involve the trunk and, in addition, the blood stream is invaded.

BACTEREMIA

Streptococci are a common cause of bacteremia, but in uncomplicated tonsillitis and pharyngitis the organisms rarely invade the blood stream. Bacteremia occurring under the age of 20

usually is secondary to otitis media, mastoiditis, or thrombosis of the lateral or cavernous sinuses. In the adult, invasion of the blood stream is especially likely to occur in women with puerperal infections, whereas after the age of 40 bacteremia is usually secondary to cellulitis and erysipelas. Metastatic abscesses develop infrequently during the course of bacteremia.

The diagnosis of bacteremia is difficult and can be made only by culturing the organisms from the blood. The sudden development of chills and high fever, either irregular or continuous, suggests invasion of the blood stream. Severe headache, nausea, vomiting, and delirium are common symptoms. In streptococcal bacteremia there may be arthritis, signs of pneumonia, petechiae, or skin eruptions. In fulminating cases anemia develops rapidly and jaundice may occur. Without specific therapy the mortality rate is 70 per cent.

PYELONEPHRITIS

Infections of the kidney and urinary passages are discussed in detail in Chapter 245. Here it should be emphasized that streptococci usually belonging to group D may be isolated from the urine of patients with infection of the urinary tract. When the organisms are present in large numbers there is usually dysuria, frequency, flank pain, fever, and pyuria.

TREATMENT

There are now several agents which may be used specifically in the therapy of aerobic streptococcal infections. The sulfonamides have been widely employed. These drugs exhibit a bacteriostatic effect against all the Lancefield groups except D. However, there are certain strains of group A that have acquired resistance to these drugs. Penicillin exhibits a much more marked antibacterial effect than the sulfonamides. Here again there are certain organisms that appear to be resistant to its action. Such streptococci are encountered in subacute bacterial endocarditis and do not produce beta-hemolysis. Erythrogenic antitoxin may be used in certain patients with scarlet fever, but it is to be emphasized that such preparations are not antibacterial. Finally, because of the nature of the reaction of the tissues to the streptococcus, surgical treatment needs to be applied in those instances where there is an

accumulation of pus, and blood transfusions administered when anemia is present.

The *sulfonamides* have been used extensively in the treatment of streptococcal infections. Today sulfadiazine and sulfamerazine are most widely used. In most infections, sulfadiazine is administered in doses of 1 Gm. every four hours after an initial dose of 2 to 4 Gm. Sulfamerazine may be given in a dose of 1 Gm. every six hours.

In the average case of tonsillitis and pharyngitis, as well as in scarlet fever, sulfonamide therapy has little influence on the natural course of the disease. Exhibition of the drug may be followed by a rapid disappearance of soreness of the throat, but it displays little effect on other symptoms. It does not appear to alter the local signs of inflammation nor does it change the course of the cutaneous rash. Following institution of chemotherapy, the leukocyte count rapidly drops toward normal and the number of streptococci in the throat decreases. These effects are temporary, for, upon withdrawal of the drug, the leukocyte count increases and streptococci can again be isolated from the throat. Although these drugs have no effect on the late nonsuppurative complications, they apparently prevent middle ear and other septic complications. In those cases where the infecting organism is sulfonamide-resistant, it is doubtful whether any beneficial effect is obtained by its administration. From this brief summary, then, it would appear that sulfonamides are not necessary in mild cases of pharyngitis or tonsillitis with or without scarlet fever. When given, their chief value is probably in the prevention of suppurative complications.

Suppurative complications may be treated with full doses of sulfonamides but, again, the beneficial results are sometimes difficult to determine. If the sulfonamides are employed in purulent otitis media, mastoiditis, and sinusitis, careful observations of the course of the infection should be observed, since these drugs may mask the destructive processes. Surgical drainage is necessary in many instances.

There are some infections caused by group A hemolytic streptococci where there appears to be little doubt as to the favorable influence of the sulfonamide drugs. In erysipelas, improvement is often marked within a period of 24 hours, and therapy may be discontinued within four or five days. The sulfonamides have reduced the mor-

tality in group A streptococcal peritonitis, bacteremia, meningitis, puerperal fever, and lymphangitis. In infections of the urinary tract they have been employed with apparent success, although group D streptococci are resistant to sulfonamide action.

Because of the high antistreptococcal activity of penicillin, this antibiotic would appear to be the drug of choice in the treatment of all infections caused by these organisms. Penicillin actually kills the streptococci if adequate concentrations remain in contact with the organisms for several hours. Its effect on the natural course of pharyngitis, tonsillitis, and scarlet fever is beneficial and is more dramatic than that observed following the use of the sulfonamides. Preliminary studies suggest that penicillin rapidly rids the inflamed throat of streptococci and, if adequate amounts are exhibited for a period of five to seven days, the organisms may be eradicated and the development of rheumatic fever prevented.

In the average case of streptococcal infection, be it scarlet fever, sore throat, or erysipelas, sufficient concentrations of penicillin may be maintained by the intramuscular injection of 20,000 units every three hours. In severe infections the same dose may be given every two hours, or the amount injected at three-hour intervals increased to 30,000 units. Procaine penicillin in 2 per cent aluminum monostearate in oil may be given in doses of 300,000 units every two days. Application of penicillin by means of troches or sprays has little effect on the local inflammatory lesion, and the organisms do not disappear from the throat.

Penicillin appears to exert a definite effect on the suppurative complications of tonsillitis and pharyngitis. Penicillin treatment of otitis media is followed by a gradual decrease in the amount of exudate; redness of the drum disappears and within 4 to 14 days there is no further aural discharge. The temperature, if elevated, returns very rapidly to normal. Complications such as mastoiditis are rare during this form of therapy. If treatment is instituted before aural discharge occurs, the drum membranes must be watched closely. A tympanic cavity filled with purulent exudate requires drainage. In general, it is wise to continue penicillin treatment for several days after all discharge has ceased and the temperature has returned to normal. Premature dis-

continuance of treatment may lead to a recurrence. It is perhaps important to emphasize that *Micrococcus aureus* infections of the middle ear are common in patients with group A streptococcal infections of the throat, and in these cases discharge is likely to be prolonged. Adequate bacteriologic studies should be made.

Infections of the mastoid and paranasal sinuses should likewise be treated by the parenteral administration of penicillin. Streptococcal pneumonia should be treated with somewhat larger amounts of penicillin; a dose of 40,000 units every three hours is suggested. From 30,000 to 50,000 units every two hours should be given to patients with puerperal sepsis and bacteremia. Empyema, purulent pericarditis, and arthritis are best treated by local instillation of 10,000 to 50,000 units of penicillin every 48 to 72 hours until sterile. In addition, full doses of parenteral penicillin should be administered. In these infections early treatment is required if surgical drainage is to be avoided.

Penicillin and the sulfonamide drugs do not affect the toxic phases of scarlet fever except in so far as bacterial growth is inhibited. Patients with moderate or severe scarlet fever should probably receive either convalescent serum or antitoxin. Convalescent serum, which is not followed by serum sickness, should be administered intramuscularly in doses of 50 to 100 ml. In children somewhat smaller amounts may be employed. Before using scarlet fever antitoxin, tests for sensitivity to horse serum should be made. In those individuals showing no sensitivity the antitoxin is injected intramuscularly and, occasionally, intravenously in severe cases. In moderately severe cases approximately 15,000 units are employed; in the severely ill, 35,000 units. The administration of antitoxin or convalescent serum early in the illness is followed by a rapid decline of fever, cessation of vomiting, and fading of the rash.

In patients developing focalized collections of pus, surgical drainage should be promptly established. Surgery should not be injudiciously employed because of the danger of spread of the infectious process. Patients with lymphangitis and arthritis should have the involved parts immobilized. Transfusions of whole blood should be administered to all patients with anemia.

General measures for the supportive and symptomatic therapy of infections should be employed

(Chapter 99). The use of saline gargles and irrigations of the throat may be effective in the relief of the angina associated with tonsillitis. The use of cold applications to erysipelas or to tender and enlarged cervical lymph nodes frequently affords symptomatic relief.

PREVENTION

It may be stated that there is no completely adequate method for the prevention of streptococcal infections. There are a number of procedures which will limit the spread of the organism to some extent. The problem is exceedingly complicated because of the fact that group A streptococci occur in the upper respiratory tract of many individuals.

In the past it has been customary to isolate all patients with scarlet fever, but today such procedures seem unwarranted, for no precautions are taken with the person with a sore throat without a rash, caused by the same bacterium. Any patient with a streptococcal infection of the upper respiratory tract may be a source of infection. During the acute stage of all such illnesses the patient should be advised against intimate contact with others. From the studies of "return cases" it is apparent that approximately 2 to 4 per cent of patients discharged from scarlet fever wards give rise to secondary cases.

Approximately 50 per cent of patients with streptococcal infections continue to carry the organism in the pharynx three weeks after the acute infection. Usually the number of organisms is small. Those individuals with suppurative complications of the sinuses are likely to harbor large numbers of streptococci and would appear to be a dangerous focus for infection.

There is no specific immunizing procedure which will protect against streptococcal infections. This is not surprising, since the evidence today is that immunity is largely type-specific. It is possible to protect an individual from scarlet fever. Such immunity may be actively or passively acquired. Active immunity is achieved by administering to Dick-positive individuals five injections of scarlet fever toxin at weekly intervals. The amounts used are 500, 2000, 8000, 25,000, and 50,000 skin test doses. Such immunization is usually followed by a reversal of the Dick skin test. Reactions following this immunization are common. No antibacterial immunity

results, so that there appears to be little justification for this type of immunization.

Scarlet fever antitoxin has been used to prevent the rash. The serum is administered following exposure. The likelihood of developing scarlet fever after exposure is about 1 in 20 and, since protection is only against the rash, this procedure is likewise seldom employed.

Individuals or groups of individuals may be protected from streptococcal infections by the prophylactic use of the sulfonamide drugs. The drug has found wide use in the armed services and in closed, small communities, such as orphanages and institutions. In such instances, in the face of an epidemic, the daily administration of 1 Gm. of sulfadiazine is usually sufficient to stop the outbreak. The sulfonamides have also been used to prevent secondary infections in subjects with common respiratory disease. It would appear more profitable to instruct such patients to remain isolated for a few days rather than to administer chemotherapeutic agents. The role of penicillin in the prophylaxis of streptococcal infections has not been adequately evaluated.

Tonsillectomy has been employed widely as a prophylactic measure for streptococcal infections. It is obvious that tonsillitis cannot occur if the organ is removed, but there is no conclusive evidence that such a procedure protects against streptococcal pharyngitis. Individuals without tonsils are less likely to harbor beta streptococci and, following an acute infection, the organisms disappear more rapidly than in persons with tonsils.

Many attempts have been made to control respiratory disease by altering certain environmental factors; these include the use of ultraviolet light, aerosols, various dust-holding procedures, and treatment of bed clothing with oils. It has been demonstrated that such methods decrease the contamination of the air with beta streptococci, but the degree of their effectiveness in preventing infection is not known. Respiratory streptococcal infections are spread primarily by droplets and droplet nuclei, so that control is difficult. Occasionally food-borne outbreaks occur. Here pasteurization of milk and proper cleanliness and handling of food are essential.

There are several local infections of various organs that require special comment. Erysipelas is difficult to control. In the few subjects who have repeated attacks, the prophylactic use of

sulfonamides would be justified. Wound infections and puerperal sepsis are best prevented by good surgical aseptic technics and the avoidance of unnecessary examinations. The sulfonamides and penicillin have been employed widely as prophylactic therapy in surgery. Thus penicillin is administered to prevent subacute bacterial endocarditis following oral manipulations, and both drugs are used to prevent peritonitis.

LATE NONSUPPURATIVE COMPLICATIONS OF BETA STREPTOCOCCAL INFECTIONS

As indicated previously, beta streptococcal infections assume importance not only because of the high morbidity and the immediate suppurative complications, but also because of the late sequelae. There is considerable evidence that rheumatic fever, acute glomerulonephritis, and scleredema adultorum are precipitated by, if not directly related to, infection with the beta streptococcus. Rheumatic fever and acute nephritis may be followed by valvular disease and chronic nephritis, respectively, and therefore these sequelae of streptococcal infection assume importance as a cause of chronic illness. In this section acute glomerulonephritis will be considered only briefly, since it is discussed in detail in Chapter 244.

ETIOLOGY AND PATHOGENESIS

The cause of rheumatic fever and acute glomerulonephritis is not known; experimental production of an analogous disease in animal or man has not been entirely successful. Most students of these nonsuppurative disease processes agree that the initial attack of rheumatic fever is usually related to a preceding group A beta-hemolytic streptococcal infection. Acute glomerulonephritis is likewise related to streptococcal infections, although there is evidence that other bacteria may be responsible for a small group of such cases.

Streptococcal infections are characterized by an acute, toxic, or septic phase which lasts from three to seven days. There are fever, constitutional symptoms, and, in those susceptible to the erythrogenic toxin, a rash. Suppurative complications may occur at any time after the onset through the third or fourth week of illness. There are local signs of inflammation which occasionally spread to surrounding tissues. At times invasion of the blood stream occurs. Following the acute

illness the patient seemingly recovers completely and, for periods varying from a few days to six to eight weeks, no symptoms occur. After this latent period (termed Phase II by Coburn) the patient may again present symptoms and signs of illness, but now these manifestations are entirely different from those observed in the primary infection, and the illnesses developing after this latent period present a varied clinical picture. These diseases have been collectively termed the late nonsuppurative complications of hemolytic streptococcal infections (fig. 148).

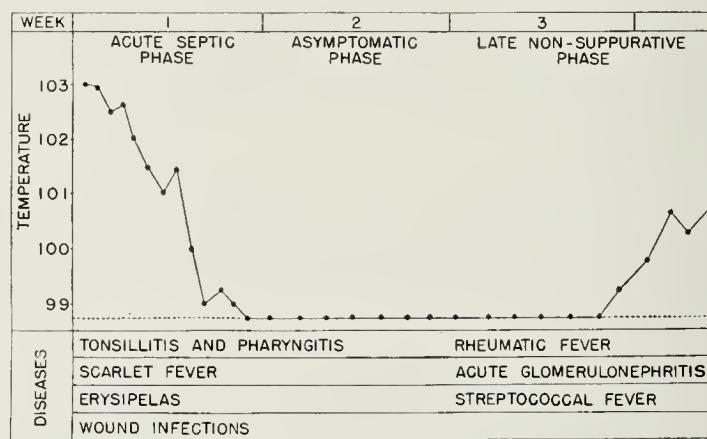


FIG. 148. The various phases of hemolytic streptococcal infections.

Certain patients develop fever without localizing signs of infection. Such cases have been called streptococcal fever. Some show fever with lymphadenitis which, after variable periods, subsides completely. In others, because of the development of polyarthritis, endocarditis, myocarditis, or pericarditis, a diagnosis of rheumatic fever is made. In a few, acute glomerulonephritis becomes manifest. Skin eruptions, such as erythema multiforme, erythema nodosum, and scleredema adultorum, occasionally appear. Once these sequelae occur, the patient is likely to suffer exacerbations following subsequent streptococcal infections, and in many instances a chronic disabling disease develops.

This sequence of (1) an acute illness due to the group A streptococcus, (2) a latent period of one or more weeks, and (3) the development of a nonsuppurative illness, occurs with sufficient frequency to suggest a causal relationship to the hemolytic streptococcus. In the family unit experiencing acute streptococcal infections and in food- and milk-borne outbreaks, it is not uncommon to observe both suppurative and nonsuppurative complications. In hospitals for conta-

gious disease, it is a relatively common experience to find that patients with scarlet fever later develop rheumatic fever. Other nonbacterial respiratory infections are not followed by rheumatic fever and acute glomerulonephritis.

Further evidence that rheumatic fever and acute glomerulonephritis are related to the hemolytic streptococcus is obtained from studies of patients with these diseases. A history of a preceding respiratory infection, usually compatible with a diagnosis of streptococcal pharyngitis or tonsillitis, is frequently obtained. Culture of the oropharynx has demonstrated that in most instances Lancefield group A streptococci may be isolated. Occasionally, these diseases follow a streptococcal wound infection. Antistreptolysin and antifibrinolysin determinations reveal high concentrations of these antibodies in the serum. These streptococcal antibody titers tend to fall as the patient recovers. Furthermore, recurrent attacks occur with sufficient frequency, following streptococcal infections, to indicate a causal relationship. Sulfonamides, by preventing streptococcal pharyngitis, have reduced the incidence of recurrent rheumatic infections.

The exact mechanism whereby rheumatic fever and acute glomerulonephritis are produced is not known. It was suggested by Schick in 1907 that the late reactions developed because of altered sensitivity to certain products of the streptococcus. Obvious analogies with serum sickness are suggested since polyarthritis, fever, skin manifestations, and leukocytosis are common to both. Experimental evidence that the tissue reactions seen in rheumatic fever may result from hypersensitivity has recently been demonstrated by Rich. In man, however, there is little direct evidence that the reactions in the various tissues, including the heart and kidneys, are due to an altered sensitivity of the cells to the streptococcus.

EPIDEMIOLOGY OF RHEUMATIC FEVER

There are no reliable figures of the incidence of rheumatic fever because the disease is not reportable and, in many instances, its manifestations are so mild that a diagnosis cannot be established definitely. That it occurs frequently is indicated from reports of streptococcal epidemics where from 3 to 6 per cent of the infected population subsequently develop recognizable rheumatic fever. Since most people experience

several streptococcal infections in a lifetime, it can be assumed that rheumatic fever is common but frequently is not recognized. More accurate information is available from studies of heart disease. It has been estimated that evidence of rheumatic heart disease exists in from 1 to 6 per cent of the population. Certainly, rheumatic heart disease is the most common cause of cardiac death in childhood and young adults. Although it was formerly believed that rheumatic fever occurred more frequently in girls than in boys, recent analyses suggest that attack rates in the two sexes are essentially identical.

The first attack of rheumatic fever usually occurs in childhood. The disease is rare before 2 and after 30 years of age. The peak of incidence occurs at about the age of 7, and from 8 to 15 years of age there is a rapid decrease in incidence. Attacks of rheumatic fever in the adult are frequently instances of recurrent infection.

Individuals who have experienced one attack of rheumatic fever are especially susceptible to subsequent attacks. It is estimated that 40 per cent of patients will experience a recurrence within one year after their initial attack. Of those who do not experience a recurrence during this period, approximately 10 per cent will develop one during the subsequent year. As stated above, these recurrences are related to infections by group A streptococci, but all group A infections are not necessarily followed by a recurrence of rheumatic fever.

So far as is known, no race or nationality is immune, and differences in racial susceptibility to rheumatic fever are not well defined. In New York City the Irish appear to be particularly susceptible.

Rheumatic fever occurs in those areas of the world where streptococcal infections are prevalent. Classic rheumatic fever appears to be more prevalent in the northeastern portion of this country than in the southern states. It is seen especially in the Temperate Zones. The disease must exist in the tropics since rheumatic heart disease occurs in these areas. Rheumatic heart disease is frequently observed in the southern states even though rheumatic fever appears to occur less frequently in these areas. Like many diseases, rheumatic fever appears most frequently in population groups receiving a low income. Crowding, dampness, and poor nutrition are common in such populations, but the role of

these factors in the production of rheumatic fever has not been defined. It is suggested that similar factors also affect the spread of streptococcal infections, which may account for the high incidence of rheumatic fever. That diet may not be important is suggested by the fact that rheumatic fever frequently occurred among personnel in army and navy training camps.

There is a definite seasonal variation in the incidence of rheumatic fever. The disease occurs in the colder months of the year. In the southeastern United States it is most prevalent in March and April, whereas in the states bordering the Pacific Ocean it occurs earlier in the year.

It is well recognized that rheumatic fever tends to affect more than one member of a family. Wilson has shown that the attack rates of rheumatic fever in siblings of rheumatic parents is higher than in siblings of parents free of the disease. It has been shown, however, that the incidence of rheumatic fever in such families is affected by contact with a case of acute rheumatic fever. The exact nature of the increased susceptibility of children born to rheumatic parents remains to be defined.

PATHOLOGY OF RHEUMATIC FEVER

The essential tissue changes occurring during the course of rheumatic fever are found in the fibrous tissues located throughout the body. The pathologic changes are widespread but, because alterations in certain organs result in abnormal function, the clinician and the pathologist have been especially interested in the changes occurring in the heart, joints, and brain. The characteristic change evoked by acute rheumatic fever is the development of minute nodules, called Aschoff bodies. This lesion is considered specific for rheumatic fever. The Aschoff nodule develops as a result of swelling and fusion of the collagenous ground substances of the connective tissues. Around these areas, which are usually oval or spindle-shaped, there may be collections of lymphocytes and, occasionally, polymorphonuclear leukocytes. The typical Aschoff cell is usually a centrally located large cell containing several vesicular nuclei. As the lesion ages, fibrosis occurs, leaving a minute scar.

In patients dying with acute rheumatic myocarditis, the heart shows few gross abnormalities. The left ventricle is enlarged and there is widen-

ing of the atrioventricular valves. Occasionally, Aschoff bodies, appearing as gray specks, may be seen beneath the endocardium of the left atrium and ventricle. The leaflets of the mitral valve may be slightly swollen and thickened, and along the point of contact of the cusps a row of small, beadlike vegetations are observed. In patients with pericarditis, there may be several ounces of fluid in the pericardial sac and the heart may be covered with a fibrinous exudate.

Microscopic examination reveals small areas of inflammation scattered throughout the myocardium. These Aschoff nodules appear to be especially prominent in the base of the interventricular septum and beneath the endocardium of the left atrium. It is easy to visualize that these lesions, associated with an inflammatory reaction, give rise to alterations in the conductive mechanism of the heart. The Aschoff nodule is found in the tissues immediately surrounding the small branches of the coronary arteries.

The endocardial lesions are most frequently found in the valves and the left atrium. In the valve leaflets there is edema and subendothelial infiltration by lymphocytes and occasionally by polymorphonuclear leukocytes. The endothelium is damaged, and it is in these areas that fibrin is deposited, producing the beadlike vegetations. The cordae tendineae are also involved in this inflammatory process. As the disease continues, fibrosis develops with subsequent contraction of the tissues, producing the valvular deformities that are so characteristic of chronic rheumatic heart disease.

In both the large and small blood vessels there may be collections of small round cells in the perivascular tissues as well as a diffuse reaction in the intima. Such changes may be responsible for abdominal pain observed in patients with rheumatic fever. Like pericarditis, pleurisy is not uncommon. The pleurisy is at first dry; later, fluid may accumulate.

The joints become red, swollen, and tender. The periarticular tissues and synovia are edematous and show collections of mononuclear cells. The synovial fluid becomes increased in amount. Involvement of the tendons, especially the hamstring and Achilles tendons, gives rise to the so-called "growing pains" of childhood. Subcutaneous nodules, which are loosely connected to the tendon sheaths, are likely to be found during the acute phase of the disease in children.

In the brain true Aschoff bodies are seldom observed; instead, there is a perivascular collection of round cells. There may be proliferation of the intima and thrombosis of vessels.

Inflammatory reactions have been described in the tissues of other organs of the body. In the lung there may be an interstitial pneumonia and hemorrhage.

CLINICAL MANIFESTATIONS

One of the outstanding characteristics of the late nonsuppurative complications of streptococcal infections is the variation of the clinical features that are manifested. Frequently a definite diagnosis of rheumatic fever is easily made, but there are also many instances where such a diagnosis is difficult, if not impossible. The correct diagnosis may become apparent only after a long period of observation.

Streptococcal fever is a term applied to those patients who exhibit fever, usually of mild degree, without other signs of rheumatic activity or of a suppurative process. A history of a preceding pharyngitis is usually obtained. There may be some cervical lymphadenitis, but in many instances the glands are not prominent or tender. In some patients the temperature may be normal except during the late afternoon. An increase in the total leukocyte count or in the sedimentation rate may accompany the fever.

Rheumatic fever may be insidious in onset or develop rapidly. Although it is common for patients to give a history of a preceding streptococcal respiratory infection followed by a latent period of several days to six weeks, occasionally symptoms of rheumatic fever develop without a latent, symptom-free period. Usually the patient complains of general lack of sense of well-being which is soon followed by feverishness, perspiration, prostration, and polyarthritis.

In the absence of a specific diagnostic test, the recognition of rheumatic fever depends upon the presence of a combination of symptoms and signs of which the most important are polyarthritis, carditis, chorea, subcutaneous nodules, fever, and dramatic improvement of pain and fever following the administration of salicylates. It is important to stress that many of these manifestations may be absent in a given instance.

Although *migratory polyarthritis* is considered one of the typical symptoms of rheumatic fever, it is also a confusing symptom, since arthralgia

may be caused by other diseases. In rheumatic fever, painful joints develop rapidly and are likely to involve the ankles, knees, hips, shoulders, elbows, and wrists. Occasionally the small joints become involved. The arthritis is usually migratory in type and only rarely is a single joint involved. Several joints may become involved simultaneously or they may be affected in rapid succession. As one joint becomes involved, the pain and swelling in another may be receding. Arthralgia in any one joint may last from a few hours to several days or, rarely, weeks. Commonly there are all the signs of acute inflammation with redness, swelling, heat, pain, and tenderness. There may be signs of intraarticular fluid as well as periarticular edema. Tenosynovitis is observed not infrequently and is probably responsible for "growing pains" in the absence of signs of arthritis.

In children the arthritis may not be typical, the manifestations being pain and tenderness without swelling of the joint. The arthritic joints of rheumatic fever do not suppurate, and normal function is restored following subsidence of symptoms and signs of inflammation. During the period of arthralgia, motion causes considerable pain.

Death during the course of acute rheumatic fever is due to active *carditis*. Patients with severe cardiac involvement usually appear prostrated and pale, the fever is apt to be high, the pulse is rapid and weak, and there may be associated symptoms and signs of failure of the heart. In the absence of cardiac failure, the symptoms referable to the heart in most patients are minimal. A few patients complain of precordial discomfort and, more rarely, of severe pain. The diagnosis of active carditis is established in most patients only after careful examination, including the use of the electrocardiogram.

The single sign indicative of involvement of the endocardium is a murmur. The most common murmur associated with the initial attack is the mitral systolic, which in some patients is associated with a soft aortic diastolic murmur. The mitral systolic murmur may be functional in origin. Those murmurs, which vary little with respiration, persist in various body positions with maximum intensity at the apex, are high-pitched, occur throughout most of systole and persist during the period of observation, should be considered indicative of endocarditis. The faint sys-

tolic murmur localized to the apex which is heard only while the heart rate is rapid is usually functional in origin. Unimportant murmurs frequently disappear as the patient improves. In patients with preceding rheumatic infections, a mitral diastolic or presystolic murmur indicates rheumatic heart disease.

Enlargement of the heart occurs during acute rheumatic fever associated with active carditis. Cardiac enlargement is frequently encountered in children but seldom observed in the adult. If enlargement is minimal, the diagnosis may become apparent only by comparison of serial roentgenograms. The diagnosis of involvement of the myocardium is usually based on the recognition of disturbances of rhythm and electrocardiographic abnormalities. Most patients with rheumatic fever, if examined frequently, will show evidence of myocardial involvement. Tachycardia is frequent. Gallop rhythm, usually heard during the acute phases of the illness, is especially apt to occur. In such cases the electrocardiogram reveals a prolongation of the P-R interval. The heart sounds may be muffled, or the first sound may vary in intensity. The finding of dropped beats suggests a partial heart block (Wenckebach phenomenon). Premature contractions are observed which disappear during convalescence. Auricular fibrillation, uncommon in children, may be associated with recurrent attacks of rheumatic fever in the adult.

The electrocardiographic change most frequently encountered during the course of acute rheumatic fever is prolongation in the P-R interval. This usually becomes normal as signs of infection disappear, but it may persist. Other abnormalities include partial auriculoventricular heart block, auriculoventricular dissociation, inversion of T waves, and bundle branch block.

Discomfort over the precordial area does not always indicate acute pericarditis, but the detection of a harsh to-and-fro friction rub is pathognomonic. Frequently the precordial pain is severe in patients exhibiting a friction rub. Rheumatic pericarditis in children is often associated with little pain. Effusion into the pericardial sac may develop and must be differentiated from cardiac dilatation. The lack of an apical impulse and distant heart sounds suggest fluid. The appearance of a globular cardiac silhouette on the roentgenogram indicates effusion. There is marked reduction of all waves of the electro-

cardiogram when the effusion is extensive. Constrictive pericarditis does not follow rheumatic disease of the pericardium.

Chorea, St. Vitus' dance or Sydenham's chorea, is considered a major manifestation of rheumatic fever, but rarely occurs in adults. In children Jones found chorea in about one half of all rheumatic fever patients. Chorea usually develops rather slowly so that a week or two is required before the parents realize the child is ill. Typically, the patient is restless, nervous, and emotionally unstable, and performs many purposeless movements. The entire body frequently becomes involved so that incoordination of voluntary movements of the face, arms, and legs is observed. These purposeless movements are at times so frequent that they interfere with speech, writing, or eating. Muscular weakness may be prominent and the fingers may be hyperextended. Patients with pure chorea rarely exhibit fever or leukocytosis, but most of them eventually develop other signs of rheumatic fever. Thus, in adults, a history of previous chorea is of aid in the establishment of the diagnosis of rheumatic fever or rheumatic heart disease.

One of the most characteristic features of rheumatic fever is the development of subcutaneous nodules. These nodules, which vary in size from 1 mm. to 1 or 2 cm., are especially prone to develop over the extensor tendons of the hands and feet, over the extensor aspects of the knee and elbow, and over the spine, scapulas, and skull. Usually they are distributed symmetrically and may occur in crops. They lie deep in the tissue and the skin is movable over their surfaces. They are not painful. Detection of these nodules is best accomplished by inspection of the skin when drawn taut by flexion of the joints. Larger nodules are easily palpated. The nodules persist for a few days to several weeks but always disappear. Since subcutaneous nodules are especially prone to develop in those patients with severe carditis, they are seldom helpful from the standpoint of diagnosis.

The tendency toward *recurrent attacks* is a striking feature of rheumatic fever. Approximately three fourths of all patients with recognizable rheumatic fever will develop a recurrence of the disease, so that a previous history of an attack aids in the establishment of the proper diagnosis.

There are numerous symptoms, physical signs,

and abnormalities in laboratory examinations that aid in the establishment of proper diagnosis. Fever is usually associated with acute rheumatic fever, although it may be absent in patients with chorea. Fever may be the only clinical manifestation of the disease, other studies, such as serial electrocardiograms and detection of endocardial murmurs, being required to establish the diagnosis. A diagnosis of rheumatic fever made solely on the basis of low-grade fever is not warranted, but it should be emphasized that fever may be the only sign of rheumatic activity. The possibility of rheumatic fever should be entertained in older children or young adults exhibiting a low-grade fever in whom no obvious cause exists.

Little experience is required to indicate the protean character of rheumatic fever. Studies of outbreaks of streptococcal infection emphasize that nonsuppurative sequelae include typical rheumatic fever and a low-grade, often continuous, fever without signs of rheumatic activity. It is natural to assume that such cases of so-called streptococcal fever are produced by the same mechanism that is responsible for the clinically recognizable form of rheumatic fever. A history of a preceding streptococcal infection is of help in diagnosis (fig. 149).

During the acute phase of rheumatic fever various forms of cutaneous rashes may appear.

Most typical is erythema marginatum. This rash is said to occur in 15 per cent of patients with acute rheumatic fever and probably should be considered as indicative of active rheumatic infection. It is characterized by a depressed center and an erythematous margin which may form rings. When the lesions fuse, various gyrate patterns are observed. Other rashes include erythema nodosum, urticaria, and various purpuric lesions.

Abdominal pain occurs frequently and may be incorrectly diagnosed as acute appendicitis. Since a leukocytosis occurs in both rheumatic fever and appendicitis, operation is frequently performed. Careful search for other signs of rheumatic activity should be made in all children and young adults complaining of abdominal pain and fever. Electrocardiograms are frequently necessary in the differential diagnosis.

Not only does abdominal pain occur as a manifestation of acute rheumatic fever but also pleuritic pain is observed. *Pleurisy* is usually associated with severe rheumatic fever and gives rise to pain on respiration. Rarely, it is the initial manifestation of the illness. Usually the pleurisy does not persist for more than a few days, and symptoms may be relieved as fluid accumulates in the intrapleural space. In some patients, and again especially in those with a severe illness,

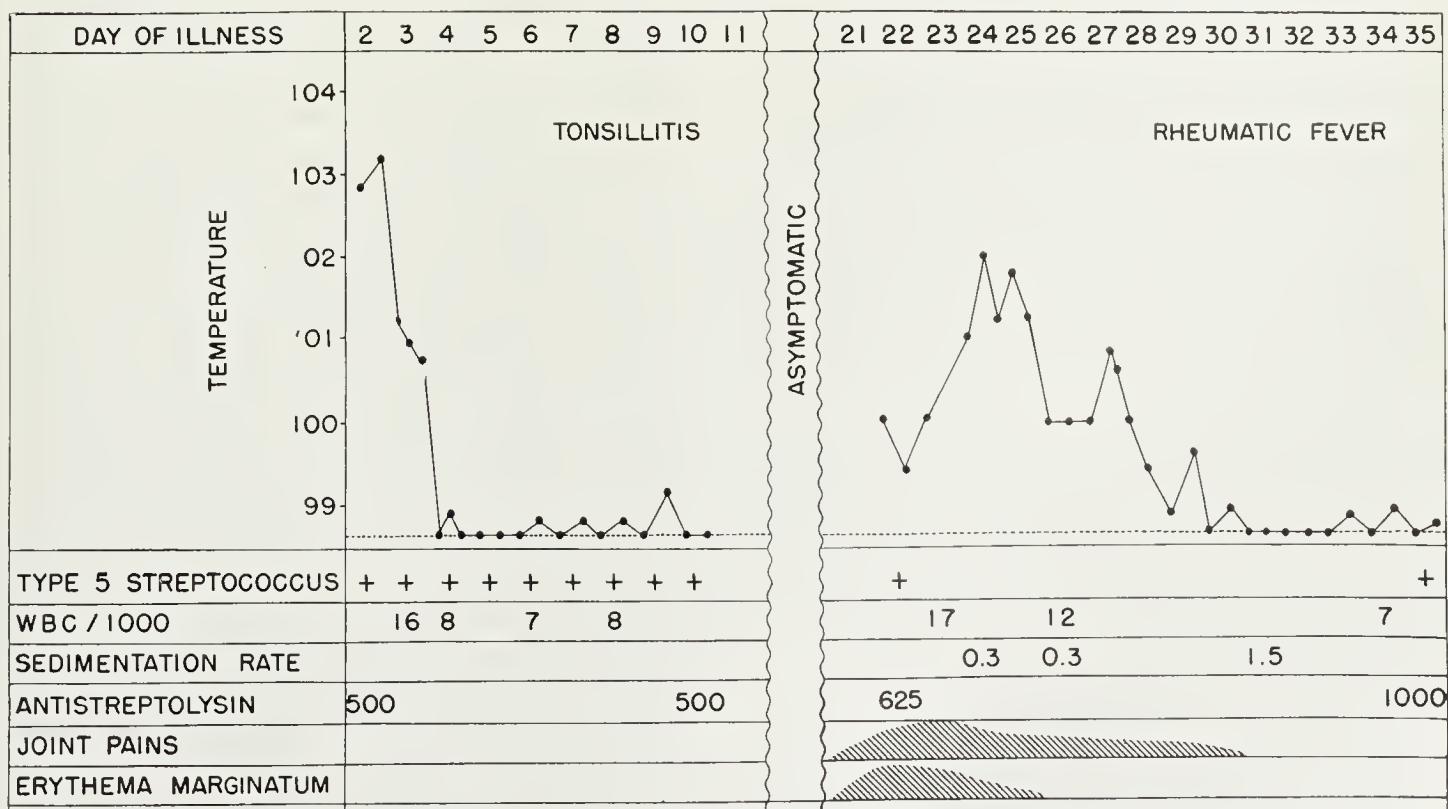


FIG. 149. The time sequence of streptococcal tonsillitis and rheumatic fever.

symptoms and signs of *pneumonia* may develop. The sputum may become blood-streaked. Physical signs are frequently difficult to interpret, for there is usually concomitant myocarditis and cardiac failure. Roentgenographic examination of the lungs is a most valuable procedure in those patients suspected of having pneumonia.

Epistaxis is commonly observed in patients with acute rheumatic fever. The bleeding may be profuse, requiring transfusions. Usually, careful examination fails to reveal any abnormalities in the nasal mucous membranes, and a history of trauma may not be obtained. The exact cause of these recurrent attacks of bleeding is not known.

LABORATORY FINDINGS

The urine is usually normal. Traces of albumin may occur during the febrile period, and hematuria is observed on occasion. In patients with severe or prolonged infections various degrees of anemia are common. There may be a reduction of both the erythrocytes and the hemoglobin concentration. A leukocyte count of from 15,000 to 30,000 is the rule during the acute phases of infection, but in some patients the count may be normal. Usually the leukocyte count reflects the course of the illness; as symptoms and signs of activity subside the leukocytes return toward normal. Persistent leukocytosis may indicate a continuing infection.

The sedimentation rate is an excellent index of rheumatic activity and is generally considered more reliable than the leukocyte count. The rate of sedimentation of the cells almost invariably increases during the acute phases of the infection; with clinical improvement the rate decreases and returns to normal. In patients with carditis and cardiac failure, normal values may be obtained, but as failure disappears the sedimentation of the cells increases.

Culture of the tonsils and oropharynx may show beta streptococci of Lancefield group A, but failure to isolate these organisms even early in the course of the disease is not unusual. Of significance is the finding of a high antistreptolysin or antifibrinolysin titer which falls as the patient improves.

DIAGNOSIS

There is no laboratory test available that establishes the diagnosis of acute rheumatic fever. *Polyarthritis*, *carditis*, *chorea*, *subcutaneous nod-*

ules, and *recurrent attacks* characterize the disease. According to Jones, the diagnosis of rheumatic fever becomes established when two or more of the above manifestations coexist.

It should be emphasized that rheumatic fever undoubtedly occurs in the absence of these conditions, but only by long observation is it usually possible to make certain of the diagnosis.

Rheumatic fever must be differentiated from other forms of acute arthritis. Under the age of 20, *gonococcal arthritis* may be confused with rheumatic fever. Both are polyarticular in their early manifestations, although gonococcal arthritis may involve only a single joint. As the disease progresses, involvement of one or two joints is usual. In many cases of gonococcal arthritis the correct diagnosis can be made only by aspiration of the joint fluid, which is turbid, contains 10,000 or more polymorphonuclear leukocytes, and, on culture, may yield gonococci. Examination of urethral or cervical discharges may give a clue to the correct diagnosis. In some cases the gonococcal complement-fixation test is a valuable aid in diagnosis.

Rheumatoid arthritis, although relatively rare in children, is generally polyarticular in its manifestations, so that it is commonly confused with acute rheumatic fever. Rheumatoid arthritis or Still's disease characteristically begins insidiously, although occasionally the onset is abrupt. A history of a preceding streptococcal infection suggests rheumatic fever. Although rheumatoid arthritis and rheumatic fever both involve the knees and wrists, the presence of fusiform swelling of the proximal interphalangeal joints bilaterally suggests the former diagnosis. Temporomandibular joint involvement is rare in rheumatic fever and common in rheumatoid arthritis. In both diseases the leukocyte count is elevated and the sedimentation rate increased. The development of signs of carditis is usually indicative of rheumatic fever, but it must be emphasized that the two diseases may coexist. The final diagnosis may not become apparent until after many months of observation. Recurrent attacks occur in both rheumatoid arthritis and rheumatic fever, but remissions in the former disease are not complete. The development of deformities or ankylosis clearly indicates rheumatoid arthritis.

Acute traumatic arthritis usually is monoarticular and is not associated with fever, and a history

of trauma is evident on inquiry. Hemarthrosis associated with hemophilia is not difficult to recognize.

Septic or *purulent arthritis* is recognized readily in most instances, and cultures of the blood and joint fluid establish the correct diagnosis. *Tuberculous arthritis* is usually monoarticular in distribution and subacute in its course. Some cases of acute *disseminated lupus erythematosus* may be difficult to distinguish from acute rheumatic fever. The former disease almost invariably occurs in females and is associated with leukopenia, hematuria, and, in most instances, a rash over the face.

In the adult, and especially in the male, *gout* must be considered. The occurrence of tophi, podagra, and an increased uric acid content of the blood, as well as the appearance of erosions of the bone in the roentgenograms, serve to differentiate gout from rheumatic fever.

The administration of salicylic acid compounds is often helpful in differential diagnosis. In rheumatic fever these drugs produce rather marked symptomatic relief, the temperature decreases, and the pulse slows.

COURSE AND PROGNOSIS

Approximately 4 per cent of patients die in their initial attack of rheumatic fever, and in every instance this is due to an active carditis. A few patients who recover may never exhibit clinical evidence of rheumatic infection, but the majority develop subsequent attacks of rheumatic fever. These attacks are especially prone to occur following streptococcal respiratory infections. Again approximately 5 per cent will succumb to an active carditis. In general, serious cardiac injury is the result of repeated attacks of rheumatic fever. Since the number of recurrences is related to the age of the patient at the time of the initial infection, rheumatic fever is especially serious in the young child before puberty.

During childhood, death is usually the result of active myocarditis, whereas, in the adult, chronic valvular disease leads to mechanical failure of the heart. Such adult patients succumb to heart failure with auricular fibrillation, embolic phenomena, or bacterial endocarditis. The latter complication usually develops in those patients who exhibit no signs of failure at the time. Occasionally, active rheumatic fever is associated with cardiac failure in the adult patient.

TREATMENT

There is no drug that has a specific curative effect in the late nonsuppurative complications of streptococcal infections. Many of the symptoms observed in the patient with rheumatic fever may be relieved dramatically by the use of compounds of salicylic acid. Sodium salicylate or acetylsalicylic acid relieve such symptoms as joint pain, tachycardia, and anorexia. Unfortunately, toxic symptoms of salicylism appear early in many patients so that careful adjustments are necessary to obtain maximum therapeutic effects. In general, small doses of these compounds given at frequent intervals are preferable to large doses. In the adult at least 8 to 10 Gm. during a 24-hour period are required for maximum effect. When such symptoms as nausea, vomiting, tinnitus, difficulties in vision and hearing, or mental confusion develop, the amount of salicylate should be reduced. Enteric-coated capsules may be employed when there is intolerance to the drug administered orally. At times rectal administration of a 2 per cent solution is used.

Aminopyrine has been used in the treatment of acute rheumatic fever but, because of its tendency to produce agranulocytosis, it is not widely employed. If used, doses of 0.5 Gm. may be given every 4 hours. The leukocyte count should be followed in all patients receiving this drug.

Recently 17-hydroxy-11-dehydrocorticosterone (cortisone) has been used in the treatment of rheumatic fever. Preliminary results suggest that such therapy has a beneficial effect in that fever, tachycardia, and polyarthritis disappear and the sedimentation rate returns to normal.

The sulfonamide drugs, penicillin, and streptomycin are not of value and should not be used in the treatment of acute rheumatic fever.

At times morphine or codeine is required to control the pain associated with pericarditis or pleuritis. In those patients with cardiac failure, digitalis should be administered. The dosage of this drug is the same as that discussed in Chapter 238.

Patients with chorea require special attention. They should be placed in bed in a quiet room. Necessary precautions must be instituted so that they do not injure themselves. During the period of active choreiform movements feeding is difficult and requires a patient, understanding nurse. Sedation, usually phenobarbital, should be ad-

ministered in sufficient quantities to supply needed rest. In severe cases various forms of fever therapy may be attempted.

General measures in the treatment of acute rheumatic fever include bed rest and a nutritious diet. Probably the most important single feature in treatment is adequate rest. During the acute phases of the disease complete rest in bed is required. The patient should remain in bed for several weeks after all clinical signs of activity have disappeared. Usually the pulse rate, leukocyte count, and sedimentation rate are used as an index of the progress of the infection. In general, bed rest or at least limited activity should be required for all those patients exhibiting an abnormal elevation of these three indices. Following recovery every patient should be observed at regular intervals to watch for recurrence or the development of chronic valvular disease.

PREVENTION

There is no adequate method for the prevention of the initial attack of rheumatic fever. The evidence indicates that prompt treatment of group A streptococcal infections with penicillin does decrease the incidence of acute rheumatic fever. It is possible to reduce the number of recurrences in those patients who have already had an attack of rheumatic fever by the prevention of subsequent attacks of acute streptococcal pharyngitis.

Careful attention should be paid to avoiding contact with any person with a streptococcal infection. In certain instances it may be advisable to remove the patient to some area where streptococcal infections are infrequent.

The most effective measure in preventing recurrences of rheumatic fever, however, is to administer prophylactically one of the sulfonamide drugs. For this purpose, sulfadiazine or sulfamerazine should be given in doses of 0.5 to 1.0 Gm. orally each day throughout the year, or at least from fall to summer. Such prophylaxis is an effective measure against the development of streptococcal infections with the exception of those due to strains of streptococci which are resistant to these drugs. Patients receiving sulfonamide prophylaxis should be followed for signs of toxicity. Most toxic symptoms develop during the first few weeks of treatment, so that individuals who take the drugs for three weeks without developing symptoms will usually be able to

tolerate this form of prophylaxis. It seems entirely probable that penicillin prophylaxis will also be effective.

Those patients undergoing surgical procedures in the mouth, especially tooth extraction, should receive penicillin as a prophylactic measure before and for several days after the procedure. It is believed that such treatment will prevent the development of subacute bacterial endocarditis.

Tonsillectomy has been emphasized as a method of preventing acute rheumatic fever. There is no evidence, however, to indicate that individuals who have undergone tonsillectomy are less susceptible to rheumatic fever than those who have not had their tonsils removed. Furthermore, removal of the tonsils does not prevent streptococcal pharyngitis. Tonsillectomy is indicated in those individuals with obviously diseased tonsils, but the procedure should be performed only during the period when the rheumatic process is inactive.

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Meningococcal Infections

Paul B. Beeson

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Epidemiology
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Chronic Meningococcemia Without Meningitis
Meningoceleal Meningitis
Fulminating Meningococcemia (Waterhouse-Friderichsen Syndrome)

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HISTORY

The best-known form of meningococcal infection—meningitis—was first described accurately in France, in 1805. Because of its distinctive clinical manifestations and high fatality rate, the disease soon came to be recognized in all parts of the world. The causative agent was discovered in 1887. Efforts to find satisfactory methods of treatment met with little success until the sulfonamides were introduced in 1936. Since that time, effective chemotherapy has caused a marked reduction in the death rate, and has changed the frequency of some of the clinical manifestations of the disease.

ETIOLOGY

The meningococcus is a Gram-negative coccus, occurring singly and in pairs. This organism does not grow well except in culture mediums which have been enriched with blood or ascitic fluid. It is distinguished from other members of the genus *Neisseria*, such as the gonococcus, by its sugar fermentations and by serologic tests. Most freshly isolated strains are encapsulated, and they show capsular swelling when placed in contact with specific antiserums. Different serologic strains have been identified, and several classifications have been attempted, based upon these serologic variations. At present three principal varieties are recognized: groups I, II, and IIa. Although such grouping has been helpful to the epidemiologist, it is not of much importance to the clinician, because there is no difference in the

clinical diseases produced by the various strains, and the therapy is now the same for all.

EPIDEMIOLOGY

The meningococcus is found in the throats of normal people in all parts of the world. Various surveys have shown the incidence of positive throat cultures for meningococcus to be from 2 to 60 per cent; usually the incidence is higher in winter than in summer. Meningococcal infections may be seen in people of all ages, although infants and young children seem to be especially susceptible. Approximately one fourth of all cases of meningitis occur in children before the age of five. Males are affected a little more frequently than females.

There can be little doubt that the meningococcus is transferred from person to person, principally by airborne droplets. Crowded living conditions naturally favor this, and high carrier rates are likely to be encountered in persons living in dormitories or in barracks. In the majority of instances the meningococcus lodges in the nasopharynx and lives there for a few days or a few weeks, and then disappears without causing any subjective symptoms. Nothing is known about the factors which may favor or oppose the existence of the organism in the throat, but it is possible that the presence of certain other microorganisms has an influence. Few people seem to escape parasitism with the meningococcus. Careful studies have shown that if a group of individuals is examined repeatedly, up to 90 per cent will be found to have meningococci in their throats at one time or another during a winter season. In some cases actual invasion of tissue seems to occur, since there is a rise in titer of specific antibodies in the blood; in most instances, however, agglutinins do not change. Healthy carriers are undoubtedly the principal factor in the epidemiology of meningococcal in-

fection, and because they are so numerous it is pointless to exercise strict isolation in caring for the few patients who happen to have symptomatic meningococcal infection.

Considering the frequency with which positive cultures are obtained from normal people, it seems fair to estimate that the presence of meningococci in the throat does not carry with it a greater than 1:1,000 chance of being followed by symptomatic meningococcal infection. Why, in an occasional case, these organisms, instead of living harmlessly in the throat for a few days or weeks, are able to invade other parts of the body and initiate serious infections is not wholly understood. Certain factors seem to play a part. As noted previously, young children are particularly vulnerable. Meningococcal infections occur more frequently in winter, when acute respiratory diseases are prevalent. In military personnel it has been noted that a high proportion of all cases of meningococcal meningitis occurs in recruits during the first two weeks after induction. This may be associated with the increased frequency of respiratory infections commonly observed after taking up life in barracks, but other factors which have been suggested are fatigue and the various immunizations given at that time.

PATHOGENESIS

Although not definite, it seems probable that meningococci may at times be able to cause an inflammation in the tissues of the upper respiratory tract, producing symptoms of acute respiratory disease—i.e., coryza, pharyngitis, and cough. Proof of this point is difficult to obtain because of the associated presence of other microorganisms in the same tissues.

At times meningococci penetrate beyond the nasopharyngeal region by way of the blood stream, causing a febrile illness of variable duration. It is thought that the primary focus of the infection usually lies in the nasopharyngeal region, and that bacteria are discharged into the blood periodically from this focus. The clinical name "meningococcemia" is perhaps misleading, since there is little reason to believe that meningococci live and multiply in the circulating blood. The illness may go on for weeks, yet the majority of blood cultures taken during that time will be sterile.

It is probable that meningococcal infection of

the meninges is also established by way of the blood stream. Careful history-taking in cases of this disease nearly always reveals that there was a prodromal illness lasting for a few hours or a day or two, in which the symptoms were those of meningococcemia (i.e., chills, fever, malaise, muscle and joint pains) before the onset of meningitis. Furthermore, blood cultures are positive in the majority of cases in meningococcal meningitis. This could, of course, be due to discharge of bacteria into the blood from the meninges, but it could also be interpreted as indicating that heavy and prolonged bacteremia increases the likelihood of establishing meningeal infection. Invasion of the meninges by the meningococcus induces a rapidly progressive type of meningitis. There is acute inflammation of the arachnoid and pia mater with the formation of a purulent exudate, which is usually more extensive over the base of the brain than in the cortical areas. The meninges of the spinal region are affected to a variable extent. Inflammatory changes may also be seen in the nervous tissue subjacent to the meninges. The third, fourth, sixth, and eighth cranial nerves are especially likely to be affected, either by inflammation or by being pressed against the skull.

MANIFESTATIONS

Chronic Meningococcemia Without Meningitis. Meningococcal infection occasionally takes the form of a chronic febrile illness featured by polyarthritis and a skin eruption. The onset of symptoms is usually sudden, with fever, malaise, and headache. The temperature course is irregular, and there may be repeated chills. Occasionally, the fever is periodic in type, resembling that of malaria. Headache varies in severity according to the height of the temperature, but is seldom as severe as when there is infection of the meninges. Pain and tenderness in the muscles and joints is usually the outstanding symptom in meningococcemia. *Arthritis* involves large joints, particularly the knees, elbows, wrists, and ankles; these may be hot, swollen, and tender. The inflammation shifts from one joint to another and subsides without leaving permanent damage. At times fluid can be aspirated from an inflamed synovial cavity, but the meningococcus is seldom present in cultures of this material. *Skin lesions* appear in crops. They are most numerous on the extremities, particularly around the knees, an-

kles, and elbows. They are usually small, erythematous papules 2 to 5 mm. in diameter, but may occasionally be large and tender, resembling the lesions of erythema nodosum. Petechial spots are noted occasionally. Splenomegaly is common. Meningococcemia is nearly always associated with an increase in the number of circulating leukocytes. The combination of *fever, leukocytosis, muscle and joint pains, and skin lesions* makes a distinctive clinical syndrome which is not difficult to recognize.

Meningococcemia subsides promptly with sulfonamide therapy; consequently clinicians no longer have an opportunity to observe the natural course of the disease. Prior to the development of sulfonamide therapy, cases of meningococcemia followed variable courses. Sometimes meningitis occurred; in other cases there was meningococcal endocarditis. The commonest outcome was complete recovery after an illness of many weeks or months.

This disease may impose a difficult diagnostic problem of unexplained fever, especially if the cutaneous eruption is absent. Occasionally chronic meningococcemia causes a relapsing type of fever, resembling that of malaria.

Positive diagnosis of meningococcemia depends on isolation of the bacteria from the blood. This is often difficult, since bacteria are not constantly present there, and it may be necessary to make a dozen or more cultures before obtaining a positive result. The height of the temperature is not particularly helpful in indicating the likelihood of obtaining a positive culture. Occasionally the organisms can be demonstrated in smears or cultures of petechial skin lesions.

Meningococcal Meningitis. A prodromal illness usually precedes the appearance of signs and symptoms of meningitis. There may be respiratory symptoms: cough, coryza, and malaise. Then follows a period lasting from a few hours to a day or two, in which there are symptoms characteristic of meningococcemia: chills, fever, malaise, headache, and joint and muscle pains. The picture changes abruptly with the onset of symptoms due to meningitis. The patient develops very severe headache, as well as pains in the neck and back. He may become nauseated and vomit. Within a few hours he is likely to become stuporous and lapse into coma, but may, on the other hand, become agitated and maniacal. On physi-

cal examination the patient appears acutely ill. The skin is flushed and hot, and often shows a *petechial eruption*. The petechiae may be on any part of the body, but are especially common in the conjunctivas, or on the lateral margins of the trunk, and on the wrists and ankles. They may appear at sites of trauma, especially when the patient has had to be restrained. In very severe cases, petechiae may be large and coalescent, forming purpuric lesions. Sometimes, in addition to the hemorrhagic rash, or even in its absence, there is an erythematous papular eruption similar to that seen in chronic meningococcemia. *Herpes simplex* occurs with special frequency in this disease, being present in about half of all cases. It is usually located around the mouth and nares. Ophthalmoscopic examination may disclose small choroidal hemorrhages, or fullness of the venules, or papilledema. The patient's tongue is dry, and the pharyngeal mucosa is reddened. General physical examination is otherwise not helpful. On neurologic examination, *stiffness of the neck* is the most characteristic sign. Other evidence of meningeal irritation, such as the Kernig or Brudzinski sign, is likely to be present. Cranial nerve paralyses, especially those causing strabismus, may be noted. There may be deafness in one or both ears, but this is apt to be missed initially because of the patient's disturbance of consciousness.

The course of the disease is variable. In fulminating cases death may ensue within a day, apparently because of overwhelming infection. In others there may be a gradual progression of signs of increasing intracranial pressure, coma, and high fever, with death occurring after a week or 10 days. Before sulfonamide therapy was available, patients with meningococcal meningitis who survived the acute infection sometimes developed the complication of internal hydrocephalus, due to blocking of the foramina of the fourth ventricle by scar tissue. This complication is now rare.

Laboratory Examinations. There is nearly always a *polymorphonuclear leukocytosis*, the count varying from 12,000 to 25,000 cells per cu. mm., or more. *Blood culture* is positive for the meningococcus in 70 to 90 per cent of cases. *Lumbar puncture* is the most helpful procedure in establishing an early diagnosis, and should be done without delay. The fluid is under increased pressure. In early cases it may be grossly clear, but it later

becomes opalescent or cloudy. Some of this fluid should be cultured immediately, the remainder being used for cell count and stained-film examinations. Cell count reveals an increased number of cells, chiefly polymorphonuclear leukocytes. The count may vary from less than 100 in an early case to as many as 25,000 or 50,000 per cu. mm. Examination of stained films of the spinal fluid nearly always reveals Gram-negative cocci or "coffee-bean"-shaped diplococci. They may be intra- or extracellular. Usually they are not numerous; some searching may be necessary to find them. This is in contrast with pneumococcal meningitis, a disease in which organisms are usually plentiful in smears of the spinal fluid. When meningococci cannot be found in Gram-stained films it is advisable to try a simple methylene blue stain, as by this method the organisms are more clearly differentiated from the leukocytes. The sugar content of the spinal fluid is low. *Smears of petechiae* may show meningococci. A segment of skin containing a lesion is held firmly between the thumb and forefinger to prevent bleeding, and the lesion is incised with a sharp-pointed blade. A small quantity of "tissue juice" is squeezed out and smeared on a glass slide. This can be stained with Wright's, Gram's, or methylene blue stain, and examined for bacteria.

In the differential diagnosis various other causes of acute meningitis must be considered. In view of the importance of etiologic diagnosis and immediate institution of appropriate therapy, every effort should be made to identify the causative agent at once, in stained films of spinal fluid or petechiae. Inexperienced examiners are apt to mistake granular artifacts for Gram-positive cocci, or to decolorize so thoroughly that Gram-positive organisms appear to be Gram-negative. These mistakes can be avoided by careful technic. The only other common Gram-negative bacterial meningitis is that caused by *Hemophilus influenzae*. This infection is seen almost exclusively in children under the age of eight. Because of the pleomorphism of the organism, some of its forms may resemble the meningococcus. Careful search, however, should reveal other shapes and bacillary forms. The "quellung" reaction with specific anti-influenzae serum confirms the diagnosis of influenzal meningitis. The commonest Gram-positive bacterial meningitides are those caused by the pneumococcus

or the streptococcus. These are apt to occur as complications of manifest pyogenic infections elsewhere in the body, such as sinusitis, otitis, mastoiditis, and pneumonia. As already mentioned, these organisms are likely to be found very easily in stained films of the spinal fluid. If no organisms can be found by microscopic examination of the spinal fluid, it should be remembered that tuberculosis and mycotic infections such as torulosis can occasionally cause the picture of acute bacterial meningitis. The viral meningitides are usually characterized by a predominance of lymphocytes in the spinal fluid.

Fulminating Meningococcemia (Waterhouse-Friderichsen Syndrome). In rare instances meningococcal infection takes the form of an overwhelming systemic infection, manifested by severe prostration, purpura, low blood pressure, rapid weak pulse, and cyanosis. This is one infection in which bacterial invasion of the blood stream may be so massive that organisms can be seen in stained films of the peripheral blood. The purpura may be very extensive, and may develop so rapidly that changes can easily be observed from hour to hour. There may or may not be evidence of meningeal infection. The name "Waterhouse-Friderichsen syndrome" is often given to this clinical picture. (Actually that term can be used to describe any acute bacterial infection in which there is bacteremia, purpura, and circulatory collapse.) At autopsy it is usual to find massive hemorrhage into the adrenal glands. The relation of this lesion to the circulatory collapse cannot be defined with certainty, and there are reports of cases showing the typical Waterhouse-Friderichsen syndrome without adrenal hemorrhage. This form of meningococcal infection is usually fatal within a day or two.

TREATMENT

Sulfonamide Prophylaxis. When meningococcal infection is prevalent in a community, one method of dealing with it is to administer sulfonamides to every member of the population group. This brings about a sharp decrease in the number of asymptomatic carriers, and thus diminishes the chance of acquiring infection. The procedure was used with notable success by military medical officers during World War II. The dose given to each person was usually 2 Gm. of sulfadiazine daily, for one to three days.

Meningococcemia Without Meningitis. This condition responds dramatically to sulfonamide therapy. The temperature usually falls to normal within 24 hours, and symptoms abate in the same time. A dose of 6 Gm. of sulfadiazine daily should suffice. Treatment should be continued for three or four days after the temperature falls to normal. No other therapy is necessary.

Meningitis. The management of meningococcal meningitis may be a complex problem. Patients are often irrational or maniacal, and may be unable to take fluids, nourishment, or medication by mouth. The most important single measure in treatment is prompt and adequate sulfonamide therapy. This should be begun as soon as the diagnosis is suspected. Even when the patient can swallow tablets it is well to begin *sulfonamide therapy* by a parenteral route. This insures early establishment of a satisfactory drug concentration, without danger of loss by vomiting or poor absorption from the gastrointestinal tract. Usually the initial dose should be 5 Gm. of sodium sulfadiazine, dissolved in 1000 ml. of physiological salt solution. The relative advantages of subcutaneous and intravenous administration are discussed in Chapter 99. After this initial loading dose, an adult patient should receive 6 Gm. of sulfadiazine daily.

Penicillin is also an effective chemotherapeutic agent in meningococcal infection. Unfortunately, however, a few meningococcus strains are resistant to it; consequently, it is not safe to assume that penicillin alone will be adequate in a given case. The safest practice is to use penicillin with sulfonamides at the beginning of treatment. Penicillin has the great advantage of almost immediate antibacterial effect, whereas with sulfonamides a lag period of six to eight hours is to be expected. Such a time loss may be of great importance in this type of infection. Penicillin is also better suited to intrathecal administration than the sulfonamides. Therefore, at the time of the initial lumbar puncture, if the spinal fluid appears hazy or cloudy, penicillin should be injected intrathecally, without waiting for further diagnostic studies. The dose should be 5000 to 10,000 units, dissolved in 5 ml. of physiological salt solution. In addition, this drug should be administered intramuscularly in a dose of at least 40,000 units every three hours, during the first 24 hours. At the end of that time a satisfactory sulfonamide level should have been established,

and further penicillin therapy, by either intrathecal or intramuscular route, is probably not necessary.

Aureomycin is also an effective antibiotic for meningococcal infection, and may be employed in patients for whom sulfonamide therapy is inadvisable.

Prior to the introduction of sulfonamide therapy, antimeningococcus serum and meningococcus antitoxin were widely used in therapy. There was no conclusive evidence, however, that they were effective agents. At present there is little reason for their use.

In the general management of the patient, sedation may be a matter of urgent necessity. An agitated individual should be given an adequate dose of a quick-acting sedative before a lumbar puncture is attempted. Paraldehyde is particularly useful in these cases. It may be injected intramuscularly in a dose of 5 to 10 ml. This can be repeated every half-hour until the patient is quiet.

Even when the bacterial infection is controlled satisfactorily, the patient may not recover consciousness for one or more days. In this case it is usually advisable to pass a nasal tube down into the stomach, in order to administer fluids, nourishment, and drugs by this route. Before each injection of material through the tube, aspiration should be done to ascertain that the stomach is not retaining material previously given. Vomiting would be a very serious accident in this type of patient, because of the danger that vomitus would be aspirated into the lungs.

In patients who respond satisfactorily to chemotherapy, the temperature usually falls gradually to normal in four to seven days. Full consciousness may not be regained for three to five days. It is usually safe to discontinue sulfonamide therapy at the end of 8 to 10 days. It is not necessary to repeat the lumbar puncture either for therapy or to follow the progress of treatment.

Waterhouse-Friderichsen Syndrome. The prime indication here also is for chemotherapy against the infection. An adequate sulfonamide level should be established as quickly as possible, and penicillin should be administered in doses of 100,000 units every three hours. Treatment of the circulatory collapse by transfusion of blood or plasma seldom has any observable beneficial effect. Many experienced physicians believe,

however, that therapy with adrenal cortical extract may be of value. This can be given in doses of 30 to 50 ml. The rationale is to supply an additional amount of cortical hormone to a patient under severe stress, rather than to substitute for adrenal tissue which may have been injured by hemorrhage.

PROGNOSIS

The outlook in *chronic meningococcemia* without meningitis is excellent. Immediate and complete recovery can be expected with sulfonamide therapy. Meningococcal meningitis is still a serious disease even with the use of effective chemotherapy. The prognosis varies considerably, according to the age of the patient. In infants less than one year old the fatality rate, even with the best treatment, is 20 to 25 per cent. With older children and adolescents the outlook becomes increasingly better up to the age of 20, where the fatality rate should be not higher than 2 or 3 per cent. In older individuals, the infection again becomes more dangerous; a fatality rate of at least 50 per cent is to be expected in old people. The only serious sequel seen with any frequency

nowadays is deafness, due to nerve damage. This may affect one or both sides. The number of cases of fulminating meningococcemia (Waterhouse-Friderichsen syndrome) is too small to permit any definite statement of statistical chances. Even with present methods of chemotherapy, however, the prognosis is poor. A few recoveries have been reported in patients who received adequate chemotherapy, either with or without adrenal cortical hormone therapy. Because of the rapidity with which death may occur in this form of infection, the mortality probably will always be high.

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Gonococcal Infections

Max Michael, Jr.

Definition
Etiology
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 Gonococcal Infection of Genital Tract
 Arthritis
Pathogenesis and Pathology
Clinical Features
 Arthritis

Definition. Gonococcal infections comprise a group of syndromes with varied manifestations produced by a single etiologic agent, the gonococcus (*Neisseria gonorrhoeae*). The organism has a predilection for the mucous membranes of the genital tract of both sexes, but may incite disease processes in any region of the body, particularly in synovial tissues and on serosal surfaces.

Tenosynovitis
Catarrhal Conjunctivitis
Keratoderma Blennorrhagicum
Perihepatitis
Gonococcal Endocarditis
Bacteremia
Laboratory Diagnosis
 Bacteriologic Diagnosis
 Serologic Diagnosis
Treatment

Etiology. The gonococcus is a Gram-negative, oval coccus belonging to the genus *Neisseria*. In stained films of purulent exudates the organisms appear predominantly in pairs, the opposing surfaces being flattened or concave, resulting in a characteristic biscuit- or kidney bean-shaped appearance. In cultures, however, there is considerable variation in size and shape of single

cells, and the flattening of opposing surfaces is seldom evident. The gonococcus grows best on solid mediums enriched with protein such as blood, plasma, or ascitic fluid. Moist atmosphere with 2 to 5 per cent carbon dioxide, as attained in a "candle jar," assists growth of the organism. It is differentiated from other members of the genus *Neisseria* by its fermentation reactions on glucose, maltose, and sucrose, and by agglutination reactions. It is thought that two or more antigenic strains of the gonococcus exist. Both nucleoprotein and polysaccharide substances have been identified in the cell, but their relationship to more precise antigenic divisions has not been conclusively demonstrated. The gonococcus contains an endotoxin. No true exotoxin has been isolated.

Epidemiology. Gonococcal infection of the genital tract, or gonorrhea, is nearly always acquired by sexual exposure, and is in fact the most common venereal disease. It can be transmitted by sexual partners who have no symptoms of the infection. Gonorrhea is outranked in incidence only by the common cold and measles among the acute infectious diseases. Approximately 1,000,000 cases are acquired in the United States each year. The lack of interest of the public and physicians alike concerning gonorrhea, and the tendency to attach relatively minor significance to the infection, have detracted from general appreciation of its true public health significance and its seriousness. Although many cases of gonorrhea have relatively mild symptoms, it must be realized that severe complications, including a high incidence of sterility, may result from the disease.

Gonococcal conjunctivitis of the newborn (*ophthalmia neonatorum*) is acquired in the infected birth canal, but has been practically eliminated by routine instillation of silver compounds or penicillin into the eyes of the newborn. Vulvovaginitis in young girls is now known to be nongonococcal in origin in many instances. Most of the gonococcal vulvovaginitis can be traced to sexual contact; infected linen and toilet seats play little or no role in the spread of this form of the disease.

It has been demonstrated that individuals may harbor the gonococcus in their prostatic secretions for as long as seven years without symptoms, and hence serve as asymptomatic carriers for years.

Pathogenesis. In the majority of instances the gonococcus gains access to the body by way of the genital tract. Less frequent sites of initial infections are the conjunctivas and rectal mucosa. The type of mucosa found in a particular part of the genitourinary tract determines to a large extent the susceptibility of that tissue to gonococcal infection. Stratified squamous epithelium, which covers the external genitalia of both sexes, extends for approximately 2 cm. into the male urethra, and lines the adult female vagina, is not susceptible to infection. Columnar epithelium, which lines the anterior urethra, urethral glands, prostatic ducts and prostate, seminal vesicles, vas deferens, and epididymis in the male, and Skene's, Bartholin's, urethral, and cervical glands, Fallopian tubes, and endocervix in the female, furnishes fertile soil for growth of gonococcus. Transitional epithelium, which lines the posterior urethra of the male, the proximal half of the urethra in the female, and the bladder of both sexes, is susceptible to invasion by gonococci. Within a short period of time, however, infection is spontaneously eradicated from surfaces lined with this type of epithelium, unless they are being bathed in exudate coming from an active lesion. Adequate drainage of infected glands and tissues formerly was regarded as essential for recovery before chemotherapeutic agents were available. When no such drainage took place, destruction of tissue and abscess formation with eventual fibrosis and cyst formation ensued. Now, however, this does not appear to be such an important factor for recovery.

From the genital lesion the infection may take any of the following courses: (1) It may be completely eradicated, either spontaneously or as the result of therapy; (2) it may be spread locally by way of the lymphatics or by direct extension to involve other organs of the genitourinary tract; (3) it may remain hidden in recesses of the genital mucosa, not causing symptoms, but producing the carrier state; (4) it may invade the blood stream and set up metastatic lesions, most important of which are arthritis and endocarditis.

Since it is not possible to culture the gonococcus from many of the metastatic lesions of gonorrhea, it has been suggested that these lesions represent an allergic response to antigenic fractions of the gonococcus, or to tissues which have been altered antigenically in some fashion

by the organism. This, however, has not been definitely established.

It is possible to produce acute gonococcal infection by reinfecting a person with chronic gonorrhea. It is obvious that there is little, if any, immunity to gonorrhea, but this point will need clarification when different strains of the gonococcus are better identified. Attempts to evoke immunity to gonorrhea by vaccination have been unsuccessful.

Manifestations: GONOCOCCAL INFECTION OF GENITAL TRACT. After an incubation period of from three to five days, gonorrhea in the *male* begins as an acute anterior urethritis manifested by purulent urethral discharge and burning on urination. If not properly treated, infection may spread to the posterior urethra with symptoms of frequency, urgency, and terminal hematuria. Perineal discomfort may occur. The prostate and seminal vesicles may also be involved, and this may result in acute retention of urine and pain in the suprapubic region. Acute seminal vesiculitis may cause high fever and pain that is referred to the suprapubic, inguinal, and sacral regions, or to the hip on the involved side. Puzzling syndromes of obscure fever and pain in the above-mentioned regions are occasionally due to seminal vesiculitis. Acute prostatitis may be accompanied by urinary retention, elevation of temperature, and the feeling of fullness in the rectum. Rectal examination discloses the enlarged, tender prostate gland. More serious involvement is that of acute epididymitis which is accompanied by pain in the epididymis, swelling, and fever. The resulting tissue destruction is responsible for many cases of sterility in males.

The chronic stage of gonorrhea may be asymptomatic or may be manifested by a small amount of mucoid urethral discharge occurring in the morning (*gleet*), or by urgency and frequency of urination. Chronic prostatitis in a small number of patients is due to previous gonococcal infection.

Gonorrhea in the *female* also begins as an acute urethritis with frequency and burning on urination, and purulent discharge. Cervicitis may be present at the same time, resulting in a profuse, purulent vaginal discharge. There may be local spread to Skene's or Bartholin's glands, with resulting acute or chronic infection in these organs. Spread from the cervix into the Fallopian tubes produces the syndrome of acute salpingitis, or pelvic inflammatory disease (P.I.D.). This is

manifested by severe pain in the lower abdomen, with local spasm and tenderness, high fever and leukocytosis, vaginal discharge, and painful urination. Recurring bouts of salpingitis are prone to occur, with involvement of the ovaries, destruction of tissue, formation of abscesses, and palpable masses, resulting in the "frozen pelvis." This is an important cause of sterility.

Acute salpingitis must be differentiated chiefly from acute appendicitis and ectopic pregnancy, though all causes of acute lower abdominal pain are to be considered. A vaginal discharge caused by the gonococcus is to be differentiated from vaginal discharge caused by *Trichomonas vaginalis*, cervical erosions, and other local gynecologic disorders.

Gonorrhreal vaginitis in the *immature female* is not so common as formerly believed. Many cases previously considered to be gonococcal in origin are actually due to other microorganisms. Because of the nature of the vaginal epithelium in the immature female, the gonococcus finds susceptible tissue and causes purulent discharge, redness of the vulva and introitus, and accompanying malaise and some fever.

ARTHRITIS. Gonococcal arthritis, an acute inflammatory process, is the commonest and most disabling metastatic complication of this disease. It occurs in approximately one-tenth to three-tenths per cent of the cases, and is more frequent in patients who have had multiple attacks of urethritis.

Pathogenesis and Pathology. Two clinical syndromes are associated with gonococcal arthritis. In approximately 25 per cent of the patients the gonococcus can be cultured from the synovial fluid; in these the disease manifests itself as a specific infectious arthritis. In the remaining cases the synovial fluid is sterile and some features of the disease follow certain of the patterns of rheumatoid arthritis. In the former group the gonococcus reaches the joint by way of the blood stream and sets up a purulent infection. In the latter group it is not certain whether the organisms reach the joint spaces and are rapidly destroyed, or whether the arthritis is the result of sensitization of the synovial tissues by antigenic fractions of the gonococcus without actual bacterial invasion of the joint. Pathologic material demonstrates certain differences in the two types. In the infected type of arthritis there is an extensive inflammatory reaction of the synovial

tissue with destruction of the superficial layer of synovial cells. In the noninfected type of arthritis the synovial tissue proliferates, thickens, and is infiltrated by perivascular and subsynovial collections of lymphocytes, plasma cells, and macrophages. Occasionally neutrophils are present. The extensive exudative reaction is not seen. The superficial synovial layer is not completely destroyed and, in some phases of the tissue sequences, may be seen to proliferate. The findings in the former group are those of an acute bacterial infection, while in the latter group they suggest the picture of a hypersensitivity reaction.

The cell count of aspirated synovial fluid varies from 1800 to 160,000 white cells per cubic millimeter, in general being higher in those cases with infected fluids. The fluid always has the characteristics of an exudate with predominance of polymorphonuclear leukocytes. The sugar content of the synovial fluid is decreased, but this is of little help in differentiating gonococcal from other forms of acute arthritis.

Destruction of articular cartilage may be noted as early as three weeks after the onset of arthritis. These changes are most apt to be seen in those cases with infected synovial fluid. Associated with the changes in the joint are periarticular inflammatory reactions which may later fibrose and contribute to ankylosis of the joints.

Clinical Features: ARTHRITIS most commonly occurs one to three weeks following genital involvement, but at times the interval may be prolonged to months or years. Factors predisposing to arthritis include pregnancy, pelvic operations, or instrumentation for ureteral stricture, all of which may cause latent infection to flare up.

The arthritis of gonococcal infection is polyarticular in about 85 per cent of the cases. The joints most frequently involved are the knees, ankles, wrists, metacarpophalangeals, and shoulders, in that order, though any joint in the body may become infected. The first signs noted are those of malaise and fleeting aches in several of the large joints. Within 24 to 48 hours, pain becomes more severe and more persistent. After three or four days, two or more joints become exceedingly painful and distended with fluid. The overlying skin becomes red and the slightest motion causes severe pain. Marked muscle spasm occurs around involved joints, and is responsible for the rapid development of deformities. A

striking and rapid muscle atrophy adjacent to involved joints is a common feature.

The course of gonococcal arthritis is exceedingly variable. Some cases may be mild with transitory aches in the joints which clear rapidly in a few days without residua. At the other extreme are cases that may progress to permanent bony ankylosis of the joints. This termination occurs primarily in cases with infected fluids which are untreated, and involves principally the smaller joints of the wrists and hands.

In a small group of patients a picture of rheumatoid arthritis develops following the gonococcal infection. It is not certain whether this represents gonococcal arthritis evolving into the "rheumatoid picture," or whether it is simply rheumatoid arthritis precipitated by the gonococcal infection.

The systemic response varies considerably. Fever between 100° and 102° F. is usually present, though extremes from normal to 105° F. may be observed. Chills are infrequent, but may be seen, particularly in patients with monarticular involvement. It is in this group that bacteria are cultured from the joint fluid.

TENOSYNOVITIS. A characteristic feature is tenosynovitis. This appears in approximately 40 per cent of the patients, and occurs most frequently about the wrists, dorsum of hands and feet, and around the internal and external malleoli. Tenosynovitis may be confused with arthritis unless careful evaluation of joint mobility is made. Occasionally tenosynovitis may be the only sign of the gonococcal infection. The occurrence of tendon sheath involvement is more frequent in gonococcal arthritis than in any other type of arthritis, and may be a valuable diagnostic sign. Acute bursitis is sometimes noted.

CATARRHAL CONJUNCTIVITIS occurs in approximately 15 per cent of cases and may also be helpful in diagnosis. Organisms have not been cultured from these lesions. The conjunctivitis may precede, accompany, or follow the arthritis. A less frequent, but more serious, ophthalmic manifestation is iridocyclitis, which may lead to blindness.

KERATODERMIA BLENNORRHAGICA, an interesting but rare form of cutaneous lesion, may accompany gonococcal arthritis. This lesion occurs most frequently on the plantar surface of the feet, and consists of thickening of the skin, some of which may become necrotic. There is sharp

demarcation between involved areas and the surrounding skin.

The diagnosis of gonococcal arthritis can be simple, particularly in patients with acute polyarthritis following a urethral discharge in which the gonococcus has been demonstrated. Associated conjunctivitis and tenosynovitis are characteristic and may be of help in diagnosis.

In the differential diagnosis, rheumatic fever, rheumatoid arthritis in the acute stage, and Reiter's disease offer the greatest problems. Gout may also imitate this disease. The use of salicylates may be of diagnostic aid since gonococcal arthritis seldom responds as dramatically as rheumatic fever. The most confusing syndrome which must be differentiated is Reiter's disease, which is characterized by urethritis, arthritis, and conjunctivitis. It is only by correlation of careful clinical observations of the patient, the course of the illness, response to chemotherapy, precise bacteriologic studies, and the judicious interpretation of the gonococcal complement-fixation test that gonococcal arthritis may be differentiated from the conditions mentioned above. In those cases of gonococcal arthritis in which response to penicillin is relatively prompt, this therapeutic test serves as an important diagnostic aid.

PERIHEPATITIS. An infrequent complication of gonorrhea in the female is the occurrence of upper abdominal peritonitis or perihepatitis. Gonococci have not been cultured directly from the lesions, but the organisms are assumed to reach this area by direct extension over the posterior peritoneal gutter. When the lesions heal, characteristic "violin string" adhesions are formed. The symptoms of perihepatitis, which may occur as long as five years after the initial attack of gonorrhea, consist of a sudden onset of sharp pain in the upper abdomen, with a moderate elevation of temperature. The pain may be referred to the shoulder, and is exaggerated by coughing or deep breathing. A friction rub is occasionally heard over the liver, and infrequently small pleural effusions develop on the side of the lesion. If untreated, perihepatitis subsides gradually over a period of one to four weeks. No incapacitating sequelae are known.

GONOCOCCAL ENDOCARDITIS. The gonococcus is a rare cause of bacterial endocarditis. The clinical picture is similar to acute endocarditis caused by other microorganisms. Involvement of

the valves of the right side of the heart is not infrequent. A double daily temperature elevation is occasionally seen and may be of some assistance in diagnosis. Arthritis frequently coexists. Peripheral emboli occur as in other forms of endocarditis, but embolization to the lungs is due more frequently to involvement of the right side of the heart. Another characteristic feature is involvement of normal heart valves in 90 per cent of the cases.

BACTEREMIA. Transient invasion of the blood stream by the gonococcus probably occurs frequently, but is accompanied by no symptoms other than chill in a few patients with gonococcal arthritis. Constant invasion of the blood stream, however, produces a bacteremia characterized by chills, fever, polyarthritis, prostration, and a macular eruption of the trunk and extremities. The rash rapidly becomes vesicular, pustular, and hemorrhagic. This rare complication of gonorrhea is more common in females. Until chemotherapeutic agents were available, recovery occurred in from three weeks to three months.

The dissemination of the gonococcus by way of the blood stream accounts for some of the *rare manifestations* of the disease, such as meningitis, periostitis, suppurative myositis, perichondritis, liver abscesses, and myelitis. It is apparent that few, if any, regions or organs of the body are free from attack by the gonococcus.

Laboratory Diagnosis. The chief laboratory methods of diagnosis depend upon the demonstration of the organism by smear or by culture, and upon the detection of antibodies by means of the complement-fixation test.

BACTERIOLOGIC DIAGNOSIS. The diagnosis of acute gonococcal urethritis in both sexes may be made by smear and by confirmatory cultures. In smears of purulent exudate stained by the Gram method, the organisms are seen as the characteristic Gram-negative, "biscuit-shaped" diplococci often located within the cytoplasm of polymorphonuclear leukocytes. This is sufficient evidence for a positive diagnosis, but failure to demonstrate the organism does not rule out gonorrhea; cultural methods must be undertaken. The most commonly used mediums are chocolate agar and Pizer's mediums, the latter being a basic medium enriched with plasma and containing Nile blue to inhibit other organisms. The technic of obtaining cultures is very important, and extreme care must be taken to avoid

excess contamination. Moist, fresh inoculums must be used. The cultures of gonococci can be identified easily by their color reaction to the "oxidase reagent." This reagent (1 per cent solution of tetramethyl-*p*-phenylenediamine hydrochloride), when poured over the suspected plate, produces a deep purple discoloration of *Neisseria* colonies. Best results are obtained from direct cultures of urethral, prostatic, or cervical exudates. When these are not available, cultures of the urine sediment are often of value.

In culturing *joint fluid* for the gonococcus it is not adequate merely to streak a loopful of the material on the culture medium. Preferably the plate should be flooded with about 0.5 ml. of the fluid. Inoculation of the sediment from centrifuged fluid is helpful. Often it is possible to obtain a positive culture when joint fluid is not available by injecting a few milliliters of physiological saline solution into the periarticular structures and withdrawing some of this for culture.

SEROLOGIC DIAGNOSIS. The complement-fixation test devised by Price is of considerable value in the differential diagnosis of gonococcal arthritis, particularly in those cases in which a history of gonococcal infection cannot be obtained, and from which gonococci cannot be recovered on culture of the genitalia or of the synovial fluid. Antibodies may appear as late as six weeks after the onset of arthritis and may persist for months after infection has been eradicated. A changing antibody titer is considered to be diagnostic. The test appears to be quite specific.

Treatment. With the introduction of effective chemotherapeutic agents, the treatment of gonococcal infections has undergone radical changes. Local therapeutic manipulations now have little place in the management of gonorrhea. The sulfonamide compounds were widely used until penicillin was introduced. However, a large number of strains of gonococci resistant to sulfonamides have appeared after several years of such therapy, and at present few gonococcal infections are cured by sulfonamides. To date, however, only rarely have gonococci been reported resistant to penicillin. The gonococcus is exceedingly susceptible to this antibiotic, which at present is the drug of choice. Aureomycin is also effective, but appears to be somewhat inferior to penicillin.

Relatively small doses of penicillin are needed for the cure of *genital infections*. A total dose of

300,000 units in aqueous solution, or in absorption-delaying mediums, such as procaine and aluminum monostearate procaine, is effective in approximately 75 per cent of the cases. Re-treatment of the remaining cases with similar or slightly larger doses usually results in cure. A watery urethral discharge is noted in as high as 20 per cent of male patients after the gonococcus has been eradicated by penicillin. This discharge is noninfective, but its exact nature is not known. The small doses of penicillin administered for the treatment of gonorrhea may delay the appearance of syphilitic lesions, and follow-up studies, including serologic tests for syphilis, for four months must be made with this fact kept in mind.

Penicillin is also the drug of choice in the treatment of *gonococcal arthritis*, but the small doses that are used in cases of urethritis are inadequate for arthritis. A satisfactory regimen consists of 400,000 to 500,000 units of penicillin a day, divided into eight injections for a period of from 7 to 10 days. It is not necessary to instill penicillin into the synovial cavities since this antibiotic diffuses readily into the joint spaces. The response to chemotherapy is often not striking, and five to seven days may be required for the temperature to return to normal. In many cases the arthritis does not subside completely, and may smolder for a period of months with occasional exacerbations accompanied by further heat and swelling. Occasionally during the course of penicillin therapy, joints not previously involved become distended with fluid. Many authors feel that this syndrome represents rheumatoid arthritis precipitated or aggravated by the gonococcal infection; the writer prefers to regard it as a manifestation of gonococeal arthritis.

Physical therapy is an important adjunct in the management of gonococcal arthritis. The acutely inflamed joint should be splinted to avoid contractures. The judicious use of heat, gentle massage, and early guarded passive motion are similarly advised in selected cases. Artificial fever therapy may be of value in cases resistant to chemotherapy. Removal of fluid from distended joints often affords marked relief from pain.

Penicillin is also the drug of choice for *other complications* of gonorrhea. It has been used locally in ophthalmia neonatorum. The dose and duration of therapy must be suited to the syndrome.

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Colon and Aerogenes Infections (Coliform Bacterial Infections)

Paul B. Beeson

Etiology
Pathogenesis
Manifestations
Urinary Tract Infections
Pyogenic Infections
Appendicitis and Peritonitis
Biliary Tract Infections
Cirrhosis of the Liver
Omphalitis
Treatment

Etiology. The coliform bacteria are a group of Gram-negative bacilli which normally inhabit the intestinal tract in man. These organisms generally ferment lactose with the production of gas. The best known members are *Escherichia coli* and *Aerobacter aerogenes*. In addition, there is a third group, the paracolon bacilli. The tests commonly employed in differentiating various members of the coliform group are biochemical (Voges-Proskauer reaction, methyl red test, citrate utilization). Final identification is by means of serologic reaction.

The coliform bacteria are the predominant organisms in the feces, and their presence in milk and water is regarded as presumptive evidence of fecal contamination. Although harmless in the intestinal tract, these organisms are capable of causing severe infection when introduced into other tissues. From the standpoint of the diseases which they produce, there is no difference in the pathogenic potentialities of the different members.

Pathogenesis. Coliform organisms may be transported from the intestinal tract to other parts of the body by way of the blood stream or the lymphatic vessels, or they may be spread externally by fecal contamination. Histologically the lesions show typical acute inflammation, with pus formation. There is a common misconception that coliform bacterial infections are characterized by an exudate which has a foul, or fecal, odor. Such an odor is caused by other bac-

teria, especially the anaerobic streptococcus, which is often associated with coliform bacteria in infections.

Manifestations: URINARY TRACT INFECTIONS.

Members of the coliform group of organisms are the commonest infecting agents in pyelonephritis and cystitis, diseases which are discussed in Chapter 244. The route by which these organisms reach the urinary tract from the bowel is not definitely known, but the lymphatic vessels are probably the chief pathway. Another possibility is that bacteria are carried in the circulating blood from the intestine to the kidneys. Ascending infection through the urethra, bladder, and ureters is probably infrequent in adults, although many pediatricians believe that the pyelonephritis commonly seen in young girls is due to ascending infections, possibly facilitated by the short urethra.

PYOGENIC INFECTIONS. Coliform organisms are occasionally the cause of pyogenic infections in various parts of the body, such as chronic sinusitis, lung abscess, and endometritis. As a rule they are associated with other organisms, particularly Gram-positive cocci, the *Proteus* group, and *Pseudomonas aeruginosa* (*B. pyocyanus*). They occasionally cause abscesses at sites of insulin injection in diabetic patients. An interesting feature of these abscesses is the production of gas in the tissues, which may lead to an erroneous diagnosis of clostridial infection. It has been suggested that the gas production is related to the high sugar content of the tissues.

APPENDICITIS AND PERITONITIS. Coliform organisms can nearly always be cultured from the pus of appendiceal infection or from the exudate of generalized peritonitis following perforation of the intestinal tract. They are not found in pure culture, however, but always in association with

other organisms such as anaerobic streptococci and clostridia. It is difficult to assess the relative importance of the various bacteria in mixed infections of this type.

BILIARY TRACT INFECTIONS. Coliform organisms are the most common etiologic agents in obstructive cholangitis. The so-called "Charcot's intermittent fever" may be seen in this condition.

CIRRHOSIS OF THE LIVER. Bacteremia due to *E. coli* occurs occasionally in patients with cirrhosis of the liver without an obvious primary focus of infection. It has been suggested that the organisms reach the blood stream through venous collaterals which shunt them around the liver, thus escaping the "filtering" effect of the Kupffer cells.

OMPHALITIS. A serious infection of newborn infants is colon bacillus infection of the stump of the umbilical cord. This is accompanied by bac-

teremia and is usually fatal. It has been given the name Winckel's disease.

Treatment. Several chemotherapeutic agents are available, and in the event of failure of one of them, a trial of others is warranted. The order of preference is something like this: "Chloromyctin" (1-6 Gm. per day), aureomycin (1-6 Gm. per day), sulfadiazine (3-6 Gm. per day), streptomycin (1-2 Gm. per day). In urinary tract infections mandelic acid may be effective; the dose is usually 12 Gm. per day—enough being given to maintain the pH of the urine below 5.5.

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Proteus and *Pyocyaneus* Infections

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Etiology

Pathogenesis

Manifestations

Urinary Tract Infections

Infections of the Ear, Mastoid, and Paranasal Sinuses

Infections of the Eye

Infections of the Skin and Subcutaneous Tissues

Meningitis

Blood Stream Infections

Treatment

Etiology. The *Proteus* genus consists of a group of Gram-negative, motile bacilli which ferment dextrose and sucrose but do not act upon lactose or mannite. They split urea, producing ammonia. The several varieties differ in other biochemical and in serologic reactions. One group (X) possesses an antigen similar to that present in certain rickettsiae; this probably accounts for the appearance of *Proteus* antibodies (Weil-Felix reaction) in certain rickettsial diseases.

Bacterium pyocyaneus (*Pseudomonas aeruginosa*) is a Gram-negative, motile bacillus which does not ferment any carbohydrate. Its outstand-

ing biochemical characteristic is the production of greenish blue pigment. Coloring of exudates by this pigment has caused the organism to be designated as "the bacillus of blue-green pus." *B. pyocyaneus* and *Proteus* bacilli are normal inhabitants of the mouth, intestinal tract, and skin of human beings.

Pathogenesis. *Proteus* and *pyocyaneus* infections are usually the result of implantation of the organisms in an already damaged tissue. Ordinarily these infections remain limited to one area, but under exceptional circumstances the organisms may be disseminated in the blood stream to form metastatic pyogenic infections elsewhere. Histologically, the lesions of *B. pyocyaneus* are characterized by thrombosis of small arteries; this may produce areas of infarction, in which there is little inflammatory reaction. The lesions caused by *Proteus* bacilli show the typical changes of acute inflammation.

Manifestations. *B. pyocyanus* and *Proteus* infections can occur in many locations, including skin, subcutaneous tissue, bone, synovial cavities, lung, kidney, meninges, ear, mastoid cells, and paranasal sinuses. The most important of these are:

1. **URINARY TRACT INFECTIONS.** *B. pyocyanus* and the *Proteus* bacilli are among the commonest pathogens of the urinary tract. Infections may follow instrumentation of the urinary tract, or may develop in the kidney as a result of lymphatic or hematogenous spread from the intestinal tract. It is not unusual for both kinds of organisms to be present at the same time in chronic urinary tract infections, or one of them may be present in combination with some other pathogen such as a member of the coliform group.

2. **INFECTIONS OF THE EAR, MASTOID, AND PARANASAL SINUSES.** *B. pyocyanus* and *Proteus* are frequent secondary invaders in infections of these areas. They usually occur in combination with Gram-positive cocci. A chronic infection of the external auditory canal due to *B. pyocyanus* is sometimes a troublesome ailment, causing considerable discomfort and discharge. It may lead to thickening of the eardrum and impairment of hearing.

3. **INFECTIONS OF THE EYE.** *B. pyocyanus* may become implanted on abrasions of the cornea, and produce an infected ulceration. The infection then is liable to spread into the eyeball. This is one of the most severe ophthalmic infections, and may lead to destruction of the eyeball.

4. **INFECTIONS OF THE SKIN AND SUBCUTANEOUS TISSUES.** Chronic ulcerations of the skin such as varicose or decubitus ulcers are very frequently contaminated with *B. pyocyanus* and *Proteus* organisms. The same is true of burned areas. Draining sinuses in chronic osteomyelitis are also susceptible to this type of secondary bacterial infection.

5. **MENINGITIS.** Primary meningitis caused by these organisms does not occur. They may, however, be introduced into the subarachnoid space in the course of a lumbar puncture or by extension from a focus of infection in the mastoid cells or paranasal sinuses. The resulting meningitis is very severe and often fatal.

6. **BLOOD STREAM INFECTIONS.** In debilitated persons, local infections due to *B. pyocyanus* or

Proteus may become disseminated in the blood stream; this causes a fulminating type of illness, with hectic fever and secondary abscesses, which often ends fatally. *Pyocyanus* sepsis may be accompanied by a unique skin eruption, consisting of vesicular or bullous lesions filled with clear fluid. The vesicles rupture a day or two after their appearance; the bases then become gangrenous and eventually slough out to produce ulcers.

Treatment. The tendency of these infections to occur in damaged, ischemic, and fibrotic areas, or in persons already debilitated, makes their therapy a difficult problem. Improvement of the patient's general condition may help to eradicate the local infection. Urinary infections may subside after surgical removal of obstructive lesions. Débridement of devitalized tissues and better drainage of chronic infections are desirable. Sulfonamides are partially effective, but unfortunately all strains of *Proteus* and *B. pyocyanus* are not susceptible to these drugs. Streptomycin is effective against most strains *in vitro*, but the rapid development of streptomycin resistance *in vivo* is a serious drawback. Aureomycin and "Chloromycetin" are effective against some, though not the majority of strains of either organism, *pyocyanus* being particularly resistant. Polymyxin is the most effective antibiotic in therapy of these two bacterial infections, but its toxicity limits its usefulness to only the most serious infections. Mandelic acid therapy of urinary tract infections may be effective with *B. pyocyanus*, but is useless against *Proteus* because the production of ammonia by these organisms prevents the attaining of a strongly acid urine. Superficial infections may be benefited by local application of 1 per cent acetic acid, or nitrofurazone ointment ("Furacin").

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Friedländer Bacillus Infections

Paul B. Beeson

Etiology
Pathogenesis
Manifestations
Acute Friedländer Pneumonia
Chronic Friedländer Infection of the Lung
Diagnosis
Treatment

Etiology. The Friedländer bacilli (*Klebsiella pneumoniae* or *friedländeri*) are a group of encapsulated Gram-negative bacilli, found among the normal flora of the mouth and respiratory and intestinal tracts. They are closely related to the coliform bacteria, and cannot be differentiated by biochemical reactions, but members of the Friedländer family form characteristic large mucoid colonies on solid mediums, and are virulent for mice. The capsular polysaccharides of Friedländer bacilli are similar to those of pneumococci; in fact, serologic cross reactions occur between certain Friedländer strains and pneumococci. Friedländer bacilli have been divided serologically into groups A, B, C, D, and E and a heterogeneous group X. Most infections in human beings are due to members of group A.

Pathogenesis. Infections of the urinary and biliary tracts, the peritoneal cavity, and other serous membranes comprise the bulk of diseases caused by the Friedländer bacilli. These are similar in manifestations and pathogenesis to those produced by the coliform organisms, discussed in Chapter 105. In the lungs, however, Friedländer infections are unique; they may take the form of an acute, rapidly progressive, and often fatal pneumonia, or of a chronic lung disease, with bronchitis, bronchiectasis, and cavity formation.

Manifestations. As already mentioned, the majority of infections caused by the Friedländer bacilli are similar to those due to the coliform bacteria. Thus Friedländer bacilli may be among the infecting organisms in general peritonitis, or may be the etiologic agents in pyelonephritis or cholangitis. Occasionally they cause infections of the middle ear, mastoids, or paranasal sinuses, or meningitis secondary to one of these. A significant proportion of all reported cases of Fried-

länder bacillus meningitis has involved persons with diabetes mellitus. Another kind of Friedländer bacillus meningitis is that which complicates traumatic perforation of the skull or spinal canal, especially as encountered in war wounds.

Acute Friedländer Pneumonia. About 1 per cent of all cases of bacterial pneumonia are caused by Friedländer bacilli. These usually occur in males past middle age. The manifestations are generally similar to those of pneumococcal pneumonia. The onset of symptoms is usually sudden; there may be chill, followed by fever and severe pleuritic pain. The fever is likely to be more remittent than in pneumococcal pneumonia, and physical signs of consolidation are less striking. In about half of the cases the sputum is dark brown or red and is so sticky that the patient has difficulty in expelling it from his mouth and lips. This form of pneumonia usually progresses rapidly, spreading from lobe to lobe and from one lung to another within a few days. Lung abscess and empyema are frequent complications. Previous to the introduction of sulfonamides and streptomycin, the fatality rate reported in different clinics varied from 50 to 80 per cent.

Chronic Friedländer Infection of the Lung. This may follow acute Friedländer pneumonia, but is also seen in patients who give no history of acute onset. The principal manifestations are productive cough, weakness, and anemia. Hemoptysis is not common. Chronic empyema or sterile serous effusion is observed in about one fourth of the cases. Cavity formation frequently occurs, and is usually located in the upper lung fields. There is very little inflammatory reaction around the cavities, so that in roentgenograms they appear to have very thin walls. A number of patients with chronic Friedländer infection of the lung have had an erroneous diagnosis of pulmonary tuberculosis and have been given sanatorium treatment. The course of this disease is quite variable. Some cases have been observed for 10 or 20 years with very little change in symp-

toms and signs, whereas others have shown gradual improvement after several months.

Diagnosis. Diagnosis can be made only by the isolation of Friedländer bacilli. A presumptive diagnosis of Friedländer pneumonia can be made on the basis of Gram stain of the sputum; this shows numerous short, plump, Gram-negative bacilli, each surrounded by a clear space due to the capsule. Culture of the sputum on a solid medium shows almost pure growth of Friedländer colonies. Certain proof is afforded by isolation of the organisms from the blood, pleural exudate, or fluid aspirated from the lung.

Treatment. Specific antiserums have been employed in the treatment of acute Friedländer pneumonia, but the results have not been encouraging. In vitro, Friedländer bacilli are usually susceptible to sulfonamides, streptomycin, aureomycin, and "Chloromycetin," and results

of therapy of experimental Friedländer infections with all of these agents have been quite satisfactory. Reliable statistics on results of therapy of Friedländer infections in human beings with these agents are not available because of the fact that only a small number of cases are observed annually even in large clinics. In view of the high fatality rate in acute Friedländer pneumonia, it seems justifiable to employ a combination of therapeutic agents—e.g., sulfadiazine plus one or more of the antibiotics.

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Typhoid Fever

Paul B. Beeson

Definition
History
Etiology
Epidemiology
Pathogenesis
Manifestations
Complications
The Carrier State
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. Typhoid fever is a febrile illness of several weeks' duration due to infection with *Salmonella typhosa* characterized by fever, cough, headache, skin eruption, splenomegaly, and leukopenia.

History. Descriptions of typhoid-like illnesses have been given since ancient times. The name typhoid fever was first used by French clinicians in the early part of the nineteenth century. In 1836 Gerhard, of Philadelphia, presented the first satisfactory clinical differentiation between typhoid and typhus fevers. Between 1855 and 1870

Budd, an English practitioner, studied the epidemiology of the disease and correctly concluded that the source of contagion was the fecal discharges of affected persons. In 1880 Eberth isolated the typhoid bacillus.

Typhoid fever has been a prominent disease of military groups, and was an important cause of disability and death in wars previous to World War I. Between 1900 and 1910 prophylactic vaccination was developed, and the use of this procedure in World War I reduced the incidence of the disease very remarkably. As a result of widespread prophylactic vaccination in civilian populations, and of improved methods of sanitation, typhoid is far less common now than 50 years ago. The introduction of "Chloromycetin" therapy, in 1948, brought about a drastic change in the duration and prognosis of the disease.

Etiology. *Salmonella typhosa* is a motile, Gram-negative bacillus, which ferments dextrose, maltose and mannite without the production of gas,

and does not ferment lactose or sucrose. At least 20 different strains of the organism have been distinguished by testing their susceptibility to lysis by bacteriophages. Such typing has been of great assistance in tracing the sources of outbreaks of typhoid fever but is of no particular value to clinicians, since there is no distinct difference in the character of diseases produced by the different phage types. *S. typhosa* has flagellar (H) antigens and somatic (O) antigens which cross-react serologically with H and O antigens of certain other *Salmonella*.

Epidemiology. Human beings are the only known natural hosts of typhoid infection. Infection is transferred from the intestinal tract of one person to the mouth of another. Great epidemics have resulted from fecal contamination of water or milk supplies, but modern methods of sanitation are rendering this mode of spread less common. The principal source of infection now is typhoid "carriers"—i.e., persons who have recovered from the disease but continue to harbor the causative organisms. Such individuals are particularly dangerous if they are food handlers. Transmission by flies is a possibility and is particularly likely to occur where outdoor toilets are used. Contamination of water supplies from improperly constructed toilets can also occur. Epidemics have resulted from the eating of shellfish caught in areas of sewage disposal. Formerly, typhoid fever was especially prevalent in the summer and early fall. This may have been due to such factors as better bacterial growth in warm weather, fly season, and vacation travel. At present, however, there is no marked seasonal variation; cases are acquired from "carriers" sporadically throughout the year.

Pathogenesis. There can be no question that the portal of infection is the gastrointestinal tract. The point at which bacteria actually enter the tissues is not so certain, however. It is commonly stated that the bacilli are first taken up by the lymphoid tissue of the intestinal wall, especially the Peyer's patches, and that drainage from there involves the mesenteric lymph nodes. It has been proposed by some workers, on the other hand, that invasion of the tissues may occur in the pharynx and tonsils. Whatever the primary point of invasion, the next significant factor in the development of typhoid fever is the presence of bacilli in the circulating blood. This is undoubtedly due to a constant feeding of or-

ganisms into the blood from some focus such as the mesenteric lymph nodes. The bacteremia permits secondary infection of the other areas: liver, spleen, bone marrow and other lymph nodes. At the end of the first week of infection, antibodies appear in the blood and the bacteremia usually ceases. From this stage onward the infection which has been established in the biliary tract is particularly important, since it furnishes a flood of infected material to the upper part of the small intestine. This probably is responsible for the heavy involvement of the Peyer's patches during the second and third weeks of the disease, and for the presence of organisms in the fecal discharges.

The gross autopsy findings in patients dying of typhoid fever are those of inflammatory involvement of lymphoid tissues, especially in the wall of the intestine, and in the mesenteric lymph nodes and the spleen. The spleen is enlarged, as is the liver. The Peyer's patches become swollen and may undergo necrosis, leaving oval-shaped ulcers; these are most numerous in the terminal ileum but may extend as high as the jejunum or as low as the appendix and cecum. They are responsible for the most serious complications of typhoid fever: perforation and hemorrhage.

The common denominator underlying typhoid lesions, wherever encountered, consists in a marked proliferation of large mononuclear cells derived from the reticuloendothelial system. This proliferation encroaches on blood vessels and leads to necrosis of tissue. Microscopic examination of the intestinal lesions reveals few bacilli in the extracellular spaces; most of them appear to be located within macrophages. Goodpasture has reported that typhoid bacilli can also be found within plasma cells. This phagocytosis may serve the parasite better than the host, since intracellular existence of the organisms may protect them from such agents as antibodies and drugs. This may explain why the disease seems to continue without observable clinical change after the appearance of antibodies in the blood, and why signs of clinical improvement do not become manifest until two or three days after beginning "Chloromycetin" therapy.

Because the most prominent inflammatory changes are found in the intestine, there is a tendency to regard typhoid fever as a primary enteric infection. A consideration of the observed facts, however, leads to the conclusion that the intesti-

nal infection is largely secondary to the biliary tract infection, which in turn is a sequel to the initial bacteremia. The fact that organisms are constantly present in the blood during the early period, while they do not appear in the stools until the second or third week, speaks for an important extraintestinal focus of the infection.

Manifestations. The incubation period of typhoid fever usually cannot be determined, but in epidemics which have followed a single exposure the incubation periods showed considerable variation, averaging 10 to 12 days.

The clinical manifestations of typhoid fever are exceedingly variable. Some persons can be infected without any disability whatever, or suffer only a brief febrile illness. In others, the disease takes the form of an overwhelming infection leading to death within a few days. In the majority of cases recovery occurs after an illness of several weeks. The description to follow will deal chiefly with cases of average severity, but it should be emphasized that the clinician must always have in mind the great variability of typhoid fever.

The first symptoms are usually malaise, feverishness, headache, and cough, and their onset is so insidious that the patient does not go to bed for several days. The fever is remittent in type, gradually increasing in height until about the tenth day, when it may fluctuate between 103° and 105° F. This continues for the next 10 days or two weeks; then the daily remissions begin to be greater and there is a gradual fall over a period of several days, with fever terminating after a total period of about 30 days. Chills may occur during the early part of the infection; occasionally the first sign of illness is a chill. Nosebleeds may be troublesome. Bronchitis is prominent and typhoid is frequently mistaken for some form of primary pulmonary infection in the early stage. The headache is of great severity and may be the chief complaint. Curiously, herpes simplex is very rare in typhoid fever. The patient is likely to suffer from abdominal distention and colicky pain. There may be either diarrhea or constipation, the latter being more frequent at the onset. At the height of the disease diarrhea may supervene, and numerous "pea soup" stools may be passed daily. When the fever has reached its peak the patient may be apathetic and drowsy, or he may show delirium. The appearance is that of severe toxemia. The typhoid patient seldom

seems alert. Muscular twitching and picking at the bedclothes may be noted in patients who have had prolonged high fever.

The eruption usually appears during the second week. The lesions, which are called "rose spots," are found most often on the anterior surface of the trunk between the level of the nipples and the umbilicus. They are small, rose red spots, 2 to 4 mm. in diameter, and usually have a small central peak, which is palpable. Their color fades completely on pressure. They are not numerous; usually only 6 to 12 may be seen at a time. They tend to appear in crops and to disappear without leaving any discoloration. When extensive, they may also be present on the proximal parts of the extremities, but are seldom seen on the face, and practically never on the palms or soles.

The spleen becomes palpable by the end of the first week in the majority of cases. It is soft and may be missed if the examiner palpates too deeply. It rarely extends more than 2 or 3 cm. below the costal margin, and recedes by the time the fever begins to subside.

During the first week or two of typhoid fever the pulse rate is usually comparatively slow in relation to the fever; this is sometimes of assistance in diagnosis. After the third week, however, the pulse rate is proportional to the temperature. A dicrotic pulse is often present, but this is not particularly helpful in diagnosis.

With the beginning of the subsidence of the fever there is gradual improvement in symptoms and a return of the patient's appetite. Usually, however, a marked weakness persists for many days after the temperature has returned to normal.

Relapse is not uncommon in typhoid fever. Some reports indicate that the frequency is as high as 10 per cent. The clinical features are similar to, although milder than, those of the initial illness. There may be a recurrence of the bacteremia, and even of the skin eruption. Fatalities are uncommon during relapses.

Complications. *Hemorrhage from the bowel* is the most important complication of typhoid fever. Gross bleeding occurs in about 20 per cent of cases. This is usually during the third week of the disease, at the time when the intestinal ulcerations have reached their greatest extent. Severe hemorrhage is accompanied by the signs and symptoms of acute blood loss—i.e., rapid, weak pulse, low blood pressure, sweating, pallor, and

drowsiness—and by the appearance of gross blood in the stools. One sign which is occasionally of value as an indication of massive hemorrhage is rapid fall in body temperature: a decrease of 5° or 6° F. in the course of a few hours.

Perforation of the intestine is a very dangerous complication, and one which accounts for many of the deaths in typhoid fever. Fortunately it is far less common than hemorrhage (1 to 2 per cent of cases). Perforation takes place at the site of an ulcer, usually in the terminal ileum, but occasionally in the appendix or in the proximal part of the colon. The clinical manifestations are pain, usually in the right lower quadrant, followed by rigidity and diminished peristalsis. The pulse rate may increase, there is usually a rise in leukocyte count, and the temperature may fall. Diagnosis of perforation may be very difficult, because of preexisting abdominal distention, tenderness, and pain. Frequent examinations throughout the course of the disease by the attending physician assist him in recognizing and evaluating the changes which occur with perforation.

Bacterial pneumonia occasionally complicates typhoid fever. If suspected, this can be verified by physical examination and x-ray, and by appropriate bacteriologic studies. Many other complications of typhoid fever can be mentioned; they include the various infections which are likely to arise in a severely ill patient, such as *parotitis*, *sinusitis*, *conjunctivitis*, etc. *Thromboembolic disease* may occur. *Meningitis* and *arthritis*, due to *S. typhosa*, are rare complications.

Three late sequels of this disease deserve mention. *Periostitis* may develop months or even years after the original illness. It may involve almost any of the long bones or the spine. The lesion is, as the name implies, on the outside of the bone; clinically, there is a tendency to abscess formation with periodic rupture through the skin and healing. The second complication is *gallbladder disease*. Signs of cholecystitis occasionally are noted during the acute illness. Years later the subject may suffer from cholecystitis and cholelithiasis. Gallbladder stones containing live typhoid bacilli are said to have been removed 20 or 30 years after the original attack of typhoid fever. Finally, a *chronic pyelonephritis* or *pyonephrosis* due to *S. typhosa* may develop.

The Carrier State. Approximately 2 or 3 per cent of patients with typhoid fever can be expected to become typhoid "carriers"—i.e., to

continue excreting the organisms in the feces for months or years after clinical recovery. In most instances the carrier state is due to persistence of infection in the biliary tract, and cholecystectomy is usually effective in eradicating the condition. Urinary carriers are occasionally encountered, but they constitute a much less serious problem than intestinal carriers.

Laboratory Findings. The *leukocyte count* during the first week or two is usually in the low normal range (i.e., 5000 to 8000); during the third and fourth weeks it may become even lower (3000 to 6000). During convalescence there is a rise. The *red blood corpuscle count* falls progressively during the course of the disease, and often reaches a level of 3,000,000 to 3,500,000 in the third and fourth weeks. The *urine* contains some albumin during the febrile stage, but is otherwise not remarkable. Tests for *occult blood in the feces* are usually positive from the second to the fourth week of the disease.

Culture of the blood is positive for *S. typhosa* during the first week of the disease in about 90 per cent of cases. After that time the likelihood of a positive blood culture decreases rapidly. *Culture of the feces* is rarely positive for *S. typhosa* before the tenth day of the disease. The incidence then increases rapidly up to the fourth week of illness; the organisms can be recovered from the feces in at least 90 per cent of cases, if good bacteriologic technic is employed. Bismuth sulfite agar, in conjunction with selenite F or tetrathionate enrichment medium, gives excellent results. *Culture of the urine* is positive during the third and fourth weeks in about 20 per cent of cases of typhoid fever.

Examination of the blood for *specific agglutinins* (*Widal test*) usually gives a positive result at the end of 7 to 10 days of illness. The titer of agglutinins rises during the next 10 days, reaching a peak about the third or fourth week of illness. The titer then falls gradually during the succeeding months. There has been much discussion of the relative values of H and O agglutination tests in diagnosis. The titer of H antibody is usually higher than that for O, and the H sometimes appears a few days earlier. No definite figure of certain diagnostic significance can be given. As with all serologic tests, a rising titer during the course of the illness is more significant than any individual figure. In general, titers higher than 1:160 with both antigens are proba-

bly significant, and the O antigen is more specific than the H. In about 10 per cent of cases the Widal test never reaches "diagnostic" titers. Previous immunization with typhoid vaccine has to be taken into consideration in evaluating the results of Widal tests. A person who has received an immunization during the preceding six months would be likely to show specific agglutinins in his serum. Furthermore, an anamnestic response to any infection may cause the reappearance of antityphoid antibodies in the serum of a previously inoculated person.

Differential Diagnosis. The sporadic cases of typhoid fever seen nowadays nearly always present diagnostic problems, and positive differentiation often has to wait for laboratory tests. Repeated negative cultures and agglutination tests should direct attention away from typhoid, since it would be a rare experience to encounter typhoid fever with negative Widal test and negative cultures of blood, feces, and urine. The following diseases should receive particular consideration:

TYPHUS FEVER. The onset is usually sudden, with chill followed by sustained high fever. The rash is more profuse, and the individual lesions are not palpable. The Weil-Felix test is positive.

ATYPICAL PNEUMONIA. The insidious onset with respiratory symptoms resembles typhoid, but abdominal discomfort and gastrointestinal symptoms are lacking. X-ray reveals an area of pulmonary consolidation which is rare in early typhoid. Cold agglutinins, if present, will establish the diagnosis.

BRUCELLOSIS. The clinical picture may be indistinguishable except for absence of "rose spots," and the fact that the pulse rate is usually elevated in proportion to the fever. Blood and feces cultures and agglutination tests will differentiate.

TULAREMIA. Rarely this disease appears in the so-called "typhoidal" form. History of contact with rabbits or squirrels or tick bite should suggest tularemia. There is usually a leukocytosis. The agglutination test is nearly always positive by the end of the second week. Rapid improvement under streptomycin treatment points to this disease.

MILIARY TUBERCULOSIS. The chest x-ray may not show lesions until late in the disease, and occasionally is negative throughout. Spinal fluid examination may be of assistance.

HODGKIN'S DISEASE. When the main lymph node involvement is in the abdomen, this condition may mimic typhoid fever. Here again, repeated negative cultures and agglutination tests should help to rule it out. The finding of large lymph nodes in the thorax or other areas may eventually lead to a correct diagnosis.

Treatment. Precautions should be taken to prevent spread of infection from the patient to others. Attendants should wear gowns to avoid contamination of clothing and should wash their hands thoroughly with soap and water after contact with the patient or his bedclothes. The principal sources of danger are the patient's dejecta. The best method of disposal in localities with properly constructed sewage systems is by way of flush toilets. Chemical disinfection of urine is not difficult, but disinfection of fecal material is almost impossible. Bedpans, urinals, eating utensils, bedclothes, and bedding should be sterilized by boiling.

It has always been maintained that nursing care and general supportive treatment are of paramount importance in the treatment of typhoid fever, and the disease has been used as the prototype for discussions of care of patients with febrile illnesses, as outlined in Chapter 98. While these measures still deserve consideration, their relative importance has shrunk substantially because of the introduction of "Chloromycetin" therapy.

"Chloromycetin" is a highly effective specific drug for the treatment of typhoid fever. Bacteremia ceases within a few hours after the first dose. During the next two days the patient begins to feel somewhat better, although the fever shows little change. During the third or fourth day there is dramatic improvement, with fall in temperature, disappearance of symptoms, and fading of the skin eruption. The patient is now on the road to recovery.

A dose of 3 Gm. of "Chloromycetin" per day, administered at six- or eight-hour intervals, is adequate. Treatment can be discontinued at the end of seven days in most cases, but relapse will occur occasionally, necessitating a second course. Relapse can probably be prevented entirely by continuing "Chloromycetin" in every case for three weeks. In a few instances hemorrhage and perforation have occurred several days after apparent favorable response to "Chloromycetin"; consequently it is desirable to keep the patient

under observation for at least two weeks.

In the event of massive intestinal bleeding the patient must be given blood transfusions. Intestinal perforation has always been regarded as indication for incision and drainage. The question should now be raised whether better results might follow conservative management, with administration of large doses of penicillin and "Chloromycetin."

During convalescence, culture of the feces and urine should be done at intervals, and the patient should not be discharged until three consecutive negative cultures have been obtained. In the event that cultures remain positive long after clinical recovery, the patient should be instructed about the danger, and health authorities should be notified before his release from the hospital. Cholecystectomy is not justified until the patient has continued to excrete typhoid bacilli for at least one year, since the carrier state may cease spontaneously during that period of time. The operation will successfully eradicate the "carrier" state in about 90 per cent of cases. Chemotherapy of typhoid "carriers" has not

been effective previous to introduction of "Chloromycetin," and initial experience with that has not been encouraging.

Prognosis. The fatality rate in typhoid fever before "Chloromycetin" was 8 to 12 per cent, the greatest incidence of deaths being in young infants and in the aged. Massive hemorrhage and intestinal perforation account for a considerable proportion of deaths. With "Chloromycetin" therapy the fatality rate will probably be not more than 1 or 2 per cent.

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Salmonella Infections

Paul B. Beeson

Etiology

Epidemiology

Pathogenesis

Manifestations

Paratyphoid Fever

Salmonella Food Poisoning

Bacteremic *Salmonella* Infections

Local Pyogenic Infections

Treatment

Etiology. The genus *Salmonella* includes a group of Gram-negative motile bacilli which ferment dextrose, maltose, and mannite with the production of gas, but do not attack lactose or sucrose. (*Salmonella typhosa*, the causative agent in typhoid fever, differs from other species of *Salmonella* in failing to produce gas. Typhoid fever is described in Chapter 108.) More than

100 serologic varieties have been differentiated, on the basis of their various somatic ("O") and flagellar ("H") antigens. The custom now is to name each newly discovered strain for the locality in which it was first isolated—e.g., *Salmonella panama*, *Salmonella kentucky*, etc. Accurate serologic identification requires special typing serums and technical skill not available in ordinary clinical laboratories. Such typing is important in epidemiologic studies, and has served to emphasize certain differences in the clinical potentialities of various members of the genus.

Epidemiology. The *Salmonella* organisms are found in all parts of the world. They may be found in the intestinal flora of various wild ani-

mals, and in domestic fowl, such as chickens and ducks. They are sometimes present in freshly laid eggs, including those of chickens. Commercial dried egg preparations, because they are pooled from large numbers of eggs, not infrequently contain *Salmonella* organisms. Healthy human "carriers" are found occasionally; many of these people give no history suggestive of previous *Salmonella* infection.

The usual mode of human infection is by ingestion of contaminated food or drink. The contamination may originate in infection of the animal from which the food was derived, or it may be the result of contact with an infected human being or rodent during the course of preparation of the food.

Pathogenesis. After being ingested in food, the organisms multiply in the intestinal tract. This may induce an irritation in the small and large intestines, lasting only a few days—*Salmonella* food poisoning. The short duration of symptoms suggests the possibility that the irritation is not due to actual invasion of the intestinal wall, but instead that absorption of some product of the bacterial growth is responsible. In at least a small proportion of cases, however, the organisms do penetrate the intestinal wall, and invade the blood stream. Then, depending upon the potentialities of the organism, and undoubtedly also on the resistance of the host, different types of illness may result. In some instances systemic *Salmonella* infections follow a pattern identical with that of typhoid fever. In some instances there is only prolonged fever, without localizing manifestations. In other cases foci of suppuration may appear in such tissues as bone, lung, pleura, meninges, etc.

It is sometimes stated that any of the *Salmonellas* may produce any of the known clinical syndromes. However, some types seem much more likely to invade the blood stream than others. For example, *Salmonella choleraesuis* is markedly invasive, bacteremia having been reported in approximately 60 per cent of recorded infections with that organism. Some of the other *Salmonellas*, on the other hand, rarely give rise to any illness other than symptoms of transient irritation of the gastrointestinal tract.

Manifestations. The various forms of clinical disease produced by *Salmonella* may be grouped into four types: paratyphoid fever, food poisoning, bacteremia, and local pyogenic infections.

1. **PARATYPHOID FEVER.** Certain of the *Salmonellas* produce an illness which is clinically indistinguishable from typhoid fever—i.e., a prolonged febrile illness, with "rose spots," splenomegaly, leukopenia, gastrointestinal symptoms, and positive blood and stool cultures. (See Chapter 108. A detailed description of this form of illness need not be given here.) Strains capable of producing this picture are *Salmonella paratyphi A*, *S. paratyphi B*, and *S. choleraesuis*. In general, the paratyphoid fevers tend to be somewhat milder than *S. typhosa* infections, but, in a given case, differentiation between typhoid and paratyphoid fever cannot be made on clinical grounds.

2. **SALMONELLA Food POISONING.** This is an illness which usually occurs in epidemics and which is characterized by the sudden appearance of symptoms of food poisoning in a group of individuals who have partaken of the same food. The incubation period is usually from 8 to 20 hours. The onset of symptoms is sudden, with nausea, colicky abdominal pain, and diarrhea. The stools are usually loose and watery, but may contain mucus or blood. There may be a chill at the onset, and there is nearly always a temperature elevation to 101° or 102° F. (Fever is a useful sign in differential diagnosis between *Salmonella* and staphylococcal toxin food poisoning, since in the latter condition the temperature remains normal.) The usual duration of symptoms in *Salmonella* food poisoning is one to three days. Fatalities are very rare, clinical recovery usually being complete within a few days.

Salmonella organisms sometimes can be recovered from the suspected food. They may occasionally be cultured from the stools during the acute phase. In nearly all cases the stool culture becomes negative for pathogenic organisms at the time of clinical recovery; rarely, patients continue to excrete organisms for a few weeks or months.

3. **BACTEREMIC SALMONELLA INFECTIONS.** The strain which most often gives the bacteremic type of illness is *S. choleraesuis*, which seems to have peculiar invasive properties. Various other *Salmonellas* have been known to produce the same picture, however. These illnesses are usually encountered sporadically, without obvious relation to cases of food poisoning. Infants and young children are affected more frequently than adults. In some cases there are no localizing signs, the only manifestation being prolonged fever,

with its accompanying symptoms—headache, malaise, sweats, loss of appetite, etc. The characteristic features of typhoid and paratyphoid fevers, such as "rose spots," gastrointestinal symptoms, and positive stool culture, are lacking. This infection is one which should be considered in cases of fever of unknown origin; repeated blood cultures may be needed before the organism can be recovered. At any time in the course of the bacteremic type of illness, localizing signs of infection may appear. Pneumonia and pleurisy are the most common; the organisms have been recovered both from sputum and from pleural fluid. Involvement of bone may occur, with periostitis and abscess formation. One or more of the large joints may become infected. There may be invasion of the meninges, or bacterial endocarditis may develop.

4. LOCAL PYOGENIC INFECTIONS. These include subcutaneous abscesses, periostitis, arthritis, sinusitis, cholecystitis, pyelonephritis, pneumonia, pleurisy, and salpingitis. They may occur independently of previous symptoms of enteritis or bacteremia, or, as already described, they may be complications of the other types of illness. One unusual epidemic which occurred in Cuba consisted of 21 cases of meningitis among infants in a nursery; there were no manifestations other than those of meningitis. There is nothing unique about the pyogenic *Salmonella* infections; the diagnosis is rarely if ever made on clinical grounds. Most such cases are regarded as

Gram-positive coccal infections until the cultural diagnosis is made.

Treatment. In most instances *Salmonella* food poisoning requires no specific treatment. When dehydration and prostration are severe, parenteral administration of fluids and electrolytes is required. Morphine or camphorated opium tincture may be useful in diminishing the diarrhea. Further purgation is not logical or beneficial. It is improbable that chemotherapy ever will be proved helpful in the management of these brief illnesses.

Sulfonamides and streptomycin have been tried in treating the paratyphoid fevers, but without benefit. In view of the remarkable effect of "Chloromycetin" in typhoid fever, this drug deserves a trial in cases of paratyphoid fever.

Information is also needed on the value of streptomycin, aureomycin, and "Chloromycetin" in the bacteremic and suppurative forms of *Salmonella* infection. Tests of these drugs in *Salmonella* infections of mice have not been encouraging.

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Bacillary Dysentery (*Shigella* Infections)

Paul B. Beeson

Definition
History
Bacteriology
Epidemiology
Pathogenesis

Manifestations
Diagnosis
Treatment
Prognosis

Definition. These infections are acute infectious diseases caused by microorganisms belonging to the genus *Shigella*, and characterized by diarrhea, abdominal pain, and fever. In clinical

practice the term "bacillary dysentery" is the one most commonly employed. The term "shigellosis" has been proposed, but, while preferable, has not achieved wide usage.

History. Acute diarrheal diseases have been described since ancient times. Epidemics have been particularly serious among soldiers living under conditions of war, and in inmates of institutions for the insane. They occur also, however, among the general population, especially in tropical regions. The first member of the *Shigella* genus was isolated by Shiga in 1898. Many others have since been studied, and further varieties are constantly being added to the list.

Bacteriology. The genus *Shigella* includes a group of more or less closely related, Gram-negative, nonmotile, nonencapsulated bacilli which either do not ferment lactose or ferment it very slowly. The members which are of most importance from the clinical standpoint are *Sh. dysenteriae* (*shigae*), *Sh. paradyENTERiae* (*flexneri*) (*sonnei*) (*schmitzii*), and the Boyd and Newcastle bacilli. Most of the cases of bacillary dysentery which occur in the United States are caused by either the Flexner or the Sonne types of organisms. Mannite fermentation and other differential biochemical tests are used in distinguishing between the *Shigella* organisms. From the standpoint of serologic classification, members of the Shiga group are homogeneous, but in all of the other varieties there is some serologic variation and overlapping.

The Shiga bacillus produces an exotoxin, but its role in human infections is not clearly established. In experimental animals this toxin produces injury in the intestinal tract and in the nervous system, but analogous lesions are not found in human Shiga dysentery. All members of the *Shigella* genus possess an endotoxin, associated with the somatic antigen, similar to that in the somatic antigens of *Salmonella* and typhoid bacilli. However, the manifestations of bacillary dysentery cannot be attributed to this endotoxin.

Epidemiology. Outbreaks develop over a period of several weeks. The principal means of contagion seems to be indirect contact between people by means of towels, eating utensils, food, faucets, etc. Asymptomatic or convalescent carriers are particularly important in this mode of spread. Cultural surveys by Watt and Hardy in representative samples of the general population revealed varying prevalence of *Shigella* organisms, from 11 per cent in New Mexico to 0.1 per cent in New York City. These investigators found that the number of asymptomatic cases of *Shigella* infection in a community at a given

time was usually much greater than the number of manifest cases of dysentery. They found, furthermore, that organisms could be recovered frequently from the surface of the hands of carriers. Some strains can survive in sea water for three days, and sewage contamination of sea water may lead to infection of naval personnel. Contamination of the milk or water supply has frequently been suspected as the cause of dysentery epidemics, but has only occasionally been proved. Similarly, transmission by flies is not often a major factor, although it could be in circumstances where fecal matter is left uncovered.

Pathogenesis. Although many different *Shigella* organisms can give rise to diarrheal illness in man, it has not been possible to reproduce the infection in ordinary laboratory animals. Under special circumstances a disease similar to human bacillary dysentery can be demonstrated in monkeys and dogs. Man himself is not highly susceptible, since comparatively large doses have been required to establish the disease in volunteer subjects. Presumably the mouth is the portal of entry, and the organisms pass down through the gastrointestinal tract until they reach the large intestine. There they are able to establish an inflammation in the mucosa. There is little tendency for the bacteria to invade the blood stream and set up metastatic infection elsewhere. The principal injurious systemic effect of the infection lies in the disturbance in fluid and electrolyte balance secondary to severe diarrhea.

The pathologic findings are mainly in the lower part of the intestinal tract. The rectum and sigmoid colon are nearly always affected; in the severest cases the entire colon and even the lower third of the small bowel may be involved. The mucosa is uniformly inflamed, and there is exudation of a fibrinous material, producing a thin superficial membrane. Necrosis of the mucosa produces superficial ulcerations which bleed. The inflammation may progress from the mucosa out into the submucous and muscular coats, causing marked thickening of the intestinal wall. Perforation very seldom occurs, however.

Manifestations. As a rule the incubation period cannot be ascertained, but such evidence as can be obtained indicates that it is short: rarely more than 24 hours. The first evidence of illness is usually the abrupt appearance of diarrhea. Temperature elevation, as high as 103° to 104° F., occurs with, or soon after, this. Chills occur oc-

casionally. There is usually some nausea, vomiting, and headache. Cramplike abdominal pain and tenesmus are likely to be symptoms in severe cases. The number of bowel movements in 24 hours may be from as few as two or three to as many as 50. The stools are loose and watery, often greenish in color, and may contain shreds of mucus. In perhaps 20 per cent of cases, gross blood can be seen in the stools. This varies from a few pink flecks to a profuse bloody diarrhea.

The general appearance of a patient depends upon the severity of the diarrhea and the height of the fever. In severe cases such signs of dehydration as wrinkling of the skin and dryness of the mouth may be prominent. On palpation of the abdomen there is no muscular rigidity but there may be general soreness and tenderness, most marked in the lower quadrants. Rarely, the spleen is palpable. *Sigmoidoscopic examination* reveals a diffusely inflamed mucosa, the surface of which may be covered with a thin fibrinous membrane. In severe cases there are areas of ulceration from which blood oozes. These may be so numerous as to leave only scattered islands of intact mucosa.

Microscopic examination of the stool shows clumps of pus cells, and, in the severer cases, red blood cells. The *leukocyte count of the blood* is usually in the normal range.

The course of the disease depends to a large extent on the age of the patient and on the infecting organism. As usually encountered in the United States, bacillary dysentery is a self-limited disease of short duration. In the majority of cases clinical recovery commences in from one to four days. *Relapse* may occur in 10 to 15 per cent of cases, unless adequate chemotherapy is employed. Children under two years of age and adults past middle age may be severely ill. Shiga infections are the most dangerous; fortunately these are not common in the United States.

Chronic bacillary dysentery has been reported in the tropics, and the incidence is stated by some writers to be as high as 2 per cent. This seems to be a rare occurrence in America, where there has seldom been proof of persistence of these organisms in the intestinal tract for as long as 12 months.

Complications are uncommon in bacillary dysentery. *Perforation of the colon* has been reported only a few times. Acute *arthritis* with effusion, involving one or more of the larger joints, may

develop during the convalescent phase. The joint fluid is nearly always sterile. This condition was observed more frequently before the introduction of sulfonamide therapy, in cases which had prolonged courses. Several authors have suggested that *Reiter's syndrome* (urethritis, arthritis, and conjunctivitis) is a late sequel to bacillary dysentery, but proof of this association is far from conclusive. Other writers have sought to incriminate bacillary dysentery in the etiology of *chronic ulcerative colitis*, but the evidence for this is not persuasive.

Diagnosis. A positive diagnosis can be made only by cultural demonstration of a pathogenic member of the genus *Shigella*. The organism can be isolated from fecal material by employing selective mediums such as SS agar or desoxycholate citrate agar. The best results in cultural diagnosis are obtained by using rectal swabs. This involves the insertion into the rectum of a sterile swab moistened with saline. The swab is rotated against the rectal wall, then drawn back and streaked on the differential mediums. Using this technic one or more times in each case, a positive diagnosis should be obtained in at least 80 per cent of patients with bacillary dysentery. *Blood culture* is very rarely positive. *Serologic diagnosis* by the demonstration of rising titer of agglutinins is not of much practical value because of the serologic heterogeneity within the *Shigella* group of organisms and cross reactions with other enteric bacteria.

In the differential diagnosis it is necessary to consider both enteric and extraenteric causes of diarrhea. The latter group is particularly important in children, in whom such acute infections as pneumonia, tonsillitis, and even osteomyelitis may provoke diarrhea. As a rule, diarrheal diseases of this type can be identified by a careful clinical examination. Among the enteric infections, early correct diagnosis can often be helped by considering epidemiologic as well as clinical evidence. *Staphylococcal toxin* diarrheas are apt to occur in explosive epidemics, involving a group of people within an hour or two after a meal. The afflicted individuals often appear to be severely stricken, with nausea, vomiting, and watery diarrhea. An important clinical characteristic is absence of temperature elevation. The symptoms usually subside within 24 hours. *Salmonella food poisoning* may also occur in an explosive outbreak, 8 to 20 hours after a

meal. Clinically this illness cannot be distinguished from bacillary dysentery, since there may be pus and blood in the stools, and there is usually fever. *Acute amebic colitis* rarely occurs in epidemics. There are mucus and blood in the stools, and motile amebas can be seen on microscopic examination. *Poliomyelitis* may have diarrhea as an early manifestation, but careful examination should reveal evidence of central nervous system involvement.

Treatment. The sulfonamides are effective in vitro against all members of the genus. Clinical assay of their effectiveness has been difficult because of the natural tendency of bacillary dysentery to subside promptly. Nevertheless, extensive clinical usage leaves little question that sulfonamide therapy is effective and that it should be employed as a routine procedure. Comparisons have been made between poorly absorbed drugs, such as sulfasuxidine, sulfaguanidine, and sulfathalidine, and the well-absorbed drugs, sulfadiazine, sulfamerazine, and sulfanilamide. There is little advantage in the poorly absorbed sulfonamides, except that sulfasuxidine occasionally seems to be more effective in treating asymptomatic or convalescent carriers. In general, sulfadiazine is the drug of choice. The initial dose is 3 or 4 Gm., to be followed by 1 Gm. every six hours. Because of the associated fluid loss, it is particularly important to maintain an adequate urine output during this form of therapy. The dose of sulfasuxidine is 4 to 6 Gm. four times daily. Therapy with any sulfonamide should be continued for 7 to 10 days, and the criterion of cure should be negative stool cultures. In the event of failure to obtain negative cultures with one sulfonamide, it is advisable to repeat the course with a different one. Unfortunately, some strains of *Shigella* are now being encountered which are sulfonamide-resistant. This may limit the usefulness of sulfonamide therapy.

Oral or intramuscular administration of streptomycin may be tried in patients who do not re-

spond to sulfonamide therapy. Although clinical trials have not been numerous, some experience with this drug indicates that it is highly effective. Aureomycin and chloromycetin will require extensive clinical usage before their place in therapy can be evaluated.

Serum therapy has had an extensive trial in Shiga bacillus infections, and many favorable reports have appeared. If serum is available, its use seems justified, as an adjunct to sulfonamide therapy, in severe cases of Shiga infection.

In the general care of the patient, adequate fluid intake is of importance. Sufficient fluids should be given to insure a urine output of 1000 ml. daily. Occasionally persons with very severe diarrhea and circulatory collapse require in addition the administration of colloids: blood, blood plasma, or human serum albumin.

Diet is not a matter of major importance, since the acute infection usually lasts only a few days. Some patients seem to suffer aggravation of symptoms if they attempt to eat or drink, and in them it is advisable to give nothing by mouth during the acute phase, relying on parenteral administration of fluids, electrolytes, and chemotherapeutic agents. *Purgation*, much used in the past, has no place in modern therapy.

Prognosis. As indicated previously, the outcome depends on the infecting organism and on the age of the patient. With Shiga dysentery, case fatality rates as high as 25 or 50 per cent have been observed. With Sonne and Flexner dysentery, the rate in the general population is less than 5 per cent; most of those fatalities occur in young infants or in old or debilitated people.

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Cholera

W. Elizabeth Gambrell

Definition
Etiology
Epidemiology
Clinical Symptoms
Laboratory Findings
Pathology
Differential Diagnosis
Treatment
Prevention

Definition. Cholera is an acute infectious disease, caused by a spirillum, the *Vibrio comma*, localized in the gastrointestinal tract and characterized by diarrhea, vomiting, and extreme dehydration.

Etiology. The causative agent is a comma-shaped, Gram-negative bacillus, with a single polar flagellum. It is actively motile, aerobic, and easily stained by the aeridine dyes. Antigenically there is a single flagellar antigen, the H antigen, and one common somatic or O antigen and several secondary somatic antigens by which different serologic strains can be distinguished.

Epidemiology. The original home of cholera is the delta of the Ganges, where it has occurred year after year for centuries. It has not been a problem in the United States since the epidemic of 1873, but it is still endemic and often epidemic in India, China, and other countries of the Orient. The great epidemics of the nineteenth century spread to all but the coldest parts of the world. The potential distribution of cholera is practically world-wide, and in the Far East the danger of epidemics is always present.

The organism may persist in nature for a short period of time, but is usually spread from person to person by patients in the incubation or convalescent stages, or by those with subclinical infections. True carriers probably do not exist, but convalescent patients may remain carriers for a short period of time. The organisms are transmitted in food, drink, or other material contaminated by infected feces. Diet which is largely vegetarian and previous enteric infections predispose to cholera. The disease cannot spread when sanitary facilities are in efficient operation.

Clinical Symptoms. There is great difference in the susceptibility of individuals who contract the disease, as some show very acute reactions, while others have very mild attacks characterized by slight malaise and diarrhea. The incubation period is usually one to three days, followed by a sudden onset. In the usual clinical course, profuse watery stools occur which are voluminous and frequent and lack all fecal characteristics. They are generally light gray in color ("rice water") and contain small flecks of mucus. Tenesmus does not occur. Vomiting is copious, and may be projectile without nausea or retching. With the tremendous loss of fluid, dehydration and hypochloremia become severe, and prostration is marked. Patients remain mentally clear but are very apathetic. The circulation is markedly affected and peripheral collapse develops rapidly. Renal failure with anuria and uremia occurs in severe cases. The skin temperature may be subnormal while the rectal temperature is elevated. In some cases high temperature results when complications develop, such as pneumonia. The disease runs its course in three to five days. In properly treated cases the fatality rate is low, but during epidemics among neglected patients even now, 50 to 70 per cent may die, although these estimates do not include the milder cases which escape notice.

Laboratory Findings. The rapid dehydration leads to hemoconcentration, and the specific gravity of the blood may rise to 1.070. Large amounts of mineral metabolites are lost, especially chlorine, sodium, and calcium, and acidosis results with a marked shift in the acid-base balance of the blood.

Pathology. The pathologic picture is unique in its simplicity, as the effects of the infection strongly resemble the results of an overdose of a drastic purgative or of severe food poisoning. The major changes which take place in the intestine are those of dehydration, resulting in a peach color and some swelling of the Peyer's patches. The cholera vibrio, when killed, liberates

an endotoxin which acts as a severe intestinal irritant. The diarrhea results from an increased permeability of the intestinal mucosa with outpouring of fluid. The organisms live in the intestinal lumen and rarely penetrate the wall. Fatalities apparently result from dehydration, the loss of salts with the resulting acidosis, rather than from the generalized dissemination of a toxin.

Differential Diagnosis. Diagnosis of cholera in areas where the disease is known to be endemic is usually made on clinical findings. It is essential to recognize the mild ambulatory cases which are important potential carriers. In the presence of an epidemic, every person with any type of gastrointestinal disturbance should be suspected of having cholera until it is proved otherwise. The diseases often confused with cholera are: acute bacillary dysentery, in which the stool appearance is different, tenesmus is present, and collapse is rare in adults; *Salmonella* food poisoning, which is usually accompanied by nausea and retching with vomiting; clinical forms of malaria, in which intestinal symptoms with collapse occur; heat exhaustion and other conditions leading to a state of shock.

The specific diagnosis is based on bacteriologic identification of the *Vibrio comma* from stool cultures or rectal swabs. Smears of feces stained with diluted carbolfuchsin and showing comma forms with the fish-in-stream appearance are suggestive. Cultures from stools in alkaline peptone water usually show the typical organisms concentrated at the surface in six hours. Suspected colonies from streaks of nutrient agar may be tested with specific V_1 comma agglutinating serum by means of a slide technic.

Treatment. The natural course of the disease is short and the infection is self-limited. Sulfonamides and streptomycin, while effective against *Vibrio comma* in vitro, are of questionable value in treatment of the disease. The real emergency

in treatment is to replace the enormous losses of water, sodium, and potassium. Treatment can be begun with physiological sodium chloride solution, giving from 2 to 8 liters intravenously during the first 24 hours, depending on the initial deficit. This should be supplemented after the first few hours with solutions containing potassium chloride; 8 to 16 Gm. of this should be administered during the first 24 hours. Dextrose may be added to these solutions if desired. Nourishment by mouth can be resumed gradually as the gastrointestinal symptoms subside.

Prevention. Cholera occurs where sanitary safeguards are ineffective. Particular emphasis should be placed on proper water supply and food handling. All cases and suspected carriers must be isolated. Fly control by adequate screening of kitchens, wards, and latrines is important, and destruction of flies and larvae by DDT sprays is effective.

Cholera vaccine is employed, but in protective value this is definitely secondary to proper sanitation of water and food.

"Chloromycetin" has been shown to be considerably more effective than sulfadiazine in therapy of *Vibrio comma* infections in mice, but its place in therapy of human cholera remains to be determined. The suggestion has been made that "Chloromycetin" could be administered prophylactically to exposed persons in the face of a cholera epidemic. This seems worthy of trial.

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Section 5—Infections Due to Bacteria of the *Hemophilus* Group

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Pertussis

Gladys J. Fashena and E. Strauss

Pathology
Symptomatology
Complications
Prognosis
Differential Diagnosis
Treatment

Pertussis (whooping cough) is an acute infectious communicable disease of the respiratory tract, which is common in children and rare in adults, characterized by recurrent paroxysmal attacks of coughing which are usually followed by an inspiratory whoop. The causative agent is the *Hemophilus pertussis* in the smooth phase. The disease is universal in distribution and occurs most commonly in the spring. Although individual susceptibility varies, the majority of nonimmune individuals who are definitely exposed contract the disease. One attack usually confers permanent immunity. The period of infectiousness reaches its peak during the catarrhal stage, and gradually declines and disappears during the paroxysmal stage. It is estimated that, on the average, the patient is infectious for approximately four weeks. Transmission occurs by droplet infection or contact with fomites. The incubation period varies from 7 to 14 days, but more often approximates the latter.

Pathology. During the first or catarrhal stage of the infection there is general inflammation of the mucosa of the larynx, trachea, bronchi, and bronchioles. As the disease progresses, a stringy, tenacious, mucoïd secretion forms on the mucous membrane. This material contains mucus, organisms, and cellular debris. The organisms are also present in large numbers on the surface of the membrane and between the cilia of the cells. Enlargement of the tracheal and bronchial lymph nodes may occur. Emphysema, bronchiectasis, pneumothorax, pneumonia, and central nervous system changes may be encountered as complications of the disease.

Symptomatology. The clinical course may be divided into three phases—namely, the catarrhal, the paroxysmal, and the convalescent phase. The first phase is initiated by a dry, hacking, irritative, nonproductive cough, occurring either during the day or during the night, but more severe at night. Associated findings are listlessness, mild coryza, and slight conjunctivitis. Temperature elevation is uncommon and signs of pulmonary disease are absent on physical examination. The duration of this phase varies, but usually averages 12 to 14 days. The second or paroxysmal stage is characterized by a series of paroxysms of severe coughing which may or may not be followed by the familiar whoop and vomiting. The number of paroxysms per day varies with each individual. The average duration of this phase is from 14 to 18 days, following which the patient enters into the period of convalescence, indicated by a decrease in both frequency and severity of the attacks and by general improvement in the condition of the patient. This phase ordinarily lasts two weeks, but may persist for three or four weeks in certain individuals. If the patient contracts a respiratory infection within a few months after having had pertussis, the clinical signs and symptoms of the disease may reappear, although the causative organism is no longer present.

The blood count usually reflects an absolute lymphocytosis which may be of diagnostic value during the catarrhal stage. The total cell count is between 15,000 and 30,000 per cu. mm. of blood, with a lymphocytosis of 80 to 90 per cent. Occasionally, the white count may be as high as 150,000 to 200,000, and in such instances a mistaken diagnosis of acute lymphatic leukemia may be made.

Complications. Bronchitis due to a secondary invader is common during the final stages of the disease. Bronchopneumonia, the commonest

complication, may develop during the paroxysmal stage or at any time during the course. This complication is seen most frequently among very young infants and debilitated children. Other pulmonary complications are emphysema, bronchiectasis, and pneumothorax. The marked increase in intraabdominal pressure which occurs during a paroxysm of coughing may initiate prolapse of the rectum or the development of an umbilical hernia. Epistaxis, rupture of the esophageal vessels, hemorrhage into the scleras, and the development of petechiae on the face and upper part of the body are common occurrences. Second in order of seriousness are the complications involving the central nervous system. Convulsions may develop as a result of intracranial hemorrhage or encephalitis. The development of convulsions during the course of whooping cough constitutes an unfavorable prognostic sign, and may be followed by spastic paralysis, other residual neurologic disturbances, or death.

Prognosis. In general, the prognosis in whooping cough depends upon the age and general health of the individual at the time of the illness. The younger the patient, the more serious the disease. Of the 10,000 deaths from pertussis which are estimated to occur annually, approximately 70 per cent occur among infants under one year of age, and 90 per cent of all deaths occur among children under five years of age. Chronically ill and debilitated individuals of any age may die from a complicating pneumonia. Paroxysmal attacks, *per se*, rarely kill, although small infants may strangle to death from secretions that have collected in the pharynx. Death due to spasm of the glottis has been reported, but is not common. Second to pneumonia, complications of the central nervous system are the most common cause of death.

Differential Diagnosis. The typical case of whooping cough in the paroxysmal stage presents little difficulty in diagnosis. However, establishment of the diagnosis in the early stages of the disease may be most difficult. A history of exposure, followed in one or two weeks by a dry, nonproductive, persistent cough, should raise suspicion of the existence of the infection. In such instances a leukocytosis with lymphocytosis furnishes presumptive evidence for the diagnosis. The recovery of the organism from cough plate or nasopharyngeal smears is positive evidence of the existence of the infection, but negative bae-

teriologic findings do not necessarily exclude the possibility of pertussis. Spasmodic bronchitis, foreign bodies, and blood dyscrasias can usually be distinguished by appropriate x-ray and hematologic studies. Mild cases, and those cases in which the whoop is absent, may offer a difficult diagnostic problem, and not infrequently one has to base the diagnosis simply on the duration of the illness or on the development of a secondary case in the family. Confirmatory serologic studies are available only late in the course of the disease, and hence are of little value at the time when help is needed.

The diagnosis of whooping cough in adults is rarely made. Most adults are immune by virtue of previous childhood infection. Individuals from rural areas presumably may escape infection until adult life. Whooping cough is rarely recognized in military groups during periods of mobilization, although under similar circumstances measles, chickenpox and other contagious diseases of childhood are common. Whooping cough is milder in adults and the characteristic whoop may be absent.

Treatment: PROPHYLACTIC. It is axiomatic to state that the unnecessary exposure of nonimmune individuals, especially infants and young children, should be avoided. Recent experiences with the immunization of young children against the disease indicates that this procedure will prevent the disease in a high proportion of individuals so immunized. If an unprotected susceptible individual is inadvertently exposed, the administration of hyperimmune human or rabbit serum as soon as possible after the exposure will either prevent the disease entirely or modify it so that the ensuing attack of whooping cough is a mild one.

ACTIVE. During the early course of the disease, isolation and rest in bed is desirable. Sudden changes in temperature are to be avoided, since this will often produce a paroxysm of coughing. When vomiting is severe enough to threaten nutrition, the refeeding of the patient shortly after vomiting will tend to minimize this disturbance. Drugs are not particularly effective in controlling the paroxysms, but barbiturates or other sedatives may be used to control sleeplessness. Expectorants used late in the course of the disease may facilitate the removal of the tenacious mucus. The value of vaccines employed as therapeutic agents is still disputed, but some evidence

has indicated that human or rabbit hyperimmune serum, when given in large amounts, may modify the course of the infection, and in small infants this may be a life-saving measure. Oxygen therapy and intelligent nursing care are of extreme importance in the management of young infants. Streptomycin and aureomycin are effective against the organism in vitro, but insufficient evidence has been accumulated to make any definite statement concerning their therapeutic efficacy in man. Preliminary reports suggest that aureomycin shortens the clinical course of the disease.

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Influenza Bacillus Infections

Paul B. Beeson

Etiology	
Epidemiology and Pathogenesis	
Manifestations	
Laboratory Findings	
Differential Diagnosis	
Treatment	
Prognosis	

Etiology. The genus *Hemophilus* includes a group of nonmotile, pleomorphic, Gram-negative coccobacilli, which grow best on mediums containing whole blood. The most important member of the genus from the standpoint of clinical medicine is *H. influenzae*. This organism requires both the "X" factor (hemin) and the "V" factor (probably di- or triphosphopyridine nucleotide). Some of the strains of *H. influenzae* found in the human body are encapsulated, while others are not. Only the encapsulated forms are virulent. The capsules contain carbohydrates similar to those of pneumococci, and serologic typing of *H. influenzae* can be done by the same methods used for pneumococci. Types A to F have been distinguished; most infections in human beings are due to type B.

Epidemiology and Pathogenesis. Influenza bacillus infections are seen almost exclusively in children under eight years of age. It has been shown that nearly all persons over that age have

specific antibody in the blood against this organism. Between the time when the passively transferred antibody from the mother has been lost and the time when the child acquires his own antibody, he is susceptible to influenza bacillus infections. The peak incidence in children is, therefore, between two months and three years of age.

Influenza bacilli are commonly found in the throat and upper respiratory passages. The circumstances by which they set up infections there and in other areas of the body are not fully understood. It is likely that infection of the respiratory passages is by direct airborne communication and that infection of the meninges is by way of the blood stream. Pathologically, the lesions are characterized by acute inflammation, with edema and infiltration by polymorphonuclear leukocytes. There may be heavy deposits of fibrin, and the tendency to form a plastic exudate contributes to the chronicity in some cases of influenzal meningitis, as well as the tendency to subsequent development of hydrocephalus after meningitis.

Manifestations: MISCELLANEOUS INFECTIONS. *H. influenzae* may be found in various types of

infection of the upper respiratory tract, usually in association with other bacteria. For example, it is present in the majority of cases of chronic bronchitis and bronchiectasis. In children this organism may occasionally be recovered in pure culture in cases of acute pharyngitis or otitis media, and it has been isolated from the synovial fluid in cases of acute arthritis. Acute purulent conjunctivitis ("pinkeye") in children is frequently caused by *H. influenzae*. Rarely, this organism is the cause of subacute bacterial endocarditis. The infections which are of major importance from the standpoint of clinical medicine are meningitis and croup.

MENINGITIS. *H. influenzae* meningitis is one of the commonest types of meningitis seen in young children. Its manifestations are similar to those of other bacterial meningitides. Usually there is a prodromal period of one to seven days, during which the child has symptoms of an upper respiratory tract infection. With the onset of meningeal infection there may or may not be an abrupt change. The temperature tends to be higher, the child becomes fretful, cries frequently, and appears to be having pain. Convulsive seizures may occur. Vomiting is a common symptom. Recognition of this condition in the early stages may be difficult. On examination there may be bulging of the fontanels, stiffness of the neck, and Brudzinski's and Kernig's signs. In the later stages there is coma, opisthotonus, and a staring expression of the eyes. Very rarely, *H. influenzae* meningitis follows a fulminating course, with purpura, producing a clinical picture of the Waterhouse-Friderichsen syndrome. Previous to the introduction of specific therapeutic measures, influenzal meningitis was fatal in more than 95 per cent of cases, and even when recovery occurred there was a high incidence of disabling sequelae, such as chronic hydrocephalus, idiocy, blindness, deafness, and paralysis.

***H. Influenzae* CROUP.** A rare, but serious, fulminating infection due to *H. influenzae* occurs in young children, characterized by high fever and acute laryngitis with respiratory obstruction. A few hours after the onset of symptoms the child appears seriously ill, with fever, prostration, and respiratory obstruction evidenced by cyanosis and retraction of the supraclavicular and intercostal spaces on respiration. There is marked redness and edema of the larynx. Tracheotomy may have to be done as an emergency measure

for relief of the respiratory obstruction. The early occurrence of a shocklike state and severe respiratory obstruction are characteristic of this infection. Without specific therapy this condition usually causes death within one to four days.

Laboratory Findings. There is a moderate to marked leukocytosis. *H. influenzae* can be obtained in the blood culture in nearly all cases of laryngitis, and in the majority of cases of meningitis. In meningitis there is a pleocytosis in the spinal fluid, the majority of cells being polymorphonuclear leukocytes. The cell count ranges from a few to many thousands, and there is a reduction in dextrose content of the spinal fluid.

An early specific diagnosis of influenzal meningitis can be made by demonstration of *H. influenzae* in the spinal fluid. The diagnosis is suggested by the finding of Gram-negative bacteria which show a marked pleomorphism, some appearing as long, slender bacilli, others as short, plump rods, and still others appearing as cocci, which may be mistaken for meningococci. Marked variation in configuration of Gram-negative bacteria should strongly suggest the possibility of influenza bacillus infection. Since the great majority of infections are due to type B, an immediate diagnosis can usually be made by demonstration of capsular swelling of organisms in the spinal fluid, when type B rabbit antiserum is mixed with the fluid. Cultivation of *H. influenzae* requires use of mediums containing blood. Ordinary blood agar is satisfactory, although chocolate agar usually gives better growth.

Differential Diagnosis. Acute laryngitis or croup due to *H. influenzae* needs to be distinguished from virus croup, laryngeal diphtheria, and streptococcal or staphylococcal laryngotracheobronchitis. Children with virus croup seldom have as severe respiratory obstruction or as rapid progression of symptoms and usually do not appear gravely ill. In diphtheria a membrane may be visible, and the course of the illness is not usually so fulminating as in either of the other two infections. In streptococcal infection the pharyngeal and laryngeal mucosa may also be fiery red and edematous. Accurate differentiation between the bacterial infections will depend on isolation of one of the causative bacteria from the throat, larynx, or blood. *H. influenzae* meningitis closely resembles meningococcal or pneumococcal meningitis and, occasionally, acute tubercu-

lous meningitis. Differentiation can usually be made by careful examination of stained smears of the spinal fluid; final diagnosis depends on cultural isolation of the infecting organism.

Treatment. Three specific therapeutic agents are available: sulfonamides, streptomycin, and type-specific rabbit antiserum. In such severe infections as laryngitis and meningitis it is probably good practice to employ a combination of two or even three of these forms of therapy. Sulfadiazine can be given orally or parenterally in a dose of .075 to 0.1 Gm. per pound of body weight daily in children under three years of age, and 4 to 6 Gm. for older children. The dose of streptomycin is 250 mg. every six hours, and in cases of meningitis an additional 25 mg. should be injected intrathecally every 24 hours. *H. influenzae* rabbit antiserum is available for type B and is used only in the treatment of very severe infections. The dose is expressed in terms of antibody nitrogen, and the usual requirement is 100 to 200 mg. The serum is injected intravenously or intramuscularly. The patient's blood serum should be tested daily for capacity to induce capsular swelling of the infecting organism. If antibody sufficient to produce capsular swelling is present, the dose of antiserum already given is adequate.

Prognosis. Without specific therapy, *H. influenzae* meningitis or laryngitis is fatal in nearly all cases. With specific therapy, these fatality rates have fallen very markedly. Very few infants die of laryngitis if treatment is begun early. The prognosis in meningitis also depends to a considerable extent on the early administration of specific therapy. If treatment is begun within the first few days, nearly every patient can be saved. If the infection has been allowed to progress to an advanced stage where there is a large amount of plastic exudate with adhesions, cure may not be achieved even with all three therapeutic agents.

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114 Chancroid

Albert Heyman

Definition
Etiology
Incidence
Pathogenesis
Clinical Manifestations
Diagnosis
Treatment

Definition. Chancroid is an acute, localized, venereal disease caused by the Ducrey bacillus. It is characterized by ulceration at the site of inoculation and enlargement and suppuration of the regional lymph nodes.

Etiology. The etiologic agent of chancroid, the Ducrey bacillus, is a short, plump, Gram-negative organism with rounded ends. When stained by special methods, the bacillus exhibits bipolar staining. In the stained smears of genital lesions the organisms usually appear singly or in small clusters, but may be arranged in long parallel columns between cells or shreds of mucus. Occasionally, the bacilli are situated intracellularly. The organism can be cultivated in whole de-

fibrinated blood or nutrient broth containing blood. When grown in pure culture in a liquid medium, the Ducrey bacillus appears in long tangled chains composed of both coccal and bacillary forms.

Incidence. The number of cases of chancroid occurring every year cannot be determined satisfactorily, since accurate diagnosis of this condition is not generally attempted. A diagnosis of chancroid is frequently applied to genital lesions improving with sulfonamide therapy in which the *Treponema pallidum* cannot be demonstrated. The disease is encountered in the West Indies, North Africa, and the Orient, particularly in the lower economic groups of the population. It is also prevalent in the southeastern part of the United States, and is more frequent in Negroes than in whites. Approximately 9000 cases are reported in the United States annually.

Pathogenesis. Chancroid is usually contracted by sexual intercourse, and the lesions are almost always located about the genitalia. The disease can apparently be acquired from sexual partners who show no evidence of an active chancroidal infection. The organism has been cultivated from the smegma and vaginal secretions in patients without clinical manifestations of the disease. Such individuals may be carriers of the Ducrey bacillus. The organism readily produces an infection when inoculated into open or slightly abraded areas of the skin or mucous membranes. Chancroidal ulcerations frequently occur in areas of the genitalia where minor abrasions may be present (fourchette of the vulva, edge of phimotic prepuce, and frenum). After an incubation period of two to five days, a localized ulceration appears at the site of inoculation. This may be followed later by inflammation and suppuration of the regional lymph nodes.

Chancroidal infection produces a distinct histologic appearance. The base of the ulcer is a shallow zone made up of polymorphonuclear leukocytes, fibrin, red blood cells, and necrotic tissue. Below this is a fairly wide layer, consisting chiefly of proliferating endothelial cells and newly formed blood vessels, some of which show degeneration of their walls. Finally, there is a deep zone in which a dense infiltration of plasma cells and lymphocytes occurs. This histologic pattern is sufficiently characteristic to permit differentiation from other genital lesions. Biopsy is a valuable diagnostic procedure.

Clinical Manifestations. The typical chancroidal lesion is a painful, shallow, irregular ulcer with ragged undermined edges, a granular, friable base, and a dirty, yellow exudate. The lesion is characteristically nonindurated, and for this reason has been called *soft chancre*. The size of the ulceration varies, but seldom exceeds 2 cm. in diameter. Multiple lesions are frequent. Occasionally, extensive destructive ulcerations occur. At times the lesions resemble a folliculitis or pyogenic infection. Almost any portion of the genitalia may be involved, but extragenital lesions are rare. In about 50 per cent of the patients inflammation and suppuration of the inguinal lymph nodes will occur. The term *bubo* is given to this type of lymphadenitis. The chancroidal bubo develops rapidly and becomes a very painful, inflammatory inguinal mass. When suppuration occurs, the mass may become tensely fluctuant and rupture spontaneously, leaving a large, single, crater-like abscess. Mild constitutional symptoms may accompany the involvement of the inguinal lymph nodes, and the patient may complain of headache, malaise, fever, or anorexia.

Diagnosis. Although the clinical appearance of chancroid is often sufficiently characteristic to suggest the correct diagnosis, laboratory confirmation is desirable. Stained smears or culture of the exudate taken from the undermined edge of the lesion will reveal the Ducrey bacillus in the majority of the early cases. The organism is not easily demonstrated, however, in larger lesions when secondary bacterial contamination has occurred. Biopsy is feasible in such cases and is an efficient method of diagnosis. Attempts to demonstrate the organism in the buboes by either culture or smear usually are not successful. The majority of patients with chancroidal infection will exhibit a positive skin reaction to an intradermal injection of killed Ducrey bacillus. The value of this skin test is limited by the fact that a positive reaction persists for years after exposure to the infection. One cannot be certain, therefore, whether a positive skin test in an individual patient represents the existing chancroidal infection, or a previous one. Early syphilis may be present concurrently with chancroid in these patients. Serologic tests and darkfield examination of the lesions and regional lymph nodes should be done to rule out this possibility.

Treatment. The sulfonamides are the treatment of choice in chancroid. Doses of 4 Gm. a day of sulfathiazole or sulfadiazine are usually curative in 5 to 10 days. Local medication is not necessary, but saline soaks and cleanliness are advised. Although the buboes usually subside with sulfonamide therapy, fluctuation may persist and the node should be aspirated in order to prevent spontaneous rupture. Streptomycin and aureomycin have recently been shown to be of

value in this infection, but their use is rarely necessary, since the sulfonamides are generally effective.

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Brucellosis

Wesley W. Spink

Definition
History
Etiology
Epidemiology
Pathogenesis
Manifestations
Laboratory Procedures
Differential Diagnosis
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Prevention

Definition. Brucellosis is an infectious disease due to microorganisms belonging to the genus *Brucella*, and is transmitted to man from lower animals. The acute form of the illness is frequently characterized by a febrile illness without localizing findings, while the chronic form is featured by fever, weakness, and vague complaints, which may persist for months and years.

History. Accurate clinical descriptions of brucellosis have been ascribed to Hippocrates, but the first clear-cut picture of the disease was presented in 1863 by Marston, who, as a British Army surgeon in Malta, detailed his own case and those of others. The etiologic agent was discovered by Bruce in 1886. The outstanding clinical description of the disease is contained in the monograph by Hughes published in 1897. Wright and Semple in 1897 demonstrated agglutinins for *Brucella* in human blood. In the same year, Bang reported that *Bacillus abortus* was the cause of contagious abortion in cattle in Denmark. The Mediterranean Fever Commission Reports of 1905 to 1907 detail the classic studies on epidemiology. The first recognized human case of brucellosis in the United States occurred in a nurse in Washington, D. C., and was described by Craig in 1906. In 1911 brucellosis was found to be endemic in the goats of Texas, and Gentry and Ferenbaugh traced human cases to this source. Traum first identified *Brucella* from aborting sows in 1914, and Evans in 1918 distinguished the difference between *Brucella meli-*

tensis and *Brucella abortus*, and suggested that raw milk from infected cows would be the source of human cases. In 1924 Keefer described the first human case of brucellosis in this country due to organisms other than *melitensis*.

Etiology. Human brucellosis is due to one of three species of *Brucella*—namely, *Br. melitensis* (goats), *Br. suis* (hogs), and *Br. abortus* (cattle). *Brucella* are small, nonmotile, nonspore-forming rods staining Gram-negative. Growth is supported at 37° C. in tryptose phosphate broth and in liver infusion broth having a pH of 6.6 to 6.8. The primary isolation of *Br. abortus* requires displacement of 10 per cent of the air by carbon dioxide. The differentiation of the three species is dependent upon biochemical and serologic reaction. In general, *Br. melitensis* is the most invasive of the three species, which is reflected in the severity of human infections, while *Br. abortus* is the least virulent.

Epidemiology. The natural reservoir of brucellosis is in domestic animals, particularly cattle, swine, and goats. The disease is but very rarely transmitted from human to human. By and large, man acquires brucellosis through the ingestion of milk or milk products containing viable *Brucella*, or through contact of the skin with infected tissues, excretions, and secretions. There is some evidence that brucellosis may be airborne, with the disease resulting from the inhalation of *Brucella*. Infections caused by *Br. abortus* are spread through cow's milk or through dermal contact with *Brucella*. Epidemics of brucellosis traced to raw cow's milk have been caused by *Br. suis*. Contact with infected porcine tissue is a common cause of infections due to *Br. suis*. While infections due to *Br. melitensis* result from eating goat's cheese or drinking unpasteurized goat's milk, recent studies in Minnesota and Iowa have shown that contact with infected hogs

has been the source of *melitensis* infections. It is readily appreciated why brucellosis is primarily a disease of rural areas and why it is considered to be an occupational disease involving meatpacking plant employees, farmers, veterinarians, and livestock producers.

Pathogenesis. Following invasion of the body by *Brucella* through the oropharynx or through the skin, the organisms tend to localize in tissues of the reticuloendothelial system, such as the bone marrow, lymph nodes, liver, spleen, and also the kidneys. A characteristic but nonspecific reaction of these tissues to the *Brucella* is the appearance of epithelioid cells, giant cells of the foreign body and Langhans' types, and lymphocytes and plasma cells. Necrosis and caseation may or may not occur in these granulomatous areas. The granulomas are similar to those of sarcoidosis and tuberculosis. Other less frequent sites of localization of *Brucella* are the bones, especially the spine, endocardium, and testes. While the central nervous system and peripheral nerves are commonly affected deleteriously by *Brucella*, the mechanism whereby this takes place is not known. Like other blood-borne infections, *Brucella* may on occasion localize in any tissue or organ in the body. Though brucellosis is a common cause of abortions in cattle, swine, and goats, authentic cases of human abortions occur no more frequently in this disease than in other bacteremias. Orchitis in the male is rarely the cause of subsequent sterility.

Manifestations. The incubation period varies between 5 and 21 days. The onset in many instances may be insidious, the patients exhibiting a low-grade fever with no localizing findings, and complaining of headache, weakness, insomnia, sweats, anorexia, constipation, pain over the spine, and generalized aches and pains. Less frequently, the disease may be ushered in by chills, high fever, and prostration, but, again, localizing abnormal physical findings may be absent. In general, about 50 per cent of the patients exhibit enlarged lymph nodes, especially of the cervical region, and splenomegaly is detected in about one third of the cases. An enlarged and tender spleen is usually associated with the more severe cases. Pain on pressure over the vertebrae occurs occasionally. Pain distributed over the course of the peripheral nerves, particularly the sciatic nerve, is encountered. Orchitis appears after several days of illness and, like the orchitis of mumps,

is ushered in with a chill or chilliness, high fever, and tender and enlarged testes. Painful and swollen joints are seen occasionally, but persistent and deforming arthritis is not specific for the disease. Signs and symptoms referable to the lungs and pleurae are uncommon. A rare but serious complication is subacute bacterial endocarditis. Ocular disorders are associated with the more chronic forms of the disease.

The initial febrile stage of the illness may endure for only a few days or up to several weeks. The persistence of fever and symptoms is definitely related to physical activity. Rest in bed during the acute illness is frequently associated with prompt improvement. The natural course of the disease in the majority of patients is marked by a permanent remission of fever and symptoms within three to six months. A small number of bacteriologic-proved cases may have an illness that persists longer than one year.

The present status of chronic brucellosis is extremely difficult to assess. There is no doubt that the infection may persist in some individuals for months and years. Such patients exhibit a state of ill health manifested by weakness, fatigue, mental depression, vague aches and pains, and no abnormal physical findings. Intermittent fever may occur. The precise incidence of chronic brucellosis awaits further investigation. Much of the data now available are based upon uncritical clinical and laboratory studies.

Laboratory Procedures. A precise diagnosis of brucellosis is dependent upon the results of laboratory procedures.

BLOOD. The total leukocyte count is usually normal or slightly reduced, but rarely over 10,000 cells per cubic millimeter. The differential count reveals a relative lymphocytosis. The erythrocyte sedimentation rate is of no specific diagnostic aid, the rates being normal or accelerated.

The most practical method for screening suspected cases of brucellosis is the *agglutination* reaction. Agglutinins usually appear during the second or third week of illness. If proper techniques and antigen are employed, agglutinins are demonstrated in the vast majority of bacteriologic-proved cases. Active brucellosis is usually associated with titers of 1 to 100 or above. Agglutinins for brucellosis are not always specific, since cross reactions occur with the cholera vibrio and *Pasteurella tularensis*. Agglutinins may persist

in the blood long after the patient has recovered, and subsequent unrelated infections may provoke an anamnestic rise.

At least one *culture* of blood, and preferably more, should be carried out in every suspected case of brucellosis. Cultures of *Brucella* have been isolated from aspirated sternal bone marrow, when simultaneous blood cultures remained sterile. It is too impractical for routine purposes to attempt to isolate *Brucella* from the urine, bile, or feces.

The *opsonocytophagic* test, which is a measure of the phagocytosis of *Brucella* by polymorphonuclear neutrophil leukocytes, is of extremely doubtful diagnostic aid. The *complement-fixation test* does not contribute enough additional information to warrant its use.

INTRADERMAL TESTS. Various antigenic preparations such as killed organisms and the nucleoprotein fraction of *Brucella* are used widely for diagnostic purposes. A positive reaction has no more significance than that obtained with tuberculin in suspected cases of tuberculosis. A positive reaction indicates previous invasion of the body by *Brucella*, and does not mean that active disease is present. Unfortunately, many instances of chronic brucellosis are being diagnosed on the basis of a vague illness and positive intradermal tests. When agglutinins are absent and cultures remain sterile, considerable caution must be exercised before making a diagnosis of brucellosis, even though the skin test is positive. Negative skin tests are encountered in severe cases of brucellosis where a high titer of agglutinins is present and a bacteremia is demonstrated.

In summary, the diagnosis of brucellosis depends upon a correlation of epidemiologic data, the nature of the illness, and laboratory information such as the presence of agglutinins and isolation of *Brucella* from the tissues or blood.

Differential Diagnosis. Brucellosis must be differentiated from other acute febrile illnesses such as *influenza* and other *upper respiratory diseases* of doubtful etiology. Brucellosis is not commonly associated with coryza or pharyngitis. Other diseases from which it must be differentiated include *malaria* and *typhoid fever*. Brucellosis may be confused with *infectious mononucleosis*, but the characteristic blood picture and the elevated titer of heterophil antibodies in the latter disease are helpful differential aids.

Chronic brucellosis simulates *psychoneurosis*,

anxiety states, and *chronic nervous exhaustion*. Indeed, a patient with brucellosis may suffer from the foregoing states of nervous disorders. Some confusion may arise in differentiating it from other diseases including *tuberculosis* and lymphoblastoma, especially Hodgkin's disease.

Treatment. Unfortunately, much information of a popular nature on brucellosis has been disseminated widely. The general public has heard or read that brucellosis is a chronic disease which may last for years, and that no satisfactory treatment is available. Therefore, any physician who believes that he is dealing with a case of brucellosis should reassure the patient that the disease is self-limiting, and complete recovery will ensue. Psychotherapy is extremely important in the management of these mentally depressed and tired patients. This is particularly applicable to individuals having chronic brucellosis. The acutely ill and febrile patient should be kept in bed. Many patients will recover completely following a period of rest.

Over the years the lack of specific treatment for brucellosis has been emphasized by the number of agents and procedures that have been recommended and then discarded one by one. There is no doubt that an occasional case of acute brucellosis has responded satisfactorily to sulfonamide therapy. Penicillin is of little or no use in this disease. Relatively large doses of streptomycin have altered the clinical course of brucellosis favorably in some instances. A most encouraging development was the observation that a combination of streptomycin and sulfadiazine yielded more satisfactory results, especially in the more severe cases with complications. Experimental evidence showed that these two agents acted synergistically on all three species of *Brucella*. While various schedules of doses have been recommended, the following has given encouraging results: Streptomycin is administered intramuscularly in a dose of 0.5 Gm. every eight hours for 10 days to two weeks. At the same time that treatment is started with streptomycin, 3 to 4 Gm. of sulfadiazine are given orally, and then 1 Gm. every four hours, omitting the early morning dose. Sulfonamide therapy is continued as long as streptomycin is administered. This treatment is recommended only for proved cases of brucellosis, because of the danger of toxic complications resulting from either one of these drugs. Streptomycin can produce vestibular dys-

function that may be more disabling than the disease for which the drug has been administered. Since dihydrostreptomycin is just as active against *Brucella* as streptomycin, and since it probably provokes less dysfunction of the eighth nerve, it is now recommended that dihydrostreptomycin be substituted for streptomycin in the same doses as given above.

The antibiotic aureomycin yields more satisfactory therapeutic results than does the combination of streptomycin (or dihydrostreptomycin) and sulfadiazine. Aureomycin may be administered orally and the toxic reactions are less severe than those encountered with the combination of drugs. The oral dose is 0.5 Gm. every six hours for 10 days to two weeks. If nausea or vomiting occurs, the reduction of the dose or omission of a dose or two will obviate these side effects from the drug. Relapses may be successfully treated with a second course of aureomycin.

Another antibiotic introduced for the treatment of human brucellosis is "Chloromycetin." There is evidence that, following the oral use of this agent, clinical results are as satisfactory as those obtained with aureomycin. A recommended dosage schedule is 1.0 Gm. of "Chloromycetin" every six hours for the first 24 hours, and then 0.5 Gm. four times a day for the succeeding 13 days.

A common therapeutic practice in the more chronic cases is to attempt "desensitization" of the tissues to *Brucella* by treating patients with one of the several antigenic preparations, such as heat-killed *Brucella* cells or filtrates of *Brucella* cultures. While hypersensitivity to *Brucella* may be a factor in the symptomatology, and the use of ascending doses of antigenic material may be sound therapy, the results are difficult to evaluate, and treatment must often be continued for several months. Violent local and systemic reactions often occur, even following the injection of minute amounts of antigen.

For the relief of headache and the generalized aches and pains, salicylates may be prescribed, while the occasional use of barbiturates is desirable for the insomnia which is so commonly a part of the disease.

Prognosis. While brucellosis may be a chronic and disabling disease, the overall mortality rate is not more than 2 to 3 per cent. The physician today may learn a great deal about the prognosis of this disease by turning back and looking over

the rich experience of the Mediterranean Fever Commission, which was recorded in 1905 to 1907. In a day when specific treatment was lacking, careful clinical observations were made. In an analysis of hundreds of *melitensis* cases, Eyre stated the following in 1908:

One may safely say that not more than 10 per cent are convalescent in a shorter period than one month from the onset of symptoms. In 50 per cent, the disease extends over two months, in 25 per cent to three months, and in fully 15 per cent, a duration of three months is exceeded.

Over the succeeding years, it has been observed that a relatively small, but important, number of cases will have a protracted illness. Cases of bacteriologic-proved brucellosis in which the disease has continued for over a year, have been studied at the University of Minnesota Hospitals. But such cases are not commonly encountered. One cannot escape the conviction that so-called chronic brucellosis is being mislabeled too often on the basis of procedures of doubtful value, especially the intradermal test with *Brucella* antigen.

Relapses do occur in the more chronic cases of brucellosis. These recurrences are manifested by fever, and mental and physical disability with generalized aches and pains. But too little attention has been given to the problem of reinfections. Clinical observations in meat-packing plant employees have confirmed studies made with experimentally infected animals in that the immunity induced by one attack of brucellosis is only relative. Second and third infections do take place. Thus, in individuals who continue to be exposed to the disease, it may be quite difficult to differentiate between relapses and reinfections.

Prevention. As long as the reservoir of brucellosis persists in domestic animals, human brucellosis will occur. The only practical means of eliminating the disease in human beings is to eradicate the disease from cattle, hogs, sheep, and goats. Such control measures in animals are being worked out in several areas in the United States. Since human brucellosis is contracted through the ingestion of contaminated milk and milk products, it is essential that only properly pasteurized milk should be utilized for human consumption. Brucellosis is an occupational disease involving farmers, livestock workers, veterinarians, and those working in packing plants.

There are no dependable means available for immunizing these groups against the disease.

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Tularemia

Edward S. Miller

Definition
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Definition. Tularemia is an acute infectious disease caused by a bacterium, *Pasteurella tularensis*. It is a severe systemic illness, but is frequently accompanied by localized infections in the skin, conjunctiva, lungs, lymph nodes, or other organs.

History. Tularemia was first identified in 1912 as an infectious disease of California ground squirrels, caused by a small Gram-negative bacillus. Shortly thereafter, this organism was implicated as the cause of an unusual human conjunctival infection, and during succeeding years other manifestations of tularemia were recognized. One of these is an endemic disease of Utah, previously known as deer fly fever. It is probable that a syndrome described in Japan more than a century previously was the same disease.

Etiology. *P. tularensis* is a tiny, pleomorphic, Gram-negative, nonmotile coccobacillus. It grows aerobically on artificial mediums enriched with blood, glucose, and cystine. It does not form spores and is killed readily by heating to 58° C. for 10 minutes. Thorough cooking therefore renders infected meat safe for consumption. In

the animal host the organism often grows intracellularly.

Epidemiology and Pathogenesis. Tularemia is primarily a disease of rodents and other animals. Man is only an incidental and occasional host. In the United States infection occurs naturally in rabbits, rats, squirrels, beavers, woodchucks, opossums, skunks, and many other species. It is estimated that 1 per cent of wild rabbits in this country are infected. Tularemia is disseminated in the rabbit population by rabbit ticks, rabbit lice, and rabbit fleas—species which do not attack man. Several other arthropods function as vectors in transmitting *P. tularensis* to animals and to man. Ticks are of particular importance, for they acquire tularemia not only by feeding on diseased animals, but also by congenital transfer of organisms from the parent tick to its progeny. Among the ticks found infected in nature which feed on man are *Dermacentor andersoni*, *D. variabilis*, *D. occidentalis*, and *Amblyomma americanum*. Another vector is the deer fly or horsefly (*Chrysops discalis*), a biting insect prevalent in some western states. It feeds at frequent intervals on animals or on human beings, and since its mouth parts thus become mechanically contaminated, the organisms are transmitted readily from one host to another.

Though man is only an incidental host, he is highly susceptible to the disease. The portal of

entry may be via the skin, the conjunctiva or other mucous membranes, or the respiratory or alimentary tract. In animals, experimental infection follows mere deposition of the bacteria on the unbroken skin.

Ninety per cent of human cases are the result of direct contact with diseased animals, chiefly wild rabbits. Tularemia is thus particularly common in hunters, in butchers, and in housewives. In the course of dressing the game the organisms effect an entry through the skin of the hands or, less commonly, are rubbed into the eye. Human infections also arise from a number of other sources. Some follow the bites of ticks or deer flies. Cases have resulted from the ingestion of incompletely cooked meat and from the drinking of stream water contaminated by infected rats. Accidental infections are common among bacteriologists; the organism is known to be one of the most dangerous agents to be handled in the laboratory. One case of congenital infection is on record. Despite the highly infectious nature of tularemia, it is a remarkable fact that man-to-man transmission practically never occurs, even in the presence of the pneumonic form of the disease.

The agent is disseminated by the blood throughout the body of the human host. The portal of entry may be marked by an ulcer on the skin or the mucous surface. In addition, there are numerous visceral lesions, particularly in the liver, spleen, lymph nodes, lungs, and kidneys. A typical lesion is 1 to 15 mm. in diameter and consists of a caseous center surrounded by polymorphonuclear leukocytes and lymphoid, epithelioid, and giant cells.

Tularemia occurs in Japan, in Turkey, and in many parts of Europe, as well as in North America. In this country the disease has been reported from all states except Vermont, and appears to be especially common in the south central states. Cases arising from contact with rabbits are most common during the winter months, when game laws permit hunting. Those resulting from deer fly bites are seen chiefly in the summer when flies are most active, while cases contracted from ticks are seen in the spring and summer.

Manifestations. The incubation period is usually 2 to 5 days, though it may vary from 1 to 21 days. The onset of illness is abrupt, with fever, chills, drenching sweats, headache, weakness, and generalized aching. There may be gastroin-

testinal symptoms: nausea, vomiting, or diarrhea. The subsequent course is influenced by the localization of lesions, and on this basis tularemia is commonly divided into a number of clinical varieties.

The *ulceroglandular* form of the disease is seen in 80 per cent or more of cases. One or two days after the onset of systemic symptoms, the lymph nodes draining the portal of entry become enlarged, painful, and tender. At the same time or shortly thereafter, a painful papule appears on the skin at the site of inoculation, which is most commonly on the hands. This soon becomes pustular, then breaks down to leave a punched-out ulcer 0.5 to 1 cm. in diameter. There may be several local lesions. In some cases subcutaneous nodules appear along the course of the lymphatics leading to the regional glands. All of these lesions are inflamed and painful during the acute phase of illness. In one half of the cases the lymphadenitis then subsides slowly over a period of one to two months, while in the remainder the glands or nodules eventually undergo necrosis and drain superficially.

The *glandular* variety is characterized by regional, and occasionally by generalized, lymphadenitis. There is no local lesion, though presumably the portal of entry of the organisms lies within the area drained by the enlarged regional nodes. Suppuration may occur as in the ulceroglandular variety.

The *oculoglandular* or *ophthalmic* type of tularemia results from conjunctival inoculation of *P. tularensis*. The conjunctiva, the lids, and the periorbital tissues become inflamed and edematous, and there are symptoms of pain, photophobia, and lacrimation. Tiny yellow papules appear on the conjunctiva and soon ulcerate. If lesions localize on the cornea, they may lead to scarring or to actual perforation of the eyeball. Dacryocystitis occasionally occurs, and, rarely, atrophy of the optic nerve. The ocular syndrome is accompanied by adenitis involving the corresponding preauricular, submaxillary, anterior cervical, and sometimes the axillary lymph glands. These too may suppurate and drain through the skin.

The infecting organisms may be ingested, giving rise to the rare *gastrointestinal* variety of disease. Lesions appear in the mouth, in the pharynx, or anywhere along the alimentary tract, and are associated with regional adenitis.

Patients are severely ill with symptoms of nausea, vomiting, diarrhea, and abdominal pain. There may be extensive bleeding into the intestine.

Typhoidal tularemia is characterized by systemic symptoms and signs without a primary lesion or lymphadenitis. This type is often accompanied by pneumonia, and is frequently fatal. Accidental infections acquired by laboratory workers are usually of this variety.

In *pleuropulmonary* tularemia the chief manifestation is pneumonia, often accompanied by pleurisy with effusion. Infection in the lung is primary in one third of the cases, while in the others it develops secondarily to some other type of the disease. In the latter instances the pneumonia may appear days or months after the onset of illness. Pneumonia occurs in one half of the patients with typhoidal tularemia, and in 7 per cent of ulceroglandular cases. The serious nature of this condition is indicated by the fatality rate of 30 to 40 per cent, and by the fact that 60 to 70 per cent of fatal cases of tularemia have pneumonia. The usual symptoms are marked prostration with cough and pleuritic pain. Sputum, if present, is scanty and mucoid or tinged with blood. The physical signs of consolidation are often minimal. Pleural effusion occurs in one half of the cases; the fluid is usually greenish yellow and moderately turbid. It may be grossly bloody. Lung abscess, pneumothorax, and atelectasis are rare complications. By x-ray the pulmonary infiltration has a patchy, ground glass appearance, and lesions are sometimes multiple. Any portion of the lung may be involved, but the pneumonitis tends to be hilar in distribution, with extension into the lower lobes. The hilar lymph nodes often are enlarged. It is evident that the clinical and x-ray characteristics of this syndrome may resemble those of severe cases of primary atypical pneumonia.

Uncommonly, the infectious process may localize in the peritoneal cavity, in the meninges, in the pericardial sac, in the appendix, or in bone. The clinical pattern so induced may simulate closely that of miliary tuberculosis.

The categories described above are, of course, purely arbitrary, though useful, clinical designations. Patients often exhibit combinations of syndromes. Regardless of the type of tularemia, most patients are severely ill and prostrated. Fever persists for 10 to 30 days, is usually re-

mittent in type, and ranges between 101° and 105° F. A transitory remission in fever and symptoms often occurs a day or two after the onset of illness. A rash is seen occasionally, occurring on any part of the body. It may appear at any time during the acute illness, and lasts for days to weeks. It may be erythematous or purpuric, macular, papular, or pustular. In a small proportion of patients the spleen and the liver become enlarged and tender.

In the untreated case of average severity the acute phase of illness lasts for two to three weeks, after which the fever falls by lysis, symptoms abate, the ulcerations begin to heal, and glandular enlargement diminishes. Convalescence is characterized by marked lassitude and weakness which persist for three months or longer. Mild cases of tularemia are sometimes observed, in which there is only a low-grade fever with minimal constitutional symptoms.

The course of illness in the more severely ill patient is characterized by great prostration, with high fever lasting three or four weeks or longer. An unfavorable outcome is heralded by such signs as sustained high fever, delirium, and rapid enlargement of the liver and the spleen. Death usually occurs between the second and fourth weeks.

The most common complication is suppuration of lymph glands, which may occur during the acute illness or after a lapse of weeks or months. Sometimes the lymphadenitis subsides completely, only to reappear many months later. Relapses are unusual in tularemia, but have occurred as long as 24 months after the initial illness. A prolonged, chronic type of illness has been reported in a few instances.

Laboratory Findings. The most satisfactory means of specific diagnosis is afforded by the agglutination test. Agglutinating antibodies almost invariably appear in the blood during the second or third week of illness, a titer of 1:80 being considered significant. The level rises to a maximum of 1:640 to 1:5120 during the fourth to eighth week, then drops slowly; significant titers persist for many years, sometimes for life. There is some cross agglutination between tularemia and brucellosis, but the titer is higher with the homologous antigen.

P. tularensis often can be recovered from the patient by suitable technics, but this is accompanied by great risk of infection to the laboratory

workers, and therefore is not recommended. The organisms can be recovered from ulcer exudate, in blood early in the disease or just before death in fatal cases, in bubo pus, and in the sputum and pleural fluid of pulmonary infection. The best means of isolation is by intraperitoneal inoculation of material into a guinea pig. Primary isolation from the patient directly to artificial media usually fails.

A diagnostic skin test can be performed, using a suitable antigen in high dilution (1:1000). An erythematous reaction developing in 48 hours indicates present or past infection; sensitivity persists for many years.

In acute tularemia the white blood count is normal or moderately increased. The erythrocyte sedimentation rate is elevated.

Differential Diagnosis. The various clinical manifestations of tularemia may be confused with a number of other infectious diseases. A history of exposure to potentially infected animals or arthropod vectors is of great assistance. The tularemic agglutination test is, of course, important in diagnosis. Ulceroglandular lesions may be differentiated from the more common staphylococcal and streptococcal infections by culture. Subcutaneous nodules may suggest the diagnosis of sporotrichosis; the latter is identified by smear and culture. Symptoms and signs in the typhoidal variety are in no way pathognomonic, and are similar to those encountered in a number of other infectious diseases. Brucellosis and typhoid fever are identified by suitable cultures and by agglutination tests. Typhus and Rocky Mountain spotted fever are distinguished by their exanthems and by serologic tests. In infectious mononucleosis, the clinical course is usually milder, blood cells are abnormal, and the heterophil agglutination test is positive. The pneumonic form of tularemia may be clinically indistinguishable from several nonbacterial pulmonary infections. In primary atypical pneumonia the cold agglutinin titer is often elevated. Psittacosis and Q fever are identified by complement-fixation tests.

Prophylaxis and Treatment. Foshay has prepared a killed bacterial vaccine which is used for active immunization. Judgment as to its efficacy must be reserved; it probably does not reduce the incidence of infection, but it may modify the severity of illness.

Therapy with streptomycin has proved to be

a revolutionary development in the treatment of tularemia. *P. tularensis* is highly sensitive to this drug in vitro, and extensive trials in man attest to its effectiveness in vivo. The drug is most effective when administered early in the course of illness, at which time a marked diminution in symptoms and fever usually takes place within 24 to 72 hours. Primary lesions heal rapidly, and in the majority of cases the lymphadenitis regresses. Patients with pneumonia show an equally striking clinical response, though the pulmonary infiltration as seen by x-ray may require several weeks to resolve. Tularemic adenitis is the lesion most resistant to therapy. The incidence of suppuration has probably been decreased; nevertheless, in a significant number of cases the nodes enlarge, liquefy, and drain in spite of antibiotic treatment, subsiding only after several weeks or months.

Streptomycin is administered intramuscularly for a period of five to seven days. In practically all cases a dose totaling 1 Gm. per day is sufficient. The drug should be given promptly to any patient who presents clinical evidence of tularemia. It is unwarranted to wait for serologic proof of the diagnosis, for that will not be forthcoming until the second or third week of illness, and in the meantime the patient may die. Therapy is especially to be considered in patients who are seriously ill with the syndrome of atypical pneumonia; a therapeutic trial of the antibiotic is often fully justified.

In experimental infections, and in a very limited clinical trial, aureomycin also appears to be an effective therapeutic agent for tularemia. Whether it will prove to have any advantage over streptomycin remains to be determined.

Other measures include the usual types of symptomatic remedies. Buboës are incised and drained only if they become fluctuant.

Prognosis. The over-all fatality rate in untreated tularemia averages 6 to 7 per cent. The prognosis is grave in the pneumonic and gastrointestinal types of disease, but the fatality rate fortunately is lower in the more common ulceroglandular and oculoglandular varieties. Fatalities are more common in the aged, in the obese, and in those with preexisting cardiovascular disease. The prognosis has, however, been markedly altered by the introduction of streptomycin therapy. The acute phase of illness is ameliorated, the period of convalescence is shortened, and fatali-

ties are now unusual, even in the more serious forms of the disease.

Permanent sequelae are rare following recovery, and patients acquire a prolonged active immunity.

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Plague

Edward S. Miller

Definition
 History
 Etiologic Agent
 Epidemiology and Pathogenesis
 Manifestations
 Laboratory Findings
 Differential Diagnosis
 Treatment
 Prophylaxis and Control
 Prognosis

Definition. Human plague is an acute, severe, frequently fatal infection characterized by fever, prostration, and suppurative lesions of the lymphatic system. Sometimes there is an associated pneumonia. *Pasteurella pestis* is the etiologic agent, rodents are the primary hosts, and the usual vectors are fleas.

History. Plague is one of the ancient pestilences of man. Descriptions of a plaugelike disease are found in the Old Testament. Early Greek and Roman manuscripts testify to its existence in the Mediterranean region long before the Christian era. The disease has been endemic in Asia and in Europe for many centuries, where from time to time great pandemics have destroyed large segments of the human population. The last major outbreak originated in China in the late nineteenth century, spread to all the continents, and in 1900, entered the United States through the port of San Francisco. Whether the disease existed in this country prior to that time is un-

known, but certainly it has since become a permanent resident.

Etiologic Agent. *P. pestis* is an encapsulated, nonmotile, Gram-negative bacterium which produces no spores and will grow under either aerobic or anaerobic conditions. Though it is predominantly bacillary in shape, coccal, ovoid, and other pleomorphic forms are often seen. When stained with carbolfuchsin or carboltionin, the organisms display a characteristic bipolar appearance. Growth occurs on ordinary mediums. On agar the colonies are small, round, transparent, colorless, and viscous. There are no important antigenic differences among strains collected from different animal species in various parts of the world. *P. pestis* produces no exotoxin.

Epidemiology and Pathogenesis. As with other infectious organisms spread through the agency of vectors, *P. pestis* is enabled to survive and be transmitted by means of a series of intricate ecologic adaptations. Plague is fundamentally an affection of rodents; from them it is sometimes, and quite incidentally, transmitted to man. A great many varieties of wild rodents are found infected in nature. In the United States alone, the endemic reservoir includes at least 38 species of rats, mice, marmots, rabbits, prairie dogs, squirrels, and chipmunks. Rats are the most im-

portant animal hosts because they are found all over the world, travel widely, and live in close association with man. Large human outbreaks usually arise in urban areas and in the wake of rat epizootics. Under circumstances of poor sanitation, the concentration of people and of rats provides ample opportunity for the exchange of parasites. In rural or wooded regions plague may be enzootic in many other species of rodent hosts. Such infection is referred to as *sylvatic plague*, in contrast to rat or *murine plague*. Devastating epizootics of sylvatic plague sometimes occur, yet they give rise only to sporadic human cases because man rarely comes into close contact with these animals.

The flea is the usual transmitting agent, the most important species being the rat flea, *Xenopsylla cheopis*. Other arthropods occasionally function as vectors, including lice, ticks, and possibly bedbugs. The flea becomes infected by ingesting the blood of a bacteremic animal, following which the organisms multiply in the alimentary tract of the insect. When the flea feeds on a new host, the bite wound is inoculated by the regurgitation of organisms, or as a result of simple mechanical contamination by the mouth parts. Plague bacilli are also present in the flea feces, and infection may follow the scratching of this material into the skin. Rat fleas will accept other hosts, including man, particularly if rats are not immediately available. When an epizootic decimates the rat population, fleas are encouraged to transfer from the dead rodents to humans.

Human bubonic plague results chiefly from the bite of the rat flea. Infection can also be acquired by direct contact with the tissues of an infected animal, or by its bite, for the organisms can penetrate through skin abrasions and through intact mucous membranes. Not a few accidental infections have occurred in laboratory workers as a result of handling cultures and infected animals. Direct transmission of the bubonic form of the disease from man to man is unusual, in contradistinction to the mode of spread of primary pneumonic plague. A person who develops plague pneumonia excretes large quantities of organisms in his sputum. The infection may then be airborne, in droplet nuclei, directly to a human contact, without an intermediary insect vector. This type of plague is highly contagious, secondary cases are common among those attending

a patient, and under suitable circumstances tremendous outbreaks may occur.

The most prominent lesions are ordinarily in the lymphatic system. In bubonic plague a hemorrhagic zone of edema surrounds an inflamed and suppurating group of regional lymph glands. The latter are hyperplastic, and show areas of focal necrosis containing many organisms. Similar metastatic lesions may develop in distant groups of glands or in other viscera. In pulmonic infections there is a lobular pneumonia with hemorrhagic exudate in the alveolar spaces, with accompanying pleuritis and bronchitis. Hemorrhages may be found in any organ, or beneath epithelial surfaces.

It is now clear that plague is widely and permanently entrenched in the rodent population of the United States, chiefly in the West. Naturally occurring infection has been found in California, Oregon, Washington, Utah, Idaho, Nevada, Montana, New Mexico, Colorado, Texas, Oklahoma, Kansas, North Dakota, Louisiana, and Florida. Susceptible rodent hosts exist in all parts of the country, and there is reason to believe that sylvatic plague is gradually extending eastward. There have been 504 reported human cases in the United States since 1900, of whom 318 died. Vigorous control measures have eliminated plague whenever it has made its appearance in cities. However, sylvatic plague is impossible to eradicate, and offers a constant threat of retrograde extension back to the domestic rat population.

Manifestations. Symptoms appear after an incubation period of 2 to 12 days. The disease can assume several different clinical forms, of which the *bubonic* variety is the most common. Illness begins abruptly with chills, a rise in temperature to 102° to 105° F.; tachycardia, headache, vomiting, uncertain gait, marked prostration, and delirium. The spleen is sometimes palpable. The flea bite which represents the portal of entry rarely can be seen; if present it is marked by a papule or vesicle which ultimately becomes pustular. Only after a lapse of one to five days do localizing symptoms of extreme pain and tenderness point to the regional glandular lesions which give the disease its name. They are in the inginal or femoral regions in the majority of cases, less often in the axilla or neck, and uncommon elsewhere. The infection may extend secondarily to other superficial or deeply situated groups of

glands. The bubo consists of a firm, matted group of glands, measuring 2 to 5 cm. in diameter, and surrounded by a boggy and frequently hemorrhagic zone of edema. It usually suppurates and drains spontaneously after one or two weeks, though sometimes complete resorption occurs.

There is a marked hemorrhagic tendency, presumably due to an endotoxic effect on blood vessels. Petechiae or ecchymoses are often seen beneath cutaneous or mucous surfaces. Bleeding may occur into a viscous or a serous cavity, or from the nose, alimentary, respiratory, or urinary tracts.

The course of bubonic plague is marked by an irregular or remittent fever. It often drops at the time of appearance of the bubo, only to rise again. In favorable cases the temperature falls gradually during the second week, concomitant with improvement in the general clinical condition. A rise to hyperpyrexic levels, or a precipitous fall to normal or to subnormal, frequently heralds approaching death. Most fatalities occur during the first week of illness. Though bubonic plague is usually a severe illness, mild cases are sometimes seen during epidemics; to these is applied the name *pestis minor*.

The second clinical form which plague may take is that of *pneumonia*. The initial cases appear in patients with bubonic plague, of whom as many as 5 per cent develop secondary lesions in the lungs. These individuals may provide the starting point for a man-to-man epidemiologic cycle of airborne primary pneumonic plague. It is a fulminating infection accompanied by great prostration, cough, dyspnea, and, in the later stages, cyanosis. The sputum is abundant, blood-stained, and teeming with *P. pestis*. Often there are no clear-cut pulmonary signs, though scattered rales or areas of dullness may be found. In the absence of specific therapy, plague pneumonia invariably ends in death within two to five days.

The third variety of plague is the so-called *primary septicemic* form, in which the patient experiences a sudden and overwhelming systemic illness. There is a marked constitutional reaction with chills, low-grade fever, rapid pulse, severe headache, nausea, vomiting, and delirium. Death terminates the course within a few days, before localizing lesions become clinically apparent. Nevertheless, autopsy usually reveals inflammation in some part of the lymphatic system.

The infectious process may localize in other regions of the body. Subcutaneous abscesses and cutaneous ulcerations sometimes occur, and the meninges are occasionally invaded.

Laboratory Findings. Since plague is an uncommon disease in the United States, the diagnosis often has been overlooked until the patient has succumbed, or until multiple cases have developed. Nevertheless, the epidemiology and the clinical features provide highly characteristic leads to the clinician. Once a suspicion of plague is entertained, it can readily be verified by smear, culture, and animal inoculation of appropriate specimens. If a bubo is present, a small quantity of interstitial fluid should be aspirated from its center. Large numbers of morphologically characteristic bacilli are usually to be seen in a stained smear. Infected sputum likewise contains many organisms. Bacteremia of varying degrees occurs sometime during the course of nearly all cases. Pus and sputum should be cultured on blood agar plates, while blood is inoculated into hormone-cystine or other nutrient broth. Organisms are identified by their morphologic and colonial characteristics, and by agglutination with specific antiserum. Guinea pig inoculation is the final step in identification. In this animal the gross and microscopic lesions are highly characteristic. It is to be emphasized that the handling of infected materials or animals involves great danger of infection of the laboratory workers. Except as mentioned above, serologic tests have not been satisfactory or useful in diagnosis.

The white blood cell count is elevated to levels of 20,000 to 40,000, with a predominance of polymorphonuclear leukocytes. There is little or no change in the red blood corpuscles.

Differential Diagnosis. Before the appearance of localizing signs, plague may be confused with severe systemic illnesses such as typhoid or typhus. The bubonic form bears certain resemblances to other varieties of infectious lymphadenitis, including tularemia, syphilis, and lymphogranuloma venereum, or to those of staphylococcal or streptococcal origin. Pneumonic plague must be distinguished from tularemic, pneumococcal, and other bacterial pneumonias, as well as from psittacosis and primary atypical pneumonia. A consideration of epidemiologic factors, plus bacteriologic studies, will aid in the differentiation.

Treatment. The therapy and the prognosis of plague have been revolutionized by the introduction of streptomycin and sulfonamides, for even pneumonic and septicemic cases can be treated successfully. Streptomycin is the most effective of all presently known drugs. It is administered in doses of 2 to 4 Gm. a day for 6 to 10 days. Sulfonamides have also proved efficacious, the best one being sulfadiazine. Sulfonamide blood levels of 10 to 20 mg. % should be maintained, and administration continued for at least two weeks after the temperature has returned to normal. Considering the gravity of the disease, the safest practice is to administer both of these drugs simultaneously. An antiplague serum has been in use for a number of years, though it is of only limited value in bubonic plague, and does not alter the mortality rate in the more severe types of infection. Streptomycin and sulfadiazine will render therapeutic serum obsolete. Buboes are treated with hot, moist applications; incision and drainage are postponed until the lesion becomes well localized and fluctuant.

Prophylaxis and Control. The control of plague in endemic urban areas demands unceasing vigilance in detecting rodent epizootics, and vigorous measures in combating outbreaks. The most important control measures are those aimed at extermination of rats and their ectoparasites. Rats are attacked by poisoning and trapping, by elimination of harborage areas, and by separating them from their food supplies. Recently DDT

has been used with brilliant success in diminishing the flea population infesting both rodents and human beings, thereby interrupting the rat-flea-rat and the rat-flea-man cycles of transmission.

Patients must be disinfested and carefully isolated, while other intimately exposed persons should be quarantined. Good results have been obtained in preventing secondary cases among contacts by treating them with sulfadiazine, 3 to 8 Gm. a day for seven days. If the danger of an epidemic is sufficiently threatening, the entire exposed population should be immunized. Two types of bacterial vaccines are in use, one composed of dead organisms, and the other containing a special avirulent strain of living bacilli. Both provide limited and transitory active immunity.

Prognosis. Formerly the fatality rate of bubonic plague averaged 50 per cent to 90 per cent, while the pneumonic and septicemic forms were almost uniformly fatal. However, even the gravest varieties of infection respond to streptomycin and to sulfadiazine therapy, so it appears probable that the over-all fatality rate will be reduced to 5 to 10 per cent.

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Glanders

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Definition and Etiology
 Epidemiology and Pathogenesis
 Manifestations
 Diagnosis
 Treatment

Definition and Etiology. Glanders is a grave infectious disorder characterized by the development of numerous granulomatous abscesses throughout the body. The causative agent is

Malleomyces mallei, a small, aerobic, nonmotile, nonsporulating, Gram-negative bacillus.

Epidemiology and Pathogenesis. This is another of the interesting group of infectious diseases of animals which are sometimes transmitted to man. In this instance, the principal natural hosts are horses, mules, and asses. Glanders once was a common equine disease in America, but

stringent control measures virtually have eradicated it. However, it is still prevalent in certain sections of central Europe, North Africa, and Asia. The infection may be acquired by handling diseased animals. Organisms may gain entry through cutaneous abrasions, by implantation on the conjunctiva, by ingestion, or by inhalation. Human beings are highly susceptible, as evidenced by the large number of laboratory workers who have contracted the disease. Nevertheless, with the elimination of animal glanders in the United States, the infection also has become rare in man.

Manifestations. Human glanders usually runs an acute and stormy course. After an incubation period of several days, illness begins abruptly with chills, high fever, and marked prostration. At the portal of entry, commonly on the skin, a nodule forms and breaks down to become a painful ulcer. The regional lymph nodes are involved, and lymphatic and vascular dissemination soon results in a generalized pyemic state. Miliary lesions develop along the course of lymphatics, in subcutaneous and submucous tissues, in muscle, in the lungs, and in other viscera. The lesions gradually enlarge, coalesce, and undergo central caseous necrosis. The superficial nodules ulcerate, while more deeply situated abscesses often form fistulous tracts which extrude discharges onto the surface. Areas of consolidation appear in the lungs, and the liver and the spleen become inflamed and enlarged. Many patients exhibit ulcerations of the upper respiratory tract with erosion of adjacent cartilaginous and bony structures. Among other septic manifestations are meningitis, osteomyelitis, and purulent polyarthritis. A generalized purplish, papulopustular eruption sometimes is seen preterminally.

Acute glanders progresses with great rapidity, ending fatally in one to three weeks in the majority of cases. Recently, however, a milder syndrome was described in a group of laboratory workers who were accidentally infected via the respiratory tract. In these cases, the clinical picture was not unlike that of viral pneumonia of average severity.

A chronic form of glanders sometimes is seen. The onset is generally insidious, with low-grade fever and milder initial symptoms. The course is characterized by exacerbations and remissions and punctuated by the irregular appearance of

painful ulcers and draining abscesses. Chronic glanders may at any time assume the fulminating qualities of the acute form. More than half of the patients die after months or years of exhausting illness.

Diagnosis. Specific diagnosis can be established by culture, by animal inoculation, by serologic testing, by the demonstration of derinal sensitivity, and by biopsy. *M. mallei* can be recovered from exudates, sputum, scrapings from a local lesion, and terminally from the blood. Straus's reaction is elicited by injecting infected material into the peritoneal cavity of a male hamster or a male guinea pig. Scrotal swelling becomes apparent in two to four days, and organisms then can be recovered from the tunica vaginalis. Both agglutinating and complement-fixing antibodies appear in the blood during the second to fourth weeks of illness; they are specific when present in high titer, except for some cross reaction with the antigens of *Malleomyces pseudomallei*. The latter organism causes melioidosis, a disease closely related to glanders. Patients who survive the initial onslaught of illness develop a persistent skin sensitivity to mallein, which is an antigen prepared from cultures of *M. mallei*. The test is performed by intradermal injection of 0.1 ml. of a 1:10,000 dilution of commercial mallein; it is considered positive if an erythema is present 48 hours later. Skin and mucous membrane lesions show characteristic histologic features and are readily accessible to biopsy.

Treatment. Sulfadiazine has proved to be a potent chemotherapeutic agent in experimental animal infections, and has been used successfully in several human cases. The drug should be administered for a minimum of 20 days, in doses sufficient to maintain blood levels of 10 to 15 mg. %. Penicillin and streptomycin are ineffectual.

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Melioidosis

Edward S. Miller

Definition
Etiology
Epidemiology
Manifestations
Diagnosis
Treatment

Definition. Melioidosis is a fulminating, usually fatal, infectious disease in which granulomatous lesions develop throughout the body. Etiologically, pathologically, and clinically it bears a striking resemblance to glanders.

Etiology. The causative organism is *Malleomyces pseudomallei*, a motile, aerobic, Gram-negative bacillus. This bacterium is closely related to *Malleomyces mallei*, the causative agent of glanders, but the two can be differentiated by bacteriologic and serologic methods. There is also an important epidemiologic difference, for melioidosis finds its primary hosts and principal reservoir in rats, whereas glanders is chiefly an affection of horses. The mode of transmission has not been established but is thought to result from contamination of food and water with the excreta of infected rodents.

Epidemiology. The disease was first identified in Rangoon in 1911, and some 300 cases have since been observed in Indo-China, the Malay States, Thailand, Ceylon, and contiguous regions. It may have a much broader geographic distribution than has heretofore been suspected, for recently two cases were reported as originating in Guam and one in the United States.

Manifestations. The clinical course of melioidosis is much like glanders, except that it is even more virulent and lethal. Nearly all untreated cases have ended fatally. In the most acute form, illness is sudden in onset, with shaking chills, high fever, and marked prostration, often associated with vomiting and severe diarrhea. Bacteremia occurs early and results in the development of widely disseminated granulomatous abscesses. The patient passes into a state of stupor or coma and dies within 3 to 14 days. In subacute cases the course of disease is similar except that

the patient survives sufficiently long (three to four weeks) for some of the disseminated lesions to become clinically evident, and additional symptoms and signs depend on their location. They are prone to develop in the skin, subcutaneous tissues, muscles, lungs, bones, liver, and spleen. Pyelonephritis, orchitis, epididymitis, and prostatitis sometimes are seen. A pustular rash has been observed. In rare cases melioidosis becomes chronic, with deep-seated lesions and draining sinuses which persist for years.

Diagnosis. Cultural methods afford the best means of prompt diagnosis, for *M. pseudomallei* can be recovered readily from blood, sputum, exudates, and urine. As in glanders, Straus's reaction can be elicited by intraperitoneal injection of infected material into male hamsters and guinea pigs. The agglutination and complement-fixation tests become positive after two to four weeks. Biopsy specimens reveal characteristic pathologic changes which are indistinguishable from those seen in glanders.

Treatment. The reported fatality rate of 95 per cent attests to the inefficacy of older methods of treatment. Sulfadiazine is curative in experimental infections in animals and should receive adequate trial in man. It is suggested that full therapeutic doses be given for a minimum of 20 days. Streptomycin, aureomycin, and "Chloromycetin" have yet to be evaluated in this disease.

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Section 7—Anaerobic Infections

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Anaerobic Streptococcal Infections

Max Michael, Jr.

Definition
Etiology
Pathogenesis of Infections
Clinical Features
Treatment
Significance and Prognosis

Definition. Many *anaerobic streptococci* are normal inhabitants of the body, but they may under certain circumstances cause infection which is characterized by tissue destruction and by the production of foul-smelling pus. The sites most often involved by such infection are the parturient uterus, lungs, pleura, paranasal sinuses, and the brain.

Etiology. Anaerobic streptococci are Gram-positive cocci which grow in short chains; the individual cells appear quite small on initial isolation. They require anaerobiosis for isolation from the body and, while most strains remain strictly anaerobic, some strains, on further subculture, are able to grow without conditions of anaerobiosis and may then closely resemble *Streptococcus pyogenes*.

Attempts at division of anaerobic streptococci into groups on the basis of cultural characteristics, of biochemical reactions, and of antigenic groupings, are unsatisfactory. Antigenic analyses, while incomplete, suggest that there are separate types; there are at least two acid extractable antigens which are identified by precipitin methods. Certain of the anaerobic streptococci are related antigenically to *beta-hemolytic streptococci* of groups A, B, and C.

Pathogenesis of Infections. Anaerobic streptococci form a part of the normal throat flora and have been isolated from apparently normal paranasal sinuses and from tooth sockets. The presence of these organisms in the normal gastrointestinal tract may be the result of swallowing those normally in the throat. They are found in the vagina of as many as 40 per cent of normal females.

Conditions appear to be most favorable for invasion and infection by anaerobic streptococci when necrotic tissue is present, such as the lochia of the parturient uterus, devitalized tissue such as that occurring in the postpneumonic lung or the necrotic tissue which may follow pulmonary infarction. The occurrence of anaerobic streptococcal infection depends upon the patient's susceptibility, the type of tissue involved, and the status of the tissue where the organisms are found. Since these organisms are so frequently present in the mixed flora, it is often difficult to assess their etiologic role in cases of pulmonary suppuration. There appears to be no correlation between the type of anaerobic streptococcus and the type of infection produced. The ability of some strains to ferment various carbohydrates, with the production of gas, is responsible for the appearance of lesions, particularly in muscles, which may simulate gas gangrene. Antibodies have not been demonstrated in the serums of patients recovering spontaneously from anaerobic streptococcal infections.

Clinical Features: PLEUROPULMONARY INVOLVEMENT. Anaerobic streptococcal infections of the lungs and pleura are characterized by the destruction of tissue and by the production of large amounts of foul-smelling pus. The organisms may reach the lungs by two routes. The first of these is by *aspiration*. The bacteria which are present around infected tooth sockets and infected gums or as part of the normal throat flora become incorporated into plugs of mucus and, as such, are inhaled into the lungs. This is most apt to occur following operations such as tonsillectomy, or after aspiration of vomitus, as in an alcoholic stupor or in the postepileptic state. The second mode of access to the lungs is by *embolization*. Septic thrombi which are apt to form in the uterine veins during post-partum anaerobic streptococcal infection may become detached and

travel to the lungs, provoking abscess formation. It is thought by some that pulmonary abscesses following certain neck infections or following operations on the throat represent such embolization rather than aspiration. Patients developing putrid lung abscesses are apt to be profoundly ill. A septic temperature, frequent sweats, and a cough productive of large amounts of foul, musty sputum are often noted. Hemoptysis, embolization of the brain, rupture into the pleural space, and spill-over of the putrid material to the other lung may occur. Chronic lung abscess may develop in such a patient. It is often difficult in such cases to evaluate adequately the role of the streptococcus because of the abundance of other organisms as demonstrated by cultural methods. When, however, bronchopleural fistulas develop, with resulting *putrid empyema*, the role of anaerobic streptococci becomes more clearly defined. Stained smears from such empyemas reveal a wide variety of organisms; on culture, however, the anaerobic streptococcus is quite often the only organism isolated. The fluid from such an empyema is foul-smelling, thin, and usually reddish brown in color.

Another type of pulmonary involvement caused by anaerobic streptococci is the so-called *spontaneous putrid empyema*. The sudden onset of the signs and symptoms of empyema without preceding pulmonary symptoms frequently suggests an otherwise normal respiratory tract, but closer scrutiny demonstrates underlying pulmonary disease such as small abscesses with development of small bronchopleural fistulas. A patient with putrid empyema is usually acutely and gravely ill, with pinched facies, profuse sweating, grunting expiration, dyspnea, and chest pain. The physical findings are those of any empyema. A striking feature sometimes noted is the rather rapid accumulation of gas in the pleural space, which may be produced not only by the bronchopleural fistula, but also, perhaps, by the fermentation of various carbohydrates in the pus by the anaerobic streptococci. Often an area of cellulitis will be noted in the thoracic wall over the site of the empyema. Blood stream invasion may occur.

OTHER INFECTIONS. As high as 40 per cent of *post-partum uterine* infections are caused by anaerobic streptococci. These organisms, normal inhabitants of the female genital tract in a large number of individuals, may, under the conditions existing in the parturient uterus, produce several

syndromes. The mildest of these is putrid endometritis which is characterized by a low-grade fever, foul lochial discharge, and a soft, tender, subinvolved uterus. The more serious infections spread to the peritoneal cavity, producing peritonitis. With invasion of the pelvic veins and resulting thrombophlebitis, the organisms may enter the blood stream and establish metastatic foci in various parts of the body, particularly in the lungs, leading to pulmonary gangrene, suppuration, and later empyema.

As would be expected from the fact that this infection is endogenous, it does not assume epidemic proportions in maternity wards, as may be the case with *beta-hemolytic streptococci*, which are introduced into the uterus from the throats of those attending the patient.

Infection of the *paranasal sinuses* by anaerobic streptococci results in acute or chronic sinusitis comparable to that incited by other bacteria. On occasions, however, anaerobic streptococci invade the frontal bone from the frontal sinuses with resulting osteomyelitis. Direct extension to the brain may then occur, with abscess formation and meningitis. A similar state of affairs may follow from infected mastoid cells.

The capabilities of anaerobic streptococci to produce a syndrome simulating clostridial *gas gangrene* was brought out forcibly in reports from the North African campaigns in World War II. Although the lesions produced by these gas-producing streptococci resembled those due to the clostridia in their local effects, they were not accompanied by the overwhelming toxemia noted in patients with true clostridial gas gangrene.

A serious infection is that resulting from anaerobic streptococcal infection following *human bites*. The organisms are introduced into subcutaneous tissue by the teeth. Such infections are characterized by intense edema, gangrene, and a foul discharge. Later, extension may take place into joints and bones. Other bacteria are usually present in such infections.

Relatively few parts of the body are free from attack by anaerobic streptococci. The organisms have been recovered from many cases of appendicitis and of appendiceal abscess where they are usually present in association with other organisms such as coliforms and clostridia.

Other lesions in which anaerobic streptococci are apparently etiologic agents include perirectal abscesses, osteomyelitis, postoperative wound in-

fection, liver abscesses, bacterial endocarditis, otitis media, and deep cellulitis of the neck.

Treatment. Penicillin is the drug of choice in the treatment of these infections. This antibiotic should be administered in doses of at least 100,000 units every two to three hours, and should be continued until the temperature has returned to normal for at least a week and until the local foul discharge has ceased. If the infection does not appear to be affected by these doses, the amount of the drug should be increased to much larger amounts, since many strains of anaerobic streptococci are relatively resistant to penicillin. For infections such as empyema and meningitis, penicillin must also be instilled locally.

It is becoming apparent that the administration of large doses of penicillin systemically, plus repeated thoracentesis with removal of pus and instillation of penicillin, will result in a favorable outcome in many cases of putrid empyema. In those individuals who do not respond to such management, closed thoracotomy, or rib resection and open drainage, may be indicated. By the same token, the need for surgical attack is becoming less in patients with putrid lung abscess. If they are treated early with massive doses of penicillin and frequent bronchoscopic drainage, recovery may ensue. Breathing exercises aimed at

re-expansion of the lung are indicated for both the empyema and lung abscess patients.

Significance and Prognosis. It is of great importance to recognize infection caused by anaerobic streptococci. These organisms may invade any region of the body and set up infection which may vary from an insignificant pyogenic lesion to an overwhelming, rapidly fatal infection. Furthermore, because these organisms are relatively resistant to penicillin, large doses may be required. Unless anaerobic cultures are made routinely, the etiology of many infections will remain obscure, since the usual aerobic cultures will fail to reveal organisms in many cases.

The ultimate outcome of a given anaerobic streptococcal infection will depend upon prompt clinical and bacteriologic diagnosis, intensive chemotherapy, and judicious surgical drainage of pus accompanied by appropriate supportive measures.

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Bacteroides Infections

Paul B. Beeson

Etiology
Pathogenesis
Manifestations
Septicemia Following Tonsillar Infection
Post-partum and Postabortal Infection
Laboratory Findings
Treatment
Prognosis

Etiology. The genus *Bacteroides* includes a group of Gram-negative, nonspore-bearing anaerobic bacilli. Members of this genus are nor-

mally found among the flora of the mouth, intestinal tract, and vagina. The species which is of the greatest interest from the standpoint of human infections is *Bacteroides funduliformis*, also called *Bacillus funduliformis* and *Fusiformis necrophorus*.

Pathogenesis. *Bacteroides* infections probably occur more commonly than is indicated by published case reports. Some of them go unrecog-

nized because of the difficulties associated with isolation and identification of anaerobes. The usual source of infection is presumed to be the alimentary tract of the host. Organisms may be transported to other parts of the body by direct extension or by way of the blood and lymph. Members of the genus have been isolated from many different types of infections, including tonsillitis, otitis media, lung abscess, empyema, arthritis, appendicitis, peritonitis, and endometritis. Usually other intestinal bacteria such as *Escherichia coli*, *Clostridium welchii* and anaerobic streptococci are present, in addition to the *Bacteroides*. From such mixed infections, however, *Bacteroides* may invade the blood stream and be transported elsewhere, producing metastatic infections, especially in the lungs, joints, and liver. This septicemic form of *Bacteroides* infection occurs most frequently when thrombophlebitis develops in the vicinity of the primary infection.

Manifestations. In mixed infections such as otitis media, appendiceal abscess, etc., the course and symptoms are variable, and the role of the *Bacteroides* cannot be evaluated. The outcome in these cases usually depends on the possibility of surgical treatment.

Septicemia Following Tonsillar Infection. A characteristic disease pattern may be encountered in primary *Bacteroides* infection of the tonsils. The patient usually suffers from sore throat for a few days, then abruptly becomes extremely ill. A hectic type of fever, ranging between 101° and 104° F. is common, and temperature elevations of 106° to 108° F. may occur. Signs of acute inflammation in the tonsils and pharynx may have subsided, but there is usually tenderness in the region of the tonsillar lymph nodes. Palpation along the course of one of the internal jugular veins discloses a firm, tender cord, indicating the presence of a thrombus. Septic emboli become lodged in the lungs, forming lung abscesses, and pleural empyema may develop. Productive cough and pleuritic pain are common at this stage. Purulent arthritis may develop in one of the large joints—e.g., the elbow, shoulder, knee, or ankle. The liver becomes enlarged and tender as a result of acute hepatitis, and there may be icterus. Without appropriate therapy this form of *Bacteroides* infection usually causes death within a few days.

Post-partum and Postabortal Infection. *Bacteroides* septicemia similar to that which compli-

cates tonsillar infection is occasionally encountered in the post-partum or postabortal state. Here the primary infection is endometritis, with thrombophlebitis in the pelvic veins. The manifestations are similar to those just described, including septic fever, pulmonary symptoms, arthritis, icterus, and hepatitis.

Laboratory Findings. There is usually a leukocytosis ranging from 12,000 to 25,000. Patients with hepatitis have elevated serum bilirubin and positive test for bilirubin in the urine, but the stools do not become acholic. The only method of specific diagnosis is demonstration of *Bacteroides* by cultural methods. As already mentioned, the organisms are often associated with other bacteria common to the gastrointestinal tract, and this makes cultural demonstration technically difficult. In bacteremia or metastatic infections, however, *Bacteroides* can be isolated relatively easily, provided that incubation is carried out under anaerobic conditions. Thioglycollate broth is suitable. The possibility of this type of infection should be considered in appropriate cases, and anaerobic cultures made. After one or two weeks it is possible to make a diagnosis by demonstration of a rising titer of agglutinins for stock strains of *Bacteroides* organisms.

Treatment. The effect of various chemotherapeutic agents has not been thoroughly investigated, but clinical and experimental evidence indicates that the sulfonamides are effective against *Bacteroides* infections. Penicillin apparently has no clinical value. All purulent foci which are accessible should be drained surgically. Ligation of veins proximal to areas of thrombophlebitis has not appeared to be helpful.

Prognosis. The paucity of clinical reports makes it impossible to present reliable statistics regarding prognosis. In mixed local infections the course is variable. The fatality rate of septicemic cases formerly was almost 100 per cent, but a very considerable reduction has been effected since the introduction of sulfonamide therapy.

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Section 8—Miscellaneous Bacterial Infections

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Anthrax

Edward S. Miller

Definition
Epidemiology
Manifestations
Diagnosis
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Prognosis

Definition. Anthrax is an uncommon infectious disease of man in which the primary lesion may be in the skin, the lung, or the gastrointestinal tract. The etiologic agent is *Bacillus anthracis*, a large, Gram-positive, aerobic, nonmotile, encapsulated bacillus. The spores produced by this organism are notably resistant to destruction and will survive in contaminated soil for many years. The anthrax bacillus causes an acute, fatal, highly contagious systemic disease in cattle, horses, sheep, and a variety of other animals. The disease is world-wide in distribution and is prevalent in livestock in many parts of the United States.

Epidemiology. Most human infections are acquired by individuals who are occupationally exposed to domestic animals or to animal products, on which the hardy spores may survive indefinitely. Sixty to 80 cases are reported in the United States annually, chiefly in farmers, veterinarians, butchers, and those who work with hides, leather, and animal hair. Infection occurs primarily as a result of direct contact, the organisms entering particularly through abrasions in the skin. The respiratory and the gastrointestinal tracts are rare portals of entry in man. Biting flies also can transmit the disease.

Manifestations. Human anthrax nearly always takes the form of a cutaneous lesion ("malignant pustule"). Following an incubation period of one to several days, a tiny red maculopapule appears on the skin, usually on an exposed surface such as the hand, arm, face, or neck. The papule becomes a vesicle, around which daughter vesicles may develop. The lesion soon ruptures, leaving a shallow ulcer surrounded by a raised

erythematous rim. Serosanguineous fluid oozes into the crater and dries to form a tough black eschar. Simultaneously it becomes surrounded by a firm, nonpitting edema, which in some cases becomes very extensive ("malignant edema"). The local lesion itself is characteristically pruritic but painless. The regional lymph nodes are somewhat enlarged, moderately painful, and tender. After three to six days, the pustule reaches a maximum diameter of 1 to 3 cm., while the edema extends for a radius of 2 to 20 cm. In nonfatal cases the inflammatory process then gradually recedes, the eschar ultimately sloughs off, and a permanent scar is left. Cutaneous anthrax usually evokes mild to moderate symptoms of fever, headache, and malaise. In fatal cases the infection spreads to the meninges, lungs, or other viscera, and constitutional symptoms are severe.

Other clinical varieties are rare. A primary pneumonia ("woolsorter's disease") may follow exposure to airborne spores. The ingestion of uncooked meat from infected animals has resulted in a rapidly fatal form of enteritis with peritonitis. Meningitis may follow the bacteremic spread of organisms.

Diagnosis. The diagnosis of anthrax can be confirmed readily by bacteriologic methods. Typical Gram-positive rods are present in large numbers in the vesicle fluid of cutaneous lesions and in the sputum in pneumonic cases. When so found in smears, a presumptive diagnosis is justified. *B. anthracis* grows readily on ordinary mediums. Unlike its nonpathogenic cousins (e.g., *Bacillus subtilis*, *Bacillus anthracoides*, etc.), it produces a fatal infection when injected into mice.

Treatment. Penicillin is effective, in doses of 30,000 units every three hours until signs of inflammation have receded. Pulmonary and other internal forms of anthrax have been almost universally fatal in the past, but these, too, will

probably yield to antibiotic treatment. The results of animal experiments indicate that streptomycin may be an even more potent therapeutic agent than penicillin.

Prognosis. The fatality rate in cutaneous anthrax formerly was 5 to 20%, but penicillin therapy has reduced this to negligible proportions. The prognosis in internal anthrax probably will be materially improved also.

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Streptobacillus moniliformis Infection (Haverhill Fever, Rat Bite Fever)

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Definition
Etiology
Epidemiology
Manifestations
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Differential Diagnosis
Treatment
Prognosis

Definition. An acute infectious disease caused by *Streptobacillus moniliformis*, and characterized by fever, arthritis, and skin eruption.

Etiology. The causative organism is a pleomorphic microorganism which grows in chains, with beadlike structures interposed. It stains irregularly by Gram's method, and is more easily demonstrated with the Giemsa or Wayson methods. This organism is regarded by some workers as a fungus because of its morphologic appearance, and is sometimes called *Actinomyces muris*, or *Streptothrix muris ratti*. The L_1 pleuropneumonia-like microorganism of Klieneberger has often been found in association with it, but there is dispute as to whether the relationship between them is that of symbiosis or variation in morphology. *Streptobacillus moniliformis* grows readily in liquid cultures enriched with blood or

ascitic fluid. The organism is pathogenic for mice, in which it may cause acute polyarthritis.

Epidemiology. *Streptobacillus moniliformis* infection may be acquired in two different ways. Nearly all sporadic cases result from the bites of rats. These are most common in infants and children, and in laboratory workers. The other type of infection occurs in epidemics. One such epidemic occurred in Haverhill, Massachusetts, the other in Chester, Pennsylvania; both were thought to have been caused by the ingestion of contaminated milk. The names *Haverhill fever* and *erythema arthriticum epidemicum* have been applied to cases in which there was no history of rat bite. The clinical picture is the same in both types of infection.

Manifestations. The incubation period is comparatively short. The interval between rat bite and the development of symptoms is usually three to seven days, while in the Haverhill epidemic the incubation period appeared to be only one to three days. The onset of symptoms is sudden, with malaise and fever, headache and vomiting. About half of the patients have one or more

chills. The temperature course is quite variable; usually there is an intermittent or remittent type of fever. Occasionally the fever is relapsing in type, with two or three days of normal temperature interspersed between one or more days of fever. *Arthritis* usually appears during the first week of the disease, and involves one or more of the larger joints. These become hot, swollen, and tender. In addition, there are generalized muscle aches. A *skin eruption* appears in over 90 per cent of cases. This is usually most prominent on the extremities, in the vicinity of joints, and consists of reddened, flat papules 1 to 4 mm. in diameter. When infection has been acquired by rat bite there are usually signs of mild inflammation at the site, and regional lymph nodes may be enlarged and tender.

The natural duration of the disease is variable. It may subside after a few days or it may persist for several weeks. Recovery is the rule, even without specific treatment, and permanent disability due to joint involvement seldom occurs.

Laboratory Findings. A moderate leukocytosis, with a leukocyte count of 10,000 to 15,000, is often observed, although the leukocyte count remains normal in some cases. A specific diagnosis is made by isolation of the causative organism from the blood or from a joint fluid. Growth is usually visible after 48 hours as small "puff-ball" colonies at the bottom of the flask of liquid medium. These show the characteristic pleomorphic configuration. Agglutinins for *Streptobacillus moniliformis*

moniliformis can be demonstrated in the blood after the second week of disease.

Differential Diagnosis. In patients with a history of rat bite, the principal difficulty is in differentiating *Streptobacillus moniliformis* from *Spirillum minus* infection. The clinical features of the two diseases may be very similar, and positive diagnosis can be made only by demonstration of the causative organism in the patient's blood. A tentative diagnosis of *Streptobacillus moniliformis* infection may be based on a short incubation period, prominence of joint symptoms, and failure to respond to arsenical therapy. Where there is no history of rat bite, differentiation from such diseases as rheumatic fever, chronic meningococcemia, and malaria must be made.

Treatment. Penicillin is an effective agent in the treatment of *Streptobacillus moniliformis* infection. A dose of 400,000 units a day should produce clinical improvement within 48 hours. Treatment should be continued for about a week.

Prognosis. This infection is always benign unless complicated by other illness.

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Bartonellosis

W. Elizabeth Gambrell

Epidemiology
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 Oroya Fever
 Verruga Peruana
 Asymptomatic Infection

The term bartonellosis indicates infection with *Bartonella bacilliformis* transmitted by certain species of the sandfly, *Phlebotomus*. The infection, often referred to as Carrion's disease, may

develop in one of three forms—an acute febrile anemia of rapid onset and high mortality, designated Oroya fever; a profuse cutaneous eruption of fairly long duration, called verruga peruana; or an asymptomatic invasion of the erythrocytes in patients who become carriers.

Epidemiology. The disease is limited geographically to certain valleys in the Andes chain

of mountains in South America, comprising parts of Peru, Ecuador, and Colombia. It is further restricted to regions of definite altitudes, between 2400 and 8000 feet, where the insect vector, *Phlebotomus*, propagates.

Manifestations. The incubation period is approximately three weeks, but may be much longer. The initial symptoms are pain and fever. Aching pains of the bones, joints, and muscles, intermittent and variable in intensity, appear, accompanied by fever which may be as high as 104° F. at the beginning, but soon becomes milder. In the early stages the disease often resembles influenza or malaria, and, even though anemia is absent, blood cultures for *Bartonella* will be positive. After this, the patient develops in days or months one of the two classic types of the disease.

OROYA FEVER. This type is characterized by acute illness, extreme pallor, fever, delirium, and weakness. The erythrocyte count falls very rapidly, often being less than one million in a few days. The slightest movement brings on vertigo and often syncope, and is accompanied by pain so that the patients assume a fixed statuesque position to decrease faintness and pain. Death may occur within 10 days, but usually in three to four weeks. Parasites are numerous in the blood, and 90 per cent of the red blood corpuscles may be parasitized when the erythrocyte count is one million. The organisms may be found in the circulating monocytes and in the fixed phagocytes of the reticuloendothelial system. Reticulocytes are abundant, often comprising 70 per cent of the red blood corpuscles. Neither hemolysins nor agglutinins are found in the serum. Recovery results if the Bartonellae decrease and fever abates. The erythrocyte count stabilizes, then increases

to approach normal values in approximately six weeks, when convalescence begins.

VERRUGA PERUANA. In most cases the disease does not terminate, but in about one month merges with the second form, verruga peruana. This is characterized by a profuse skin eruption of miliary verrugas varying in color from red to purple. Three types of lesions may occur, according to size and location. These are *miliary*, which are about 1 cm. in diameter and project above the skin, *nodular*, which involve the skin and subcutaneous tissue and at first do not project above the skin, and *mulaire*, which press against the skin and finally erode it. The three types may occur together, and since eruption takes place in successive crops, verrugas of all types and at all stages of development may be found on the same patient. These occur on covered and exposed areas, chiefly the limbs and face, and more rarely on the genitalia, scalp, and mucosa. They may persist from one month to two years, the *miliary* disappearing first and leaving no scars unless infected. The *mulaire* persist longer and usually scar. The eruption is accompanied by pain, fever, and moderate anemia. *Bartonella* may be demonstrated in the lesions and cultured from the blood. Prognosis is good. No effective treatment is available against the etiologic agent.

ASYMPTOMATIC INFECTION. The form of greatest epidemiologic importance is the asymptomatic infection in man, where 10 per cent of certain populations are carriers as demonstrated by blood cultures. These constitute a reservoir for further transmission by the only proved vector, the sandfly.

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Diphtheria

Paul B. Beeson

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Definition. Diphtheria is an acute infectious disease, caused by *Corynebacterium diphtheriae*, characterized by a local inflammatory lesion, usually in the upper respiratory passages, and by distant effects, particularly on the heart and peripheral nerves, due to specific exotoxin.

History. The first accurate description of the disease was given by Bretonneau in 1826. In 1883 Klebs described the morphologic appearance of *C. diphtheriae* in stained preparations from diphtheritic membranes. A year later Loeffler isolated the organism in pure culture and showed that it was capable of producing lesions resembling those of human diphtheria in experimental animals. In 1888 Roux and Yersin showed that some of the manifestations of diphtheria in guinea pigs could be produced by sterile filtrates of *C. diphtheriae* cultures. By 1893, von Behring had demonstrated the neutralizing effect of antiserum on diphtheria toxin in experimental animals; this was soon followed by the treatment of human diphtheria with antitoxin. Schick described the skin test for susceptibility to diphtheria in 1913. Ramon in 1923 showed that the toxin

could be altered in such a way as to render it noninjurious without destroying its antigenic property (toxoid); this was the basis for present methods of active immunization against diphtheria.

Etiology. *C. diphtheriae* is a Gram-positive, pleomorphic, unevenly staining bacillus. Three principal types are recognized: mitis, intermedius, and gravis. These are distinguished by the appearance of their colonies on tellurite medium, and by their capacity to ferment glycogen and dextrose. European workers, particularly those in the British Isles, believe that there is a significant difference in the clinical manifestations of diphtheria produced by the different varieties, gravis and intermedius diphtheria being associated with severe toxic manifestations, whereas the chief danger of mitis diphtheria is in laryngeal obstruction. In the United States the gravis type is comparatively uncommon, and less significance is attached to the relationship of the type of organism to the clinical form of the illness.

The exotoxin produced by *C. diphtheriae* is a potent poison having the chemical properties of a protein. In highly purified preparations the minimum lethal dose for guinea pigs is as little as .0001 mg.

Epidemiology. Diphtheria can occur at any age, but is most frequently encountered in children between the ages of two and five years. There is no marked difference in sex incidence. The principal mode of transmission is apparently by droplet infection, especially from asymptomatic carriers. Fomites probably play little part in the spread of diphtheria, but *C. diphtheriae* can remain alive and virulent in dust of a darkened room for several weeks. This could serve as a means of spread of the infection.

Pathogenesis. In the majority of cases the growth of diphtheria bacilli is confined to a superficial area, there being little tendency for the

organisms to invade deeper tissues, or to enter the lymphatics or blood stream except in terminal stages of the disease. The exotoxin produced by bacilli in the local lesion is, however, carried by the blood to all parts of the body. Dissemination of this toxin, with damage to remote areas, appears to be greater when the primary lesion is in the nasopharynx, and less when it is in other sites such as the larynx or on the anterior nasal mucosa.

The *primary lesion* of diphtheria is a superficial ulceration covered by a membrane. It is most often located on the mucosal surface of the tonsils, uvula, soft palate, nasopharynx, nose, larynx, trachea, or bronchi. The membrane consists of a coherent mass of bacteria, necrotic epithelium, phagocytes, and fibrin, and is firmly attached to the underlying tissues. The deeper tissues become intensely congested and edematous. There is acute inflammation of the regional lymph nodes, which are packed with phagocytes and necrotic material.

In addition to the local lesion, morphologic changes may be found in many tissues after death from diphtheria. *Peripheral nerves* show degenerative changes in the medullary sheaths; less commonly there is degeneration of the axis cylinders. The *heart* is often dilated; there may be cloudy swelling and hyaline changes in the myocardium. Cloudy swelling is nearly always present in the *kidney*. *Petechial hemorrhages* are occasionally found in the kidneys, skin, and adrenal glands.

Death in diphtheria may result from respiratory obstruction due to the membrane and edema, or it may be caused by the action of the toxin on the heart, nervous tissue, and other organs. The mechanism of circulatory failure in diphtheria has been the subject of some controversy. Unquestionably the myocardium often suffers damage. In addition, however, some authorities believe that the toxin interferes with neuromuscular control of the peripheral circulation.

There is strong evidence that diphtheria toxin affects the body tissues by interfering with the cytochrome B enzyme system.

Immunity. The chief factor which governs susceptibility to clinical diphtheria is the presence or absence of antibody to the exotoxin. This has been demonstrated unequivocably in experimental animals, and is also supported by an im-

pressive accumulation of observations on human beings.

The *Schick test* is a rough method of determining the amount of antitoxin present in the circulating blood. A standard quantity of diphtheria toxin in 0.1 ml. of fluid is injected intradermally and, as a control, an equal quantity of toxin previously heated to 70° C. is injected into the opposite arm. The result is read after four to seven days. A positive reaction is indicated by induration and erythema at the site of the toxin injection, significantly greater than at the site of the control injection. A negative test is indicated by absence of reaction, or by reactions of equal intensity at the two test areas. A negative Schick test can generally be interpreted as indicating a blood antitoxin level greater than 0.01 unit per ml. of serum.

Antitoxic immunity is not necessarily complete, and Schick-negative individuals occasionally contract the disease, especially if subjected to heavy exposure. On the other hand, many Schick-positive individuals escape diphtheria after being exposed. Only about 50 per cent of adults in America are Schick-negative, yet diphtheria is comparatively uncommon in adult life. Furthermore, second attacks of diphtheria are very rare, despite the fact that only about 90 per cent of patients convalescent from the disease have become Schick-negative. The implication is, therefore, that factors other than antitoxic immunity play a part in determining susceptibility to clinical diphtheria. There may be resistance to tissue invasion by the organisms themselves. In general it may be said that a positive Schick test in a young child is strong evidence of susceptibility, whereas in an older subject the finding has less significance.

Manifestations. The incubation period is short, usually one to seven days, and the early symptoms vary according to the location of the primary lesion.

FAUCIAL DIPHTHERIA. About half of all cases of diphtheria are of this variety. The onset is insidious, with slight soreness of the throat, malaise, and low-grade fever, gradually increasing in intensity during the next two or three days. The patient usually appears quiet and does not complain excessively of sore throat. The body temperature fluctuates between 100° and 102° F. The blood pressure is normal and the pulse rate is moderately increased.

The characteristic physical findings are in the throat. The *diphtheritic membrane* may begin on one or both tonsils. It is usually confluent and tends to spread to the adjacent pharyngeal mucosa, often upward onto the soft palate and uvula. Sometimes it extends across from one faucial area to the other. There is little redness elsewhere, so that the mucosa only a few millimeters away from the edge of the membrane usually appears normal. At first the membrane is rather gelatinous, but it soon becomes tough and coherent. It may be gray, yellow, or white. When an attempt is made to loosen it with an applicator, there is bleeding of the underlying tissue. When healing begins, the membrane separates at the margins, rolls up, and breaks away in large pieces. Therapy with antitoxin usually hastens the separation of the membrane and the return of the mucosa to normal appearance.

NASOPHARYNGEAL DIPHTHERIA. The membrane may spread from the faucial areas over the posterior pharyngeal wall up into the nasopharynx and even out into the anterior portion of the nose. In such instances the patient is always severely ill, and subsequent development of toxic manifestations in the heart or nervous system is to be expected.

In severe cases of faucial or nasopharyngeal diphtheria there is marked edema and swelling in the anterior and lateral parts of the neck, in addition to enlargement of the regional lymph nodes. This is sometimes referred to as "bull neck" diphtheria, and is generally the severest form of the disease.

ANTERIOR NASAL DIPHTHERIA. Lesions which are restricted to this area usually produce mild illness, the chief symptom being persistent, thin, watery, sometimes bloody, nasal discharge, which is irritating and gives the upper lip a raw appearance. Toxic manifestations are rare.

LARYNGEAL DIPHTHERIA. This may result from extension of nasopharyngeal diphtheria, or the lesion may originate in the larynx. The first symptom of laryngeal involvement is hoarseness. As edema develops in the larynx or as the membrane increases in thickness or extends down into the trachea and bronchi, there may be serious encroachment on the air passage. Loose edges may flap into the lumen during one of the respiratory phases, tending to cause valvelike obstruction. Because of the small diameter of the larynx and trachea in young children, the danger of re-

spiratory obstruction is greatest in them. A croupy stridor, dilatation of the nares, anxiety, restlessness, increased pulse rate, sweating, and flushing of the face are the early signs of obstruction. Later there is retraction of the suprasternal regions, lower rib margins, and the sternum with each inspiration, and cyanosis is evident.

EXTRARESPIRATORY DIPHTHERIA. Primary lesions occasionally develop in other parts of the body. They may appear on the vulva or urethra, or on wounds, burns or chronic ulcers. Wound diphtheria is a special problem in tropical areas and is one of the causes of "jungle sores." These chronic ulcerated areas do not have a characteristic appearance; diagnosis depends on cultural identification of *C. diphtheriae*. As a rule toxic manifestations, especially as related to the cardiovascular system, are not prominent, but peripheral neuritis may occur. Healing of such lesions is speeded by administration of antitoxin.

CARDIOVASCULAR SYSTEM. The frequency of cardiac involvement in diphtheria is illustrated by the fact that abnormal electrocardiograms can be demonstrated in about one half of all patients. Various types of disturbance in rate and rhythm are observed. The *pulse rate* may be rapid—130 to 170 per minute—or heart block may occur during the second and third weeks, with the rate falling to 40 or 50 per minute. The effects on the circulation are usually severest during the second week of illness. The *blood pressure* tends to be low; in some cases hypotension on the order of 70/40 persists for several days. This is a grave prognostic sign. Patients with severe cardiovascular involvement commonly exhibit marked pallor, nausea, and vomiting. There may be gallop rhythm; muffled heart sounds, premature ventricular contractions, or dropped beats. When congestive failure becomes fully developed, there is shortness of breath, pain in the region of the liver, and distention of the neck veins. Death is the usual outcome in such cases. Occasionally a patient in whom no previous manifestation of cardiac damage has been noted dies suddenly after some slight exertion; it is presumed that there has been an acute disturbance in cardiac excitation, with either ventricular fibrillation or ventricular standstill.

PERIPHERAL NEURITIS. Evidence of the neurologic complications is seldom observed before the second week of illness, and may develop as

late as the fifth or sixth week. The commonest initial sign of neural involvement is paralysis of the palate, leading to difficulty in swallowing and regurgitation of fluids into the nose. There is also a characteristic nasal quality in the voice. Second in frequency is involvement of the third cranial nerve, giving rise to extraocular paralysis or to impairment of ciliary function and difficulty in accommodation. The seventh, ninth, and tenth cranial nerves may also be affected. Less frequent is neuritis of the spinal nerves, with paresthesias or weakness of the muscles of the abdomen, neck, or lower extremities. Respiratory paralysis, due to involvement of the intercostal and abdominal muscles, is rare. Loss of the patellar and Achilles tendon reflexes is occasionally seen. These neurologic manifestations are not associated with pain. Increased spinal fluid protein has been observed in a small proportion of cases of diphtheria, and this in combination with postdiphtheritic neuritis may constitute a picture which closely resembles the Guillain-Barré syndrome. Symptoms of postdiphtheritic neuritis persist from a few days to several weeks; usually they improve after the sixth week, but instances have been reported in which disability persisted for several months. Permanent sequelae, however, are virtually never encountered.

Laboratory Aids. Diagnosis by identification of *C. diphtheriae* in stained smears from the membranous lesion is unreliable. Nonpathogenic diphtheroid bacilli may lead to confusion, or true diphtheria bacilli may not be detected. A specific diagnosis depends on cultural demonstration of *C. diphtheriae*. In addition to routine throat cultures on blood agar, material swabbed from the membranous lesion should be inoculated onto Loeffler's and tellurite media. Loeffler's medium provides rapid presumptive diagnosis; organisms with characteristic morphology may be identified in smears from the culture after only 8 to 12 hours' incubation. For practical purposes, this identification, if made by a competent bacteriologist, and in conjunction with a compatible clinical picture, is adequate. Further identification, if desired, may be made from the culture on tellurite medium, which also is of assistance in distinguishing the type of *C. diphtheriae*. Virulence tests need not be done on typical organisms isolated during the acute stage of the disease, but are indicated when the organism is cultured from

the throat or nose of an asymptomatic or convalescent carrier.

The *leukocyte count* in diphtheria is usually normal, but there may be a moderate leukocytosis. *Proteinuria* of slight or moderate degree is common during the acute stage and during convalescence. Marked proteinuria usually signifies a severe toxemia.

Differential Diagnosis. The differential diagnosis of lesions resembling faecal diphtheria is discussed in the section on streptococcal infections (p. 808). Laryngeal diphtheria must be distinguished from "croup" and streptococcal laryngotracheobronchitis. Croup usually comes on at night, improves by morning, and is without fever or local membrane. In *streptococcal laryngotracheobronchitis* there is high fever, leukocytosis, and diffuse redness and edema of the air passages. *Hemophilus influenzae* also may cause an acute laryngotracheobronchitis with symptoms similar to those in streptococcal infections. *Foreign body in the nose* may resemble anterior nasal diphtheria.

Complications. *Purpura* occurs occasionally in cases with very severe toxemia. *Streptococcal infection* is a frequent complication and may cause diffuse redness and edema of the palate and fauces with enlargement and unusual tenderness of the regional lymph nodes. (This is one of the reasons why the throat culture should always be made with media suitable for both types of organisms.) *Relapse* is very rare in diphtheria. *Serum sickness* occurs in a variable proportion of patients convalescent from the disease, depending upon the amount and kind of antitoxin which has been administered.

Specific Treatment: Antitoxin. Every patient in whom the diagnosis of diphtheria appears probable should receive antitoxin without delay. It is not justifiable to wait until the result of a culture is available. The total dose of antitoxin should be given at once; a second injection should never be necessary. The dose required depends on the severity of the disease, not on the age or body weight. The severity of the disease is estimated on the basis of the extent of the membrane, the amount of edema in the neck, the pulse rate, the blood pressure, and the general appearance of the patient. Patients with extensive nasopharyngeal or "bull neck" diphtheria should receive maximal doses. In mild cases a dose of 20,000 units is adequate, whereas in

severe cases considerably larger quantities are needed. Many authorities believe that no advantage can be derived from doses of antitoxin in excess of 100,000 units, although it is the practice in some clinics to give as much as 200,000 units. The antitoxin may be injected intramuscularly, intravenously, or by both routes. In severe cases it is a good plan to give half the total dose intravenously and the remainder intramuscularly.

Penicillin Therapy. Most strains of *C. diphtheriae* are sensitive to penicillin in vitro, and the drug is employed generally in the treatment of diphtheria. Evaluation of its effect has been difficult, because of variability in the natural course of the disease, and because physicians have been unwilling to withhold antitoxin therapy in order to assay the effectiveness of penicillin alone. Certainly penicillin does not neutralize the exotoxin. The general experience is, however, that penicillin therapy has been beneficial in a considerable proportion of the cases, and should be used as a routine measure. Throat cultures become negative earlier in patients who receive penicillin, and the therapy is also of value in preventing or treating pyogenic complications caused by streptococcal infection. A dose of 300,000 units daily for 10 or 12 days should certainly be adequate.

Treatment of Laryngeal Obstruction. In laryngeal diphtheria death may result from obstruction of the air passages. Management of this complication requires experience, skill, and judgment. Patients with laryngeal diphtheria should be observed carefully for signs of obstruction, described previously. In mild cases some benefit may be afforded by having the patient breathe warm moist air from a steam kettle. If obstruction becomes more marked it must be relieved either by intubation or by tracheotomy. Intubation is the preferable method in an institution with experienced medical and nursing staff, whereas in the hands of less experienced personnel tracheotomy is probably the safer measure. Where either of these procedures has been done special nurses should be on duty at all times, since the tubes may suddenly become obstructed, requiring removal, cleansing, or reinsertion. It must be remembered that the patient is unable to call for assistance. Tracheotomy or intubation has to be maintained at least three or four days, and occasionally a tracheotomy tube is left in place for several weeks. One danger of this is that

laryngeal stenosis may occur, especially in cases where there has been secondary pyogenic infection around the site of the opening.

General Management. Isolation precautions should be observed. Strict bed rest is indicated, and physical effort should be reduced to a minimum during the acute stage as well as during early convalescence from diphtheria. Soreness of the throat is usually moderate, and swallowing not excessively painful; hence local measures such as gargles and irrigations are not advisable, as they may facilitate the absorption of toxin.

A liquid or soft diet should be prescribed, according to the patient's preference. Diet high in carbohydrate and in vitamin C is usually advised, but the basis for this has not been very well established. If the patient receives an adequate caloric and fluid intake by mouth, there is no reason for supplementing the diet with parenteral feeding.

The patient should be observed carefully for evidence of effect of the toxin on the cardiovascular system, which is usually at its height during the second week of illness. The pulse and blood pressure should be recorded frequently. In patients with hypotension it is common practice to raise the foot of the bed. (This is also good procedure in individuals with palatal paralysis, since it may help to prevent aspiration of material which collects in the throat.) Numerous methods have been employed in combating heart failure in diphtheria, but nothing seems of much benefit. Digitalization is not helpful. Injections of "Pitressin" and epinephrine are sometimes recommended for hypotension but are of questionable value. Intravenous administration of glucose solution is often advocated in treatment of patients with myocardial impairment, but there is no proof that this is beneficial. Similarly, there is no proof that therapy with adrenal cortex extracts is indicated.

Six weeks of bed rest is a minimum for patients convalescent from a severe attack of diphtheria. In cases where there has been little evidence of toxemia two or three weeks in bed is sufficient.

Treatment of Carriers. *C. diphtheriae* usually disappears from the throat between the second and fourth weeks, but in a small proportion of patients it may persist longer, despite a second course of penicillin. In such instances test for virulence of the organism is indicated; if negative

the patient need not be kept under isolation. Tonsillectomy is effective in terminating the carrier state in some instances. If these measures fail, theoretically isolation should be maintained until the throat culture is negative, but as a matter of fact experience suggests that after about six weeks patients seem to have less tendency to infect others, and there is little danger in releasing them.

Prophylaxis Against Diphtheria. Active immunization with diphtheria toxoid should be given to every child. The first immunization should be carried out at about six months of age, and the antitoxin response should be checked by a Schick test six months later. If the child is still Schick-positive, the course of immunization should be repeated. It is advisable to give a booster dose at the time of beginning school—i.e., at five or six years of age.

Active immunization of adults presents a more difficult problem because toxoid often causes severe local and general reactions in them. Unless an individual is very likely to be exposed to diphtheria, toxoid injections are not indicated after the age of 12. If the decision is made to give toxoid to an adult, the so-called Moloney test for sensitivity can be employed. One-tenth ml. of fluid toxoid diluted 1:100 or 1:200 is injected intradermally. If this provokes extensive erythema

after 12 to 24 hours, it is probable that injection of a standard immunizing dose will cause a severe reaction. It is advisable then to defer further prophylactic measures and repeat the Schick test a few weeks later, because these intradermal tests often provide antigenic stimulus sufficient to immunize the individual.

Passive immunization is occasionally of value. It may be given to the other children in a family or in a hospital ward where a case of diphtheria has developed. A dose of 1500 units of antitoxin can be expected to confer immunity for about two weeks.

Prognosis. The general fatality rate from diphtheria varies in different parts of the world from 5 to 12 per cent. The prognosis in individual cases is poor if there is an extensive membrane with marked edema and lymphadenopathy. The usual causes of death are laryngeal obstruction and circulatory failure.

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Tetanus

Edward S. Miller

Definition
 History
 Etiologic Agent
 Pathogenesis and Epidemiology
 Manifestations
 Laboratory Findings
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 Treatment

Definition. Tetanus is a severe intoxication characterized by generalized hypertonicity of skeletal muscles and convulsive seizures. The manifestations result from the action of an exotoxin produced by *Clostridium tetani*.

Sedation
 Antiserum
 Treatment of Local Lesion
 Nursing Care
 Feeding
 Other Therapy
 Prophylaxis
 Prognosis

History. Tetanus has been known since ancient times as a scourge of parturient women, newborn babies, and wounded soldiers. As recently as the eighteenth century one out of every six infants born in the Rotunda Hospital in Dub-

lin died of tetanus neonatorum. The record was no more enviable in other parts of the world. Studies beginning in 1884 demonstrated that the disease is caused by a toxin-producing *Clostridium*. In succeeding years immunologic methods were developed for the prevention of the disease.

Etiologic Agent. *Cl. tetani* is a large, motile, spore-forming, Gram-positive bacillus without a capsule. It is an obligate anaerobe and can be cultivated on artificial mediums in the absence of atmospheric oxygen. Characteristic spherical terminal spores are produced, which are highly resistant; if protected from direct sunlight, they can survive in nature for many years. Tetanus spores are often present in the intestinal contents of man and animals, and have been found in soil and street dust in many parts of the world. Under suitable conditions of growth *Cl. tetani* elaborates a powerful exotoxin. At least 10 antigen types of the organism have been distinguished, but differentiation is of no practical importance, since all of their exotoxins have the same immunologic properties.

The vegetative forms of *Cl. tetani* and the exotoxin are destroyed by heating to 65° C. for 10 minutes. Spores can be killed by autoclaving at a temperature of 115° C. for 20 minutes.

Pathogenesis and Epidemiology. The etiologic agent is carried into human tissues by contamination of a wound. A variety of lesions, both large and small, may offer a suitable haven for growth: lacerations, compound fractures, gunshot wounds, burns, frostbites, bedsores, and penetrating lesions produced by nails, human and animal bites, and insignificant slivers. Cases have resulted from the use of unsterile surgical supplies and biologic materials. Infections of the post-partum uterus and of the umbilical stump (tetanus neonatorum) were once extremely common, but have diminished in numbers with the introduction of aseptic obstetric technics. *Cl. tetani* is so ubiquitous in the human environment that almost any contaminated wound may contain the organisms.

The mere fact that *Cl. tetani* is present does not necessarily mean that tetanus will develop; local conditions in the wound must be suitable. The organisms will proliferate only in the presence of an oxidation-reduction potential far lower than that existing in normal living tissue. Such a fall in potential may occur as a result of the presence in the wound of necrotic tissue, of soil, of bits of

cloth, metal or wood, or of tetanus toxin. Once the organism begins to grow it produces toxin, and thereafter can itself maintain the conditions necessary for continued multiplication. If the conditions for growth are not optimal, tetanus spores may persist in the tissues for many months in a viable but dormant state. Some may be carried by phagocytes to distant parts of the body. If such tissues are later traumatized (as by surgical procedure), tetanus may then develop.

Tetanus bacilli grow locally in a wound, show little capacity to invade, and are in themselves harmless. They cause disease by virtue of a soluble exotoxin elaborated in the course of growth. Actually, two toxins are produced, tetanolysin and tetanospasmin. Tetanolysin has a lytic effect on red blood corpuscles in vitro, but has not been shown to contribute to the production of symptoms in tetanus. Tetanospasmin is a protein substance with potent neurotoxic properties. It is estimated that a dose of 0.13 mg. is lethal for man. The toxin acts at two points in the body: on the neuromuscular end organs, causing sustained muscle spasm, and on the motor nerve cells of the spinal cord, medulla, and pons, causing convulsive seizures. Tetanospasmin has a strong affinity for nerve tissue of susceptible animals and, when once combined with it in vivo, cannot be neutralized by any amount of antitoxin. The means by which toxin travels from the local lesion to the nervous system is still a matter of controversy. According to one theory, the toxin enters the neuromuscular end organs, passes centripetally up the axones of motor nerves to the cord, then spreads throughout the nervous system. However, recent evidence makes it seem more likely that the toxin is carried to the nervous system via the circulating blood.

Manifestations. The incubation period varies from two days to several months, but in two thirds of cases it falls within the range of 6 to 15 days. Some patients have prodromal symptoms of restlessness and headache. In others the first symptoms are those stemming from the developing muscular rigidity, with vague discomfort in the jaws, neck, or lumbar region. Among the first muscles to show involvement are those innervated by cranial nerves, particularly the fifth, seventh, ninth, tenth, eleventh, and twelfth. Spasm of the muscles of mastication causes trismus and difficulty with chewing. This highly characteristic phenomenon gives to the disease

its common name of "lockjaw." Sustained contraction of the facial muscles produces a distorted grin which is called "risus sardonicus." Spasm of the pharyngeal muscles makes swallowing difficult. Stiff neck and opisthotonus are also among the early signs. Progressively, other muscle groups become involved, with tightness of the chest and rigidity of the abdominal wall, the back, and the limbs.

The patient is conscious and mentally clear, suffering great pain from muscular spasms. There is profuse perspiration. Fever may or may not be present. The wound through which *Cl. tetani* was introduced is usually evident, although in 10 to 20 per cent of patients it cannot be found. Neurologic examination discloses hyperactive tendon reflexes, often with sustained clonus. There are no sensory changes.

In the untreated patient the symptoms and signs increase in severity for several days, then continue for a variable period. A sudden noise, a hypodermic injection, or any other stimulus may precipitate a generalized tonic convulsion of great intensity, accompanied by spasm of the larynx and muscles of respiration. The resulting acute asphyxia may end fatally. If the patient survives, the intensity of the muscle spasm begins to clear slowly during the second week, but it may be as long as several months before recovery is complete.

Occasionally *mild cases* occur in which there is only moderate muscle rigidity without tetanic seizures. Sometimes the administration of tetanus antitoxin forestalls the development of generalized tetanus but not of *local tetanus* involving the muscles around the site of injury.

Complications are frequent in tetanus. Pulmonary atelectasis is common and may be followed by pneumonia, which is especially to be dreaded, for it seriously lessens the chance of recovery. Constipation, with fecal impaction, and urinary retention are often encountered. Cystitis and pyelitis may develop in patients requiring catheterization. Compression fractures of the vertebrae may result from the convulsive seizures. Decubitus ulcers are likely to occur in patients under heavy sedation who are not turned frequently. Serum sickness may appear one to three weeks after administration of antitoxin. Foot drop and muscle contractures may follow prolonged unconsciousness with the limbs in poor position. Asphyxia from respiratory muscle or laryngeal

spasm, from massive aspiration of secretions, vomitus, or food, or from extensive pneumonia may be the immediate cause of death.

Laboratory Findings. The diagnosis of tetanus must be based on the clinical picture, for laboratory examinations are of little assistance. It is difficult to isolate the organism from the local lesion, and it is a laborious task to identify it precisely. Furthermore, the presence of *Cl. tetani* in a wound does not necessarily indicate that the patient has tetanus. The intoxication itself produces no change in the leukocyte count, but leukocytosis may accompany secondary infection. The cerebrospinal fluid is often under increased pressure, but is otherwise not remarkable. The urine is normal unless secondary urinary tract infection is present.

Differential Diagnosis. The incipient stages may resemble certain other conditions, but fully developed tetanus is likely to be confused with few other diseases. The most frequent diagnostic problem is differentiation of *serum sickness* from early tetanus. Many patients with injuries are given tetanus antitoxin; sometimes serum sickness, developing one to three weeks later, involves the temporomandibular joint, thus limiting the opening of the mouth and superficially resembling the trismus seen at the onset of tetanus. Usually arthralgia or arthritis of other joints is also present, together with urticaria, generalized adenitis, and eosinophilia. Other conditions in which trismus occurs include *peritonsillar abscess* and local infections of the mouth and cervical region. The finding of a normal spinal fluid in tetanus eliminates confusion with *meningitis*. The clinical picture of *strychnine poisoning*, with hyperexcitability of the muscles, opisthotonus, "risus sardonicus," and tonic convulsions, may closely mimic tetanus, except that the muscles are relaxed between seizures in strychnine intoxication, while spasm tends to persist in tetanus. In *rabies* inability to swallow is often an early symptom, with drooling of saliva and spasms of the muscles of deglutition, followed by fever, anxiety, excitement, delirium, hyperesthesia, and convulsions both tonic and clonic. Paryses develop, and death occurs in two to eight days. History of a bite by a dog, cat, or other animal several weeks previously is usually obtainable.

Treatment. This is a grave disease for which, unfortunately, there is no specific treatment.

Nevertheless, meticulous attention to certain supportive measures will in a number of instances change the outcome from death to recovery.

1. SEDATION. The most important feature in therapy is the continuous use of sedatives in quantities sufficient to induce partial relaxation of muscle spasm, and to prevent the dangerous acute tetanic seizure. To accomplish this, it often becomes necessary to induce a state of unconsciousness, yet one must avoid depression of respiration. Various drugs have been used, including barbiturates, paraldehyde, chloral hydrate, magnesium sulfate, and tribromoethanol, periodically alternated. "Sodium Amytal" is administered subcutaneously, or in an emergency, intravenously, in a dose of 0.25 to 0.5 Gm. Tribromoethanol is administered per rectum in a dose of 15 to 30 mg. per kilogram of body weight. Precise dosage schedules must be determined empirically, as indicated by the patient's condition.

2. ANTISERUM. As soon as the patient has received adequate sedation, he is given 100,000 units of tetanus toxin intravenously or intramuscularly, but never intrathecally. The usual tests for horse serum sensitivity must be performed beforehand. Beef serum antitoxin is available for individuals sensitive to horse serum. This dose is sufficiently large to provide a safe excess of circulating antitoxin for a month or longer. Repeated doses are not necessary except in unusual cases involving extensive, slow-healing wounds, where readministration of antitoxin may have to be considered at three- or four-week intervals. Antitoxin has no curative action in tetanus, for it has no effect on the toxin which is already combined with nerve tissue. Its only action is to neutralize newly formed toxin as it is produced in the lesion.

3. TREATMENT OF LOCAL LESION. The patient should receive sedatives and antiserum before the site of infection is manipulated. The local lesion is then treated according to the same surgical principles that would be applicable if tetanus were not present. Specifically, a limb should not be amputated simply because the patient has tetanus.

4. NURSING CARE. There is no disease in which meticulous, gentle nursing care is of greater importance. Constant attendance by special nurses is desirable. The patient should be in a quiet, darkened room, where all external stimuli such as noise, drafts, and jarring are kept

to a minimum. His position should be changed frequently. Secretions which accumulate in the pharynx should be removed by suction, and postural drainage aided by raising the foot of the bed. A padded tongue depressor should be placed between the teeth to prevent biting of the tongue during convulsions. Bedsores should be avoided by special attention to care of the skin. An indwelling catheter may be necessitated by persistent urinary retention. Enemas should be given as needed to overcome constipation and prevent fecal impaction. Foot drop and wrist drop can be prevented by suitable positioning with pillows, sandbags, or splints.

5. FEEDING. Oral feeding is contraindicated if the patient is unconscious, because of the danger of vomiting and aspiration of vomitus. Suitable quantities of glucose, saline, and amino acid solutions should be administered intravenously. It is best not to give infusions subcutaneously because the attendant pain stimulates the patient unduly.

6. OTHER THERAPY. Penicillin can be administered as a prophylactic measure against pneumonia. The drug does not neutralize tetanus toxin, but it probably aids in controlling the tetanial infection itself. If a urethral catheter is used the patient should also receive sulfadiazine daily to control infection in the urinary tract.

Tracheotomy is a highly useful procedure in selected cases, and should be employed more often in the treatment of tetanus. It is indicated in patients who have repeated episodes of laryngeal spasm.

Prophylaxis. In the prevention of tetanus it is important that contaminated wounds receive thorough and prompt debridement. In addition, either active or passive immunization is used to raise the resistance of the patient. Immediate passive protection is achieved by administering horse serum antitoxin parenterally in a dose of 1500 to 10,000 units, depending on the extent of the lesion and the lapse of time between injury and treatment. It acts by neutralizing free toxin, and has no bactericidal effect. Its use has been attended by great success; only rarely does tetanus follow serum prophylaxis. However, there are serious disadvantages to its use. It provides protection for only a week or two. A significant proportion of patients become sensitized to horse serum and may have serum sickness with the initial injection, or anaphylactic

reactions with subsequent ones. Furthermore, tetanus sometimes follows a wound so trivial that it is disregarded by the patient; or the physician may hesitate to give serum antitoxin when the lesion is insignificant in appearance.

Active immunization provides the most satisfactory type of prophylaxis. A toxoid is used, and initial immunization is achieved by giving two doses of an alum-precipitated preparation, or three doses of fluid toxoid, at monthly intervals. A booster dose is administered after one year, and thereafter at two- or three-year intervals. The antibody response to initial immunization is slow, so that if active immunization is begun at the time of injury, the patient will not get the immediate protection he needs. However, if he has previously received toxoid, a satisfactory rise in serum antibody titer will occur within two to five days after a "booster" dose; this is within the incubation period of the disease. By the use of active immunization tetanus was rendered almost nonexistent in the United States armed forces during World War II.

Prognosis. The prognosis of tetanus is very serious. The over-all fatality rate is 30 to 40 per cent. The outlook is especially grave in young children, in the aged, and in patients who develop pneumonia or other secondary infections. It is also worse if the period of incubation is short. Most deaths occur within the first 10 days of illness, and if life can be maintained through this critical period the chances of survival are good. Recovery from symptoms is complete, but does not convey permanent immunity to reinfection.

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Botulism

Edward S. Miller

Definition
 History
 Etiology
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Definition. Botulism is an intoxication resulting from ingestion of a poisonous substance produced by *Clostridium botulinum*. The illness is characterized by generalized muscular weakness, and frequently ends in death.

History. This disease was first described in Germany over 100 years ago, where it was seen in individuals who had eaten contaminated sausages. For this reason the name of the illness is

derived from the Latin word for sausage. Outbreaks of botulism have been observed in the United States for many years, chiefly in association with the consumption of inadequately processed canned foods.

Etiology. *Cl. botulinum* is a motile, Gram-positive bacillus which produces subterminal spores. It grows readily on artificial media, but only under anaerobic conditions. The organisms are natural inhabitants of the soil and are found in abundance in many parts of the world. They are frequently present on fruits and vegetables, and thus not uncommonly are carried into the gastrointestinal tracts of animals and of man.

The bacillus is not in itself pathogenic, and is harmless when present in the alimentary tract.

However, it produces an extremely potent exotoxin under suitable conditions of anaerobic growth, in a variety of foodstuffs of animal and plant origin. The toxin, called botulin, has been isolated in pure crystalline form and identified as a globulin with a molecular weight of approximately one million. There are five different immunologic varieties of *Cl. botulinum*, designated as types A, B, C, D, and E. They differ in that each produces a specific exotoxin. There are no qualitative differences in the effects of the different types of toxins, but there are marked species differences in host susceptibility to the different varieties. Only types A and B, and rarely E, have been implicated in human disease. These toxins are the most potent human poisons known. The lethal dose for man has been calculated as 0.25 microgram.

The spores can withstand boiling for as long as 22 hours, but are killed by moist heat at 120° C. in 4 to 20 minutes. The exotoxin is much more labile. It is inactivated by boiling for 10 minutes.

Pathogenesis. Botulism occurs as a result of the ingestion of toxin which has been previously formed in food. The clostridium frequently contaminates foodstuffs, but no human cases have resulted from the consumption of fresh food. However, the spores will survive and produce toxin if improper methods of preservation are employed. The products implicated are canned fruits and vegetables and canned or preserved fish and meats. Commercial packers in this country now use sterilizing technics which are adequate to destroy all spores. The chief danger lies in home-canned products, particularly when high-pressure steam methods are not employed. Because of this, most outbreaks of botulism in the United States have occurred in individual families, or other small groups of people.

Spoilage of food may be suspected because of abnormal taste, odor, gas, turbidity, or softening; but, on the other hand, there may be no observable alterations. Therefore, whenever possible, home-preserved products should be boiled for 10 minutes before use. Needless to say, any item which appears to be spoiled must be destroyed without being tasted.

Botulism is not limited to man. The disease occurs in a varied assortment of wild and domesticated animals and birds, while still others are susceptible to experimental inoculation. Outbreaks are sometimes seen in chickens, dogs, or cats, in

relation to human outbreaks when these animals are fed scraps from the table.

The only natural portal of entry for botulin is the gastrointestinal tract, though it can be shown, experimentally, that animals are far more susceptible to parenteral routes of administration. The toxin is a protein, yet it resists digestion in the alimentary tract. It is absorbed intact from the small intestine, possibly also from the stomach, but poorly from the colon. Care must be taken to prevent contact of contaminated food with cuts on the hand, for a dangerous quantity of botulin may thus be absorbed.

The principal site of action of the toxin is at the myoneural junction. The nerve impulse is interrupted, and production of acetylcholine at the junction is inhibited. The toxin also acts on parasympathetic end organs, resulting in transient stimulation followed by depression. There is no definite evidence of any effect on the central nervous system.

Manifestations. Following ingestion of botulin, there is a latent period, usually in the range of 12 to 36 hours, though it may be as short as 2 hours or as long as 14 days before any symptoms appear. The incubation period is shortened and the severity of illness increased as the size of the dose is increased.

Illness begins insidiously with fatigue, weakness, headache, and dizziness. Digestive complaints are observed in only one third of cases, and probably are due to local irritation from other substances in the spoiled food, rather than to the toxin. They consist of nausea, vomiting, upper abdominal discomfort, and diarrhea. Such symptoms subside after a few hours and thereafter there is obstipation, with abdominal distention but without tenderness or pain. Botulism is essentially a generalized paralytic disease, and these manifestations soon dominate the clinical picture. Weakness is noted during the first 24 hours in the muscles innervated by the cranial nerves. Soon it spreads to the rest of the skeletal system. Except for headache, botulism does not give rise to pain.

The patient is clear mentally, and remains so throughout the course of his illness. There is no fever until secondary infection occurs. Initially, there may be hypersecretion of the lacrimal, salivary, and sweat glands, but this is soon followed by diminished function. Early in the illness excessive vagal tone sometimes causes the pulse

rate to drop below 50 per minute. Subsequently, there is vagal depression and tachycardia. Hypotension may occur as a result of peripheral vascular dilatation.

The most significant physical alterations are seen in the nervous system. Nearly all patients exhibit cranial nerve palsies involving any except the olfactory and optic nerves. Weakness of the intrinsic and extrinsic eye muscles results in loss of the light and accommodation reflexes, mydriasis, ptosis, strabismus, diplopia, or nystagmus. The face becomes expressionless because of seventh-nerve paralysis. Chewing, swallowing, and phonation are interfered with, and the tongue cannot be controlled. The neck muscles are unable to support the head. The limbs become progressively weaker and movements may be incoördinated. Complete paralysis of a limb is rarely encountered, since death supervenes before this occurs. Pulmonary ventilation is diminished as a result of weakness of the intercostal muscles and the diaphragm, and cyanosis appears. The superficial and deep reflexes are diminished but rarely absent. The sensory system is intact.

The paralysis may progress to a fatal termination after 2 to 10 days of illness. Death results from paralysis of the respiratory muscles, from obstruction of the airway, or from attendant pulmonary infection. In nonfatal cases the muscular weakness increases over a period of 10 days; then almost imperceptibly function begins to return. The muscles involved in respiration, deglutition, and speech are the first to show improvement. Visual abnormalities persist for weeks or months. Two to six months elapse before all the symptoms disappear.

Laboratory Findings. The clinical diagnosis can be substantiated by identifying botulinus toxin either in the food or in the body of the patient. A suspected specimen is suspended in saline and inoculated into mice. If toxin is present, the animals become paralyzed, whereas control mice passively immunized with specific antiserum are protected. The toxin can occasionally be demonstrated in the stomach or intestinal contents, or in the peripheral blood during life, and in organ extracts after death. Additional evidence may be gained by culturing *Cl. botulinum* from the food, although it must not be forgotten that the organism may be a harmless contaminant.

The disease produces no characteristic changes

in the leukocyte or red blood corpuscle counts, in the urine, or in the spinal fluid.

Differential Diagnosis. Botulism may be confused with other diseases of toxic or infectious origin. One should seek a history of recent consumption of home-preserved foods, and of co-incident illness among other humans or animals that shared the food. Cranial nerve palsies and other paralytic phenomena are similarly seen at times in poliomyelitis, and in viral types of encephalitis. These diseases are accompanied by fever and by spinal fluid abnormalities. In post-diphtheritic paralysis a history of preceding sore throat usually can be obtained. The paralysis of shellfish poisoning appears a few minutes after ingestion of the seafood, and is accompanied by paresthesia, giddiness, and somnolence. In mushroom poisoning there are severe pains with marked vomiting and diarrhea. Intoxication with the belladonna group of alkaloids leads to fever, tachycardia, and delirium. An overdose of curare results in the rapid onset of widespread paralysis, with death or recovery in the course of minutes or a few hours.

Treatment. Botulism is most satisfactorily controlled by prevention, for methods of treatment are inadequate. Practically all cases of human botulism are due to either type A or type B toxin, and a bivalent antitoxin is available for prophylaxis and for therapy. When the diagnosis is suspected on clinical grounds, the antitoxin should be administered immediately by the intravenous route in a total dose of 100,000 units. The antiserum will not reverse the effects of toxin which has already damaged the myoneural junction, but it will neutralize toxin which has not yet been fixed by the receptor cells. Early administration, therefore, is important. The same dose is given prophylactically to other individuals who have eaten the contaminated food but have not yet developed symptoms.

The patient should be kept at strict bed rest, in order to conserve his strength. There may be residual toxin in the gastrointestinal tract; therefore, it should be emptied by gastric lavage, by enema, and by catharsis. Animal experiments would indicate that fall in blood pressure should be counteracted most effectively by the use of the vasoconstrictor drug, "Paredrine Hydrobromide," 10 to 20 mg., subcutaneously.

Strenuous measures may be necessary to fore-

stall death from pulmonary infection or respiratory failure. When the swallowing reflex is lost, oral feeding becomes dangerous and must be replaced by tube feeding or by intravenous alimentation. Pharyngeal secretions are removed by suction. Penicillin is administered prophylactically. Narcotics, sedatives, and other respiratory depressants are strictly contraindicated, even though patients are often apprehensive and restless. If laryngeal paralysis causes obstruction of the airway, tracheotomy may be necessary. With the approach of respiratory insufficiency, the patient should be placed in a mechanical respirator.

Prognosis. The fatality rate of 65 per cent indicates the grave nature of botulism and the inadequacy of therapy. If a patient survives the first 10 days of illness, his chances of recovery are good. Though convalescence may take as long as six months, it leads eventually to complete restoration of function.

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Section 10—Mycobacterial Infections

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Tuberculosis

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DEFINITION

Tuberculosis is an infectious disease of protean manifestations, which is widespread among both man and animals. The initial lesion is usually located in the lung, and from it tubercle bacilli may spread by intrabronchial dissemination, or by direct extension; or they may be carried in the blood stream to many organs throughout the body, causing destructive lesions at the time of dissemination or after long periods of latency. In the majority of individuals the primary infection becomes arrested, but it causes alterations in the immunologic state of the host which modify the response of the tissues to subsequent reinfection or to exacerbation of the primary infection. Pathologically, varying degrees of exudation, production, tubercle formation, necrosis, and fibrosis are observed, depending on the organ involved, the number of infecting bacilli, the virulence of the organisms, and the immunologic state of the patient.

HISTORY

The discovery of lesions involving the bones of a Neolithic man and of Egyptian mummies indicates that man has been afflicted with tuberculosis during much of his evolutionary development. The contagiousness of tuberculosis was recog-

nized by Aristotle, and the name "phthisis" was conferred by Hippocrates because of the marked bodily wasting produced by the disease. An important advance occurred in 1819 when Laennec asserted in his treatise on the use of the stethoscope that tubercles, wherever present, were manifestations of a single disease process. This disputed doctrine was supported by the inoculation experiments of Villemin in 1865, and was finally proved by the discovery of the tubercle bacillus by Koch in 1882. Subdivision of the tubercle bacilli pathogenic for man into three types followed, the avian bacillus being isolated by Magucci in 1890, and human and bovine types being differentiated by Theobald Smith in 1898.

Following centuries of fanciful therapeutic regimens, the value of bed rest and sanatorium care was demonstrated by Dettweiler, whose sanatorium was opened in Germany in 1876. Although not the first to perform the procedure, Forlanini is credited with establishing and perfecting the technic of artificial pneumothorax, beginning in 1888. The efficacy of pneumothorax was enhanced by the recognition by Ascoli, in 1912, that better results were obtained with negative (less than atmospheric) than with positive intrapleural pressures; and by the introduction of pneumonolysis by Jacobaeus in 1913.

De Cerenville's resection of ribs to collapse the lung of a tuberculous patient in 1885 was the forerunner of the modern type of thoracoplasty. Modifications and additions soon followed: multiple stage operations and subperiosteal resections were introduced by Brauer about 1910; Sauerbruch, in 1909, found it feasible to remove the first rib; and apicolysis was added by Semb in 1930.

A most important development in the history of tuberculosis was the discovery of streptomycin by Waksman and his associates in 1944. The

early studies of Hinshaw and Feldman indicated that streptomycin possesses therapeutic potentialities unapproached by earlier chemotherapeutic agents, and the clinical uses and limitations of this antibiotic gradually are being elucidated.

PREVALENCE AND INCIDENCE

Tuberculin surveys and autopsy studies 50 years ago indicated that virtually 100 per cent of the population was infected prior to the age of 20. The situation has changed considerably since that time; in the United States, for example, tuberculin surveys now reveal only 20 to 30 per cent of positive reactors in young adults, and it is estimated that only approximately 50 per cent of the total population is infected. Skin hypersensitivity is known to disappear in a certain percentage of individuals, and, consequently, autopsy studies yield higher figures than tuberculin surveys. Post-mortem studies reported by Carnes in Baltimore in 1942 showed that 90 per cent of the adult population of that city had been infected. Autopsies performed by Medlar in New York City from 1944 to 1946 revealed figures considerably lower than this for young adults, but the incidence of infection in individuals over 50 years of age was above 80 per cent. These studies indicate that the decline in the incidence of infection has occurred chiefly among the younger age groups. It also appears that the over-all decline in the incidence of infection is less striking than the marked decrease in the mortality rate.

The *morbidity*—i.e., the frequency of actual tuberculous disease—is difficult to estimate accurately, but most authorities agree that it is in the neighborhood of 0.5 to 1.0 per cent, or that there are approximately 500,000 to 1,000,000 active cases in the United States today. Of those drafted for military service in World War II, 0.3 per cent were found to have active tuberculosis; in the general population, the figure is higher than this in older age groups. Thus, although half the total population is infected, clinically significant disease develops in only a relatively small number of individuals. This ability to withstand and arrest tuberculous infections in the great majority of instances is indicative of a generally high degree of native resistance. It should be pointed out, of course, that factors

which lower native resistance, such as malnutrition and overwork, are minimized under modern living conditions.

There has been a striking decline in the *mortality rate* from tuberculosis during the past 50 years. From first place in 1900 with over 200 deaths per 100,000 population, tuberculosis by 1940 had fallen to seventh place as a leading cause of death, with a mortality rate of only 45.9 per 100,000. It is generally agreed that the most important factor in this decline has been the improvement in living standards, with better nutrition and housing, shorter working hours, and earlier diagnosis and treatment. Tuberculosis remains, however, one of the major causes of death in young adults, accounting in 1940 for 18.6 per cent of all deaths in persons from 15 to 24 years of age, and for 14.3 per cent of deaths among individuals from 25 to 44. As a matter of fact, except for deaths due to accidents, tuberculosis remains the leading cause of death in the age group 25 to 44.

Mortality from tuberculosis is lowest in the Middle West, higher in the West, and highest along the Eastern Seaboard. The disease is especially common in congested urban areas, and among low-income groups. In 1940, tuberculosis caused 5.4 per cent of all deaths in the United States in the white race, 11.3 per cent in the Negro, and 21.8 per cent among the Indians. Forty-two per cent of patients dying of tuberculosis were 45 or older, as compared with the figure of 24.4 per cent in 1900. Thus, although tuberculosis remains a leading cause of death in young adults, there is an increasing tendency for fatalities to occur in higher age groups. Another interesting trend is the decrease in deaths due to disseminated forms of tuberculosis. In 1910, 13.4 per cent of deaths were attributed to disseminated forms; by 1940 this figure had dropped to 8 per cent.

Despite the decline in the mortality rate, the *fatality rate* for tuberculosis remains high. In other words, a relatively high percentage of patients who contract the disease eventually die of it. It is estimated that there are approximately 10 active cases for each annual death; in 1945, for example, there were 52,398 deaths for an estimated 500,000 active cases. In addition to 10 active cases for each annual death, it is estimated that there are another 10 individuals with inactive disease.

ETIOLOGY

Three types of tubercle bacilli—human, bovine, and avian—are known to infect man. The latter is of the least importance; only a small number of proved cases of avian infection have been reported in humans. Morphologic and cultural differences between the three types are somewhat variable, and animal inoculation is resorted to for positive identification. The human type causes disease in the guinea pig but not in the rabbit, the bovine type in both the guinea pig and the rabbit, and the avian type in birds and rabbits, but not in the guinea pig. Atypical strains are encountered occasionally. For example, a strain with the usual cultural characteristics of the human type may cause disease in the rabbit as well as in the guinea pig; in this case inoculation of calves, which are highly resistant to the human type, is helpful in making a definite differentiation.

The tubercle bacillus is a rod, about 1.0 to 4.0 microns in length and 0.3 micron in thickness. Beaded and granular forms have been observed with both modified Gram and acid-fast stains, but recent evidence indicates that many of these forms are artefacts of the staining process. True granular forms do occur, particularly in older cultures, and are identified by their red rather than purple color, lack of distention of the cell wall, and failure to disappear with the addition of alcohol. Evidence for a filtrable virus or zoogloal stage in the life cycle of the tubercle bacillus is not entirely convincing; for the present it must be assumed that reproduction occurs by fission. The distinguishing tinctorial property of the tubercle bacillus—namely, its ability to resist decolorization by acid alcohol when stained with basic fuchsin—is known to be related to the waxy component, and probably specifically to mycolic acid. Curiously, the structural integrity of the cell is also involved, for grinding the bacilli between glass slides destroys acid-fastness, whereas prolonged extraction with fat solvents does not.

Avirulent dissociates of virulent strains of tubercle bacilli may be produced by appropriate cultural technics, and occasionally tubercle bacilli of unusually low virulence for laboratory animals have been isolated from man. It has not been definitely established, however, that true dissociation can occur in the human body. A

simple morphologic differentiation between virulent and avirulent dissociates has been described by Middlebrook and Dubos—namely, that virulent cultures grow in long, tightly formed cords, with individual bacilli parallel to each other, whereas avirulent organisms are haphazardly arranged and show no tendency toward cord formation.

Chemically, the tubercle bacillus is unique in its high lipid content, which makes up one fourth to one third of its dry weight. The lipids are composed of phosphatides, acetone-soluble fats, and waxes. These substances probably account for the unusual resistance of the tubercle bacillus to bactericidal agents, to drying, and to wide temperature variations. They are not, however, as was once thought, situated on the surface of the cell as a thick capsule, but are distributed throughout the body of the bacillus.

Tubercle bacilli are strict aerobes, and are usually isolated on solid mediums containing as their principal ingredients potato, egg yolk, and glycerin. Growth is slow, four to six weeks being required for colonies to develop. Because of their high lipid content, tubercle bacilli are hydrophobic, and grow in clumps on the surface of ordinary liquid mediums. Dubos has developed a liquid medium containing a complex ester of oleic acid, "Tween 80," which coats the bacilli, making them hydrophilic, and provides rapid, diffuse, submerged growth. The diagnostic and investigative potentialities of this medium are great, and are being explored in many laboratories.

TRANSMISSION

Inhalation of air containing tubercle bacilli is the most important means of acquiring tuberculous infection in man. The bacilli may be transmitted in droplets of saliva or sputum as a tuberculous subject coughs or expectorates in the presence of others. Transmission also may occur from inhalation of particles of dust laden with viable organisms, a method which is possible because of the peculiar resistance of the tubercle bacillus to desiccation and exposure. Tubercle bacilli are killed within a few hours in direct sunlight, but survive up to five days in a well-lighted room, up to five months in the dark, and as long as a year and a half in the refrigerator.

In addition to inhalation, tubercle bacilli may enter the mouth and pharynx by direct or indi-

rect contact with infected material. Tuberculous food handlers, for example, may deposit organisms on food or eating utensils, which are then placed in the mouths of uninfected subjects. Similarly, tuberculous sinuses, and urine and feces, may occasionally be sources of infection. Kissing is an example of transmission by direct contact, and is probably an important source of infection in infants. Dogs are susceptible to both the human and the bovine bacillus, and may occasionally transmit tuberculosis. Cats are said to be highly resistant to the human type of bacillus but susceptible to the bovine form. Placental transmission of tuberculosis in the human does occur but is of negligible significance because of its rarity and its uniformly fatal outcome within a few weeks after birth.

The various sources of infection described above apply chiefly to the human bacillus, which is responsible for over 95 per cent of tuberculous infections in this country at the present time. The intensive campaign of the last 40 years to destroy tuberculous cattle and to encourage pasteurization of milk has practically eliminated the milk-borne bovine type of tuberculosis in the United States. In other countries, such as the British Isles, ingestion of contaminated milk is still responsible for a large number of cases of cervical adenitis and abdominal tuberculosis, especially in infants and children. Infection of the lungs by the bovine bacillus is uncommon, even in areas in which it is responsible for a high incidence of intestinal tuberculosis. Cummings, for example, recovered bovine bacilli from only 17 of 1269 cases of pulmonary tuberculosis in a section of England where bovine infection was prevalent. The tubercle bacillus is destroyed by boiling in water for two minutes, or by pasteurization at 60° C. for 20 minutes. The likelihood of contracting the disease from eating tissues of infected animals is small, since tubercle bacilli do not survive the temperature at which meat ordinarily is cooked.

PATHOLOGIC ANATOMY

This subject is considered exhaustively in textbooks of pathology; a brief summary of the broader aspects will provide adequate reorientation for the purposes of this discussion. In general, two types of tissue response predominate in tuberculosis—namely, exudative and productive. They may exist separately or in combination.

According to Pinner, exudative reactions tend to occur in association with loose tissue structure, large doses of highly virulent organisms, and bronchogenic spread to parenchymal tissues. Productive reactions are commonly observed with small doses, low virulence, and firm tissue structure, and in lesions in interstitial tissues resulting from hematogenous dissemination.

In the exudative lesion in the lung, polymorphonuclear leukocytes, large mononuclear cells, and fibrin infiltrate the alveolar spaces. After a variable period of time this pneumonic type of lesion may undergo partial or complete resorption, or it may caseate. If caseation occurs, areas of caseous pneumonia become liquefied, beginning at their centers, a process which leads to cavitation, with liquefied leukocytes and exudative material being expelled as sputum. Caseous areas may also be replaced gradually by fibrosis and calcification. The fibrosis following exudation is often greater than that associated with productive lesions which by their very nature are fibrotic. It should be emphasized that the exudative reaction may be misdiagnosed easily, even by histologic examination, since epithelioid cells, Langhans' giant cells, and caseation may be absent.

In contrast to the exudative lesion, formation of the productive lesion or tubercle involves growth of new granulation tissue, supported by a definite reticulum which pushes the normal tissue aside. The tubercle consists of Langhans' giant cells, epithelioid cells, and a surrounding layer of lymphocytes. Later, the granulation tissue making up the tubercle forms a fibrous capsule around the periphery, differing in this respect from the exudative lesion, in which the surrounding fibrosis is produced by collagenous tissue normally present in the peribronchial, perivascular, and septal spaces. Once formed, productive reactions rarely undergo resolution to the extent observed with exudative lesions. The tubercle may gradually undergo complete fibrosis, or it may caseate in essentially the same manner as the exudative lesion. The caseous tissue may gradually become inspissated and later calcified, or liquefaction and cavity formation may supervene.

Rarely, primary tissue necrosis may occur in tuberculous infection. This is observed in the so-called "acute caseating miliary tuberculosis," and presumably results from the sudden hema-

togenous dissemination of large numbers of tubercle bacilli in extremely hypersensitive individuals.

IMMUNITY

Native Resistance. Man possesses a relatively high degree of native resistance to tuberculosis, as manifested by his ability to arrest the infection in the great majority of instances. Susceptible animals, such as the guinea pig, possess much less native resistance, and almost invariably succumb to the disease. It is probable that no differences in actual native resistance exist among various white races; the higher mortality rate in this country of city-dwelling Irish, as compared with Jews, is most likely due to a long period of natural selection of resistant individuals among the latter. Negroes and Indians, on the other hand, possess distinctly lower native resistance than whites. This is evidenced chiefly by a less favorable clinical course, a higher mortality rate, and a greater tendency toward enlargement and caseation of the hilar lymph nodes when the disease occurs in adults.

Heredity. In addition to racial differences, there are undoubtedly great individual variations in resistance to tuberculosis which, to some extent at least, are influenced by heredity. Animal experiments with inbred families indicate that resistance is dominant over susceptibility. In humans, the studies of Kallmann and Reisner demonstrate a close concordance in morbidity and mortality in tuberculosis in monozygotic twins. These studies indicate that whereas the calculated expected tuberculosis morbidity of the general population is 1.37, for monozygotic twins it is 87.3. Other evidence, such as the relative infrequency of infection in the consorts of tuberculous patients, the fact that some but not all children of tuberculous parents contract the disease, and the relatively small percentage of individuals infected who develop manifest disease, has persuaded some students of the problem that heredity is the chief factor in determining the occurrence of clinical tuberculosis. These arguments for the dominant role of heredity are countered by the close correlation of tuberculous mortality with economic and hygienic alterations, so clearly demonstrated during wartime, which indicate that environmental influences causing fluctuations in native and acquired resistance are certainly of the greatest importance.

As in many other fields, the relative influence of heredity and environment cannot be finally stated at present.

Sex. Marked differences in mortality from tuberculosis are observed in the two sexes. The total mortality rate is higher in males, but in certain age periods deaths occur much more frequently in females. Little difference is observed up to the time of puberty, but from the ages of 15 to 30 the mortality rate among females is considerably higher than that of males. This difference is somehow associated with menstruation and childbearing, but the specific factors involved, hormonal and otherwise, are not known. After the age of 30, when the incidence of pregnancies is decreased, and men are more exposed to occupational stresses which tend to lower resistance, the male mortality rises considerably above that of the female, and remains so until about the age of 60, following which the curves tend to approach each other again. It is of interest that in certain rural areas with a relatively high birth rate in women over 30, the predominance in female mortality is prolonged past the third decade.

Age. In relation to the total number of individuals infected at any age period, tuberculosis is more highly fatal during the first year of life than at any other time. From one to five, the mortality rate is lower than during the first year, but remains appreciably above that of subsequent age periods. The high mortality rate of infants and young children is probably related to a large infecting dose of bacilli, and to deficiencies in the ability to develop acquired resistance. From the age of five until puberty, the mortality rate is the lowest of any age period. This may be due to the full development of immune mechanisms and the relatively sheltered life children lead at this time; there is no evidence of a specific increase in the native resistance of the school-age child. During puberty, a specific lowering of resistance does appear to occur, which, together with the stresses and strains of earning a living and of childbearing, accounts for the abrupt rise in mortality in adolescents and young adults. The mortality rate remains high throughout adult life, despite the fact that native resistance appears to be as high as at any other period (Rich). It seems paradoxical that, although pathologic lesions observed in children are indicative of a degree of native resistance which is lower than

that of adults, the relative mortality from tuberculosis is higher in adults than in children from the ages of 5 to 12. The explanation, according to Rich, probably lies in the greater exposure of adults to influences that tend to depress resistance, again emphasizing the importance of environmental factors.

Acquired Resistance. The basic facts concerning the altered response of the tissues to reinfection in tuberculosis are well illustrated by the Koch phenomenon. Koch observed that cutaneously inoculated guinea pigs slowly developed an indolent ulcer at the local site, with rapid spread to, and marked enlargement of, the regional lymph nodes, and eventual death from generalized tuberculosis. In contrast, animals previously infected developed much more rapidly, within a day or two, an intense local skin reaction followed by ulceration and healing. Spread from the local site was greatly inhibited, and there was little involvement and enlargement of the tributary lymph nodes. Subsequent experimentation has confirmed and elucidated the chief characteristics of the lesion of reinfection, which are as follows: (1) An intense local inflammatory reaction, which develops much more rapidly than with the primary infection; (2) suppression of multiplication of the organism; and (3) inhibition of spread of the bacilli, with little or no involvement of the regional lymph nodes, and a greatly decreased tendency toward hematogenous dissemination.

Correlated with these observations is clear-cut evidence of protection, manifested by increased survival time and less involvement of the organs of immunized animals as compared with non-immunized controls. Unfortunately, susceptible animals invariably die of tuberculosis in spite of immunization, a situation which differs sharply from the almost 100 per cent survival of immunized animals with many other infections. Thus the degree of acquired resistance in experimental tuberculosis is not sufficient to give complete protection, but is easily demonstrable and confers a definite, limited increase in the ability to withstand subsequent reinfection.

Controlled observations of survival time are not possible in man, but here, as in animals, there is well-documented evidence of the development of a limited degree of acquired resistance as a result of immunization with living, dead, or attenuated tubercle bacilli (BCG). The evolution

of the great majority of primary infections is one convincing demonstration of acquired resistance in man. Having gained a foothold, tubercle bacilli multiply freely for a time in the primary focus and its regional lymph node component. Then, as acquired resistance makes its appearance, a further increase in the number of bacilli is inhibited, and some or all of them are destroyed and disappear. This phenomenon can be explained only by the assumption that some immune mechanism comes into play which restrains the further proliferation and spread of the infecting organisms. Another demonstration of acquired resistance in man is the infrequency with which a secondary primary complex appears, once the initial one has been formed and arrested. Exceptions have been described, but they are rare and would appear to occur in individuals whose resistance has, for some reason, declined to the point where the immunologic state of the tissues is similar to that which existed prior to the initial infection. Other evidence indicates that acquired resistance not only alters the response of the tissues, but also acts in some instances actually to prevent the development of subsequent reinfections. This is demonstrated by the relative infrequency with which tuberculin-positive children, living in close contact with open cases of tuberculosis, develop new pulmonary lesions from exogenous reinfections. Finally, the results of BCG vaccination (to be discussed in detail later) offer at least suggestive evidence of the development of acquired resistance following immunization.

Role of Hypersensitivity. The role of tuberculin hypersensitivity in acquired resistance has long been a subject of controversy. The delayed tuberculin type of hypersensitivity, which differs in a number of important respects from anaphylaxis and the pollen type of hypersensitivity, appears together with acquired resistance a few weeks after the onset of a tuberculous infection, and represents essentially a hypersensitivity to tuberculoprotein. Down through the years an impressive mass of evidence has accumulated, indicating that tuberculin hypersensitivity plays a major role in the development of acquired resistance to tuberculosis. When it was found that, contrary to virtually all other infections, protective antibodies apparently played no role in immunity to tuberculosis, it became necessary to search for other mechanisms which could ac-

count for the manifestations of acquired resistance described above. It was observed that tuberculin hypersensitivity, which appears at approximately the same time as acquired resistance and undergoes apparently parallel fluctuations, gives rise to an intense local inflammatory reaction capable of immobilizing bacilli at the local site. The significance of this observation was emphasized when it was found that foreign proteins in general tend to be immobilized at the site of injection in experimental animals previously sensitized to those proteins. From this evidence the theory arose that, since humoral mechanisms were apparently lacking, and immobilization of bacilli could be accounted for on the basis of an acute local inflammatory reaction, acquired resistance in tuberculosis could be attributed largely to the presence of tuberculin hypersensitivity.

This view, supported by the experiments of Krause and others in this country, became generally accepted. However, beginning about 1929, Rich and his associates, and later others, introduced evidence which cast considerable doubt upon the importance of tuberculin hypersensitivity in the functioning of acquired resistance. Specifically, it was shown that immobilization of bacilli at the local site occurs not after, but prior to, the appearance of the local inflammatory reaction. Further, in desensitization experiments it was demonstrated that the ability to inhibit proliferation and spread of the bacilli was in no way impaired when the local hypersensitive inflammatory reaction was abolished altogether; indeed, the resistance of the desensitized animals often appeared to be greater than that of the hypersensitive controls.

These observations have been confirmed repeatedly, and have been extended by Rich and his associates to a number of other infections. Taken together, the above evidence would seem to indicate that tuberculin hypersensitivity is a phenomenon which appears at approximately the same time as acquired resistance, but is not responsible for its operation, and at times may even be harmful because of tissue destruction caused by the intense inflammatory reaction. Rich's views on the subject are concisely summarized in the following statement: "Hypersensitive inflammation has never been satisfactorily shown to be necessary for the successful operation of acquired immunity at any stage of

any infection under any condition whatsoever."

Clinical observations are entirely in accord with this point of view. The early hopes that hypersensitivity would closely parallel the patient's resistance to tuberculosis and be of important prognostic value have not been realized. On the contrary, in some individuals, particularly Negroes, marked hypersensitivity appears to be associated with an unusually low degree of acquired resistance. Evidence that measles, pregnancy, and the terminal stages of tuberculosis cause a lowering of hypersensitivity, and therefore of acquired resistance, is not convincing. The diminished tuberculin hypersensitivity noted in these conditions is probably due in most instances to a nonspecific depression of the reactivity of the cutaneous capillaries. Clinical experience has proved time and again that the correlation between tuberculin skin hypersensitivity and the clinical course is not sufficiently close to allow reliable predictions concerning prognosis.

Tuberculin therapy was at one time practiced widely, and still has its advocates. One scheme is to administer small doses, hoping to increase hypersensitivity. In view of what has been said concerning the relation of hypersensitivity to acquired resistance, this would appear a futile approach. Tuberculin also is given in gradually increasing doses, in an attempt to desensitize the tissues to tuberculoprotein. This procedure seems rational, but is regarded by most authorities as impractical and dangerous because of the severe focal and constitutional reactions caused by excessive doses. The clinical results achieved are not often sufficiently striking to warrant these risks. One hesitates to condemn tuberculin therapy altogether because of the favorable results occasionally reported, especially in tuberculosis of the skin and eye, where the lesions are under direct observation. If it is to be given, however, tuberculin should be administered under controlled conditions, using carefully graded doses.

Mechanism of Native and Acquired Resistance. The basic mechanisms underlying native and acquired resistance to the tubercle bacillus are unknown. Native resistance seems to be determined by conditions existing within the mononuclear phagocytes, in which large numbers of tubercle bacilli become segregated soon after entering the body. In the susceptible body, bacilli

multiply freely in the monocytes, while in the natively resistant body the environment is, for some unknown reason, unfavorable, causing the organisms to be inhibited and gradually to die. The factors responsible for inhibition of tubercle bacilli in the phagocytes of the resistant body, and for their survival and proliferation in the susceptible host, constitute one of the major unsolved problems of tuberculous infection.

In acquired resistance, humoral immunity has not been found to play the important role it does in most other infections. Humoral antibodies have been demonstrated repeatedly in animals and patients infected with the tubercle bacillus, but they appear irregularly, do not increase the resistance of normal animals to tuberculosis, and have not been found *in vitro* to render tubercle bacilli more easily phagocytized by opsonization. In contrast to these negative findings with humoral antibodies, it has become well established that tubercle bacilli are more readily inhibited and destroyed in the phagocytes of immunized than of nonimmunized animals.

As a result of these observations, a theory of specific cellular immunity has arisen, which postulates that alterations occurring within the phagocytes themselves play the major role in the operation of acquired resistance. This theory is supported by the experiments of Lurie, showing rapid mobilization of macrophages at the site of infection in immunized animals, with marked inhibition of bacilli occurring apparently without the aid of antibodies. Convincing as these demonstrations may be, they should be regarded with skepticism, in view of the association between protective antibodies and acquired resistance in virtually every other infection. It is possible that appropriate methods for demonstrating the role of antibodies are simply not yet available, a situation similar to that which existed with syphilis and malaria until recent years. It is not unlikely that appropriate methods will show that in tuberculosis, too, humoral immunity plays a role in acquired resistance.

PATHOGENESIS

Primary Tuberculosis. The initial site of infection of the body tissues by the tubercle bacillus is called the primary focus. Most tissues exposed to direct contact with bacilli are protected by local mechanical defenses under ordinary circumstances, but may become infected when these de-

fenses are broken. Thus, the primary focus is observed occasionally on the fingers, on ear lobes that have been pierced, on the prepuce following ritual circumcision, on the tonsils, and on the conjunctiva. In countries in which tuberculosis in cattle is still common, the initial lesion is frequently located in the intestinal tract. In the study of Blacklock in Glasgow, autopsies of 283 children revealed a primary infection in the lung in only 61.1 per cent, and in the intestinal tract in 35.7 per cent. In the United States, in contrast, well over 95 per cent of primary infections occur as a result of inhalation of contaminated air, and the primary focus is located in the lung.

This focus, often referred to as the "Ghon focus," is usually situated near the pleura, and occurs most frequently in the best-aerated portions of the lung, the upper part of the lower lobe, or the lower part of the upper lobe. Initially exudative in character, the primary focus rapidly undergoes caseation. Tubercl bacilli escape freely from this focus and are carried by the lymphatics to the tributary bronchopulmonary and tracheobronchial lymph nodes, which become greatly enlarged and undergo exudation and caseation similar to that of the parenchymal focus. The combination of the primary focus and the enlarged caseous regional lymph nodes is commonly referred to as the "primary complex." Roentgenologically, the most characteristic feature of the primary complex as it is observed in infants and children is the marked enlargement of the bronchopulmonary and tracheobronchial lymph nodes draining the primary focus. In many instances the parenchymal focus cannot be distinguished from the lymph node component on the x-ray; in others, a characteristic dumbbell-shaped shadow is seen with a narrow zone of lymphatic drainage connecting the parenchymal and lymph node components.

In recent years, with the declining incidence of infection, it has become increasingly common for individuals to attain adult life without contracting a primary tuberculous infection. It is a curious fact, however, that in white adults who develop presumably primary parenchymal tuberculous foci, it is unusual to observe the x-ray enlargement of the tracheobronchial lymph nodes so characteristic of primary infections in childhood. Both from the standpoint of x-ray appearance and clinical course, lesions in recently tuberculin-negative adults are indistinguishable

from those clearly due to reinfection tuberculosis, presently to be described. Exceptions have been observed, but are uncommon in view of the large number of individuals who now presumably reach adulthood without having been infected by the tubercle bacillus. In Negroes, on the other hand, typical primary complexes are observed in adults as well as in children. This racial difference suggests that an age-determined native resistance may modify the characteristics of primary infections in white adults as compared with children, while in Negroes, who have a lower degree of native resistance, the age-determined difference is lacking. The crux of this problem lies in the determination of whether lesions observed in recently tuberculin-negative white adults actually represent primary infections, or are merely reinfections in individuals who have lost their skin hypersensitivity. Further clinical and pathologic studies are needed.

Deviations from the classic primary complex have been described by Terplan. The parenchymal focus and the lymph node component have been observed to occur separately, each in the absence of the other, and new typical primary complexes have been noted in lungs in which the true initial complexes are in a relatively advanced state of healing.

In the great majority of instances the primary complex undergoes gradual healing, with encapsulation of the parenchymal and lymph node components, and eventual calcification which may progress to true bone formation. By x-ray the lesions gradually recede from the periphery, and eventually result after a year or more in small areas of calcific density, usually less than 1 cm. in diameter. Bacteriologically, in over 80 per cent of adults who have arrested a primary infection in childhood, the calcified primary complex is sterile. In these instances the possibilities of endogenous exacerbation are not completely excluded, however, for tubercle bacilli may remain viable in lesions beyond the confines of the primary complex *per se*, such as the paratracheal or upper mediastinal nodes.

In a small percentage of cases there is progression of the primary complex, which accounts for most of the fatalities in infants and children. Progression occurs in the following ways: (1) direct extension or intrabronchial spread from the primary focus; (2) massive lymph node caseation with rupture of a node into a bronchus,

resulting in tuberculous pneumonia; and (3) hematogenous dissemination from either the parenchymal or the lymph node component. Hematogenous dissemination occurs frequently during the course of primary tuberculosis, and may result in the full-blown picture of miliary tuberculosis, with death in a few weeks, or may merely give rise to seeding in various organs. Seeding is common in the upper parts of the lungs, where the lesions, which appear on the x-rays as small, indistinct areas of density, have come to be called Simon foci. These foci tend to heal with fibrosis and calcification, and are often recognizable, in roentgenograms taken years later, as nodular fibrotic and calcific apical densities. Focal hematogenous lesions in other organs may regress and heal, or they may lie dormant for many years, and eventually cause progressive destructive lesions.

Reinfection Tuberculosis. In contrast to the classic form of primary tuberculosis in children, tuberculosis in the adult is regarded as usually being reinfectious in character; i.e., infection in individuals whose immunologic state and tissue response have been altered by previous contact with the tubercle bacillus. The basic manifestations of this altered response are, as indicated in the section on Immunity, an intense local inflammatory reaction, suppression of proliferation of the bacilli, and inhibition of their spread. These features are observed in cases of reinfection tuberculosis in human beings just as they are in experimental animals in the Koch phenomenon; in fact, adult reinfection pulmonary tuberculosis (*phthisis*) is in essence, as pointed out by Pinner, a Koch phenomenon in the lung. There is an intense local reaction of the tissues with a tendency to chronicity, marked fibrosis, excavation, and restriction in the involvement of the tributary lymph nodes.

Reinfection tuberculosis in the adult has its inception usually in a small caseopneumonic focus which is located most frequently in the posterior portion of the upper lobe; less commonly, it may be present in the apical portion of a lower lobe. When large enough to be roentgenologically demonstrable, but while the patient is still asymptomatic, this lesion may be seen as a small area of density with indistinct borders located most frequently in the infra-clavicular region between the first and third anterior ribs. Minimal in extent, this focus is com-

monly referred to as an "early infiltrate," or "Assmann focus." For historical accuracy it should perhaps be stated that the lesions described by Assmann were larger than those now regarded as early infiltrates, and were observed in patients who had symptoms. Assmann, however, deserves credit for being among the first to recognize the phthisiogenetic significance of unstable, exudative infraclavicular infiltrations.

One of the unsolved problems of tuberculosis is the source of the tubercle bacilli which are responsible for the early infiltrate. Broadly, there are two main possibilities. One is inhalation of bacilli from without, giving rise to an entirely new infection in the upper portion of the lung—i.e., the establishment of a true exogenous reinfection. The other possibility is local exacerbation, or transmission to the local site of bacilli which have lain dormant somewhere in the body for varying periods following subsidence of the primary infection; this is known as endogenous exacerbation. Tuberculous foci which may be potential sources of endogenous exacerbation following a primary infection probably exist in the body in two principal locations. One consists of apical nodular foci, remnants of the so-called Simon foci resulting from lymphohematogenous dissemination during the active primary phase. With reactivation, there may be extension by contiguity in a caudal direction, or extension to the infraclavicular region may occur, presumably as a result of intrabronchial spread. The other chief focus which may be responsible for endogenous exacerbation is the lymphatic system draining the primary complex, including the hilar, parastracheal, and mediastinal nodes. From this focus tubercle bacilli are presumably carried to the lung parenchyma by lymphohematogenous dissemination. A vast literature has sprung up concerning these possibilities of exogenous reinfection and endogenous exacerbation. The matter is important for practical as well as theoretic reasons, for if phthisis is largely exogenous in origin the main factor in prevention would be avoidance of contact. If, on the other hand, most cases of pulmonary tuberculosis in adults result from endogenous exacerbation of old primary infections, the chief emphasis should be placed on factors which tend to minimize such exacerbations, and which will maintain resistance at the highest possible level. Unfortunately, at the present time the relative frequency with which exog-

enous reinfection and endogenous exacerbation are responsible for the early infiltrate is not known, and the methods for settling the matter are not available. Indirect evidence indicates that both methods probably occur, but speculation as to which is the most important appears to be futile. For the present, programs aimed at eradication of the disease should include the important preventive measures concerned with both possibilities.

Adult tuberculosis as discussed in the preceding paragraphs is assumed to be largely reinfectious in nature. It should be stated again, however, that an increasingly large number of individuals are reaching adult life without having been infected by the tubercle bacillus. It is reasonable to assume, therefore, that an increasingly large number of cases of adult tuberculosis will be instances of primary infection, and unequivocally exogenous in origin. As indicated in the section on the primary complex, it is difficult at present to distinguish clinically and roentgenologically between primary and reinfection tuberculosis in adults. This entire subject needs further clarification.

Pulmonary tuberculosis in the adult usually, but not invariably, begins as an early infiltrate. In an occasional instance aspiration tuberculous pneumonia may follow the rupture of a caseous hilar lymph node; this is seen with increasing frequency in older individuals. Clinically suggestive but not proved evidence also indicates that pneumonic lesions may develop when a large inoculum of bacilli is carried suddenly to a portion of the lung from some endogenous focus. Contiguous spread in an apicocaudal direction from nodular foci at the extreme pulmonary apex, a mode of development thought at one time to account for virtually all phthisis, unquestionably occurs in a certain percentage of cases. Finally, hematogenous seeding may give rise to bilateral foci, usually in the upper parts of the lungs, which may remain interstitial and cause relatively few symptoms, or may ulcerate through the bronchi and gradually produce a picture which is predominantly that of bronchogenic phthisis.

Once formed, the early infiltrate may regress and heal completely. This may occur in ambulatory, asymptomatic individuals, but the value of bed rest in aiding this process is well established. All too often the early infiltrate progresses to the

characteristic chronic, destructive form of pulmonary tuberculosis known as phthisis. Caseation occurs and is followed by liquefaction and discharge of the pus, leading to cavitation. Intra-bronchial aspiration follows, giving rise to new parenchymal foci where the process is repeated. The presence of bacilliferous sputum also gives rise in a large percentage of cases to lesions of the bronchial and tracheal mucosa. Reparative processes supervene, with some resorption and marked fibrosis, but the nature of the lesions, especially the cavities which continually discharge infective material into the bronchial passages and thence to other parts of the lung, tends to foster the chronicity and gradual extension of the disease.

As pulmonary tuberculosis progresses, increasingly large numbers of tubercle bacilli are expelled in the bronchopulmonary secretions, and are responsible for lesions which may appear in the larynx, the mouth, and, through swallowing, in the intestinal tract. The pathogenesis of other forms of extrapulmonary tuberculosis may be stated briefly. Tuberculosis of the kidneys, epididymis, prostate, Fallopian tubes, adrenals, bones, brain, eyes, lymph nodes, and other organs not in direct contact with the external environment, is lymphohematogenous in origin. Hematogenous seeding of these organs may occur during the active primary stage of infection, causing progressive, destructive lesions at that time, or after many years of latency when for some reason the resistance of the body is depressed. Hematogenous dissemination may also occur during the course of reinfection tuberculosis in adults, giving rise to single or widespread lesions. The internal organs vary considerably in their susceptibility to tuberculous infection. Some, such as those listed above, are relatively frequently involved, while others, including the pancreas, thyroid, ovary, spleen, heart, liver, and skeletal muscles, are rarely the site of progressive lesions.

PULMONARY TUBERCULOSIS

Manifestations. The onset of symptoms of pulmonary tuberculosis is in many instances *insidious*. This is particularly true when the disease begins with a small area of exudative bronchopneumonia—an early infiltrate—which enlarges slowly over a period of months as a result of contiguous or bronchogenic spread. In the

early stages, and at times when moderate progression has occurred, the patient is usually *entirely asymptomatic*, and may remain so for a considerable period. This cannot be emphasized too strongly, for an increasingly large percentage of early asymptomatic cases are being discovered as a result of routine films and x-ray surveys. Failure to realize this important point may deprive the patient of treatment at the time when the chances for complete recovery are maximal.

The earliest symptoms are constitutional, and result chiefly from the absorption of tuberculo-protein into the circulation of the hypersensitive body. As the lesions enlarge, greater amounts of tuberculoprotein are absorbed, and the constitutional symptoms become more pronounced. *Fever* is one of the commonest constitutional symptoms of tuberculosis, and usually begins as a slight elevation of the temperature in the late afternoon or evening. This elevation may occur daily, gradually attaining higher levels over a period of weeks or months, or it may subside altogether for an interval, and reappear intermittently as the patient passes through a series of grippelike episodes. It is characteristic for fever to be relatively well tolerated in patients with tuberculosis, even with a temperature elevation to 102° or 103° F. Except for sensations of warmth and flushing, the patient is often quite comfortable, and in some instances is even euphoric.

Fatigue and *malaise* are among the earliest constitutional symptoms noticed by the patient. They usually first manifest themselves as excessive tiredness at the end of the day, and may lead the patient to restrict his activities in the evening in order to get more rest. In other instances, particularly when the subject refuses to modify his routine, he may become irritable and morose. Fatigue and malaise become gradually more noticeable as the toxemia progresses, and may be the main complaints when the patient first seeks medical advice. Eventually, in far advanced disease, profound asthenia is often present.

Weight loss is usually noted somewhat later than the above symptoms, and may not be present to a marked extent for many months unless the disease runs a malignant course. Anorexia and indigestion are associated symptoms and seem to vary with the severity of the other constitutional manifestations. Anorexia may provide a clue from the standpoint of differential diagno-

sis; tuberculosis at this stage can be confused with diabetes and thyrotoxicosis, and in both of these conditions loss of weight is characteristically associated with an increase in appetite.

Chilly sensations may be noted as the toxemia progresses, particularly when the temperature rises abruptly in the evening. *Night sweats* are considered classic manifestations of tuberculosis, but actually do not occur in most instances until the disease is fairly far advanced. *Tachycardia* of a mild or moderate degree occurs along with the fever and other constitutional symptoms. *Headache* is noted in some individuals in the evening when the temperature is elevated, but usually subsides by morning and is absent during the daytime.

Menstruation is said to be disturbed in tuberculosis, but this statement is based upon the situation occurring in far advanced disease. In the early stages the menses are usually normal, and become irregular and scanty only as the disease progresses. Amenorrhea may occur in the later stages, particularly when the condition becomes terminal. For reasons not entirely clear, hemoptysis seems to occur more frequently during the menstrual period.

It should be realized that the constitutional symptoms referred to above are nonspecific in character, and do not provide the basis for more than a suspicion of the diagnosis of pulmonary tuberculosis. Since examination of the lungs in the early stages is negative in most instances, and the blood count and sedimentation rate may be entirely normal, the importance of the chest x-ray cannot be overemphasized.

In at least half of all patients with pulmonary tuberculosis, the onset of symptoms is not insidious as described above, but is *relatively sudden*. A characteristic story is that of a "bad cold," or "influenza," without awareness of symptoms of any sort prior to the acute episode. The "cold"—especially the cough—persists, while the constitutional manifestations may subside temporarily, giving the patient the feeling that he is recovering. Some individuals may recall a slight morning cough of some months' duration, attributed usually to irritation from smoking. Cough is characteristically first noted in the morning because secretions formed in the lungs during the night flow into the bronchi and trachea, and stimulate the cough reflex on arising. Once these passages are cleared, the patient

coughs infrequently or not at all until the next morning, when another mild paroxysm occurs. As the disease progresses, and secretions are formed in larger amounts, the cough becomes more troublesome, occurring throughout the day and night. Severe paroxysms of coughing often occur, especially in the morning; these may prevent the normal caloric intake, or may lead to vomiting if the patient does attempt to eat.

Along with cough, there is expectoration of *sputum*, except in the very early stages when the cough may be dry, or productive of only small amounts of mucus. In early cases a few flecks of pus may be seen in the mucus, and later the sputum becomes predominantly purulent in character. As cavitation progresses, liquefied caseous material is formed in increasing amounts, until 2 or 3 ounces of sputum are produced daily. In caseous pneumonic lesions with cavitation and liquefaction, the purulent matter is usually green or greenish yellow in color. Later, as the clinical condition improves, the greenish color tends to disappear, and the sputum is yellowish, with less purulent material and more mucus. Tuberculous sputum is not foul except in rare instances in which the pulmonary lesions become secondarily infected with anaerobes. Layering does not usually occur, a feature which is at times helpful in differentiating tuberculous from nontuberculous lung abscesses. Late in the course of the disease, secondary infection of tuberculous cavities frequently develops, and the patient may become exhausted by his efforts to bring up 300 or 400 ml. of sputum daily. In some such instances sulfonamides and penicillin are helpful from a palliative standpoint.

Hemoptysis is commonly associated with cough and expectoration, and ordinarily consists of streaking of the sputum, with only small amounts of blood being present. Occasionally, a gross hemoptysis may usher in the disease, the patient being unaware of any previous symptoms. Bleeding results usually from the ulceration of vessels in tuberculous cavities, and the natural tendency of the infectious process to cause vascular thrombosis is an important factor in preventing massive hemorrhages in the majority of patients with cavitary disease. Large hemoptyses usually occur without warning, and frequently begin during the night when the patient is asleep. Ordinarily, not more than 300 ml. of blood is produced; a clot then forms and seals

off the site of the bleeding. Dark clots of blood are usually brought up for several days, but if the cough mechanism is inadequate there may be blockage of a main bronchus with collapse of one or more lobes. The bleeding may recur at frequent intervals, and transfusions are indicated if this leads to severe blood loss. In an occasional instance the hemorrhage is massive and fatal; this usually occurs with old fibrotic disease, and the patient drowns within a few minutes in the large amount of blood that flows into his lungs. One of the greatest hazards of hemoptysis is the danger of spreading the infection throughout the lungs. Depending on the number of tubercle bacilli present in the bloody fluid, posthemoptysic spreads vary in extent from scattered finely mottled infiltrations to massive tuberculous pneumonia.

As pulmonary tuberculosis progresses, and especially with cavitary disease, ulcerations or granulomatous infiltrations frequently appear in portions of the tracheobronchial tree draining affected lung tissue, with *wheezing* as a common symptom. Endobronchial disease may alter the treatment, and therefore this symptom should be carefully sought for. Wheezing may also occur in the absence of demonstrable ulcerations or granulations, and is then presumably caused by mucosal swelling or retained secretions. It should be noted that tuberculous tracheobronchitis occasionally occurs in the absence of demonstrable parenchymal disease. When the sputum is copious in amount and contains large numbers of tubercle bacilli, the larynx also frequently becomes involved, with hoarseness being the most prominent symptom. Later, severe pain accompanies tuberculous laryngitis, and often interferes with eating and drinking. Tubercle bacilli may ascend the Eustachian tubes to cause otitis media, which usually begins insidiously with slightly impaired hearing and a sense of fullness in the ear. The mouth or the tongue may become the site of a persistent ulcer, which biopsy shows to be tuberculous. Finally, swallowing large numbers of bacilli may cause intestinal tuberculosis, with intermittent cramplike pain, diarrhea, and, at times, constipation.

Tuberculous Pneumonia. The clinical onset of tuberculosis occasionally may be an acute pneumonic episode, especially in Negroes, in children, and in elderly individuals both white and colored. The sudden aspiration of a dose of bacilli suffi-

ciently large to cause a pneumonic lesion results usually from the abrupt emptying of a cavity, from a hemoptysis, or from the rupture of a caseous node into a bronchus. Fever, chilly sensations, cough, and chest pain are noted, and the condition can easily be confused with primary atypical pneumonia. The temperature is usually not above 102° F., though it may rise to 104° or 105° F., and the white blood count is in most instances not elevated above 15,000. Tuberculous pneumonia may run a malignant course, with death in from one to three months, or the process may gradually subside and become a chronic condition.

Pleurisy with Effusion. This condition is common among young adults, and its pathogenesis and significance need to be emphasized. The pleura usually becomes involved as a result of direct or lymphatic extension from an underlying parenchymal process, and the lesion in the lung often is not of sufficient size to be visible on the x-ray. Whether the pleura can also be infected directly by way of the blood stream is a matter of dispute. Animal experiments indicate that parenteral injections of tubercle bacilli rarely result in direct infection of serous cavities. The not infrequent occurrence of bilateral effusions, on the other hand, is often cited as evidence that infection of the pleural surfaces may result from direct hematogenous seeding. Chest pain and fever are the initial symptoms; the pain may be sharp and pleuritic in character, or it may begin as a dull ache or uncomfortable sensation in the lower chest. In the more acute cases there is marked prostration with a high fever and a stormy course for two or three weeks. More commonly the temperature is only moderately elevated, and the patient does not feel particularly ill except for the pain in the chest. Clear yellow fluid is obtained by aspiration, and tubercle bacilli are recovered by culture or guinea pig inoculation in approximately 50 per cent of the cases. Whether the organism is recovered or not, experience has shown that, without treatment, 30 to 50 per cent of the patients develop clinical and x-ray signs of active pulmonary tuberculosis within five years. These figures are sufficiently high to warrant the assumption that all cases of "nonspecific" pleurisy with effusion are caused by tuberculosis, and they should be treated accordingly. Details of management will be outlined in a subsequent section.

PHYSICAL AND X-RAY EXAMINATION

The widespread use of the x-ray during the past 25 years has demonstrated the marked limitations of physical examination in detecting and appraising the lesions of pulmonary tuberculosis. As a result, the tendency at present in many quarters is virtually to ignore the physical examination altogether; this is lamentable, for the physical signs contribute information which, when correlated with the x-ray findings, gives a more complete understanding of the nature and activity of the parenchymal disease.

Early asymptomatic infiltrations are usually missed on routine physical examination, and indeed it is often surprising how extensive the x-ray infiltrations may become before definite physical abnormalities are detected. Crepitant post-tussic rales may be noted over a small area in minimal lesions, although rales are not of themselves conclusive evidence of activity. With larger lesions, especially after cavitation develops, dullness and moderately coarse rales are usually elicited. In far advanced disease all varieties of physical signs may be present. With pneumonic lesions the classic signs of consolidation are noted, and as cavitation develops coarse bubbling rales appear, especially at the base of the cavities where liquefied pus tends to accumulate. Even with large cavities demonstrable on the x-ray, however, the classic signs of tympany and amphoric breath sounds are often absent because the soft, shaggy cavity walls and surrounding structures do not act as good resonators. In old fibrocaseous lesions, on the other hand, the walls are relatively thick and rigid, and the classic signs of cavitation may be present. Tension cavities, associated with bronchial disease preventing normal egress of air during expiration, also produce atypical signs of cavitation. With long-standing disease, extensive fibrosis causes contraction and distortion of the pulmonary tissue, with deviation of the mediastinum and greater or lesser immobilization of the rib cage. In such instances a wide variety of physical signs, such as bronchial breath sounds, coarse rales, deviation of the trachea, spasm and atrophy of various chest and neck muscles, and diminished movements of one hemithorax, are noted.

From an x-ray standpoint, the early infiltrate is usually observed in the infraclavicular region, although it may be located entirely above the

clavicle, or in the midlung field. As the infiltrations progress and enlarge, the x-ray appearance of pulmonary tuberculosis may be indistinguishable from various nontuberculous conditions. Tuberculous cavities, especially when located in the lower lung fields, closely simulate nontuberculous lung abscesses. Similarly, the tuberculous nature of bronchopneumonic or lobar consolidations cannot be determined on the basis of the x-ray alone. The limitations of a single film in determining whether an infiltration is tuberculous, and of assessing its activity, is too often ignored, and leads to serious diagnostic and therapeutic errors.

Aside from its diagnostic limitations, the x-ray film may at times give misleading impressions concerning the functional status of the lungs. For example, in patients who have had pleural effusions, or extensive nodular bronchogenic disseminations following hemoptysis, the lung fields may eventually become almost entirely clear by x-ray, although pulmonary function remains markedly impaired. Careful physical examination will reveal the presence of impaired function in such cases, and will lead to more precise pulmonary function studies if surgery is contemplated.

TUBERCULIN TEST

Tissue hypersensitivity to tuberculoprotein results from the production of tuberculous tissue in the body by intact whole tubercle bacilli, either living, attenuated, or dead. A positive tuberculin test indicates, therefore, that an individual has, or has had, such a focus of tuberculous tissue in his body. It does not indicate that he harbors a clinically significant lesion, or that any of his present signs or symptoms are necessarily due to tuberculosis, active or inactive. The chief value of the test lies in exclusion. If negative, it can be fairly reliably concluded that the patient does not have active tuberculosis; virtually all individuals with active tuberculosis have a positive tuberculin reaction. Exceptions are sometimes noted during the course of certain intercurrent infections, especially measles and influenza, late in the course of pregnancy, and in some terminal cases of tuberculosis. The tuberculin skin reaction may turn negative after a period of years in individuals who have arrested and healed a primary tuberculous infection; the frequency with which this occurs is not known, but many well documented instances are on record.

The increasing incidence of negative tuberculin reactions in young adults has enhanced the diagnostic value of the test in recent years. Only 20 to 30 per cent of young men in the armed forces during World War II were tuberculin positive; in this age group the skin reaction is particularly helpful in ruling out tuberculosis in the presence of obscure fevers and undiagnosed pulmonary conditions.

The most reliable and accurate method of performing the tuberculin test is the intracutaneous, or Mantoux test, in which 0.1 ml. of suitably diluted tuberculin is injected intradermally into the skin of the forearm. If positive, induration (5 mm. or more) appears at the local site in 24 to 72 hours, and is surrounded by an area of inflammation varying from 1 to several centimeters. Intense local reactions occur if the dose of tuberculoprotein is too large, causing tissue necrosis and lymphangitis extending to the regional nodes. Absorption of tuberculoprotein into the circulation of the highly hypersensitive body causes constitutional symptoms, chiefly malaise, aching, and fever, and may produce focal reactions around tuberculous lesions throughout the body. To avoid these untoward reactions, small doses of tuberculin should be used for the initial test, with gradually increasing amounts thereafter at intervals of three or four days until the test becomes positive. If old tuberculin (O.T.) is used, the initial dose is usually 0.01 mg. (0.1 ml. of a 1:10,000 dilution); in individuals suspected of being unusually hypersensitive, the initial dose may be reduced to 0.001 mg. If the reaction is negative, tenfold increments in the amount of O.T. are employed for subsequent tests. An individual is ordinarily considered tuberculin negative if he fails to react to 1.0 mg., although some observers prefer to increase the amount to 10 mg. In recent years the purified protein derivative (P.P.D.) of Seibert has partially replaced old tuberculin because it gives more uniform results and minimizes false positive reactions. It is available commercially in two strengths, the first (0.00002 mg.) being roughly equivalent to 0.01 mg. O.T., and the second (0.005 mg.) corresponding to 1.0 mg. O.T.

The tuberculin patch test is often used in children to avoid the use of needles. It is less reliable, however, and, if negative, should be followed by the intracutaneous test if an accurate appraisal of the skin reactivity is desired.

LABORATORY FINDINGS

Recovery of Tubercl Bacillus. Aside from the x-ray, the most important laboratory procedures used in the diagnosis and management of patients with tuberculosis are those concerned with the isolation of tubercle bacilli from sputum, gastric washings, urine, feces, spinal fluid, serous and purulent effusions, abscesses, and draining sinuses.

Sputum may be absent, or present in only small amounts early in the morning in patients with minimal tuberculosis, and a few flecks of muco-purulent material obtained at this time may be adequate to make the diagnosis. The material is usually examined first by the direct smear. The Ziehl-Neelsen method of staining is the most widely used, although a fluorescent dye, carbolauream, has become popular in recent years. In the Ziehl-Neelsen method tubercle bacilli are stained with basic fuchsin, and resist decolorization by acid alcohol; a counterstain such as methylene blue is then added to provide a background against which the red-colored acid-fast bacilli are easily seen. Fairly large numbers of tubercle bacilli must be present to be seen on the direct smear. Therefore, if this is negative, 20 ml. or more of sputum is collected, digested with acid or alkali, concentrated by centrifugation, neutralized, and the sediment smeared, stained, and examined. With this technic a significantly higher percentage of specimens is positive than on direct smear of the untreated specimen, but again small numbers of bacilli may be missed. If negative on smear, the concentrated sediment is cultured or inoculated into guinea pigs, or both. Twenty to 30 per cent more positives are obtained by culture or guinea pig inoculation than by smear of the concentrated sediment. The relative merits of cultures and guinea pig inoculations are still being debated, but the results with cultures are so favorable that in many laboratories the more laborious and expensive guinea pig method has been abandoned.

If no sputum is produced, the *gastric contents* should be aspirated shortly after the patient awakens in the morning. Smears of the gastric contents may give false positive results; therefore the material is digested, concentrated, and cultured or inoculated into guinea pigs. In minimal cases of pulmonary tuberculosis, prior to the development of cavitation, discharges carried

into the bronchial tree and swallowed by the patient are small in amount, and many cultures of the gastric contents may be necessary to recover tubercle bacilli. For example, in one recent study it was found that 68 per cent of minimal cases had at least three negative specimens before a positive was obtained; and in another series of 61 patients, from 5 to 14 negatives were reported prior to the first positive culture. Once cavitation develops, the discharges increase in amount, and bacilli should be recovered by cultures of the sputum or gastric contents with comparative ease. A series of negative sputum or gastric cultures in the presence of cavitation provides strong presumptive evidence against the diagnosis of active pulmonary tuberculosis.

The basic principles outlined for sputum and gastric contents apply to the recovery of tubercle bacilli from other sources. Minor modifications are necessary, especially in preparing and concentrating urine and stool specimens. With spinal fluid, tubercle bacilli are often detected by smear or culture of the pellicle which forms if the specimen is left in the icebox overnight.

Sedimentation Rate. The sedimentation rate is normal in the majority of individuals with minimal tuberculosis, and is, therefore, of little value in determining the presence of activity of such lesions. In more advanced febrile cases the sedimentation rate usually is elevated, and often is used as an index of the progression or regression of the disease. This use has definite limitations, however, since the rate may be normal in patients on absolute bed rest in spite of progressive intrabronchial disseminations; and, conversely, a sudden increase in the rate may accompany the onset of a relatively insignificant complication such as mild pleurisy. When normal, the sedimentation rate cannot necessarily be interpreted as signifying inactivity or favorable progression. When elevated, it is indicative of some abnormality; whether this is of serious significance, or whether it is even tuberculous in nature, must be ascertained in other ways.

Blood. Hematologic changes in tuberculosis are relatively slight. In minimal cases the blood count is usually normal, but as the disease progresses there may develop a mild hypochromic microcytic anemia. Even in far advanced cases the anemia usually is not marked except in the presence of extrapulmonary complications such as intestinal tuberculosis or amyloidosis. A mild leu-

kocytosis may be present in progressive, febrile stages, with a count of 10,000 to 15,000, but even in acute tuberculous pneumonia the total white count is rarely above 15,000. Polymorphonuclear leukocytes may be moderately increased, with a shift to the left. An increase in monocytes with a decrease in lymphocytes is regarded by some observers as indicative of progression of the disease, and in experimental animals this appears to be well substantiated. In man, however, the lymphocyte-monocyte ratio and other prognostic guides, such as the Medlar index, are of limited value because they are markedly affected by various intercurrent processes, and they merely confirm the more reliable prognostic evidence obtained by physical examination, serial x-rays, and sputum studies. The total white and differential counts may, therefore, be regarded as of greater value in differential diagnosis than in determining prognosis. Exceptions to some of the above statements should be noted; in widespread acute tuberculous pneumonia, for example, the total white count may occasionally be well above 20,000, with a polymorphonuclear count of over 95 per cent. Similarly, in acute miliary tuberculosis, there may occur a high-grade leukocytosis and at times even a leukemoid blood picture, or there may be a marked leukopenia.

Urine. Changes in the urine in pulmonary tuberculosis, as in other chronic febrile diseases, consist chiefly of intermittent traces of albumin without other significant abnormalities. With amyloid disease, marked proteinuria appears, together with epithelial cells and casts indicative of a degenerative renal lesion. Renal tuberculosis is not uncommon, and therefore frequent urine examinations should be made, noting especially persistent proteinuria and an abnormal number of erythrocytes and leukocytes. If these are present, pyelograms are indicated, and concentrated urine specimens should be cultured and inoculated into guinea pigs. Tubercle bacilli occasionally have been isolated from the urine of individuals with no gross or microscopic urinary abnormalities, and in whom follow-up examinations reveal no evidence of renal tuberculosis. Such individuals should be regarded as harboring latent tuberculous foci in the kidney, and should be followed at frequent intervals with urine examinations and cultures.

Other Laboratory Tests. A number of serologic tests have been employed in tuberculosis, but

none has been found to be of practical diagnostic or prognostic value. The complement-fixation reaction, for example, is positive in less than 50 per cent of patients with minimal lesions, and false positive reactions are obtained in over 10 per cent of individuals with no evidence of active tuberculosis. Various nonspecific procedures have also been disappointing, although recent electrophoretic serum protein studies may eventually lead to tests which are of use to the clinician. Tests for renal insufficiency, hyperthyroidism, diabetes, and amyloidosis are of value in the diagnosis and management of conditions which frequently complicate pulmonary tuberculosis.

DIFFERENTIAL DIAGNOSIS

The onset and course of pulmonary tuberculosis varies widely, and may simulate a great number of other disease states. The outstanding conditions which may be confused with tuberculosis, and the main differential features, will be considered briefly.

Psychoneurosis. Patients with purely functional disorders frequently present complaints similar to those of early pulmonary tuberculosis. Malaise, easy fatigability, and inability to concentrate are common symptoms, and there may be anorexia with slight weight loss. A chronic hacking cough may be present, due to irritation of the respiratory passages from smoking. A careful evaluation of these complaints will usually give a clue to the correct diagnosis. Clinical findings, including the failure to detect abnormalities on physical examination of the chest, do not provide sufficient grounds for exclusion of the diagnosis of pulmonary tuberculosis. A chest x-ray is an essential part of the examination of patients with the symptoms described above.

Endocrine Disorders. Two endocrine disorders, *hyperthyroidism* and *diabetes*, are commonly manifested by weight loss and easy fatigability. In contrast to tuberculosis, however, the weight loss is associated with an increased appetite rather than with anorexia. Negative chest x-rays, in addition to glycosuria and an abnormal glucose tolerance test in diabetes, and an elevation of the basal metabolic rate in hyperthyroidism, lead to the correct diagnosis.

Obscure Fevers. Tuberculosis is always to be considered in the differential diagnosis of fevers of unknown origin. With a negative chest x-ray, the fever may be caused by early miliary tubercu-

losis, or by an extrapulmonary tuberculous focus, and localizing signs should be sought for. Smears and cultures of the sternal marrow may facilitate early diagnosis in such cases. A negative tuberculin test is strong presumptive evidence that the underlying process is not tuberculous. Cultures, serologic procedures, biopsies, and other appropriate studies will usually clarify the etiology of fevers caused by brucellosis, subacute bacterial endocarditis, lymphomas, and other conditions.

Pulmonary Fibrosis and Emphysema. Pulmonary fibrosis and emphysema with cough, weakness, dyspnea, and at times streaking of the sputum, are relatively common in older individuals. Tuberculosis is in some cases the cause, or is an associated condition, and therefore the sputum should be examined carefully for tubercle bacilli. Pneumoconioses, especially silicosis, should be kept in mind, and the patient questioned concerning possible industrial exposure. Nodulation, more dense near the hilar regions and extending peripherally through both lung fields, is the characteristic x-ray appearance of silicosis. With the development of a superimposed tuberculous infection, larger, confluent shadows appear, and the constitutional manifestations of tuberculosis are usually present, although it may be very difficult to recover tubercle bacilli from the sputum.

Nontuberculous Lung Abscess. This affection, which may be roentgenologically indistinguishable from tuberculosis, usually has an acute onset with chills, fever, and leukocytosis. The sputum may or may not be foul, depending on the organisms involved. The differential diagnosis is usually relatively simple, since acid-fast bacilli are almost always readily demonstrable in patients with tuberculous cavities. Clubbing of the fingers may develop in four to eight weeks in the presence of a nontuberculous abscess. Nontuberculous abscesses may become chronic and, when seen at this stage, especially in conjunction with hemoptysis, may be very suggestive of tuberculosis. Sputum studies, plus a careful review of the original signs and symptoms, usually will clarify the situation.

Bronchiectasis. Bronchiectasis is usually, although not invariably, associated with a chronic productive cough, and is one of the commonest causes of hemoptysis. Clubbing of the fingers is common, while in tuberculosis it is rare. Bronchiectasis usually involves the lower portions of

one or both lungs, but in an occasional instance is situated at the apex. The x-ray may be completely negative, or there may be increased linear densities extending outward and downward from the hilar regions. Moderately coarse rales usually are noted over the involved areas. The failure to find acid-fast bacilli in the sputum, and the instillation of iodized oil into the bronchial tree, confirm the diagnosis. Not infrequently, tuberculosis and bronchiectasis are found to coexist.

Primary Atypical Pneumonia. This presents a clinical and x-ray picture which may be indistinguishable from pulmonary tuberculosis. The absence of cavitation, the failure to find tubercle bacilli in repeated examinations of the sputum, and the eventual complete clearing of the parenchymal lesions, are the important differential features. The infiltrations in primary atypical pneumonia usually clear completely within two to four weeks, but in an occasional case may persist for two to three months. In borderline cases, especially those involving the upper lobes, the diagnosis may remain in doubt for many weeks.

Pneumococcal Lobar Pneumonia. This disease may be confused with acute tuberculous pneumonia at times, although in the latter the temperature is in general not so high, the patient is not so acutely ill, and the white blood count usually is not elevated above 15,000 with only a moderate shift to the left. In many instances tuberculous pneumonias represent disseminations from a cavity, and therefore physical and x-ray signs of cavitation may be present unless masked by massive consolidation. Tubercle bacilli usually are demonstrated easily.

Mycotic Diseases. *Coccidioidomycosis*, a mycotic infection endemic in the San Joaquin Valley of California and in certain parts of Arizona and western Texas, presents a clinical and x-ray picture similar to pulmonary tuberculosis. This condition is of national importance because of the large number of individuals who were in the endemic areas during World War II. A history of potential exposure, the coccidioidin skin test, smears and cultures of the sputum for *Coccidioides immitis*, and precipitin and complement-fixation tests of the patient's serum, are the procedures used in confirming or excluding the diagnosis. *Histoplasmosis* recently has been suspected of causing pulmonary calcifications similar to those occurring in tuberculosis, because of the observation that many individuals in the

south central states with pulmonary calcifications have positive histoplasmin skin tests and negative tuberculin reactions. Other mycotic infections, such as *actinomycosis* and *blastomycosis*, may at times simulate tuberculosis, but the fungi usually can be readily recovered from the sputum. If the possibility of mycotic diseases is kept in mind in obscure pulmonary disorders in which tubercle bacilli are not present, the diagnosis usually presents no great problems. Certain fungi, such as *Aspergillus* and *Monilia*, which may on occasion be pathogenic, are often present in the sputum as contaminants, and their presence requires careful evaluation.

Carcinoma of Lung. Carcinoma of the lung, with chronic cough, blood-streaked sputum, fever, and weight loss, may present a clinical picture very similar to tuberculosis in older individuals. Carcinomas located peripherally produce fewer symptoms, but may present an x-ray appearance indistinguishable from that of tuberculosis. Bronchoscopy with biopsy if possible, study of the sputum or bronchial secretions for cancer cells, and a careful search for metastatic foci, are important steps in the diagnosis of carcinoma. Patients with lesions suspected of being carcinomatous, from whom tubercle bacilli cannot be recovered, should be subjected to early thoracotomy. It should be noted that tuberculosis and carcinoma are occasionally both present in the same patient.

Cardiovascular Disorders. These may produce symptoms suggestive of tuberculosis. Hemoptysis occurs frequently with mitral stenosis and is occasionally observed with hypertension. Every long-standing pulmonary congestion, such as occurs in patients with mitral stenosis, causes pulmonary fibrosis; infected pulmonary infarcts may develop into abscesses suggestive of tuberculous cavitation.

Other Conditions. Mediastinal cysts, lymphomas, amebiasis, aortic aneurysms, sarcoidosis, and metastatic neoplasms, may be confused with tuberculosis. Careful evaluation and study, including the exclusion of tuberculosis by the failure to find tubercle bacilli, usually will lead to the correct diagnosis.

EVALUATION OF NEED FOR TREATMENT

In patients with progressive symptomatic pulmonary tuberculosis the clinical and x-ray find-

ings are usually characteristic, and the diagnosis and need for treatment are established readily. In some situations, however, the diagnosis and degree of activity and, therefore, the need for treatment, are more difficult to ascertain. At the outset it may be stated that old calcified primary complexes, nodular fibrotic areas at the extreme apices, and adhesions and scarring due to old pleurisy are not indications for treatment. Individuals with these lesions should, however, have yearly physical and x-ray examinations, since dormant foci may give rise to active disease during periods of lowered resistance.

Minimal infraclavicular infiltrations, detected in increasing numbers in recent years as a result of x-ray surveys, require careful evaluation, which in most instances should be carried out with the patient at bed rest. This is particularly true of individuals under 25 years of age, in whom the infiltrations usually represent early, unstable lesions which may undergo rapid progression and excavation. In older persons, the appearance of the lesion on the x-ray is a useful guide as to whether the patient should be put to bed during the initial period of observation. Hazy, poorly circumscribed shadows indicate exudative, unstable lesions, while dense, sharply circumscribed infiltrations usually represent old arrested disease which is unlikely to show progression. Serial x-rays are the most valuable means of following the lesion and determining its activity. These should be made at least once a month, and sometimes more frequently in young adults with exudative lesions. The sedimentation rate may give useful information if elevated, but usually it is normal. Gastric washings should be cultured repeatedly for acid-fast bacilli, but negative results do not necessarily indicate inactivity. Careful clinical observations and serial roentgenograms over a period of at least six months are usually adequate to determine the activity of the lesion. If active, as determined by either progressive or regressive changes, prolonged rest is indicated. If inactive, the individual may be allowed to resume his normal life, with further observations at less frequent intervals.

TREATMENT

Rest. Through trial and error and empiric observation, it has gradually become recognized that the fundamental principle in the treatment of tuberculosis is rest. Mechanisms underlying

the beneficial effects of rest are not completely understood, but some aspects of the problem have been at least partially elucidated. A reduction in the general metabolic needs of the body results in a decreased rate and amplitude of respiratory excursions, putting the lungs themselves partially at rest. The decreased motion of the lungs also diminishes the tendency to aspirate infective material into healthy pulmonary tissues, and relieves local strains which may predispose to hemoptysis. Along with the decrease in body metabolism and motion of the lungs, there is a reduction in the amount of blood flowing through the pulmonary parenchyma; this minimizes the absorption of toxic products and thereby alleviates toxic manifestations such as malaise, fever, and tachycardia. It is possible that rest exerts additional effects which are less clearly defined but which may be classified under the general heading of "physiologic tone." Endocrine function, vascular permeability, and other obscure mechanisms which combine to give high resistance, are included in this category. Whatever the mechanisms are that build up resistance and promote healing, the value of complete rest, mental and physical, is established beyond any doubt.

Since the benefits to be gained are great, rest should be instituted as soon as an active or potentially active case of tuberculosis is discovered by the physician. In older individuals with fibrocaseous disease, a few days may be allowed to straighten out personal affairs. Exceptions also may be made in some patients with hopelessly far advanced disease. Otherwise, it is the duty of the physician to insist upon bed rest immediately, and to explain its importance and advantages.

Sanatorium Treatment. With few exceptions, treatment should be instituted and carried out in a sanatorium. This is often difficult to arrange, for resting in bed at home surrounded by family and friends is much more appealing to the patient than going to a hospital. Sanatorium treatment is greatly to be preferred, however, and the reasons for this need to be outlined persuasively to the patient and his family. The education and instruction which provide the basis for understanding and complete coöperation on the part of the patient can be accomplished more effectively in a sanatorium. Strict bed rest is such an onerous discipline to many that it is helpful to be

in an environment where others have carried out this routine for long periods, and show the obvious benefits of it. Patients who have failed to coöperate will also be present to demonstrate the tragic consequences of their neglect. Too often, in spite of the best intentions, the patient at home tends to fit into the customary routine and activities of the family, whereas actually their routine should be modified to fit his own needs. In the home it is difficult to restrict visits of friends to certain designated periods, and their presence keeps the patient too closely in contact with worries and problems which should be put aside temporarily. The danger of transmitting the disease to other members of the family is always present, and is a compelling reason for moving to another environment if there are children in the household. Finally, the lack of facilities in the home for frequent and complete laboratory follow-up, and for the institution of collapse therapy when indicated, deprives the patient of the advantages which modern treatment has to offer. The chief exceptions to the rule for sanatorium treatment are patients with long-standing, far advanced disease who will not benefit from bed rest, and who merely need domiciliary care in an environment where they will not be a hazard to others.

Climate. Climate was at one time considered an important part of the treatment of pulmonary tuberculosis, but the excellent results obtained in many different environments, including hospitals in the busiest portions of our larger cities, have made it apparent that climate exerts a relatively insignificant influence on the course of the disease. In general, patients should be treated in sanatoriums located in or near their own communities, where they are near their families and friends and, if indigent, can be supported by local welfare agencies. When economic factors are not a consideration, a dry, temperate climate such as that of southern Arizona is well tolerated, particularly by patients who are chronically afflicted and need to lead a sheltered life for long periods. Cool, fresh air seems to have an invigorating effect but possesses no known specific advantages aside from this. This statement is not intended to discount treatment in the open air, which is widely practiced and is conducive to remaining strictly in bed. High altitudes are claimed by some to exert a favorable effect by decreasing the oxygen supply to tubercle bacilli in infected tis-

sues. Tubercle bacilli are strict aerobes, but it is doubtful that, at the elevation of even the highest sanatoriums, the oxygen supply is sufficiently decreased to seriously impair their growth. Experimental evidence tends to support this view. High altitudes are, on the other hand, contraindicated in patients with advanced emphysema and diminished respiratory reserve.

Diet. This factor deserves brief mention. Aside from the elements comprising a good, well-balanced diet, no specific vitamins or other substances are known which specifically promote healing, and which should, therefore, be given in excessive doses. This statement is made despite the enthusiasm of some for vitamin D, ascorbic acid, calcium, etc., the benefits of which are far from proved. The total caloric intake should be designed to enable the patient to regain and maintain his ideal weight. There is no virtue in becoming fat, and many patients have great difficulty in losing excess pounds once their disease is arrested.

During at least the initial period of observation and treatment the patient should be at strict bed rest, which means remaining in bed at all times. This may occasionally have to be modified for patients who have great difficulty with the bedpan, and exert less energy in using a commode at the bedside. Except for those who are acutely ill, the patient is usually allowed to sit up and feed himself at meal times. Otherwise, he should remain in bed as quietly as possible, and preferably should be flat in bed. The value of remaining supine is given weight by the recent theoretic considerations of Dock, which suggest that apical localization of phthisis is due to low pulmonary artery pressure at the apex of the lung in the upright position. This theory is in need of direct experimental proof, but is plausible and in keeping with the known facts, and provides a rational basis for remaining flat in bed which can be readily understood by the patient as well as the physician.

Clinical and Laboratory Observations During Treatment. Once the patient is on strict bed rest, a systematic series of clinical and laboratory examinations should be planned to ascertain his response to treatment, and to follow his progress. The temperature should be recorded every four hours during the daytime, preferably by rectum, since this is more accurate than the oral method. The latter is quite dependable, however, if the

thermometer is kept under the tongue for at least five minutes, and the patient has had nothing to eat or drink during the preceding half-hour. The pulse rate is recorded each time the temperature is taken, and is a sensitive indicator of toxemia, often remaining elevated after the temperature is normal. The patient should be weighed every two weeks unless he is too ill, or unless the psychologic trauma associated with failure to gain is so great that it is better to omit the procedure. A complete blood count should be performed once a month, or oftener if there is a sudden change in the patient's condition. The sedimentation rate also may be determined monthly, and at times gives helpful information concerning the patient's progress, favorable or unfavorable.

The patient should be visited every day or two by his physician, who should make repeated observations concerning his general physical and mental status, his vegetative functions, and any special complaints such as diarrhea, hoarseness, headache, or dysuria, which would direct attention to complications or extrapulmonary involvement. Repeated physical examinations are essential, and must be correlated with the other data in assessing the patient's progress.

Aside from clinical observations, the most important information in follow-up examinations is obtained from repeated sputum studies and serial roentgenograms. Sputum is collected in disposable containers, and measured every 24 hours. Its color, odor, layering, and consistency, whether mucoid, mucopurulent, or purulent, should be noted by the physician when he makes his rounds. Attempts to recover tubercle bacilli are made at monthly intervals. This information provides an indispensable guide for decisions which are made in the treatment of tuberculous patients. Methods of searching for tubercle bacilli in sputum and gastric washings have been outlined in the section on laboratory methods.

Chest x-rays are taken at least once a month during the first several months when the patient's initial response to treatment is being evaluated. Later, except when there is a sudden change in the patient's condition, an interval of three months is usually satisfactory.

Duration of Bed Rest. The duration of strict bed rest is variable, depending upon the extent of the disease and the response of the individual patient to treatment. There is a natural tendency to make this period as brief as possible,

since complete rest in bed becomes monotonous, and constitutional symptoms usually disappear after a few weeks. Early symptomatic improvement is encouraging, but may be misleading; it signifies not that the process is healed, but merely that there is improvement, with less absorption of toxic products into the circulation. Experience has shown that relapses are frequent when patients are allowed to get up as soon as their symptoms disappear and the temperature, pulse, and sedimentation rate are normal. Healing in tuberculosis is a slow process, which is accompanied by a gradual conversion of the sputum to negative, and regression and sharpening of the shadows on the x-ray. Evidence of roentgen stability and beginning fibrosis, together with the bacteriologic results, indicate that the process of healing is well under way, and that modifications of bed rest may gradually be instituted. The duration of strict bed rest varies from 6 to 12 months, in asymptomatic patients with minimal lesions, to 18 months or 2 years, in patients with more extensive disease, in some of whom there may be progression and exacerbation before resolution is well established.

Further Management. The period during which the patient gradually resumes his activities is a crucial one and requires careful supervision, for lesions which appear stable on bed rest may not remain so when activity is increased. Amerson has shown that, even with complete roentgen resolution, caseous foci may persist for long periods, and may cause local exacerbations months or years later. The patient is allowed to sit up for only 15 or 30 minutes a day at the beginning, and, at intervals of two or three weeks, this period is gradually lengthened. Over several months or a year, if there is no elevation of the temperature, pulse, or sedimentation rate, and the x-ray remains stable, the patient may reach a point where he is walking 2 or 3 hours a day, sitting in a chair for meals and reading, and spending 12 or 14 hours in bed. From this point there is a further gradual increase until he resumes his former occupation, or some type of work which does not overtax his energies. Routine checkups should be made at frequent intervals for an indefinite period because of the ever present danger of relapse. According to the classification of the National Tuberculosis Association, the disease is considered arrested when there is x-ray stability, laboratory studies are all

negative, and the patient remains asymptomatic on moderate activity for a period of six months. A minimum of two years is necessary, however, before one can be fairly certain that relapse will not occur. After two years, follow-up studies may be made at intervals of six months to a year, but the patient should be instructed to report for a checkup whenever any unusual symptoms appear.

The above outline of treatment is that prescribed for patients with minimal and moderately advanced tuberculosis in whom the response is in most instances favorable if coöperation is obtained, and in whom rehabilitation with return to a gainful occupation is to be anticipated. A regrettably large percentage of patients do not come under medical supervision until their disease is too far advanced to allow such salutary results. Many such individuals can, with prolonged rest and proper management, become "good chronics," able to be up and about and carry on for many years in an environment where they will not be health hazards to the community. In elderly individuals, prolonged bed rest is more likely to be deleterious than beneficial, and a sheltered life free from occupational strains and financial worries is indicated.

Collapse Therapy. Statistical studies of pulmonary tuberculosis have invariably shown a worse prognosis in patients with open cavities than in those without cavitary disease. This is not surprising since bronchogenic dissemination is greatly favored by the presence of cavities, whose liquid bacilliferous contents are aspirated into other parts of the lungs. Large cavities close occasionally on bed rest alone, but usually they do not, and it is primarily in this type of case that artificial collapse therapy has its greatest usefulness.

In the opinion of the author, collapse therapy ordinarily is not indicated in noncavitory disease; healing appears to occur as rapidly and completely on bed rest alone as with the addition of collapse measures, and the discomfort and complications of the latter are avoided. There is not general agreement on this point, however; in some institutions some form of collapse therapy is attempted on virtually every patient, including those with minimal lesions, and there are many published series in which this approach is claimed to produce superior results. In patients with noncavitory lesions which fail to improve or show

progression on bed rest alone, it is generally agreed that collapse therapy should be instituted.

Collapse therapy exerts its beneficial effects by reducing pulmonary volume, diminishing respiratory excursions, decreasing the amount of blood flowing through the affected tissues, causing an inadequate supply of oxygen for the tubercle bacilli, and, most important of all, approximating the walls of cavities so that healing may occur.

ARTIFICIAL PNEUMOTHORAX. Designed originally for predominately unilateral disease with cavitation, this form of therapy produces brilliant results in carefully selected cases. The indications for pneumothorax have been broadened considerably, but its indiscriminate use in patients with far advanced bilateral disease does not meet with good results, and the incidence of complications is high. In borderline cases, complications can be minimized by promptly abandoning the pneumothorax if it is evident that adequate collapse cannot be obtained. Artificial pneumothorax is initiated by carefully inserting a blunt needle into the potential space separating the parietal and the visceral pleura, and injecting air intrapleurally under manometric control. Initially, about 300 ml. of air is introduced, and this is repeated at intervals of two to four days for several weeks. As the ability of the pleura to absorb air gradually diminishes, refills are given less frequently, once weekly, and eventually once every two or three weeks. Fluoroscopic examination of the patient is performed before and after each refill, and an attempt is made to keep the amount of collapse constant. For this reason small frequent refills are preferable to larger ones given less often.

Introduction of air into the intrapleural space under negative pressure allows the lung to retract because of its own inherent elasticity; the amount of collapse tends to be greater in diseased portions where there is impairment of the normal distensibility of pulmonary tissue. This fortuitous *selective collapse* of diseased portions provides selective rest and relaxation, but still allows effective ventilation of the healthy lobes. The establishment of selective collapse is not under control of the operator, however; it is determined by conditions which impair elasticity within the lung. Even when these conditions are ideal, selective collapse is often prevented by adhesions from without.

In favorable cases cavities should be closed and

the sputum converted to negative within a period of six months after initiating artificial pneumothorax. Exceptions occur, but in general, if this result is not attained, the pneumothorax should be abandoned or measures should be undertaken to make the collapse more effective. Once effective collapse is achieved, refills are continued for from two to five years, the longer period being necessary with extensive disease, and in cases in which the period required for initial closure of cavities is more prolonged.

Artificial pneumothorax is contraindicated in acute tuberculous pneumonia, because collapse is inadequate and the incidence of tuberculous empyema is high. Other contraindications are large apical cavities in which adequate collapse is rarely if ever possible and thoracoplasty is preferable, and extensive endobronchial tuberculosis in which tension cavities, or collapse and infection distal to the stenosis, are common.

In over two thirds of artificial pneumothoraces, adequate collapse is prevented by the presence of adhesions between the visceral and the parietal pleura. The adhesions are often so extensive that the pneumothorax must be abandoned, but in selected cases they can be effectively divided by *intrapleural pneumonolysis*. In this procedure two small openings are made in the chest wall; through one the adhesions are directly visualized through a thoracoscope, and are severed by a cauterizing instrument which is introduced through the other opening. Although fraught with potential dangers, such as hemorrhage, perforation of the lung, and the development of empyema, the incidence of complications is low in skilled hands, and in many cases this procedure converts an unsatisfactory pneumothorax into a highly successful one.

Complications of artificial pneumothorax are common, and may be serious. Air embolism, hemorrhage, and perforation of the lung are potentially fatal complications, but can be avoided, except in rare instances, by careful technic. In over 90 per cent of pneumothoraces, fluid develops, but is usually small in amount and disappears after a few weeks. If the fluid persists, it may cause adhesions and gradual obliteration of the pneumothorax space beginning usually at the base, or it may cause fibrosis of the visceral pleura which prevents later re-expansion of the lung. In a small percentage of cases the effusion develops into true tuberculous empyema. Ser-

fibrinous effusions are aspirated frequently if large in amount; if they persist for more than a few weeks, the pneumothorax usually is abandoned before the visceral pleura becomes encased in a fibrous sheath.

PNEUMOPERITONEUM. This is a form of collapse therapy which has become increasingly popular during the past decade. Attended by few of the complications of pneumothorax, administration of air into the peritoneal cavity is simple from a technical standpoint, and produces effective collapse in selected cases. Originally employed chiefly for lower lobe cavities, pneumoperitoneum probably has its greatest usefulness in cases with far advanced bilateral cavitary disease unsuitable for any other treatment aside from bed rest. Favorable results have been reported in seemingly hopeless cases, although even the enthusiasts admit that many patients are not benefited. Pneumoperitoneum may be a useful adjunct in preparing patients for surgery who would otherwise never be in condition to withstand permanent collapse measures.

PHRENEMPHRAXIS, temporary paralysis of the diaphragm, is effected by crushing the phrenic nerve. The diaphragm remains elevated and immobile for six or eight months, and then gradually resumes its normal function. Formerly used much more extensively than at present, this procedure is now thought to be contraindicated in the presence of lower lobe cavities. In some circles, phrenic crush is used as an adjunct to bed rest in treating minimal lesions which are not responding well, and it is sometimes used in conjunction with pneumoperitoneum. Its main disadvantages are gastrointestinal disturbances, especially when performed on the left side, failure of the nerve to regenerate in about 10 per cent of cases, and reduction in respiratory reserve. When thoracoplasty is contemplated, phrenemphraxis on the operative side should be avoided if possible, in view of the potential permanent impairment of bronchial drainage and respiratory reserve.

THORACOPLASTY. The classic indication for thoracoplasty is chronic fibroid disease at or near the apex of one lung, with a cavity which cannot be closed so effectively or safely by any other means. If lesions are present in the other lung, there should be x-ray stability for at least six months. When there is more urgency, the contralateral lesions may at times be controlled by

pneumothorax. Ribs are resected subperiosteally in one, two, or three stages, the apex is freed and lowered according to the technic of Semb, and the resulting compression of the lung brings about cavity closure and conversion of the sputum in the majority of patients. Too often, thoracoplasty is attempted only after other measures have been maintained inadequately until the patient's condition is hopeless; the results under these circumstances are very poor. In unilateral cases, when pneumothorax and pneumonolysis are unsuccessful, the lung should be re-expanded and thoracoplasty performed without delay. Thoracoplasty is also indicated in intractable tuberculous empyema, and is performed following pulmonary resections to prevent overdistention of the remaining lung tissue.

Resection. Resection of pulmonary tissue is indicated at times in the following conditions: persistent cavitation after thoracoplasty, severe bronchial stenosis, tuberculoma, bronchiectasis, and giant cavities. The chief disadvantages of lobectomy and pneumonectomy in pulmonary tuberculosis are the high incidence of extension of the disease to other lobes, and the high incidence of tuberculous empyema. Streptomycin therapy has markedly decreased the incidence of postoperative spreads, especially those occurring early, and has thereby made resections less hazardous than they once were.

Chemotherapy. With the advent of the sulphonamides and similar compounds, hope for a chemotherapeutic agent effective against tuberculosis was revived, and sulfone derivatives, such as promin and promizole, showed promise in experimental animals. The results in human beings have not been so favorable, however, and none of these compounds can be recommended for use in patients except in combination with streptomycin. One interesting compound, paraaminosalicylic acid, has been reported by Swedish investigators to be relatively nontoxic, and to give encouraging results in patients with pulmonary tuberculosis. Preliminary studies in this country indicate that it is considerably less active in human beings than is streptomycin, but may possibly be useful when administered in conjunction with the latter.

STREPTOMYCIN. The discovery of streptomycin, announced by Waksman and his collaborators early in 1944, was followed by laboratory and clinical observations of its effectiveness by

Hinshaw, McDermott, and others. The results of these preliminary studies led to clinical trials on a much larger scale, so that a fairly comprehensive appraisal of this remarkable antibiotic is now possible.

It has been established definitely that streptomycin modifies the course of various tuberculous lesions in a manner unapproached by earlier chemotherapeutic agents. The most striking results have been obtained in tuberculous meningitis and in acute hematogenous miliary tuberculosis, in which clinical remissions have followed treatment in a large percentage of cases. Relapses, with a fatal termination, have been common, unfortunately, but in 10 to 20 per cent of cases remissions have been complete during a follow-up period of a year or more. Tuberculous ulcers of the tongue and mouth, tuberculous laryngitis, draining tuberculous sinuses, and ulcerating lesions of the tracheobronchial tree have also responded favorably, and may be considered definite indications for treatment with streptomycin. In tuberculosis of the genitourinary tract, bones and joints, skin, eyes, intestinal tract, and lymph nodes without draining sinuses, the results are sufficiently encouraging to warrant streptomycin therapy, although years will be required to define its exact value and limitations. In chronic tuberculous empyema, streptomycin appears to have little or no beneficial effect. Details concerning treatment of some of the above-mentioned conditions are presented in subsequent sections.

In pulmonary tuberculosis the most encouraging results have followed treatment of fresh exudative lesions, particularly when these are finely disseminated. With more confluent lesions, as in tuberculous pneumonia, the response is also usually favorable, although in acute overwhelming infections the disease may, in spite of treatment, progress to a rapidly fatal termination. In general, patients with minimal and moderately advanced disease who are likely to respond to conventional forms of therapy should not be treated with streptomycin because of the hazards of toxicity and the probability that resistant organisms will develop. Streptomycin is of definite value in preventing postoperative spreads following pulmonary resection, and in treating spreads if they occur following thoracoplasty. In chronic fibroid or fibrocaseous pulmonary tuberculosis, streptomycin may give temporary

palliative relief, particularly if there are areas of recent exudation and extension, but the improvement is chiefly subjective, and cessation of therapy is usually followed by relapse. Favorable results were originally obtained by intramuscular administration of 2 to 3 Gm. of streptomycin daily in divided doses at four- to six-hour intervals for from three to four months. Later evidence demonstrated that the optimal therapeutic response often can be obtained with small doses given at less frequent intervals, and that small amounts produce less toxicity. The usual routine is to give 0.5 Gm. twice daily for six weeks, and to administer a second course if indicated and if the organisms have not become resistant. Studies are now being conducted with doses smaller than 1 Gm. daily, and the possibility of administering streptomycin only once or twice a week is also being investigated.

The most important toxic reaction from streptomycin administration is impairment of vestibular function, which occurs in the majority of patients who receive the drug in large doses (2 Gm. daily) for more than a month. This is manifested subjectively by dizziness, lightheadedness, and unsteadiness, and objectively by impaired or absent vestibular function with caloric tests. In a large percentage of patients vestibular function is lost altogether, especially in patients over 50 years of age. Compensatory mechanisms, chiefly visual, operate with remarkable effectiveness, so that the residual disability is usually minimal, but may be disturbing in the dark. In rare instances deafness occurs, but can usually be prevented by discontinuing streptomycin when impairment of hearing is first detected. Other serious toxic manifestations are fortunately not common, but occasional instances of agranulocytosis, renal damage, and exfoliative dermatitis have been reported. Contact dermatitis has occurred in a number of nurses as a result of handling streptomycin solutions without wearing rubber gloves. Mild sensitivity reactions, chiefly eosinophilia and pruritic maculopapular rashes, occur during the second or third week of streptomycin therapy in a large percentage of patients. They are of minor significance and may be disregarded; the itching is usually relieved by "Benadryl." It should be noted that the incidence of toxic reactions, especially vestibular damage, has been markedly decreased by lowering the dose to 1 Gm. daily.

In at least two thirds of patients treated with 1.8 to 2.0 Gm. of streptomycin daily for three or four months, the infecting tubercle bacilli become highly resistant to the action of streptomycin, and further therapy is presumably futile. This resistance probably represents an outgrowth of naturally resistant variants which are present among most or all virulent strains of tubercle bacilli. Once acquired, resistance is often, but not always, permanent. Resistance may develop as early as the sixth week; therefore, when streptomycin is given in conjunction with surgery to prevent postoperative spreads, the preoperative course of treatment should be brief. Sensitivity tests should be performed on tubercle bacilli isolated from all patients prior to therapy, for cases are appearing in whom the organisms are highly resistant on primary isolation, and in whom the disease was apparently contracted from streptomycin-treated patients. The development of resistance is dependent more on the duration of therapy than upon the size of the daily dose. Thus, resistance develops in only 25 per cent of cases treated for 42 days, whereas in those treated for three or four months, 75 to 80 per cent develop resistance, regardless of the daily dose.

Dihydrostreptomycin, a hydrogenated derivative of streptomycin, appears to possess the same therapeutic efficacy as streptomycin, but has the advantage of being considerably less toxic. Vestibular damage, particularly, is minimized by its administration; the majority of patients can tolerate 2 Gm. daily for at least 60 days with no manifestations of vestibular damage. Further, dihydrostreptomycin is tolerated well by patients who develop fever, rashes, and other sensitivity reactions from streptomycin. If preliminary results (late 1948) are borne out by large-scale studies, it is probable that dihydrostreptomycin will supplant streptomycin in the treatment of tuberculosis.

TREATMENT OF SPECIAL CONDITIONS ASSOCIATED WITH PULMONARY TUBERCULOSIS

The general principles underlying the treatment of pulmonary tuberculosis have been described above, but the management of certain features deserves special consideration.

Hemoptysis. Pulmonary hemorrhages are not infrequent in patients with pulmonary tuberculo-

sis, and represent a dangerous and alarming complication. Fortunately, closure of the ulcerated blood vessel occurs quite promptly in most instances, so that death from acute exsanguination is rare. Allaying fears of the patient concerning a possible fatal termination of the episode is an important part of the management of hemoptysis. The patient is instructed to lie on the affected side, to prevent sanguineous material laden with bacilli from flowing into other parts of the lungs and spreading the disease. If the side from which the blood is coming is not known to the physician from previous examination and x-rays, the patient often can sense it from a peculiar feeling in one side of the chest. Although he lies mostly on the affected side, for a few minutes every hour the patient should roll onto the other side so that bloody discharges may drain into the trachea and be removed by gentle coughing. Severe coughing is harmful because the forced inspiration preceding each cough causes material to be aspirated into all parts of the lungs. The time-honored warning against injudicious use of opiates is sound, but small doses of codeine may be a valuable aid in preventing spread of the disease by converting a severe intractable cough into one that is mild but effective. The patient usually brings up dark clots of blood over a period of several days as the episode subsides. In some instances the bleeding continues or recurs, and in such cases it may be necessary to institute artificial pneumothorax, which allows the bleeding vessel to contract, and usually terminates the hemorrhage. If possible, pneumothorax should be avoided, since collapsing the lung during the acute episode impairs drainage of the retained secretions, and the danger of pleural complications is great. If artificial pneumothorax is unsuccessful, phrenemphraxis or pneumoperitoneum is occasionally instituted in an attempt to stop the bleeding. If bleeding persists, reducing the erythrocyte count to low levels, transfusions should be given. Many drugs, such as calcium gluconate, atropine, and nitroglycerin, have been thought to be effective in isolated cases of hemoptysis, but their general use cannot be recommended. Similarly, ascorbic acid and vitamin K are often administered, but are probably helpful only in very rare instances. In spite of the best care and the patient's complete coöperation, posthemoptysic spreads are all too common. One encouraging feature of this situation is that the

fresh exudative lesions which follow hemoptysis respond extremely well to streptomycin therapy. In many instances, of course, the exudative "spread" is mostly blood, which disappears on rest alone within a few weeks; this makes it difficult to evaluate the effects of streptomycin in any given case.

Spontaneous Pneumothorax and Bronchopleural Fistula. Spontaneous pneumothorax is a relatively common occurrence in young adults. It usually begins suddenly with a sharp pain in the anterior chest, and in the majority of instances is due to the rupture of a subpleural bulla. The bulla may be secondary to fibrosis caused by tuberculosis or other infections, or it may be congenital. Following the rupture, the pleura usually does not become infected, the tear seals off promptly, and the lung re-expands in a period of weeks or months. The management of such cases consists in watchful waiting plus an attempt to demonstrate an active tuberculous focus. In many cases the pneumothorax is recurrent and, if repeated frequently, may become very troublesome. Thoracotomy with suture of the lung tissue surrounding the bulla has brought about a cure in some such instances. The available evidence indicates that only a small percentage of spontaneous pneumothoraces are tuberculous in origin, and therefore bed rest is not prescribed unless a parenchymal focus is demonstrated or tubercle bacilli are recovered. The patient's activities are restricted while the lung is re-expanding, but thereafter, except for periodic x-rays and examinations, he is allowed to resume his normal life.

Occasionally, the tear in the pleura results in a valvelike mechanism in which air enters the pleural space during inspiration, but cannot leave during expiration. This causes a tension pneumothorax, with progressively increasing intrapleural pressure and mediastinal deviation, and death may ensue unless the opening is sealed off or treatment is instituted. Treatment consists of aspirating air to relieve the increased pressure. This may be done intermittently at first, but continuous removal through a catheter attached to an aspirating apparatus, or placed under water in a bottle at the bedside, is often necessary for a period of days or weeks before the fistula is closed. In some instances lobectomy or pneumonectomy is performed if the fistula remains patent.

When tuberculous in origin, spontaneous pneumothorax results from the ulceration of a subpleural caseous focus, or the rupture of a tuberculous cavity directly into the pleural space. If possible, the lung should be re-expanded at once, using catheter drainage with controlled suction, for this is a much more serious situation than the rupture of a bulla. In this instance the fistula carries large numbers of tubercle bacilli into the pleural cavity, causing infection, fluid formation, and the development of empyema. This may be a pure tuberculous empyema, or other organisms, such as streptococci and staphylococci, may pass through the fistulous opening to form a mixed infection empyema. An open bronchopleural fistula with empyema is a dangerous situation; the empyema fluid may drain slowly through the fistula into the bronchi and lungs, causing widespread dissemination of the disease, or, if the fistula suddenly enlarges, several hundred milliliters of pus may flood into the bronchial tree, causing the patient to drown in his own secretions. A patent bronchopleural fistula is suspected when the patient coughs up material similar to pus aspirated from the chest, and may be proved by injecting methylene blue into the empyema cavity and subsequently observing the dye in the sputum. Once diagnosed, a bronchopleural fistula is an indication for surgical drainage because of the dangers mentioned above, and because of the failure of mixed-infection empyemas to respond to aspiration and irrigations. A total thoracoplasty usually is necessary at a later date.

Tuberculous Empyema. This condition is considered separately, for its management differs somewhat from that of bronchopleural fistula with mixed-infection empyema. Pure tuberculous empyema may appear spontaneously, or may represent a complication of artificial pneumothorax. In the latter instance the fluid is serous at first, and gradually thickens. There is a tendency to regard all effusions as empyemas if tubercle bacilli can be recovered. This is misleading, for with clear effusions the prognosis is much more favorable than in pure tuberculous empyemas in which the fluid is thick, purulent, and swarming with bacilli. Tuberculous empyemas sometimes are cured by repeated aspirations and irrigations, but usually they are not. Streptomycin is of little if any value in this condition. Open surgical drainage is contraindicated because of

the almost inevitable development of mixed-infection empyema from entry of pyogenic bacteria through the opening in the chest wall. Unless the lung can be re-expanded and the empyema obliterated within a relatively short period, the visceral pleura thickens and the empyema becomes chronic. Total thoracoplasty is then necessary, with aspiration of pus at frequent intervals as the operation is done in stages from above down. As unroofing procedure of the Schede type, which is dangerous and deforming, is sometimes required finally to obliterate the space.

Fibrinous and Serofibrinous Pleurisy. Pleural involvement occurs in most cases of pulmonary tuberculosis. One indication of this is the high incidence of pleural adhesions in patients receiving artificial pneumothorax. The adhesions result from localized areas of fibrinous pleurisy overlying peripherally located parenchymal foci, and the apposition of the two pleural surfaces aids in localization of the process. With fibrinous pleurisy, symptoms may be absent or there may be sharp, pleuritic pain, and a friction rub may be detectable. The course of fibrinous pleurisy is usually mild, and, except for local palliative measures, attention should be directed at the underlying parenchymal disease.

Five to 10 per cent of patients with pulmonary tuberculosis develop serofibrinous pleurisy. When parenchymal pulmonary lesions are demonstrable by x-ray, the tuberculous etiology of the serous effusion usually is readily established by sputum studies. In many instances, however, especially in young adults, no parenchymal lesions are visible and the underlying process is obscure. In 30 to 50 per cent of such effusions a diagnosis of tuberculosis can be made by culturing tubercle bacilli from the pleural fluid. In the remainder no definite etiologic cause can be demonstrated. Experience has taught, however, that without rest treatment a third to a half of individuals with "nonspecific" serofibrinous pleurisy develop clinical pulmonary tuberculosis within five years, and it is therefore now generally agreed that the cause is, in most if not all instances, tuberculosis.

Serofibrinous pleurisy results from the discharge of tubercle bacilli into the pleural cavity from an adjacent tuberculous lesion, usually a subpleural pulmonary or lymph node focus, more rarely an abscess originating in a rib or vertebral body. Hematogenous seeding is thought to ac-

count for some effusions, especially when they are bilateral, but experimental evidence indicates that tubercle bacilli do not pass freely from the blood stream into serous cavities. In patients with "nonspecific" effusions, the subpleural tuberculous focus is presumably too small to be visible on the roentgenograms.

The onset of serofibrinous pleurisy is extremely variable. It may be insidious, with gradually increasing fever, malaise, and vague discomfort in the chest, or there may be sudden, severe pleuritic pain, with high fever and marked prostration. Care must be taken to exclude other causes of serous effusions, such as pneumonia; a careful analysis of clinical signs and symptoms prior to the onset of the effusion is usually adequate to make this differential.

Fluid is aspirated initially for diagnosis. After removal of most of the effusion, 100 ml. of air may be injected into the pleural space, allowing the remainder of the fluid to fall to the base so that the pulmonary parenchyma can be visualized clearly on the x-ray. Opinion is divided as to whether repeated aspirations should be performed if the fluid persists and increases in amount after the first tap. Many authorities favor removal only when the effusion becomes so large that respirations are interfered with, or when absorption of the fluid seems unduly slow. Others, including the author, feel that fluid should be removed repeatedly to prevent incarceration of the lung. The fluid usually does not reappear after several thoracenteses have been performed, and there is a minimal degree of mediastinal shift and pleural thickening. Artificial pneumothorax was used at one time in the treatment of serous effusions, particularly in the presence of cavitary disease, but it is now generally agreed that this is contraindicated because the presence of air impedes healing, and the lung often does not re-expand after being collapsed for a prolonged period in the presence of fluid.

It should be emphasized that so-called "nonspecific" pleural effusions are to be regarded as tuberculous unless proved otherwise. Tubercle bacilli are often present in such small numbers that the most careful bacteriologic studies may fail to reveal their presence; negative cultures and guinea pig inoculations do not, therefore, exclude tuberculosis as the underlying cause of the effusion. In addition to aspirations, the treatment is that prescribed for an active mini-

mal case of pulmonary tuberculosis. Bed rest should be continued for at least 6 to 12 months after the acute process has subsided, and thereafter a period of 6 months or more is allowed for the patient to return to his normal activities. X-rays should be taken every 6 months for the next several years.

EXTRAPULMONARY TUBERCULOSIS

Laryngeal and Tracheobronchial Tuberculosis.

Tuberculous laryngitis usually occurs in patients with moderately or far advanced pulmonary tuberculosis, the infection of the larynx resulting from the continual passage of bacilliferous sputum over the vocal cords and accessory structures, which are irritated by the chronic cough. Rarely, laryngeal lesions are seen in patients with little or no active pulmonary tuberculosis, and the infection then is presumably hematogenous or lymphogenous in origin. Hoarseness and a dry sensation in the throat are the common symptoms; the diagnosis can be confirmed by direct or indirect laryngoscopy, and a biopsy. The posterior part of the larynx and vocal cords are first involved, and later there are deep, extensive ulcerations of the laryngeal cartilages, including the epiglottis. With the latter there is severe pain on swallowing, which interferes with eating. Heretofore, the treatment of tuberculous laryngitis has consisted of complete voice rest, cauterization of granulations or deep ulcerations, anesthetic sprays to relieve pain, penicillin or sulfonamides to reduce secondary infection, and careful management of the underlying pulmonary disease. With streptomycin, however, the condition usually responds so well that most of the palliative measures mentioned above are unnecessary. Streptomycin is administered intramuscularly in doses of 1.0 Gm. daily, and may also be given by aerosol, although the latter seems to add little to the patient's response. There is asymptomatic improvement within a few days, and in the majority of cases the ulcers heal within a few weeks.

Streptomycin exerts a similarly favorable influence in tuberculous tracheobronchitis. Tracheobronchial lesions consist of ulcerations, or of granulomatous infiltrations which tend to occlude the bronchial lumen as they undergo fibrosis and healing. Stenosing bronchial lesions are suspected in the presence of wheezing, especially when this is localized over one lung, or over a

single lobe. Episodes of pneumonitis occur distal to the stenosis, due to impairment of the normal drainage of secretions, and bronchiectasis may appear in the affected lobe. Bronchoscopy aids in determining the nature and extent of the tracheobronchial disease, and in assessing the efficacy of streptomycin therapy. Old fibrotic cicatricial stenoses are not benefited by streptomycin; treatment in such cases consists of topical applications or of surgical procedures, chiefly thoracoplasty or pneumonectomy. When ulcerations are present, however, or when granulomatous lesions are of relatively recent origin, the response to streptomycin therapy is usually prompt and impressive. Ulcers tend to heal within a few weeks, and local stenoses are relieved, with a marked decrease in redness, edema, and swelling of the inflamed tissue. Streptomycin is administered intramuscularly, as in tuberculous laryngitis, and may in addition be given by nebulization, although the evidence of additional benefit from the latter is not convincing.

Generalized Miliary Tuberculosis. Resulting from the sudden entry of large numbers of tubercle bacilli into the blood stream, miliary tuberculosis is characterized by seeding throughout the tissues of small foci which are all of roughly the same age and size. The source of the bacilli is probably, in most instances, a caseous hilar or mediastinal lymph node which erodes into a blood or lymph vessel. Caseous foci in other organs, such as the kidneys, bones, adrenals, and prostate, may also give rise to massive blood stream invasion. Tubercle bacilli are carried to every part of the body, but, due to curious differences in natural resistance, some organs, such as the pancreas, thyroid, skeletal muscles, brain, and stomach, show little or no involvement as contrasted with the densely scattered lesions distributed throughout the rest of the body.

Miliary tuberculosis occurs most frequently during the period when the primary complex is active; the peak is during early childhood. The condition is not rare, however, in adults. The onset may be sudden, with high fever, aching, chilliness, and prostration, or it may be gradual, with an initial period of general malaise and weakness. Cough is not a striking feature, and if present is usually mild and nonproductive. The diagnosis often remains obscure until charac-

teristic miliary lesions appear on the roentgenogram, which may not be until several weeks following the onset of symptoms. In general, when there is an acute onset with high fever and marked prostration, the lesions are exudative in character, while in patients with a more insidious onset and low fever, a productive type of reaction is predominant. The white blood count may vary from a picture of agranulocytosis to that of marked leukocytosis, or there may even be a leukemoid reaction in the presence of extensive bone marrow involvement. Other conditions such as lymphomas, sarcoidosis, and mycotic infections may present a clinical and x-ray picture very similar to that of miliary tuberculosis; and, since the lesions are interstitial, the recovery of tubercle bacilli, and therefore the establishment of a definite diagnosis, is often delayed for many weeks. Tubercle bacilli can in some instances be cultured from the blood or bone marrow.

Heretofore, miliary tuberculosis has been a highly fatal condition, with death characteristically occurring 6 to 10 weeks following the onset, usually from toxemia, occasionally from meningitis. This situation has been greatly altered by streptomycin, which modifies the course of the disease in a dramatic fashion. Fever and toxemia usually subside within a few days after the institution of streptomycin therapy, and within several weeks the pulmonary lesions begin to show regression. Improvement may continue until the patient is asymptomatic, and the x-ray is entirely clear. Unfortunately, in over half the cases who show this remarkable initial response to treatment there is a relapse, with the appearance of resistant organisms and a fatal termination following failure to respond to a second course of streptomycin therapy. A good many patients have remained well, however, and streptomycin should be administered in daily doses of 1.0 to 2.0 Gm. intramuscularly for three or four months to every patient who develops miliary tuberculosis. The best results are obtained when treatment is started early, and therefore streptomycin must often be administered on the basis of the clinical diagnosis alone, without waiting for bacteriologic confirmation. It is possible that the relapse rate will be lower when other drugs, such as promin, promizole, or para-aminosalicylic acid, are given in combination with streptomycin; the results so far ob-

tained would appear hopeful, but no definite statement is warranted.

Subacute and Chronic Hematogenous Tuberculosis. Instead of a single, massive invasion of the blood stream, smaller numbers of tubercle bacilli may escape intermittently from a caseous focus into the circulation, and give rise to a variety of clinical manifestations which are subacute or chronic in nature. Among the more common manifestations are low-grade fever, local or generalized lymphadenopathy, effusions into the pleural and peritoneal cavities, splenomegaly, and destructive lesions of the bones, kidneys, skin and eyes. Pulmonary lesions associated with this type of dissemination are located chiefly in the upper half of the lung fields, and the individual foci are larger than those seen in miliary tuberculosis. Nonmiliary hematogenous pulmonary lesions characteristically produce few signs and symptoms, and are often discovered accidentally. They show a tendency toward eventual healing, with marked fibrosis, emphysema, and hypertrophy of the right side of the heart. In some instances the pulmonary foci may enlarge and coalesce, leading to cavitation and bronchogenic phthisis.

The protean manifestations and bizarre clinical picture caused by subacute and chronic forms of hematogenous tuberculosis provide diagnostic puzzles which often can be solved only by cultures of secretions or discharges, or by biopsy of the affected tissues. It should be borne in mind that hematogenous foci may remain latent in various organs for many years before becoming active and causing destructive lesions.

Tuberculous Meningitis. As in miliary tuberculosis, tuberculous meningitis is more common during early childhood than at any other age period. Although not rare in adults, the percentage of adults infected with the tubercle bacillus who die of tuberculous meningitis is relatively small. Opinion is divided as to the mode of infection of the meninges, but the evidence of Rich indicates that it is caused by direct extension from an adjacent focus. In miliary tuberculosis, Rich postulates that meningitis results not from the direct escape of large numbers of bacilli into the meninges from the blood stream, but rather from miliary meningeal tubercles which gradually enlarge to produce direct extension, or that it arises from older, dormant foci which become reactivated and extend into the meningeal spaces.

Pathologically, in tuberculous meningitis the reaction consists of tubercles, edema and congestion, and a fibrinous exudate, most marked over the base of the brain. Various cranial nerves are commonly affected.

Tuberculous meningitis may occur in patients with known tuberculosis of the lungs, bones, kidneys, or other sites, or it may appear in individuals who previously were apparently entirely well. The symptoms of miliary tuberculosis usually precede those of tuberculous meningitis by several weeks, when the two occur together. The early symptoms of tuberculous meningitis are headache, restlessness, and irritability, and, on examination, typical signs of meningeal irritation are elicited. The spinal fluid pressure is elevated, and there is an increase in protein and cells, most of which are lymphocytes. The chlorides and sugar are depressed, moderately in some cases, markedly in others. On standing, a pellicle usually forms. Smears of the centrifuged sediment or pellicle may reveal tubercle bacilli, but in the majority of cases they do not. Repeated cultures and guinea pig inoculations are necessary at times to recover the causative organism.

Until streptomycin became available there was no urgency about establishing the diagnosis of tuberculous meningitis, since the treatment was purely supportive and the outcome almost always fatal. Now, however, there is a need for prompt diagnosis and institution of treatment. Unless tubercle bacilli are seen on direct smear of the pellicle or spinal fluid, a bacteriologic diagnosis unfortunately requires a minimum of three to six weeks; treatment must, therefore, be started in many cases before the organisms are recovered. Early differentiation between tuberculous meningitis and meningitis due to other agents, chiefly viruses, is at times impossible; in such cases streptomycin should be administered if tuberculosis seems the probable cause on the basis of a positive tuberculin test, marked depression of the spinal fluid sugar and chloride, positive Levinson test, and the general clinical picture.

Streptomycin is administered intramuscularly in doses of 1.5 to 3.0 Gm. daily for at least three or four months. Intrathecal injections of 50 to 75 mg. are given daily for the first two weeks, and three times weekly thereafter for another six to eight weeks. Superior results have been obtained by combining promizole with streptomycin in the treatment of tuberculous meningitis. Pending

final evaluation, combined therapy would appear justified, since there is little increase in toxicity, and the results with streptomycin alone leave much to be desired. In the majority of patients treatment is accompanied by a return of the temperature to normal, and a temporary disappearance of signs and symptoms of meningeal irritation. The spinal fluid may return to normal except for a persistent elevation of the protein and, at times, of the cell count.

Relapses, which have been noted in over three fourths of the patients treated, occur weeks or months after streptomycin is discontinued; there is a return of clinical symptoms and signs of meningitis, and a recurrence of the spinal fluid abnormalities. Streptomycin should again be administered, and in some cases brings about a favorable response for a second time, though in most instances the disease is now refractory to treatment and runs a rapidly downhill course. Details of the development of resistance and its relation to the response of the patient have not been thoroughly worked out, and therefore it would seem advisable to continue treatment as long as there is any indication of a beneficial effect.

Tuberculosis of Lymph Nodes. Tuberculosis of the hilar and mediastinal nodes, which is the commonest form of tuberculous lymphadenitis, has its inception during the primary infection, when tubercle bacilli escape freely from the initial pulmonary parenchymal focus and are carried by the lymphatics to the regional nodes. Children with a primary infection may have massive lymph node involvement with few if any constitutional manifestations. The symptoms in such cases are due chiefly to pressure on surrounding structures, and consist of wheezing, dyspnea, and a severe hacking cough. In addition, compression of a bronchus may cause collapse of one or more lobes, with nonspecific pneumonitis distal to the site of the narrowing. An enlarged caseous node also may occasionally ulcerate into a bronchus and liberate large numbers of tubercle bacilli, causing widespread tuberculous pneumonia. The treatment of tuberculous adenitis of the broncho-pulmonary and mediastinal nodes consists mainly of rest, and, except when there is perforation into a bronchus or when death results from a progressive primary complex, the involved nodes show a marked tendency to heal and become calcified. Even with

apparent healing, however, tubercle bacilli may remain viable in the nodes for long periods and cause a reactivation of the process with dissemination throughout the body years after the initial episode. Aside from rest, x-ray and tuberculin therapy are sometimes recommended, but are of questionable value and are potentially dangerous because excessive doses may aggravate tissue necrosis. Calcified nodes occasionally perforate into a bronchus many years after the primary complex apparently has become arrested. This condition, known as *broncholithiasis*, is characterized by pneumonitis, hemoptysis, and expectoration of small bits of calcified material.

Cervical adenitis or scrofula has become relatively uncommon in the United States in the past 50 years as a result of the elimination of tuberculous cattle and the widespread pasteurization of milk. Direct extension of tubercle bacilli through the tissues of the pharynx or tonsils has thus been virtually eliminated, but cervical adenitis of lymphohematogenous origin is still observed in both adults and children. The swelling usually begins insidiously, and may involve one or many nodes. The lymph nodes tend to be matted together, but this is not very reliable as a diagnostic feature. The skin may later become red and tender, and perforate at one or more sites, permitting the drainage of rather thick, greenish yellow pus. The treatment of tuberculous cervical adenitis is prolonged rest, which usually results in subsidence and arrest of the process, although there may be recurrences and exacerbations for many years. Surgical excision is resorted to in some instances if the nodes remain chronically inflamed, especially if there are multiple fistulas with extensive scarring. Heliotherapy is widely used, and seems of definite value in promoting the healing of sinuses. X-ray and tuberculin therapy also are advocated, but have the limitations mentioned in connection with mediastinal nodes. Streptomycin is of definite aid, especially in bringing about the closure of tuberculous sinuses. Prolonged intramuscular administration of 1 Gm. of streptomycin daily is the usual regimen; topical application is of little or no value. The efficacy of streptomycin in treating hyperplastic nodes without draining sinuses cannot be finally stated; the early results are often favorable, but relapses are not uncommon.

Tuberculosis of abdominal lymph nodes occurs

as a result of generalized hematogenous spread, or drainage from local lesions. Vague abdominal pain, indigestion, and at times constipation, may result. The treatment is rest.

Gastrointestinal Tuberculosis. Tuberculous ulcers occur occasionally on the tongue, lip, pharynx, and tonsils. The diagnosis is made by curetting or excising a small portion of the involved tissue and preparing microscopic sections. Treatment has been revolutionized by streptomycin, for in the past the ulcers have often responded very poorly to cauterization and heliotherapy. Intramuscular administration of streptomycin brings about alleviation of the pain within a few days, and complete healing of the ulcer in almost all cases within a month or two. Small doses of streptomycin, 0.5 to 1.0 Gm. given daily in one or two doses, are usually adequate.

Tuberculosis of the esophagus and stomach is rare. The *intestine*, however, especially the lower ileum and cecum, is frequently involved in patients with advanced pulmonary tuberculosis as a result of swallowing bacilli. The symptoms of ileocecal tuberculosis are variable, consisting chiefly of intermittent indigestion, colicky pain, constipation, and diarrhea. The appearance of any unusual gastrointestinal complaints should arouse suspicion, especially in patients with far advanced pulmonary involvement. A moderate to advanced blood loss type of anemia is common, and should direct attention to the intestinal tract whenever present in patients with pulmonary tuberculosis. X-ray studies of the ileocecal region following a barium meal provide valuable confirmatory evidence of spasticity and hypermotility. The treatment is directed at both the pulmonary lesions and the ulcers in the bowel. For the latter a low-residue, bland diet diminishes irritation of the bowel wall, and opium derivatives or bismuth compounds are given to relieve the pain and diarrhea. Streptomycin, administered both orally and intramuscularly, has brought about striking symptomatic improvement in most of the cases so far reported. Oral administration alone is less effective, and it is probable that the greatest benefit is derived from the parenteral route.

Tuberculous peritonitis results from extension of local lesions in the intestine, lymph nodes, or genital tract, or it may be caused by hematogenous spread from other parts of the body.

Serofibrinous peritonitis usually has an insidious onset, with mild constitutional symptoms and vague intestinal complaints. As with serofibrinous pleurisy, however, the onset may in some cases be acute, with high fever, severe abdominal pain, and marked prostration. Fluid often appears, especially in the more toxic cases, and may require repeated aspirations to relieve the distention and discomfort. Except for paracenteses, the treatment consists of bed rest, and the administration of streptomycin, which produces a favorable response in most cases. Empiric observations of improvement following laparotomy do not justify this as a routine procedure, for in many cases improvement has not been noted, and controlled studies proving the efficacy of this not innocuous procedure have not been reported. Nevertheless, since a definite diagnosis of tuberculous peritonitis often is made only at operation, a laparotomy often will be performed. With prolonged rest, and the addition of heliotherapy after the acute stage has subsided, the outlook is, in most cases, good unless the peritonitis occurs in conjunction with generalized miliary tuberculosis. As healing occurs thick adhesions may form, matting the intestines and omentum together, interfering with normal peristalsis, and causing stenosis of various portions of the bowel. Constipation then becomes a stubborn symptom, and at times complete obstruction may ensue. Unless the adhesive process is localized and surgically resectable, as it sometimes is in the region of the cecum, the treatment is symptomatic and palliative; streptomycin is of no value at this stage, except as an adjunct to surgery.

Genitourinary Tuberculosis. *Tuberculosis of the kidney* is caused in most instances by hematogenous dissemination from foci in the lungs or lymph nodes; occasionally infection may come from the genital tract. Small foci may remain latent in the kidneys for long periods before causing destructive lesions; many patients with renal tuberculosis show no evidence of active pulmonary disease. As the ulcerative lesions in the kidney enlarge, tubercle bacilli escape into the urinary tract, and often infect the ureters and bladder. Dysuria and hematuria are the main symptoms, but cases of renal tuberculosis are not infrequently diagnosed before symptoms appear. Blood and pus are found in the urine, and tubercle bacilli are recovered from the centrifuged sediment by culture or guinea pig inoculation.

Intravenous and retrograde pyelograms show more or less characteristic renal ulcerations, and retrograde studies are particularly helpful in determining whether the involvement is bilateral, and the extent of functional impairment on one or both sides. If there is moderate or marked destruction of one kidney with little or no involvement on the other side, nephrectomy should be performed to ameliorate or prevent tuberculous cystitis, and to remove the focus which is a potential source of spread to other organs. Preliminary experience with streptomycin indicates that few cases of renal tuberculosis are cured by this therapy alone. Administration of streptomycin does, however, bring about marked symptomatic improvement and causes regression of the bladder lesions in many cases. The urine may be sterile during treatment, but tubercle bacilli often reappear when streptomycin is discontinued. A judicious combination of surgery and preoperative and postoperative streptomycin therapy is probably the procedure of choice in unilateral renal tuberculosis. As in other forms of tuberculosis, the importance of prolonged rest, in addition to streptomycin and surgery, should of course be kept in mind. In far advanced bilateral cases in which nephrectomy is not possible, streptomycin may cause temporary improvement of renal function and give prolonged symptomatic relief. It may also be of value in conjunction with other surgical procedures such as transplantation of the ureters.

Genital tuberculosis is almost invariably hematogenous in origin, and in the male involves the prostate, seminal vesicles, epididymides, and occasionally the testes. Infection of the genital tract may, in occasional instances, be secondary to renal tuberculosis, with tubercle bacilli in the urine infecting the genital organs. Clinically, involvement of the epididymis is diagnosed most frequently, although pathologic examinations reveal a higher incidence of tuberculosis of the prostate and seminal vesicles. Tuberculous epididymitis often begins insidiously, with a gradual development of nodular infiltrations which are moderately tender to palpation. In some cases the onset is acute, causing sudden swelling, redness, and marked tenderness of the epididymis and surrounding structures. With rest and symptomatic measures, the acute process usually subsides in several weeks. In some clinics the epididymis is resected during the acute stage to

minimize the possibility of involvement of the testis; in the opinion of the author conservative measures are to be preferred. In the more chronic stages it is generally agreed that surgical excision is indicated, especially if the involvement is unilateral; the seminal vesicles are also removed if they are infected. Streptomycin therapy is often a valuable adjunct, particularly in the more acute stages, and in the prevention and treatment of draining sinuses when surgery is performed.

Genital tuberculosis in the female involves the Fallopian tubes more frequently than the other organs, and the lesions are more often unilateral than bilateral. Less commonly, the ovaries and uterus may be the site of destructive lesions; the cervix, vagina, and labia are rarely affected. Vague, irregular lower abdominal pain may be the only symptom of tuberculous salpingitis, and an adnexal mass, usually unilateral, may be found on pelvic examination. If the uterus is involved, tubercle bacilli may be present in the vaginal discharge, or tuberculous tissue may be removed by curettage. The menses may be normal, but in advanced cases are usually scanty or absent. Tuberculous salpingitis is a potentially dangerous condition since it may cause localized and sometimes diffuse peritonitis. For this reason surgical removal of the affected tube is indicated if the patient's condition is good and the tuberculous involvement is well localized.

PROGNOSIS

Prognosis in tuberculosis is difficult because of its chronicity and the many circumstances which influence the course of the disease. Perhaps the most important factor is the nature and extent of the lesions at the time treatment is instituted. Lesions which are limited in extent and productive in character tend to regress and heal readily with adequate treatment. Exudative infiltrations, on the other hand, are characterized by instability and a tendency to cavity formation, and the eventual outcome is more likely to be unfavorable. The presence of cavities, especially those over 2 cm. in diameter which are not amenable to collapse therapy, is a serious prognostic sign, and in the majority of cases leads to death within five years. Other important factors, which have been considered in preceding sections, are the age, sex, and color of the patient, the presence of complications or extrapulmonary

lesions, the clinical symptoms, and the patient's native resistance and response to treatment. It is assumed, of course, that the patient is willing to coöperate; all too often, unfortunately, he is not.

The advent of streptomycin has raised the hope that the outlook for patients with tuberculosis, admittedly none too good at present, will be greatly improved in the future. While not curative in itself, streptomycin exerts a profound effect on the course of the disease which favorably alters the prognosis in many cases. It is not too much to hope that other more powerful agents will be discovered which will, alone or in conjunction with surgical procedures, bring about a favorable outcome in the majority of patients.

PREVENTION AND ERADICATION OF TUBERCULOSIS

The remarkable decline in the mortality rate from tuberculosis during the first two decades of the twentieth century led a number of careful students of the problem to predict the virtual eradication of the disease by 1950 or earlier. This prediction has not come true. The decline has continued, but the curve has flattened out since 1930; the mortality rate in 1945 was still 39.7 per 100,000 population. The fallacy in the prediction lay in the assumption that the number of individuals harboring active lesions would fall so low that the disease would cease to propagate itself. This has not occurred; as pointed out in the section on Prevalence and Incidence, the decline in the mortality rate is probably due chiefly to improved living conditions and other factors which tend to increase resistance, but the incidence of infection of the population as a whole remains relatively high. This means that a large number of individuals with active disease are not hospitalized, and remain at large to infect the general populace. Evidence indicating the occurrence of such "carriers" is provided by the fact that no apparent source of contact can be found for most adults with pulmonary tuberculosis. Autopsy studies further indicate that undiagnosed cases of active tuberculosis are common in older people, especially men, and that individuals past 50 may constitute one of the chief sources of continued infection.

Preventive measures which have, in addition to the improvement in living conditions, contributed greatly to the advances accompanying

the antituberculosis campaign are: earlier diagnosis and treatment, isolation of active cases, better hospital facilities, programs for the rehabilitation of patients with arrested disease to prevent relapse, examination of close contacts of tuberculous patients, large-scale x-ray surveys, elimination of tuberculous cattle, and pasteurization of milk. Much has been accomplished, but in almost every one of the above categories the present efforts and results fall far short of what is desired.

BCG (Bacillus Calmette-Guérin), an attenuated bovine tubercle bacillus, has been used widely abroad for vaccination against tuberculosis. Controlled studies of its efficacy are difficult to conduct, but the experiments which have been made seem to provide objective and impressive evidence of its value. Protection is by no means complete, but the available evidence indicates that a sufficient degree of acquired resistance is conferred to warrant its use among tuberculin-negative groups in which exposure to tuberculosis is especially likely to occur. Examples are tuberculin-negative nurses, medical students, and individuals living under poor economic conditions in overcrowded urban areas.

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Leprosy (Hansen's Disease)

Gustave J. Dammin

Definition
History
Etiology
Epidemiology and Pathogenesis
Pathologic Anatomy
Clinical Classification
Clinical Course
Laboratory Diagnosis
Differential Diagnosis
Treatment
Prognosis
Control

Definition. Leprosy is a specific infectious disease of man caused by the *Mycobacterium leprae*. It is usually characterized by a long incubation period, a long course with exacerbations and remissions, and involvement primarily of the skin and mucous membranes and/or the peripheral nervous system.

History. Whether leprosy as it is understood today was described in the ancient records has been questioned. In Europe, leprosy appeared first in Greece in the fourth century B.C., probably having been introduced from the East. It spread northward and westward and had affected most of Europe by the end of the tenth century A.D. Leprosy was prevalent in Europe until the fourteenth century and then began slowly to decline.

As leprosy was declining in Europe, it was being spread to the Western Hemisphere by the slave traders and the discoverers from Portugal and Spain. In the United States, leprosy appeared first in Louisiana in 1758, presumably spread from the West Indies. Additional foci

were established from other sources, in Minnesota from Norway, in California from China and India.

Most dramatic has been the spread of leprosy in the Pacific islands, where today the highest rates in the world are found (Nauru—59 per 1000). There are estimated to be five million cases of leprosy in the world today.

Etiology. *Mycobacterium leprae*, described by Hansen in 1874, is accepted as the causal agent in human leprosy, even though the organism has not been cultivated and attempts to transmit leprosy to animals or human beings have not been successful.

Mycobacterium leprae is a pleomorphic, acid-fast, nonspore-forming, Gram-positive bacillus. Lepra bacilli differ from tubercle bacilli in that they (1) are found in tremendous numbers in lesions (lepromatous) in the form of packets, palisades, and globular masses (globi) both intra- and extracellularly; (2) decolorize more readily; (3) may be stained with the stronger bacterial stains; and (4) cannot be cultivated or produce disease in animals following inoculation.

Epidemiology and Pathogenesis. The exact mode of transmission is not known. A history of prolonged direct contact usually beginning in childhood is common. Leprosy may not manifest itself clinically until one to five years after the period of exposure, and appears most often during the third decade of life. Resistance to leprosy appears to increase with age.

Leprosy is not transmitted to the offspring, and it is well known that infants born of leprous parents, if removed and reared in an environment permitting no contact, do not develop the disease. Those not removed are likely to develop leprosy in early life.

Of interest are cases recognized as accidental inoculation leprosy. A recent report concerns two marines who "were tattooed successively by the same man in Melbourne, Australia, on the same day in June 1943. Both developed maculoanaesthetic leprosy in the tattoos about $2\frac{1}{2}$ years later" (Porritt and Olsen).

Lepra bacilli leave the body by many routes. In lepromatous leprosy, they may escape in the secretions and excretions and through any interruption in the involved skin and mucous membranes. The route by which they enter a new host is not exactly known, but it is believed that infection occurs by way of the skin and mucous membranes following direct contact. The cheeks, extensor surfaces of the extremities, the feet, and the buttocks commonly show the initial lesion.

Once in the body, the bacilli are probably spread by way of the lymphatics and blood stream and by autoinoculation. Localization occurs primarily in the skin and/or nerves, and in advanced cases of lepromatous leprosy, bacilli are found in many of the viscera. Bacillemia occurs more commonly in the lepromatous type.

Pathologic Anatomy. The lesions may best be classified according to their microscopic appearance. This leads to the recognition of three principal types: (1) the lepromatous (L), (2) the tuberculoid (T), and (3) the nonspecific or uncharacteristic (I). This classification, known as the "South American," is applied also to the clinical types. Since a single histologic type of lesion predominates regardless of the body systems involved, this classification has much to recommend it.

X In the lepromatous type, bacilli are numerous, they multiply intracellularly, there is little cellular response and little evidence of resistance to the disease. The cutaneous lesions are symmetric and take the form of nodules, papules, macules, and diffuse infiltrations. Most characteristic is the appearance of the leproma or nodule. It is distinguished by the "lepra cell," a large macrophage containing numerous bacilli and fat droplets. In large accumulations, bacilli form globi and rosettes (fig. 150).

The tuberculoid lesions are observed in cutaneous leprids and the affected nerves. The leprids are often macules, and usually asymmetric in distribution. Bacilli are few or absent, and epitheloid cells, giant cells, lymphocytes, and plasma



FIG. 150. Lepromatous leprosy with characteristic distribution of lesions. (Courtesy, Faget, Pogge, and Johansen; *Pub. Health Rep.*, 61:960, 1946.)

cells are present, often in the form of tubercles (fig. 151).

The nonspecific or uncharacteristic type of lesion contains few bacilli and shows a slight cellular reaction which is limited to the perivascular and perineural areas. The gross lesions in the skin and nerves are not characteristic or advanced enough to permit classification with the principal clinical types and are regarded as transitional.

Clinical Classification. The South American combined clinicopathologic classification is recommended as more logical than the Cairo classification, which recognizes lepromatous (L), neural (N), and mixed (L-N) types, since more direct clinical, immunologic, bacteriologic, and epidemiologic correlations are possible. That is, regardless of the sites involved, the lepromatous

type is characterized by a relatively rapid course, a negative lepromin reaction, and lesions containing many bacilli, and because of this, is an "open" or dangerous type for the community. The tuberculoid type has a more chronic course,



FIG. 151. Tuberculoid skin lesion in its classic form shows a central depressed area of recession and an elevated, red, sharply defined margin of activity. The lesion is anesthetic and usually bacteriologically negative. (Courtesy, Ash and Spitz; "Pathology of Tropical Diseases," Philadelphia, W. B. Saunders Co.)

shows more resistance to the disease, has a positive lepromin reaction, has few bacilli in the lesions, and is therefore a "closed" type and less of a community hazard. The nonspecific type is viewed as a transitional form. The lepromin reaction in this type has prognostic significance since many cases with negative reactions develop into the lepromatous type and those with positive reactions into the tuberculoid type. The neural type (Cairo classification) is included in the tuberculoid types of the South American classification.

Although distribution of types varies in different geographic areas, the tuberculoid type is usually preponderant.

Clinical Course. The onset is often unheralded and difficult to date. The incubation period is long, varying from months to many years, and averages about three to five years. Claims of very long incubation periods must be scrutinized, since minor lesions are likely to remain unrecognized for long periods.

Initial skin lesions of the lepromatous type usually are found on the extensor surfaces, the forehead, cheeks, and ears. Their development may be so gradual that the changes may be noted by others before the patient himself is aware of them.

Early signs of mucosal involvement in the upper respiratory and intestinal tracts may be evidenced by nasal discharge, dysphagia, and hoarseness and dyspnea due to laryngitis.

The patient with the tuberculoid type is more likely to be aware of the disease early. The initial lesions usually take the form of hypopigmented or erythematous anesthetic macules. Subjective manifestations due to neural involvement consist of numbness, tingling, and formication, and the skin may show burns or other lesions which the patient states are painless.

The progressing cutaneous leprids of tuberculoid leprosy enlarge and clear centrally. The central area is anhidrotic and anesthetic to light touch, pain, and thermal stimuli. The nerves later are thickened and tender if the disease progresses. Before nerve destruction and atrophy occur, pain of a neuritic type may be prominent. Late stages are characterized by resorption of the small distal bones of the hands and feet and painless ulcers of the extremities.

Although more marked in lepromatous leprosy, generalized lymph node enlargement is common in all types of leprosy.

The status of the so-called "lazarine type" of leprosy has been clarified recently by Pardo-Castello and Pineyro. They have observed bullous and necrotic lesions in both lepromatous and tuberculoid leprosy. For this reason, such lesions are accepted as representing a "lazarine phenomenon" rather than a particular type of leprosy.

The lepromin (Mitsuda) test is primarily of prognostic value. The test material is prepared from lepromatous nodules. Whether prepared by the Mitsuda or the Dharmendra method, the material is seen microscopically to consist almost entirely of bacilli. The latter method, involving chloroform and ether extraction, results in a bet-

ter antigen which is constant enough for standardization. Normal individuals and those with tuberculoid leprosy generally show positive reactions, and lepromatous cases, negative reactions. A satisfactory therapeutic response is shown by the transformation of a negative to a positive reaction in the lepromatous type.

The histamine test may be of assistance when the skin lesions are atypical or the neurologic examination cannot be satisfactorily performed. The normal cutaneous response to a needle prick through a drop of 1:1000 histamine consists of a wheal with surrounding erythema. When there is impairment of neural function in leprosy, only the wheal and no erythematous halo appears.

The pilocarpine test, showing impairment of the sweating response to intradermally injected pilocarpine, is helpful in identification of the leprid.

Laboratory Diagnosis. Although clinical findings are usually sufficient for diagnosis, demonstration of the bacilli or the histopathologic lesions are often desirable for confirmation or to observe response to therapy. In searching for bacilli in a suspected lepromatous case in which the skin lesions are not distinctive, the ear lobule should be examined. The lobule is held firmly enough to cause blanching. A small incision is made with a sharp scalpel and the material which can be scraped from the edges is spread on a slide. Stained by the Ziehl-Neelsen or fuchsin method, a positive lesion will show numerous acid-fast bacilli. In suspected tuberculoid leprosy, a biopsy is often helpful.

Differential Diagnosis. In nonendemic areas, leprosy is seldom diagnosed early. Once leprosy is suspected, clinical and laboratory procedures are usually successful in establishing the presence or absence of the disease. It must be differentiated from syphilis, superficial fungous infections, lupus vulgaris, lupus erythematosus, vitiligo, dermal leishmaniasis, yaws, seborrheic dermatitis, psoriasis, Boeck's sarcoid, rheumatoid arthritis, nonspecific neuritis, syringomyelia, and neurofibromatosis. Differentiation from syphilis may be difficult because of clinical similarity and the frequent appearance of positive serologic tests for syphilis in leprosy. No serologic tests currently in use, including those using cardiolipin, can differentiate between the two diseases. Important procedures in differential diagnosis are (1) the examination of cutaneous and mucosal le-

sions for *M. leprae*, (2) study of skin sensation and reaction to histamine and pilocarpine, and (3) examination of the peripheral nerves for thickening and tenderness.

Treatment. Several considerations must be heeded in evaluating the efficacy of therapy. Firstly, leprosy is an intermittently progressive chronic disease during which temporary and even permanent spontaneous arrest can occur. Secondly, the patient seeks treatment during and toward the end of an exacerbation which may naturally be followed by a remission of variable duration. Thirdly, the initial appearance of an exacerbation may be precipitated by a more or less self-limited disease—e.g., malaria or dysentery—or by an unfavorable nutritional and hygienic state, which, when corrected, may be followed by a remission. Clinical and laboratory observation over a period of years is, therefore, necessary for proper evaluation of therapy.

The use of chaulmoogra and the sulfones can only be mentioned here. Complete accounts of therapy are contained in the References. The general therapeutic regimen should resemble that for tuberculosis, since much can be accomplished by good diet and regulated rest and exercise. Chaulmoogra (*hydnocarpus*) oil was long used in Asia in the treatment of leprosy, but only during the latter nineteenth century was it introduced into Western medicine. The Cairo Congress in 1938 recognized chaulmoogra oil and its esters as the most efficacious drugs for the special treatment of leprosy. Although many cases appeared to be benefited, this opinion was not concurred in generally.

Derivatives of diaminodiphenylsulfone, especially the sulfones promin, "Diasone," and promizole have produced promising results.

Usually many months to several years of treatment are required with any of the drugs mentioned. Bacteriologic examination of the lesions affords a guide to therapy. With the sulfone derivatives, some lepromatous cases have become negative in six months. It is significant, both epidemiologically and therapeutically, that lepromatous cases have shown good responses. Nineteen cases reported by Faget were treated with promin and appraised as "disease arrested following twelve consecutive months of negative bacterioscopy."

Preliminary results with streptomycin are encouraging, and, in combination with the sulfone

derivatives, it may evolve as the treatment of choice.

Prognosis. This is dependent upon the type of leprosy, the stage in which treatment is begun and the general health of the patient. The occurrence of temporary and occasionally permanent spontaneous disease arrest must be kept in mind. The tuberculoid type has a relatively better expectancy, although disability is common, and the prognosis is relatively better in so far as disease arrest is concerned. The lepromatous type has the poorer outlook, although sulfone derivative therapy has improved the outlook for this type. With the hope which the sulfone derivatives hold, it should become easier to induce patients to seek treatment earlier. Nephritis, pneumonia, and tuberculosis, by themselves or in combination, are the commonest causes of death.

Control. Segregation and early treatment of patients, particularly those with the lepromatous type, are essential. A program of control should be directed toward encouraging voluntary admission to a leprosarium. The harm the patient may do to himself and his immediate contacts by delaying treatment, and the hopefulness with which treatment can now be regarded, should be emphasized. Cultivation of a more objective and less emotional public attitude toward the disease is fundamental to any control program.

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Introduction to Diseases Caused by Fungi

D. S. Martin

Fungous infections stand at the extreme end of the spectrum of infectious diseases. From the botanic viewpoint, the term *fungous infection* should be applied to all diseases caused by bacteria, since the latter are included as members of the Schizomycetes or fission fungi. Although it is convenient to consider the pathogenic fungi as microorganisms which differ distinctly from the bacteria, it should be emphasized that there is no clear-cut line of demarcation between the pathogenic fungi and the pathogenic bacteria, but rather a gradual transition. Thus both *Actinomyces* and *Nocardia*, some of the latter being acid-fast, are considered as fungi, yet they resemble bacteria in size and growth characteristics, differing only in that they produce longer filaments and form branches.

None of the pathogenic fungi produces either an exotoxin or endotoxin, and, compared with bacteria, most of them are poor antigens. Consequently, there is little stimulation of the resistance mechanisms of the infected animal, and the infections usually are chronic in character. As in many chronic bacterial infections, there is a marked tendency for the patient to become hypersensitive to constituents of the invading fungus, and the development of tissue necrosis and abscess formation is related more directly to the degree of hypersensitivity than to any toxic action of the organism itself.

Because of the delicate balance between the infecting fungus and its host, the clinical manifestations of any infection caused by a single species of fungus are extremely varied and depend upon factors such as the site and duration of the infection and the degree of hypersensitivity which has developed. Except for sporotrichosis and some of the dermatophyte infections, an

etiological diagnosis cannot be made unless the fungus is demonstrated in the lesion either by direct examination or by culture. A fungous disease, however, always should be considered in the differential diagnosis of any chronic infection, especially one which has failed to clear up under therapy with sulfonamides, antibiotics, or other measures used to combat the ordinary bacterial infections.

Some fungous infections are endogenous in origin, the organisms maintaining a parasitic existence in or on the body, from where they initiate infection only after trauma or some unusual circumstance has permitted the entrance of the fungus into susceptible tissues. Such endogenous infections, as would be expected, occur in all parts of the world, in contrast to those acquired from exogenous sources which characteristically are found to be highly endemic in certain geographic areas or in certain population groups. Exogenous infections occur much more frequently in males than in females, in contrast to the endogenous group in which the sexes are affected almost equally.

Except for certain of the dermatophytes or "ringworm" fungi, none of the fungous infections are transmitted from man to man and no isolation of the patient is necessary.

Practically all pathogenic fungi are capable of producing lesions of the skin, but from the clinical standpoint they can be divided into three groups: (1) those which infect the internal organs of the body as well as the skin, (2) those which affect primarily the skin and subcutaneous tissues, and (3) those which can affect only the superficial layers of the body such as the skin, hair, and nails. For convenience, the various diseases will be discussed in the three groups cited.

Actinomycosis

D. S. Martin

Definition
History
Mycology
Pathogenesis
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. Actinomycosis, caused by a single species of fungus, *Actinomyces bovis*, is a chronic infection which is characterized by the formation of granulomatous lesions which tend to soften, break down, and form chronic and multiple draining sinuses.

History. The first human cases of actinomycosis were described in 1878 by Israel, who found an organism which was similar to the *Actinomyces* described by Harz in material from "lumpy jaw" in cattle. The pathogenicity of the fungus was proved in 1891 by Wolff and Israel, who were able to isolate the fungus in pure culture by culturing it under reduced oxygen tension. The morphologically similar aerobic organism, isolated from pathologic materials by Bostroem, was not true *Actinomyces* but a contaminant.

Mycology. In sections of infected tissue or in smears of lesions, *A. bovis* appears as a densely packed mass of tangled and branched mycelial threads or filaments. The filaments at the periphery of the colony may be swollen or "clubbed," but no diagnostic significance can be attached to this finding. The filaments, which are Gram-positive, are approximately the same width as bacteria, which distinguishes this fungus from the so-called higher group of fungi or molds. The colonies of the fungus in the lesions, which often are sufficiently large to be seen with the naked eye, are referred to as "sulfur granules." In sputum, the organism may be seen as branching filaments, but often they are broken up into short diphtheroid or coccoid forms. A diagnosis should not be made on the gross appearance of sulfur granules, since a similar granule occurs in some staphylococcal infections ("botryomycosis").

A. bovis is the only pathogenic fungus which re-

quires anaerobic or microaerophilic conditions for growth. The fungus should be cultured in veal or beef infusion agar shake tube or in thioglycollate broth, or streaked on brain-heart infusion agar plates and incubated under anaerobic conditions with 5 per cent carbon dioxide. The small colonies, which appear within three to four days, are rough and irregular in appearance, and are difficult to pick up with a loop. Gram-stained smears show the same type of branching, narrow filaments that are found in crushed and stained sulfur granules, but typical "clubs" are not seen in culture.

Pathogenesis. Actinomycosis is an endogenous infection, and the fungus occurs in tonsillar crypts and in the mouth around the carious teeth of many individuals who otherwise are apparently healthy. In such a habitat, the organisms are in a favorable site to invade the local tissues in the jaw or to be inhaled into the lungs or to be swallowed. It has been established beyond question that *A. bovis* does not occur in the soil or any other place in nature, so that the older conception that the infection was carried into the mouth by chewing straws or splinters of wood has no factual basis. It is believed now that trauma from such materials may provide a mode of entrance for the oral actinomycetes.

The fungus is capable of invading the skin, subcutaneous tissues, bone, liver, intestine, and other organs. Pathologically, the reaction is that of a chronic infection with suppuration, scar, and sinus formation.

Manifestations. Actinomycosis is divided into three clinical types: (1) cervicofacial, (2) thoracic, and (3) abdominal.

CERVICOFAZIAL ACTINOMYCOSIS is observed most frequently, the organisms invading by direct extension through the mucous membranes from their site in the oropharynx. Often the patient dates the beginning of his illness to an extraction, or some trouble with an infected tooth. The infection usually proceeds to the lower jaw, but it may involve the maxillary area by exten-

sion through the salivary ducts. Lesions of the maxillary bones may extend to involve the cranial bones and, in other cases, the pharynx is involved.

The swelling at first is firm with a hardness often described as "wooden," and is not especially painful, but as it develops further the overlying skin becomes discolored and sinuses form. X-ray films, in advanced cases, show the lesions of periostitis and osteomyelitis.

THORACIC ACTINOMYCOSIS results from aspiration of the fungus. Early in the disease the symptoms are not characteristic, although there is some cough with sputum, and the patient may have irregular bouts of fever. As the infection increases, the sputum becomes more purulent and may become blood-streaked. The physical signs resemble those of pulmonary tuberculosis, but actinomycosis should be suspected if the bases of the lungs are involved. The infection may extend to the pleura, involve the chest wall, and result in the formation of multiple sinuses which drain through the skin. Such sinuses occur most frequently in the skin over the lower part of the thorax. X-rays show areas of massive consolidation, which usually are bilateral and in the lower lung fields. Formation of small abscesses and scarring may cause deformities of the thoracic cage and shifting of the mediastinum. As the disease progresses, all the symptoms increase, the patient becomes dyspneic and weaker, loses weight, and dies from all the consequences of any severe disease of the lungs.

ABDOMINAL ACTINOMYCOSIS is thought to result from invasion of the intestinal mucosa by organisms swallowed along with saliva. The infection may appear in any part of the abdomen, but the appendiceal region is affected most commonly. By the time a patient seeks a physician, a painful mass already has developed, so that the diagnosis usually is made postoperatively. Involvement of the abdominal wall results in the formation of draining sinuses. Abdominal actinomycosis has a more serious prognosis, since

the infection has a tendency to spread to other organs, including such tissues as the liver, kidneys, and vertebral bodies.

Laboratory Findings. The only significant laboratory finding is the demonstration of the fungus in the lesions or in the exudates from the draining sinuses. There usually is a leukocytosis and an increased sedimentation rate. There are no practical serologic tests, and no skin-test materials are available.

Differential Diagnosis. The presence of multiple draining sinuses should suggest the diagnosis of actinomycosis, but the clinical picture is so varied that it must be differentiated from bacterial infections such as tuberculosis, staphylococcal infections, glanders, typhoid fever, regional enteritis, and syphilis; from neoplasms such as carcinoma and sarcoma; and from other mycotic infections.

Treatment. Sulfonamide and penicillin therapy are fairly effective, especially when combined with surgical drainage. The patient should be prepared with sulfadiazine, sulfamerazine, or penicillin before operative procedures are begun, and the drugs should be continued for several months after the operation, at a sulfonamide blood level of 4 to 6 mg. %. Oral administration of potassium iodide sometimes is beneficial, and thymol has been advocated in some cases.

In severe infections of the thoracic or abdominal type, extensive operative procedures such as lobectomies or resections of parts of the bowel may be necessary.

Prognosis. The prognosis, which is best in the cervicofacial type of infection and worst in the abdominal type, depends greatly upon the extent of the infection at the time the diagnosis is established.

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Nocardiosis

D. S. Martin

The term nocardiosis is used to designate infections caused by several species of the genus *Nocardia*, which are aerobic organisms indistinguishable morphologically from *Actinomyces* in fresh unstained preparations of lesions. Some species of *Nocardia* are acid-fast.

The clinical picture, prognosis, and treatment are the same as those described under actinomycosis (see Chapter 131), except for the predilection of *Nocardia* to produce pulmonary and subcutaneous lesions (mycetomas).

The differentiation of actinomycosis from nocardiosis is mycologic. Species of *Nocardia* are aerobic and will grow on Sabouraud's slants as

waxy, wrinkled colonies which, like *Actinomyces bovis*, are composed of branching mycelial threads.

Nocardial infections are exogenous in origin, and infection occurs as a result of inhalation of the fungus from some source in nature, or introduction into the tissues by trauma.

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Cryptococcosis (Torulosis, European Blastomycosis)

D. S. Martin

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Definition. Cryptococcosis is an infectious disease caused by *Cryptococcus neoformans* (*Torula histolytica*) which can affect almost any organ of the body but which most frequently involves the brain and meninges.

History. The organism was isolated first in Europe by Busse and Buschke, in 1894, and Curtis, in 1896. Since the fungus reproduced only by the formation of buds, or blastospores, there was some confusion between this infection and the blastomycosis found in the United States,

which led to the older designation of cryptococcosis as European blastomycosis. In the United States, cases of meningitis due to this organism were reported by Stoddard and Cutler, in 1916, and *Torula histolytica* became established as the name of the etiologic agent of the disease. Benham, however, showed that the Busse-Buschke organism was identical with that isolated from cases of meningitis in the United States and, under the rules of botanical nomenclature, the name *Cryptococcus neoformans* has priority.

Mycology. In infected materials such as sputum, spinal fluid, and pus, *C. neoformans* occurs as small, round to oval, budding cells, which average about 10 microns in diameter. The most characteristic feature of the fungus is the very wide and prominent gelatinous capsule surrounding the organism. The capsule is seen easily in

sections or fresh preparations of pus if the material is examined under reduced light. However, the capsular material is so transparent that it may not be seen in a clear menstruum such as spinal fluid. If *Cryptococcus* is suspected, the material should be mixed with India ink and examined microscopically. In such a preparation the fungus is seen as a small, oval cell in the middle of a much larger colorless area surrounded by the black particles of the ink.

The organism grows readily on Sabouraud's medium at both room temperature and 37° C., and colonies usually appear within 7 to 20 days. The colony is characterized by an extremely mucoid or gelatinous appearance, and smears from the colony show budding cells like those found in the tissues. The capsule can be demonstrated by India ink preparations. The pathogenicity of the fungus can be determined by injecting 1 ml. of a cloudy suspension into mice, intraperitoneally. The animals usually succumb within three weeks and the fungus can be demonstrated in smears of peritoneal fluid or brain.

Pathogenesis. It is not known whether cryptococcosis is an endogenous or exogenous infection. *Cryptococci*, pathogenic for animals, have been isolated from the surfaces and juices of certain fruits and from spontaneously infected animals. However, the fungus also can be found on the skin and in the feces of normal individuals.

Although the organism can cause acneform lesions on the skin and produce infections in the lungs, joints, and subcutaneous tissues, meningitis is the most common form of the infection found in the United States. Although the portal of entry in meningitis has not been proved, all evidence points to the lungs and, in many cases, an antecedent history of respiratory symptoms can be obtained.

The pathologic picture in the meninges is peculiar in that usually there is very little, if any, cellular reaction to the presence of the fungus. In the skin and other tissues, there may be evidences of chronic inflammation, but a purulent reaction is rare.

Manifestations. Infections of the skin and subcutaneous tissues are not characteristic, and the lesions may be those of pustules or may simulate myxomatous tumors.

Pulmonary infections may be symptomless and picked up only by sputum examination after a lesion has been noted on routine x-ray examina-

tion. With more severe infections, there may be low-grade fever and cough, with a small amount of mucoid sputum. The physical signs may be those of dullness and changes in the breath sounds. Rales occasionally are heard.

The meningeal symptoms are those of chronic meningitis, which usually begins insidiously with intermittent headaches which later become more severe and continuous. Stiffness of the neck and positive Kernig and Brudzinski signs develop as the infection progresses.

Involvement of lymph nodes may simulate Hodgkin's disease, and infection of almost any part of the body, including bones, may occur.

Laboratory Findings. In cryptococcal meningitis, the cerebrospinal fluid usually shows increased pressure and pleocytosis, with counts ranging from 100 to 800 cells per cu. mm. The sugar content of the spinal fluid usually is decreased and the proteins are elevated.

The sedimentation rate in most cases is increased and, although there may be a leukocytosis, the white count more often is normal.

There are no serologic or skin tests which can be relied upon as diagnostic aids. Patients show little immune response and it is difficult to stimulate antibody production, even by repeated injections into animals.

The diagnosis can be established only by finding the organism or culturing the fungus from the spinal fluid or other lesions.

Differential Diagnosis. Cryptococcal meningitis must be differentiated from other meningitides due to infectious agents such as tubercle bacilli, *Listeria*, *Brucella*, and practically all of the pathogenic fungi. The neurologic symptoms also may resemble those due to a brain tumor or a brain abscess, or even some of the psychoses. Cryptococcal infections of the lung may resemble tuberculosis or nontuberculous infections, particularly those of mycotic origin.

Treatment. Cryptococcal meningitis should be treated intensively with sulfonamides, as there have been several reports of recoveries after prolonged treatment with sulfadiazine and sulfapyrazine. The treatment of pulmonary cryptococcosis is more satisfactory, and strenuous efforts to eliminate the infection should be made in order to avoid the danger of subsequent spread to the meninges. A blood level of 8 to 12 mg. % should be maintained for several weeks after apparent recovery.

The localized and subcutaneous lesions should be treated by excision and drainage after pre-operative preparation with sulfadiazine. Iodides and x-ray treatment also have been advocated.

Prognosis. The prognosis of cryptococcosis meningitis is very poor, and most patients succumb within six months after the beginning of symptoms, but an occasional patient may live for years. The few reports of recovery after sulfonamide therapy suggest that the prognosis is not always hopeless.

Pulmonary cryptococcosis offers a better prognosis, and patients have been seen who improved with sulfadiazine but died of meningitis after treatment was discontinued because of the development of hypersensitivity to the drug. Since pulmonary infections often are picked up only by routine x-ray examinations, the possibility is suggested that primary pulmonary infections

may be of such a benign character that they heal without the diagnosis being suspected. The experiences with coccidioidomycosis and histoplasmosis certainly favor such a hypothesis.

Skin and subcutaneous lesions may heal slowly or they may act as foci for spread to other parts of the body, including the meninges. Certainly, cryptococcosis skin lesions should be treated intensively to minimize the chance of spread.

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Moniliasis

D. S. Martin

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Definition. Moniliasis is an infection due to yeastlike fungi belonging to the genus *Candida* (*Monilia*), most commonly *Candida albicans*. Although the fungus can cause lesions in almost any part of the body, the skin, mouth, and vagina are infected most frequently.

History. The fungus was isolated first from a case of thrush by Langenbeck in 1839, and vaginitis due to this organism was reported by Guilini in 1891. Castellani, in 1910, described the finding of the organism in bronchial and pulmonary infections, and its etiologic role in certain dermatoses was established by Beck and Ibrahim in 1911. The organism also occurs in

abundance in the feces of patients with sprue, but it has no etiologic significance.

Mycology. In smears of infected tissues, *C. albicans* is seen as a combination of budding yeast cells and elongated filaments. The absence of a gelatinous capsule and the presence of filaments excludes cryptococcosis as a possible diagnosis, and the filaments are much wider than those seen in actinomycosis.

The fungus grows readily on Sabouraud's medium as a white, yeastlike colony which is not gelatinous or mucoid in appearance. The growth also has a characteristic yeastlike odor. The colony, which emulsifies readily in saline, is composed of budding yeast cells. Filaments are rare in the surface of the colony, but they occur in abundance in the agar beneath it. Therefore, smears should be made of material from the agar to demonstrate mycelia, thereby excluding the *Cryptococcus*.

Although the pathogenic *C. albicans* can be

distinguished from other members of the genus *Candida* by sugar fermentations, colony characteristics, and other criteria, probably the simplest method of identification is to inject a rabbit intravenously with 1 ml. of a 1 per cent suspension. The rabbit dies in about five days with kidney abscesses if *C. albicans* is present.

Pathogenesis. *C. albicans* is a definite pathogen, but the fungus occurs so frequently in the absence of lesions in normal individuals that it is obvious that disease results only when certain conditioning factors are present. The fungus is found in the mouth, in the feces, and on the skin of normal individuals. It also occurs in the sputum of a very high percentage of patients with chronic lung disease such as tuberculosis and lung abscess.

Manifestations. Thrush is an infection of the oral mucous membranes, characterized by separated or confluent white patches which, on removal from the mucosa, leave a red, moist base. Thrush occurs in young marasmic infants, in debilitated adults, and in patients with dietary deficiencies. Thrush often is seen in individuals with poorly fitting dentures. The fungus is found frequently in the local lesions of perlèche as a secondary infection in patients with riboflavin deficiency.

Cutaneous moniliasis occurs commonly in obese patients, especially in areas where the skin is macerated as a result of friction and excessive perspiration. Skin manifestations also are common in diabetics and alcoholics. Such intertriginous lesions usually are well marginated and are surrounded by small vesicles and pustules.

Sometimes the cutaneous infection becomes generalized and so severe that it terminates fatally. The lesions may be eczematous in type or they may be characterized by the formation of vesicles and pustules. Very commonly, skin infections with *C. albicans* are those of onychia and paronychia, in which redness and swelling are so severe that they resemble lesions caused by the pyogenic cocci. However, in moniliasis, such lesions are not purulent. Infection of the nails results in thickening, grooving, and discoloration. Lesions of the "id" type, resembling those due to sensitization to the dermatophytes, are not uncommon.

Vulvovaginitis is common in pregnant and diabetic patients. The lesion may be eczematoid in character, or vesicles and pustules may form and,

in severe cases, progress to ulceration. Itching is intense.

Bronchopulmonary moniliasis is characterized by chronic cough with a mucoid sputum which often contains small, grayish flakes. The physical findings are those of chronic bronchitis. Primary infection of the lungs is not common, but when it does occur it usually is severe. The sputum, which usually is mucoid, may be blood-streaked at times. The pulmonary lesions, as demonstrated by x-ray, usually are scattered and patchy, although occasionally the entire lobe may be involved. The apexes characteristically are clear; and the lesions are very labile, as can be demonstrated by a series of x-rays taken at weekly intervals. An occasional patient will have a pleural effusion and many patients complain of pleural pain.

Laboratory Findings. Except in very severe infections, there are no changes in the white blood count or sedimentation rate, and the diagnosis must be established by finding the fungus in smears or by culturing it.

Agglutinins may be found in severe cases, but the test has not been found sufficiently reliable for use as a routine diagnostic procedure. A progressively rising titer of agglutinins, however, would be diagnostic. Skin-testing materials, such as vaccines and extracts (oïdiomycin), also are unreliable, since a considerable percentage of normal individuals give positive reactions.

Differential Diagnosis. The cutaneous infections must be distinguished from other types of dermatitis, particularly those caused by the dermatophytes or "ringworm" group of fungi. The lesions also may simulate those of contact dermatitis or those caused by pyogenic organisms. The pulmonary lesions may resemble tuberculosis, bronchial pneumonia, atypical pneumonia, or fungous infections such as coccidioidomycosis, histoplasmosis, cryptococcosis, and blastomycosis.

The diagnosis of thrush and vulvovaginitis is not difficult, since the fungus can be demonstrated readily in smears from the lesions, and the organisms also can be found in cutaneous lesions, except the "ids," which are sterile.

It is important to emphasize that the finding of the pathogenic *C. albicans* in sputum is not diagnostic of lung disease, since the fungus is found frequently in pulmonary disease resulting from other causes. Every effort should be exerted

to search for the more common etiologic agents of pulmonary disease, and the patient should be followed carefully for a reasonable period of time, with repeated sputum and x-ray examinations. Tuberculosis always should be excluded by guinea pig inoculation before a diagnosis of pulmonary moniliasis can be considered.

Treatment. The predisposing factors in moniliasis are so important that much of the therapy of the infection should be directed toward their elimination. Diabetics should be regulated, ill-fitting dentures should be corrected, obese patients should be placed on a reducing diet, and intensive vitamin therapy should be given to those who are undernourished or debilitated.

More specific therapy includes the use of gentian violet (1:10,000 in 10 per cent alcohol) which can be painted on the areas of thrush, or the same dye (diluted 1:100,000) may be used as a gargle. Such local treatment should not be given for more than four to five days. Gentian violet has been used with success in some cases of pulmonary moniliasis (5 mg. per kg. of body weight), but it frequently causes local thrombosis of the veins near the injection sites.

Most patients with vulvovaginitis respond to sodium propionate in a vaginal jelly ("Sopronol"). Recurrences of the infection are not uncommon, and it is possible that reinfection may occur as a result of contamination with the fungus excreted from the gastrointestinal tract.

Potassium permanganate (1:4000), followed by the application of gentian violet (1 per cent) or ammoniated mercury (5 per cent), is beneficial in treatment of onychia, paronychia, and intertriginous lesions. X-ray therapy also may be used.

Desensitization therapy with vaccines is indicated in patients who are excessively hypersensitive to the fungus or its products. Although many normal individuals are hypersensitive, as is indicated by skin tests, it still is important to determine the degree of hypersensitivity of the infected patient. Desensitization treatment should be considered if the patient's lesions or symptoms indicate that there is an allergic component in his disease.

Prognosis. The prognosis depends upon the location and nature of the infection. Pulmonary and generalized cutaneous infections have the poorest prognosis. Intertriginous and localized skin lesions, thrush, and vulvovaginitis usually respond to treatment, but recurrences are frequent unless predisposing factors are eliminated.

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North American Blastomycosis

D. S. Martin

Definition
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Definition. North American blastomycosis is an infection caused by a single species of fungus, *Blastomyces dermatitidis*, which involves chiefly skin, lung, and bone tissues, but which also can cause lesions in most organs of the body.

Laboratory Findings
Differential Diagnosis
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History. Gilchrist, in 1894, observed large, budding, double-contoured organisms in sections from a verrucous lesion on the hand of a patient. No cultures were obtained, but in 1896, Gilchrist and Stokes were able to isolate the fungus from a

patient with similar organisms in a lesion on the face. The budding cells in sections had certain similarities to those described by Busse and Buschke, and for a time it was thought that the two organisms might be identical. Cultural studies, however, showed that the Busse-Buschke organism (*Cryptococcus neoformans*) always grew in a yeastlike form on Sabouraud's agar, whereas Gilchrist's fungus, although appearing yeastlike in tissues, grew on Sabouraud's medium as a mold with serial hyphae.

Mycology. In the lesions, *B. dermatitidis* appears as a thick-walled, double-contoured, round to oval fungus, about 10 microns in diameter, but with extremes of 5 to 15 microns. There is no capsule surrounding the organism, as in cryptococciosis, and there are no filaments, as in moniliasis.

On Sabouraud's medium at room temperature, the fungus grows slowly as a white mold, which may turn brownish with age. Smears from the colony show branching mycelial filaments, which are wider than those seen in actinomycosis, and numerous small spores along the sides of the branching myceliums.

Cultures on blood agar or beef infusion glucose agar, incubated at 37° C., are entirely different from those developed at room temperature. The colony is small, compact, and waxy in appearance, and is sufficiently soft that it can be picked up with a loop and emulsified easily. Smears of such colonies show double-contoured, budding organisms which closely resemble those seen in direct smears from lesions.

The diagnosis of *B. dermatitidis* is facilitated by incubation at room temperature, because the change in colony appearance is reversible and the moldlike colony can be made to grow as a yeast when it is incubated at the higher temperature. The pathogenicity of the fungus can be established by intraperitoneal inoculation of a mouse with 1 ml. of a 1:200 suspension of yeastlike organisms cultivated at 37° C.

Pathogenesis. Blastomycosis is an exogenous infection, and the presence of the fungus in a lesion always indicates infection. The organism gains entrance into the body either by inhalation of the fungus spores from some source in nature, or by its introduction into the tissues accompanying a wound. The clinical picture and prognosis are quite different in the two types of infection, and the pathologic reaction is very variable,

according to the degree of hypersensitivity developed by the patient. Thus, in some cases, hypertrophy of the epithelium is so marked that the changes suggest carcinoma. Under other conditions, tissue necrosis and abscess formation suggest a pyogenic infection.

Manifestations. The primary lesion in cutaneous blastomycosis is found almost invariably on some exposed part of the body, particularly the face, hands and wrists, feet and ankles. The lesion begins as a small papule which extends gradually and becomes covered with a scab. There is marked hypertrophy of the skin, resulting in a verrucous appearance, and, in the deep red or purple verrucous edges, a series of minute abscesses can be observed.

As the lesion spreads, the center has a red granulating base which heals with scarring, but there is little tendency for contraction of the scars. The lesion may spread slowly for months or years, sometimes becoming so large that it may encircle an extremity such as the wrist or ankle. Secondary lesions usually occur in the area of the first lesion or in other areas as a result of autoinoculation. There is little if any effect on the general health of the patient.

In practically all cases of systemic blastomycosis, the primary lesion occurs in the lungs, although in many instances the diagnosis is not made until after the production of skin or subcutaneous lesions. The pulmonary symptoms are variable but consist chiefly of cough, chest pain, and low-grade fever. As the disease progresses, the sputum may become purulent or blood-streaked, the fever becomes higher, and there may be severe night sweats. The patient loses weight and becomes weaker and dyspneic; abscesses appear in skin and subcutaneous tissues; and lesions in the bones, brain, and other organs appear. X-rays of pulmonary lesions in well-developed cases show dense shadows which are irregular in shape and which most often are located in the hilar region. Sometimes the shadows show no more than an apparent enlargement of the mediastinum. The shadows usually are unilateral, and the apices are affected only rarely. The masses often resemble carcinoma of the lung, especially when there are changes in the ribs which suggest metastases.

The skin lesions in the systemic form of the disease occur more often in the unexposed portions of the body, such as the thorax, abdomen,

and back. Skin involvement in systemic infections usually begins with the formation of subcutaneous abscesses which break through the skin and then develop verrucous borders which may simulate primary cutaneous lesions.

Laboratory Findings. Cutaneous blastomycosis rarely produces any changes such as leukocytosis or increased sedimentation rate, unless there is severe, superimposed bacterial infection.

A skin test, employing a heat-killed *Blastomyces* vaccine, containing yeastlike organisms diluted 1:1000 in saline, is a specific test for the disease. With the vaccine, there is no cross reaction in patients with other fungous diseases. The vaccine is injected intracutaneously, and the reaction is read in 24 and 48 hours. The degree of reaction depends upon the degree of hypersensitivity, extremely allergic patients producing a sterile abscess at the site of the injection. The determination of the extent of hypersensitivity is extremely important from the standpoint of therapy, which is discussed below.

The complement-fixation reaction, using patient's serum and *Blastomyces* antigen, is rarely positive, and then only in undiluted serums, unless the infection is extremely widespread. In cutaneous blastomycosis, however, the diagnosis can be established easily by direct examination of the pus squeezed out of the characteristic tiny abscesses at the margins of the lesion.

In systemic blastomycosis there is a leukocytosis, an increased sedimentation rate, and often anemia.

The complement-fixation test usually is positive, especially when the disease has advanced considerably. A high titer of complement-fixing antibodies usually indicates widespread disease or an almost hopeless prognosis.

The skin test is positive in only about half of the cases of systemic blastomycosis, since the patient often is not seen until he has reached a state of anergy as a result of widespread extension of his disease.

The organisms can be seen and cultured from sputum, subcutaneous abscesses, and skin lesions.

Differential Diagnosis. Cutaneous blastomycosis can resemble the lesions of syphilis, tuberculosis, epitheliomas, drug reactions, infections due to other fungi, and granuloma inguinale. The pulmonary form of the disease must be distinguished from tuberculosis, neoplasm, sarcoidosis, lung abscess, and infections due to the fungi

such as histoplasmosis, coccidioidomycosis, actinomycosis, and moniliaisis. The appearance of abscesses in subcutaneous tissues and involvement of bone often suggest a systemic pyogenic infection.

Treatment. In both cutaneous and systemic blastomycosis, it is important that a skin test be performed in order to evaluate the degree of hypersensitivity of the patient, since spreading of the lesions may occur when iodides are administered. The method of desensitization will be described below.

Cutaneous blastomycosis responds well to x-ray therapy, provided that the patient has been prepared previously by injection of small desensitizing doses of vaccine. Small doses (75 to 100 roentgen units, filtered through 1 mm. of aluminum), given at weekly intervals, are sufficient and not more than 12 to 15 treatments should be given. In open ulcerating lesions, it is important that the secondary bacterial infection be controlled by local applications of compresses containing sulfonamides.

The patient with systemic blastomycosis also should be desensitized by vaccine injections if he reacts strongly to the skin-test material. Potassium iodide should be administered very cautiously, beginning with doses no larger than 3 drops of a saturated solution three times a day. The dose should be increased 1 drop per day until it reaches 20 drops three times a day, after which the dose is dropped to 3 drops three times a day, and increased as before. The patient should be observed carefully and the drug stopped or reduced if there is any exacerbation of symptoms.

Surgical drainage of abscesses may be advisable in some cases, but in our experience such drainage should be performed only after some vaccine treatment has been given. Incision of acutely purulent bloody abscesses sometimes results in the formation of chronic ulcers.

The desensitization schedule depends upon the size of the skin test produced by the intracutaneous injection of the vaccine. If the skin test results in the production of a zone of erythema 2 cm. in diameter, the vaccine should be diluted 1:100; if a larger erythematous reaction is obtained, the vaccine should be diluted 1:1000; and in some patients the skin reaction is so large that the vaccine must be diluted 1:10,000 or higher. The first dose consists of the subcutaneous injec-

tion of 0.1 ml. of the most highly diluted material, and the dose is increased by 0.1 ml. increments, the injections being given no more often than every other day. After 0.9 ml. of the most diluted material has been injected, the patient can receive 0.1 ml. of the next lowest dilution, and the procedure is carried on as outlined previously.

The occurrence of any local or focal reaction is an indication that the dose was too high, and the next dose should be smaller than that which caused no reaction previously. After six to eight injections, the iodides can be administered slowly, as outlined above. It should be emphasized that complete desensitization is rarely obtained, and is not necessary. It is possible, however, to abolish abscess formation at the site of skin testing, and the response to iodide or x-ray treatment is much more rapid after a series of vaccine injections.

Prognosis. The prognosis in cutaneous blastomycosis is good, if treated according to the re-

gime outlined above. Untreated cutaneous blastomycosis rarely heals spontaneously, and the infection may remain localized or spread very slowly over a period of years. It is rare for primary cutaneous blastomycosis to become systemic.

Systemic blastomycosis has a grave prognosis, and the mortality is 92 per cent in patients who have been followed for at least two years. The prognosis is better in patients who have been treated early in the disease or before the skin test becomes negative, and while the complement-fixing antibody titer is low.

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South American Blastomycosis

D. S. Martin

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Definition. South American blastomycosis is a chronic granulomatous infection caused by *Blastomyces brasiliensis*, which to the present time has been reported only from South America. The fungus has a predilection for the mucous membranes of the mouth, the skin about the nose and lips, and the lymph nodes, but it also can invade the internal organs.

History. The first case was reported in Brazil in 1908 by Lutz, who considered it a case of

coccidioidomycosis. Almeida, however, in 1930 showed that the fungus was quite different from *Coccidioides immitis* and proposed the name *Paracoccidioides brasiliensis*.

Mycology. In the lesions, the fungus appears as large (10 to 60 microns), thick-walled, oval to round cells which show numerous buds around the periphery. Both small (1 to 5 microns) and large (10 to 30 microns) buds are found.

On Sabouraud's medium at room temperature, the organisms grow quite slowly, and although the colonies somewhat resemble those of *Blastomyces dermatitidis*, they are smaller and more compact and the aerial mycelium are much shorter. In smears from such colonies, many mycelial filaments can be seen along with many short, thick-walled cells, but the picture is so non-

specific that the identification is made best by cultivating the organisms on blood agar at 37° C.

On blood agar or beef infusion glucose agar, at 37° C., the organism grows as a waxy, wrinkled colony similar to that of *B. dermatitidis*. Smears of such colonies show thick-walled yeast cells with multiple small buds.

Pathogenesis. The fungus apparently exists in some unknown material in certain endemic areas in South America, particularly Brazil. Since the lesions occur most commonly in the oral or perioral regions, it is assumed that the infection gains entrance through the mouth.

Manifestations. The disease is divided into the following clinical types: (1) mucocutaneous, (2) lymphangitic, (3) visceral and (4) mixed.

The mucocutaneous type is the most common form and is characterized by lesions in the mucous membrane of the mouth and on the skin of the face, especially around the lips and the nose. The lymph nodes, which are involved early, soften and ulcerate. The lesions within the mouth often spread to involve the uvula and the vocal cords.

The lymphangitic type of infection produces massive enlargement of the lymph nodes, particularly those in the neck. This type of infection often is seen in the absence of any oral or skin lesions at the site of entrance of the fungus. The lymph nodes eventually become necrotic and drain through the overlying skin.

The visceral form of the disease is characterized by pain and severe gastrointestinal disturbances, and the liver, spleen, and other abdominal organs may become enlarged. The lungs are infected in only about one-fifth of the cases, and it is thought that such infection results from hematogenous spread from the viscera.

The term "mixed type" of infection is applied to those cases which cannot be classified into any one of the three types mentioned above.

Laboratory Findings. There is no leukocytosis unless a bacterial infection is superimposed on the fungous disease. A positive skin test, analogous to that occurring in North American blastomycosis, is obtained in patients, and complement-fixing antibodies also have been found.

Differential Diagnosis. South American blastomycosis must be distinguished from the same group of diseases listed under the differential diagnosis of North American blastomycosis, but, in addition, the lymphangitic form must be differentiated from Hodgkin's disease, aleukemic leukemia, and tuberculous adenitis. The visceral form may simulate tuberculous peritonitis or abdominal histoplasmosis. Because of the prevalence of the disease in South America, the mucocutaneous form of the disease must be distinguished from yaws and leishmaniasis. However, in endemic areas, the clinical picture of the mucocutaneous type is so characteristic that physicians have little difficulty in making the diagnosis.

Treatment. Sulfapyridine and sulfathiazole, in doses of 2 to 4 Gm. a day, are reported to cause improvement in the disease, but recurrences are quite common. It has been reported that the administration of potassium iodide causes spreading of the infection, as has been described under North American blastomycosis. It is possible that desensitization therapy might be beneficial in such patients.

Prognosis. The infection usually is fatal.

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Coccidioidomycosis

D. S. Martin

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Definition. Coccidioidomycosis is an exogenous infection, caused by *Coccidioides immitis*, which is widespread in certain areas, particularly in the southwestern United States.

History. The first case was described in Argentina by Poseidas and Wernicke in 1892, and two years later it was described in California by Rixford. At first it was thought that the organism was a protozoon, but cultures later proved it to be a fungus. Since the tissue form of the fungus is characterized by spherules which contain small spores, the appearance was not unlike that seen in coccidiosis, a protozoan infection, and the fungus therefore was named *Coccidioides immitis*.

Coccidioidomycosis used to be considered one of the most fatal of all the mycoses, but in 1936 Gifford and others described a benign primary form of the infection, and epidemiologic studies have shown that the incidence of the infection is extremely high in certain endemic areas.

Mycology. *C. immitis*, in infected tissues, appears characteristically as large (10 to 80 microns in diameter), round, thick-walled spherules which contain numerous small endospores (2 to 5 microns in diameter). The endospores may be absent in the small undeveloped forms of the fungus, and such structures may be mistaken for the cells of *Blastomyces dermatitidis*.

On Sabouraud's medium at room temperature, the fungus grows as a white mold, but turns a brownish color with age. Microscopic examination shows numerous mycelial strands, many of which have broken up into small, thick-walled, rectangular spores (arthrospores). The arthrospores are diagnostic of the fungus, but this identification can be confirmed by intratesticular inoculation of the organism into laboratory

animals and the demonstration of the typical endospore-containing spherules in fresh smears of the lesion.

It should be emphasized that *C. immitis* is a most dangerous fungus to handle in the laboratory, numerous laboratory infections having resulted from inhalation of arthrospores in cultures (Smith, 1942).

Pathogenesis. Like North American blastomycosis, the fungus may be inhaled or introduced through the skin with trauma, but the former type of infection is much more common. Occasionally the organism apparently enters through the mucosa of the nasopharynx, causing involvement of the cervical lymph nodes.

The lesions in the progressive type of infection are quite similar to those of North American blastomycosis, with involvement of lung, skin, bone, and other organs. The primary pulmonary form of infection is extremely common, and the sequence of events closely resembles that seen in primary pulmonary tuberculosis.

Manifestations. Primary pulmonary coccidioidomycosis (valley fever, desert fever) may be asymptomatic, or the patient may have symptoms either of a mild upper respiratory infection or of a more severe lung disease.

The incubation period in the clinically recognizable cases is from one to three weeks. Practically all patients are febrile, and most of them complain of coughing and pains in the chest. Chills and hemoptyses are not uncommon. Alterations in breath sounds can be detected in about one fourth of the cases, but the rest of the patients show no physical signs of any kind. Rales or changes in percussion note are rare.

The roentgenographic findings in the 75 cases of primary pulmonary coccidioidomycosis reported by Colburn were negative in 4 per cent of the group. The most common lesion (39 per cent of cases) was a fan-shaped area of increased density extending peripherally from the hilar regions. Involvement limited to the hilar lymph nodes occurred in 24 per cent of the cases, and

equally common was the finding of one or more soft nodular infiltrations in the lung fields. Thin-walled cavities were not unusual (4 per cent in Colburn's series). Some of these cavities healed within several months, while others remained open for years.

Erythema nodosum or other manifestations of hypersensitivity occur often enough to be considered as an important part of the clinical syndrome. Erythema nodosum may appear from the first to the third week after the onset, but most commonly it appears during the second week of the illness.

Progressive coccidioidomycosis is more common in the darker races, such as Negroes, Mexicans, and Filipinos. The mortality rate in Filipinos is 107 times as high as that in Caucasians, and the ratio between the mortality rates of Negroes and whites is 23 to 1.

In patients with the progressive form of the disease, there usually is evidence of dissemination within a few weeks or months after the onset of the primary infection. Skin lesions occur and symptoms of extreme lung disease, such as dyspnea, fever, night sweats, and weakness, develop rapidly, and the patient dies after an illness lasting several months or a year, with involvement of the bones, joints, brain, meninges, and other organs.

Laboratory Findings. In primary pulmonary coccidioidomycosis there is an early leukocytosis, and some eosinophilia is not unusual. The sedimentation rate is elevated but it quickly returns to normal. The persistence of an elevated sedimentation rate is strong evidence that the progressive form of the disease is developing.

Hypersensitivity to coccidioidin (an extract of the growth of the fungus in broth) develops early in primary coccidioidomycosis, usually within two weeks after the onset of symptoms. The sensitivity is so marked that, in order to avoid severe reactions, a 1:10,000 dilution must be used for the skin test. The tests are read and interpreted in the same manner as tuberculin tests. In the progressive form of the disease the sensitivity is less marked, and the patients usually are tested with coccidioidin diluted 1:1000 or 1:100. The test becomes negative in terminal infections.

Precipitins and complement-fixing antibodies

usually can be demonstrated in the serums of patients with clinically recognizable primary infections. Since the titer of complement-fixing antibodies rises as the infection becomes disseminated, this test is very important in evaluating prognosis. Positive complement-fixation tests with spinal fluid are obtained in patients with coccidioidal meningitis. According to Smith, the precipitins tend to disappear as dissemination occurs.

Differential Diagnosis. Primary coccidioidomycosis must be distinguished from pulmonary infections such as influenza and primary atypical pneumonia. The progressive form may resemble bacterial infections such as tuberculosis and glanders, or neoplasms, or infections due to other fungi such as blastomycosis, cryptococcosis, and actinomycosis.

Coccidioidomycosis should be considered as a possibility in any unusual illness in a patient who has resided in or visited an endemic area.

Treatment. The patient with primary coccidioidomycosis should be kept at bed rest until the infection has subsided, as shown by a normal white count and sedimentation rate. The patient also should be checked by x-ray examinations. The thin-walled cavities which sometimes develop usually heal over a period of several months.

Progressive coccidioidomycosis is extremely difficult to treat, and only a few cases of recovery have been reported. It is suggested that iodide treatment might have a beneficial effect if the hypersensitive patient is desensitized before the drug is administered.

Prognosis. The prognosis is excellent in primary coccidioidomycosis in whites, but it is very poor in infections of the darker-skinned races. The prognosis is almost hopeless when the infection develops into the progressive form of the disease.

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Histoplasmosis

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Definition. Histoplasmosis, caused by *Histoplasma capsulatum*, is an infection which, in its malignant form, is characterized by anemia, leukopenia, and enlargement of the liver and spleen.

History. In 1909 Darling observed small *Leishmania*-like organisms in the livers and spleens of native Panamanian patients who died of a disease resembling visceral leishmaniasis. Darling thought that the organism was a protozoon and named it *Histoplasma capsulatum*, but in 1934 it was proved to be a fungus by DeMonbreun, and by Hansmann and Schenck.

Until 1945, there had been no reports of a recovered case, and the infection was thought to be uniformly fatal. However, the epidemiologic studies of Christie and those of Palmer have shown that a high percentage of residents of the Mississippi Valley give positive tests to injections of an extract of the fungus (histoplasmin). Although a primary infection with *Histoplasma* has not been established beyond question, the evidence certainly suggests that there exists a benign type of infection, similar to that seen in coccidioidomycosis.

Mycology. In the lesions, the fungus occurs within the cytoplasm of endothelial cells as small (2 to 4 microns), oval, budding yeast cells. The organisms, when stained by Giemsa's method, superficially resemble the bodies of *Leishmania donovani* except that the central nuclear materials are lacking.

On Sabouraud's medium, the organism grows as a white, cottony mold which turns brown with age. On microscopic examination, branching septate hyphae and small, oval, pear-shaped spores are found, but the diagnostic findings are the

large, thick-walled spores, which are covered with numerous finger-like projections, the so-called tuberculate chlamydospores.

On sealed blood agar slants, incubated at 37° C., a pasty, yeastlike growth is obtained which, on microscopic examination, shows small, oval, yeastlike forms similar to those seen in lesions. A semisolid medium has been developed by Salvin, in which the yeastlike form can be obtained in large quantities.

H. capsulatum is pathogenic for laboratory animals such as mice, guinea pigs, and dogs.

Pathogenesis. Histoplasmosis is essentially a disease of the reticuloendothelial system, but lesions have been described in most tissues of the body. The pathologic findings of enlarged liver and spleen, together with the ulcerations of the gastrointestinal tract, including the mucous membranes of the mouth and pharynx, have suggested that the portal of entry of the fungus is the intestinal tract. However, the high incidence of positive histoplasmin reactions in healthy residents of the central Mississippi Valley has indicated that a more common portal of entry may be the respiratory tract. Primary skin lesions have been described, but they are rare. At autopsy, the lesions can be found scattered throughout the body in the reticuloendothelial cells, particularly in macrophages. Unlike systemic infections caused by other fungi, there is no tendency to abscess formation.

Manifestations. The highly fatal systemic form of histoplasmosis has been reported to occur in all age groups. Essentially, the clinical features are those of an infection with an insidious onset in which fever, weight loss, and gastrointestinal disturbances appear as the disease progresses. The gastrointestinal symptoms, which are very variable, may consist only of simple diarrhea, but severe ulcerative enteritis may develop. Rectal hemorrhages occur occasionally. Lesions of the eye, ear, and nose also have been reported.

The liver and spleen enlarge gradually and the patient develops anemia and leukopenia. Gen-

eralized lymph node enlargement is common, especially in adults.

Nothing is known of the manifestations of the primary pulmonary type of infection. In fact, the existence of such a type of infection is based only on the epidemiologic data obtained in certain areas of the United States in which positive histoplasmin tests are found in a high percentage of tuberculin-negative individuals who have calcified lung lesions. If such findings indicate the existence of a primary pulmonary infection, the symptoms are so mild that they are not recognized.

Laboratory Findings. In the systemic form of the disease, the average red blood count is about 2,500,000, and the white count is definitely lower than usual. There may be either no important change in the differential formula or else a definite neutropenia.

The fungus sometimes can be seen in blood smears stained by Giemsa's or Wright's methods, but the organisms are seen more often in smears made from the bone marrow. In such smears, the organisms occur in the cytoplasm of mononuclear cells.

Serologic studies have been done on only a few patients, and complement-fixing antibodies have been demonstrated. Agglutinins are produced easily in rabbits. Skin tests also have been reported as positive in infected patients, but they also are positive in normal individuals living in endemic areas.

X The significance of a positive skin test still is open to question, as there are cross reactions with other fungi. Howell, however, showed that there are considerable variations between different batches of histoplasmin, and has emphasized the necessity of a careful standardization of skin-testing materials. It should be emphasized that most fungous materials used for skin testing (histoplasmin, coccidioidin, blastomycin) are extracts obtained by culturing the fungus in broth for several months. We have not observed cross

reactions in blastomycosis when a vaccine was used, and Salvin has reported that complement-fixation and skin tests are specific when the yeast phase of the fungus is used as antigen.

Differential Diagnosis. The severe systemic form of the disease may resemble Gaucher's disease, aleukemic leukemia, or even malaria, brucellosis, infectious mononucleosis, and miliary tuberculosis. When lymph node enlargement is marked, the disease may resemble Hodgkin's disease or lymphosarcoma. The involvement of the reticuloendothelial system makes it necessary to distinguish between histoplasmosis and leishmaniasis.

Treatment. There is no satisfactory treatment of systemic infection, although many drugs have been tried. Because of the similarity of the pathologic picture to leishmaniasis, Meleney suggested the use of antimony salts, and one patient has been reported in whom temporary improvement followed the administration of "Neostam." The patient died, but the fact that the organisms could not be found at autopsy suggests that this drug might have been effective if it had been given earlier in the disease.

Prognosis. The prognosis is hopeless in patients with systemic infection.

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Section 12—Fungous Diseases Involving the Skin and Subcutaneous Tissues

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Sporotrichosis

D. S. Martin

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Definition. Sporotrichosis, caused by *Sporotrichum schenckii*, is a chronic or subacute infection of the skin and subcutaneous tissues which is characterized by a primary lesion, or sporotrichotic chancre, at the site of entrance of the fungus, and the subsequent development of a series of nodules along the course of the lymphatics which drain the initial lesion.

History. The first human case of sporotrichosis was reported from Baltimore by Schenck in 1898, and a second case in the United States was reported by Hektoen and Perkins in 1900. The latter authors named the fungus *S. schenckii*. De Beurmann and Ramond, in 1903, described a case in France, and the fungus was named *Sporotrichum beurmannii* by Matruchot and Ramond.

Mycology. The fungus has been seen only rarely in the lesions of human sporotrichosis, although it occurs abundantly in the lesions of inoculated animals. The tissue form is a small (1.5 to 4 microns), cigar-shaped body, which is found in polymorphonuclear cells and extracellularly.

Growth, on Sabouraud's medium or blood agar incubated at room temperature or 37° C., appears within four to five days as a small white colony which becomes leathery and folded as it develops. Some colonies produce a brown to black pigmentation, while others remain white. The white colonies may develop black areas spontaneously, and the black ones may turn white. Smears from such colonies are diagnostic, and show branching filaments with side branches on

which small (2 to 4 microns by 2 to 6 microns), pear-shaped spores occur in clusters.

Campbell, in 1946, made the observation that cultivation of the fungus on cystine agar at 37° C. caused a reversal to the tissue form, the colonies being soft and yeastlike, and smears made from such colonies showing numerous cigar-shaped bodies.

Pathogenesis. The portal of entry usually is the skin, the fungus being introduced with a wound. A history of a prick with a barberry thorn is obtained quite frequently. A true epidemic was reported from South Africa in 1942, in which 650 cases developed in miners working in an infected mine shaft. Although the disease may cause involvement of internal organs, the disseminated, mucosal, skeletal, and visceral forms, described by Beurmann and Gougerot, are quite rare; and by far the most common type of infection, at least in the United States, is the lymphatic type of the disease.

Manifestations. The incubation period of the primary lesion may vary from three weeks to three months, and the lesion appears first as a small, hard, painless nodule in the subcutaneous tissue, which at first is freely movable underneath the skin. As the nodule develops, it becomes adherent to the overlying skin and eventually ulcerates. Characteristically, a succession of subcutaneous nodules appears along the course of the lymphatics draining the primary lesion, and these, in turn, become attached to the skin, soften, and ulcerate.

Disseminated sporotrichosis, which is rarely seen in the United States, is characterized by lymph node enlargements all over the body. Such nodules rarely ulcerate and the disease is rapidly fatal. Infections of mucous membranes, usually in the nasopharynx, present a variety of clinical manifestations such as erythema, ulcerations,

and papillomas. Involvement of bone and internal organs is extremely rare.

Laboratory Findings. In the lymphatic form of the disease, there are no significant laboratory findings except the isolation of the fungus from the lesions.

The yeastlike cultures obtained on cystine agar permit the obtaining of suitable agglutinating suspensions. This development, however, is so recent that it has not as yet been used as a diagnostic procedure in clinical cases.

Positive skin reactions to vaccines have been obtained in patients, but they have little diagnostic value since the diagnosis, at least of the lymphatic type, can be made on clinical grounds.

Differential Diagnosis. The lymphatic form of sporotrichosis sometimes resembles tularemia, but it can be distinguished easily by the absence of agglutinins for the latter organism. The skeletal, visceral, and disseminated forms fortunately are rare, but they can be simulated by infections due to other fungi and by bacterial infections

such as tuberculosis, syphilis, glanders, and tularemia.

Treatment. The lymphatic form of the infection responds specifically to potassium iodide, which should be given as a saturated solution, beginning with 10 drops three times a day the first day, 15 drops three times a day the second day, and increasing the dose until 30 or 40 drops three times a day is given. The drug should be continued for at least six weeks after recovery.

Prognosis. The prognosis is excellent in the lymphatic form, but is very poor in patients with disseminated, visceral, or skeletal sporotrichosis.

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Chromoblastomycosis

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Definition. Chromoblastomycosis is a chronic infection of the skin and subcutaneous tissues which is characterized by the development of large, unsightly verrucous lesions. Although the infection can be produced by three different pigmented, moldlike fungi, *Hormodendrum pedrosoi*, *Hormodendrum compactum*, and *Phialophora verrucosa*, the infection cannot be differentiated on clinical or pathologic grounds.

History. The infection was seen first in Brazil in 1911 by Pedroso, who found brown bodies in

a biopsy section, but it was not until after Lane and Medlar reported their case in Boston in 1915 that Pedroso's case was reported. Numerous studies of the infection have shown that the majority of cases occur in Central and South America, but the disease has been reported from scattered areas in the United States, such as Texas, North Carolina, Missouri, and Massachusetts.

Mycology. The tissue form of the fungus is the same for all of the three fungi causing the disease. The organisms appear as dark brown, round bodies, 6 to 12 microns in diameter, and show lines of septation suggesting that in the tissues they multiply by fission rather than by budding.

On Sabouraud's medium at room temperature, the organisms grow as dark green to brown or black molds with aerial hyphae. The specific diag-

nosis is made by microscopic examination, which requires considerable experience, since the three types of fungi produce three different types of spore formation.

Pathogenesis. The infection, which usually is unilateral and occurs on an extremity, most commonly the leg, is introduced through the skin by trauma. The source of the fungus in nature is unknown, but the evidence suggests that it occurs saprophytically on wood.

Manifestations. The infection usually begins as a small papule which at first resembles a small patch of "ringworm." The lesion then progresses very slowly, and crops of new lesions may develop along the paths of lymphatic drainage. The lesions become ulcerated and warty in appearance, and may become so large that they resemble large cauliflower masses. The disease progresses very slowly, sometimes requiring 15 years or more to involve an entire extremity.

Involvement of the subcutaneous tissues leads to elephantiasis of the infected extremity, but, unless there is secondary bacterial infection, there are no generalized symptoms.

Laboratory Findings. The only significant laboratory finding is the demonstration of the brown, oval bodies in smears or sections of the lesions.

Differential Diagnosis. After the development of the typical cauliflower lesions, the diagnosis is not difficult, but the early lesions may be confused with skin infections such as tuberculosis, syphilis, leishmaniasis, yaws, and infections due to other fungi.

Treatment. Excision of very early lesions is advisable, and local treatment should be applied to control secondary infections. Sulfamerazine now is being tried in Puerto Rico by Carrion and Silva, but it is too early for the results to be evaluated. Iodides and x-ray treatments sometimes cause improvement, and the author has seen one patient who responded to iontophoresis with copper sulfate. In some cases it may be necessary to resort to amputation if the secondary infection cannot be controlled.

Prognosis. Chromoblastomycosis is not fatal, but it is difficult to eradicate infection when it has become firmly established.

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Maduromycosis

D. S. Martin

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Definition. Maduromycosis is a slow, progressive infection of the foot or hand, which is characterized by swellings and the formation of multiple sinuses. The infection may be caused by

a variety of fungi, particularly *Monosporium apiospermum* and various species of *Nocardia*. It has been suggested that the term maduromycosis be limited to infections caused by the higher moldlike fungi, and that the infections caused by the *Nocardia* group be designated as actinomycotic mycetomas.

History. The clinical disease, which was described first in 1842 by Gill, was named madura foot by Colebrook in 1846, because of its occurrence in Madura, India. The fungus has been

found in almost all parts of the world, especially where individuals go barefoot, but it also has been described in states as far north as Massachusetts and Minnesota.

Mycology. So many fungi have been described as etiologic agents of the infection that it would be impractical to describe all of them here. Regardless of the nature of the fungus causing the infection, the organisms in the tissues appear as granules which are large enough to be seen with the naked eye. The granules or "grains" produced by the *Nocardia* are of the "sulfur granule" type, described under Actinomycosis (Chapter 131) and Nocardiosis (Chapter 132), whereas those produced by the higher fungi are of various colors and may have a white, black, red, or other appearance.

In sections of tissues, it is important that a Gram's stain be done in order to distinguish between infections caused by *Nocardia* and those caused by the higher molds. In the actinomycotic mycetomas the granule is composed of tangled, narrow, mycelial filaments, whereas in maduromycosis the filaments are larger and large spores can be seen, particularly around the peripheries of the granules.

Cultures from the latter type of lesion should be made on Sabouraud's medium, and the mold then is identified by mycologic examination.

Pathogenesis. Maduromycosis is an exogenous infection and the organisms gain entrance through the skin following trauma such as a bruise or the introduction of a splinter of wood. More than 90 per cent of the lesions occur in the foot. Sometimes the lesion starts as a small papule or nodule, or as a small abscess. There may be several of these small lesions before the swellings and deformities characteristic of maduromycosis develop. The reactions of the body to all of the fungi are similar to those described under Actinomycosis (Chapter 131), namely: suppuration, scarring, and sinus formation.

Manifestations. The typical picture of maduromycosis may take months or even years to develop. The most characteristic feature of the infection is the large, swollen foot, or hand, which

may enlarge until it becomes a shapeless mass two or three times its normal size. The skin, which becomes discolored and irregular as a result of scar and sinus formation, does not lose its sensation. The infection usually is painless, even if the foot is manipulated, but there may be local tenderness over unruptured abscesses. The lesions involve the muscles, fascia, tendons, and bones. Bone involvement, which can be demonstrated by x-ray, is more common in the nocardial infections than in those which are caused by the moldlike fungi.

In the absence of secondary infections, there are no systemic manifestations.

Laboratory Findings. The only positive laboratory finding is the demonstration of the granules in material from draining sinuses or in sections of the lesions.

Differential Diagnosis. Maduromycosis must be differentiated from chronic bacterial infections such as tuberculosis, syphilis, and yaws, and from fungous infections such as blastomycosis, coccidioidomycosis, and sporotrichosis. The infection also may simulate elephantiasis and certain neoplasms.

Treatment. Sulfanilamide has been reported as curing a case of extensive maduromycosis due to a species of *Nocardia*, but in the majority of cases medical treatment has not proved satisfactory, and it has been necessary to resort to amputation. It is felt, however, that sulfonamides and antibiotics should be given extensive clinical trial, especially in nocardial infections, before resorting to such drastic surgery. Fortunately, the fact that the disease does not become systemic allows sufficient time for therapeutic experimentation under medical management.

Prognosis. The prognosis for life is excellent, but it is unusual for the local lesion to heal or become stationary.

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The Dermatomycoses

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Definition. The dermatomycoses are fungous infections of the skin, hair, or nails, caused by species of fungi belonging to the genera *Microsporum*, *Epidermophyton* or *Trichophyton*, which are referred to collectively as the dermatophytes.

History. *Achorion schoenleinii*, now known as *Trichophyton schoenleinii*, which was described by Schoenlein in 1839, was the first pathogenic microorganism to be reported. *Microsporum* and *Trichophyton* infections were found in 1843 and 1845 respectively, many years before bacteria were proved to have any etiologic relationship to infectious disease.

Mycology. The species identification of a dermatophyte is exceedingly complex, and requires such a careful mycologic examination that it cannot be discussed here. However, the diagnosis of a dermatophytic fungous infection usually can be established by a direct microscopic examination of scrapings from a lesion. All of the dermatophytes have the same appearance in such lesions, and a species diagnosis can be made only by cultural studies.

In making preparations from the skin, hair, or nails, it is essential that the scrapings be placed in 10 per cent potassium hydroxide, and the preparation warmed slightly to hasten the clearing of the keratinized material. The fungi in the lesions occur as refractile mycelial fragments or as small spores.

Pathogenesis. The dermatophytes live in the keratinized superficial structures of the body, where the fungi exist saprophytically until the infection is activated by conditions such as ex-

cessive perspiration, maceration, or other factors. The most important factor in dermatophyte infections is the state of hypersensitivity developed by the patient, which causes acute reactions at the sites of infection. Sometimes fungous products enter the general circulation, producing sterile dermatophytids or "ids" in other parts of the body.

Manifestations. It has been shown that there is no distinct correlation between the species of fungus causing an infection and the type or location of the infectious process. Thus species of *Microsporum* can infect the hair or skin, species of *Epidermophyton* can infect the skin or nails, and species of *Trichophyton* can infect all three tissues. Many dermatologists, therefore, classify the dermatomycoses according to the part of the body infected, using such terms as tinea pedis (athlete's foot), tinea unguium (infection of the toenails), tinea barbae (infection of the beard), tinea capitis (ringworm of the scalp), and others.

The clinical manifestations are so extremely varied, depending upon the degree of hypersensitivity of the patient, that it is impossible to describe any of them in this chapter. In extremely hypersensitive patients, especially after too vigorous treatment of local lesions, severe generalized symptoms appear which may be so serious that the patient is incapacitated for months.

Laboratory Findings. There are no significant laboratory findings other than the demonstration of fungi in direct smears of the lesions.

Differential Diagnosis. Because of the variability of the clinical manifestations, the dermatomycoses can be confused with almost any type of skin disease, and the specific diagnosis can be made only by direct examination and culture.

Treatment. In the management of any of the superficial mycoses, it is most important that overtreatment be avoided, since serious conse-

quences may follow the too vigorous applications of therapy, especially in extremely hypersensitive individuals. Most of the remedies used are keratolytic agents and not fungicides, and the beneficial effects of treatment result more from the removal of the substrate than from the death of the fungus.

The type of treatment depends upon the part of the body infected and the type of tissue (skin, hair, or nails) involved. Since infections of the feet are encountered most frequently, their management is presented as an illustration of the type of therapy which can be employed.

Moderately severe dermatophytosis of the feet may be treated by soaking them for 15 minutes each night in a solution of potassium permanganate (1:4000), followed by one of the fatty acid ointments (sodium propionate ointment ["Sopronol"], or undecylenic acid ointment ["Desenex"]). In the morning, any remaining ointment should be removed and a suitable dusting powder (thymol iodide, salicylic acid, or calcium propionate) applied. Half-strength Whitfield's ointment, Castellani's stain, "Pragmatar" ointment, and a variety of other medications may be more efficacious in the hands of experts, but they are more likely to cause reactions than the fatty acid derivatives.

With severe or secondarily infected dermatophytosis of the feet, the patient should be placed at bed rest and continuous wet dressings applied. Superimposed bacterial infections should be treated with preparations such as 1 per cent gentian violet solution. As the acute infection subsides, it should be controlled by following the general principles outlined above for the moderately severe dermatophytosis.

Tinea unguium is particularly difficult to treat as it is almost impossible mechanically to get through the nails to the fungus without resorting to measures such as filing, scraping, and repeated soaking.

The therapy of tinea capitis differs from the above routine in that it may be treated by daily shampoo followed by sodium propionate liquid in the morning with the application of 5 per cent salicylanide ointment or copper undecylenate ointment at night. As many hairs as possible should be epilated manually, but in extensive cases x-ray therapy may be necessary. The Wood's light is almost obligatory in performing manual epilation, since it permits the physician to distinguish between infected and noninfected hairs.

Prognosis. The prognosis for the acute exacerbations of the infection is good if the lesions are treated carefully. It is doubtful if the infection is ever eliminated completely, and the patient should be instructed in such matters as personal hygiene in order to aid him in keeping his infection under control.

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Section 14—Spirochetal Infections

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Syphilis

Albert Heyman

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DEFINITION

Syphilis is a chronic, systemic, infectious disease caused by the *Treponema pallidum* and usually transmitted by sexual contact. It is capable of producing tissue destruction and chronic inflammation in almost any organ in the body and can express itself in a great diversity of clinical manifestations.

HISTORY

The origin of syphilis has been a controversial subject. Whether syphilis existed in Europe from time immemorial or was first introduced from America by Columbus and his crew has been a matter of dispute. Most medical historians believe that the disease originated in America, since it first began to be noticed in Europe about 1495, or soon after Columbus returned from the New World.

Considerable knowledge regarding the pathology and clinical aspects of syphilis was accumulated in the sixteenth to nineteenth centuries, but it was not until early in the present century that most of the fundamental information about the disease was uncovered. The etiologic agent, the *Treponema pallidum*, was discovered by Schaudinn and Hoffmann in 1905. Soon afterward, Wassermann and his associates introduced serologic methods of diagnosis.

In 1910 Ehrlich announced the discovery of arsphenamine, and in 1917 Wagner von Jauregg demonstrated the value of malarial fever therapy for paresis. These were the two most important advances in the treatment of syphilis until 1943, when penicillin was found by Mahoney and his associates to be effective in the early stages of the disease. This drug has largely replaced other forms of chemotherapy in syphilis.

ETIOLOGY

The *Treponema pallidum* is a slender, corkscrew-like spirochete with regular, evenly spaced spirals. It varies in length from 5 to 20 μ . When viewed under the dark-field microscope, *T. pallidum* shows characteristic motility, rotating on its long axis and moving slowly backward and forward. The spirals usually keep their uniform shape and size, although the body of the organism may bend at the middle. It does not have the quick, whipping movements of other spirochetes which are often found in ulcerative lesions. The organism does not stain well with ordinary dyes, but can be demonstrated by silver impregnation methods in fixed tissues. For clinical purposes it can be demonstrated by dark-field microscopy of material from primary or secondary syphilitic lesions.

T. pallidum is readily killed by soap, ordinary antiseptics, drying, and heat. It may resist cold temperatures, however, and can be frozen and stored for long periods without affecting its virulence. The organism does not remain viable, however, in whole blood or plasma which has been stored at refrigerator temperature for more than 96 hours.

Pathogenic forms of *T. pallidum* have not been cultivated on artificial mediums. Strains of the organism which have been cultured are not virulent in animals and differ morphologically from pathogenic *T. pallidum*. Rabbits and

monkeys can be experimentally infected with syphilis, and typical lesions have been produced in these animals.

FREQUENCY OF SYPHILIS

Accurate information is not available as to the total number of persons infected with syphilis in the United States (i.e., prevalence), or the number of new infections occurring each year (i.e., incidence). Both the incidence and prevalence rates in a community depend upon numerous factors, such as age, sex, race, and the socioeconomic status of the population. The results of the serologic tests for syphilis taken during the Selective Service examinations in 1940 and 1941 revealed a prevalence of 45.3 per thousand; that is, 4.5 per cent of men of draft age (21 to 35 years) had syphilis. Considerably higher rates were found among Negroes, 252.3 per thousand, than among whites, 17.4 per thousand. Higher rates for both whites and Negroes were found in the southeastern portions of the country. The actual number of new cases of syphilis occurring each year is very difficult to determine. It has been estimated, however, on the basis of reported cases of infectious syphilis, that approximately 200,000 new cases developed in 1948.

PATHOGENESIS

Syphilis is usually transmitted by direct and intimate contact with moist infectious lesions of the skin and mucous membranes. The disease is usually spread, therefore, during the primary and secondary stages. Sexual contact is by far the commonest means of infection, but transfer of the disease by kissing or biting occasionally occurs. Indirect transmission—i.e., by contaminated objects—is exceptional, since the organisms quickly die if allowed to dry. The disease can be spread by inoculation with infected blood, as in transfusion syphilis. In pregnancy, infection is transmitted to the fetus through the placenta. *T. pallidum* is apparently capable of penetrating the intact mucous membrane, but a small abrasion is probably required for inoculation to occur through the skin. Once the spirochete has penetrated the epithelium, it enters the lymphatics and can be demonstrated in the regional lymph nodes a few hours after experimental inoculation. From the lymph nodes the organism spreads rapidly throughout the body by way of the blood

stream. This spirochetemia may occur several weeks before appearance of the primary lesion at the site of inoculation. The seeding of *T. pallidum* in various tissues at this time is the basis for many of the later manifestations of the disease.

About three to six weeks after the organism has entered the body, a primary lesion, the *chancre*, develops at the site of inoculation. The chancre is usually a single ulceration of the skin or mucous membrane, often associated with enlargement of the regional lymph nodes; it heals spontaneously. About six weeks after its appearance a generalized skin eruption, known as *secondary syphilis*, develops. In this stage systemic manifestations such as headache, fever, and malaise are common. The signs of secondary syphilis also disappear spontaneously.

This sequence of events in early syphilis is variable; either the primary lesion or the secondary manifestations, or both, may fail to develop. Infection without noticeable lesions probably occurs in a high percentage of cases, and many individuals with late syphilis are unable to recall either primary or secondary manifestations.

With the involution of the primary and secondary lesions, *T. pallidum* disappears from the surface and is harbored within the body. This stage of the disease is known as *latent syphilis* and is characterized by the absence of signs and symptoms of the infection. It is detectable only by serologic tests. During the first two years of the latent period infectious lesions may appear on the skin and mucous membranes. These lesions resemble those of secondary syphilis, but are usually less profuse and often appear insignificant. The frequency of this type of relapse in untreated cases is not known, but it is believed to occur in the majority of patients. Usually by the end of the second year, almost certainly by the end of the fourth year, the patient has developed sufficient immunity to suppress such lesions and prevent spirochetemia. In patients receiving inadequate therapy, however, resistance to the organism may not be fully developed, and redissemination of spirochetes with production of new infectious lesions may occur for as long as 10 years or more after the onset of the disease.

Following healing of the primary and secondary manifestations, the patient may show no outward signs of the infection; nevertheless,

chronic, progressive, inflammatory changes may be taking place in the visceral organs or in the cardiovascular or central nervous system. Clinical evidence of cardiovascular or neurosyphilis may not develop for 10 to 20 years or more after the onset of the disease. Occasionally the tissues of the host seem to become sensitized to the spirochetes, and large destructive lesions, called *gummas*, result. These lesions, which contain very few spirochetes, can occur in almost every organ of the body, but are most frequently found in the skin or bones.

Many patients with latent syphilis do not develop late manifestations, and show no evidence of syphilis at autopsy. A study of patients with untreated early syphilis followed for a number of years showed that approximately one third of them achieved spontaneous cures with the development of negative serologic tests. An equal number died of causes other than syphilis or developed latent syphilis with no clinical evidence of the disease other than a positive serologic test. The remaining third developed serious lesions of the cardiovascular or central nervous system or benign gummatous lesions of the skin or bones. It would appear, therefore, that the prognosis of syphilis, even if untreated, is good in two thirds or more of the cases. Modern therapy, however, will not only greatly improve this prognosis, but will also prevent the spread of the disease to others.

HISTOPATHOLOGY

The early lesions of syphilis are characterized by infiltration of the blood vessel walls and perivascular spaces with plasma cells, large mononuclear cells, and lymphocytes. Spirochetes may be numerous and can be demonstrated by silver impregnation stains. In the late lesions of syphilis there may be necrosis with granuloma or gumma formation. The necrosis is thought to be the result of an exaggerated or hypersensitive response to a small number of organisms. Spirochetes are rarely found. These lesions heal slowly and often produce considerable scar formation and tissue destruction.

IMMUNITY AND RESISTANCE IN SYPHILIS

The development of immunity in a syphilitic patient can be considered from two standpoints: the resistance the patient develops to his own

infection and the immunity he develops to reinfection.

Practically every patient with syphilis develops some resistance to his own infection, since healing of early syphilitic lesions occurs spontaneously and latency follows. The degree of immunity established, however, determines whether the patient will achieve a spontaneous cure, whether the disease will remain latent, or whether late, serious complications will develop. The factors responsible for the development of this type of immunity and the destruction of spirochetes are largely unknown. The immunity in syphilis has been generally thought to be cellular in type. The serum of experimentally infected animals and patients with syphilis, however, has been demonstrated to contain antibodies which will immobilize and render noninfectious virulent strains of *T. pallidum*. The exact relationship between these antibodies and the development of immunity has not yet been determined.

Apparently the outcome of the syphilitic infection is influenced to some extent by the sex and race of the individual. Neurosyphilis, for example, occurs more frequently in men than in women, and in a higher proportion of white individuals than Negroes. Bone and cardiovascular syphilis, however, are more common in Negroes.

Immunity to reinfection develops soon after the onset of the disease. In animals, immunity has been found to appear within three weeks after the initial infection and to increase progressively in degree during a period of six months. Reinoculation of animals who have developed partial immunity may produce asymptomatic reinfection. In humans, reinoculation usually results in a chancre if carried out within 15 days after the appearance of the primary lesion of the initial infection. Later than this a chancre seldom develops, the patient having acquired some degree of immunity. This resistance is relative. It can probably be overcome and a superinfection produced by inoculation with large numbers of spirochetes.

Adequate treatment of patients with early syphilis may abort the development of immunity, and reinfections can occur in such patients. If treatment is delayed until after this period, immunity to reinfection becomes established and may remain throughout the lifetime of the individual. Persistence of immunity in late syphilis

is thought by some to indicate that treatment is not curative. Others, however, believe that the existence of immunity does not necessarily indicate the persistence of infection, and that all organisms can be destroyed in late syphilis as well as in the early infection.

Treatment of early syphilis not only can influence the patient's immunity to reinfection, but may also prevent the patient from developing resistance to the spirochetes within his own tissues. If inadequate treatment is given during early syphilis and complete destruction of the patient's spirochetes is not obtained, redissemination of the organisms may occur and produce infectious skin and mucosal lesions or involve tissues which may previously have escaped, such as the eye or central nervous system. This type of relapse is frequently the result of inadequate treatment of early syphilis and is the basis for the statement that poor treatment is worse than none at all. Once the patient has developed immunity to his own infection (usually within four years after the onset of the disease), inadequate treatment does not result in redissemination of organisms. The treatment of early syphilis must therefore be continuous and adequate. In late syphilis continuous therapy does not seem to be essential.

The development of immunity parallels to some extent the formation within the patient of an antibody-like substance called reagin. *In vitro* this substance acts like a true antibody and can be detected by flocculation and complement-fixation tests. This substance probably has little relationship to immunity. Reinfections can occur in patients whose serum contains this substance, and large amounts of it can be produced in animals without protecting them against syphilitic infection. Furthermore, it has been shown that reagin and the antibody which immobilizes *T. pallidum* are separate substances.

CLINICAL MANIFESTATIONS OF EARLY ACQUIRED SYPHILIS

Primary Stage. About three weeks after *T. pallidum* has entered the body the primary lesion, or *chancre*, appears. The period of incubation may vary from 10 to 90 days. The typical chancre is a solitary, indurated, nonpainful ulceration, which heals slowly with scar formation. It is often accompanied by painless enlargement of the regional lymph nodes, the *satellite bubo*. It

must be emphasized that primary syphilis is often atypical and may be manifested by small, multiple, or painful lesions which resemble many other conditions. Because of the frequent atypical appearance of the chancre, the clinical diagnosis or exclusion of primary syphilis can never be relied upon and every genital lesion should have a dark-field examination.

Approximately 95 per cent of primary lesions are found on or near the genitalia. In the male the chancre frequently appears on the coronal sulcus or on the prepuce. Any part of the genitalia may be involved, however, and the glans, shaft, pubis, or scrotum may be the site of the primary infection. Occasionally intraurethral lesions occur. These cases are usually mistaken for urethritis, but *T. pallidum* can be found in the urethral exudate. Chancres of the external genitalia must be differentiated from such conditions as chancroid, granuloma inguinale, lymphogranuloma venereum, carcinoma, and many other lesions which appear in this area. In the female, the primary lesion often appears on the labia and in the fourchette, but the perineum, pubis, clitoris, or urethra may be involved. Chancres of the cervix are frequent and are often mistaken for nonspecific cervical erosions. About 5 per cent of primary lesions occur on the lips, female breasts, or in the mouth. Unusual lesions of such areas must always be suspected of being syphilitic.

In the diagnosis of primary syphilis, serologic tests cannot be relied upon entirely, since the tests are often negative in this stage of the disease. Moreover, a positive serologic reaction in a patient with a genital lesion may represent either a latent infection associated with a nonsyphilitic lesion or else a biologic false positive reaction caused by a nonsyphilitic disease (i.e., lymphogranuloma venereum or chancroid). For this reason a dark-field examination is of greatest importance in the diagnosis of this stage of the disease and should be done on the first visit of every patient suspected of having primary syphilis. If the initial dark-field examination is negative, it should be repeated on three successive days, and if spirochetes are not found, material from the regional lymph nodes should be aspirated and examined under the dark-field microscope. All local medication should be withheld, but oral sulfonamides may be administered during this period of time. If the dark-field examina-

tions and serologic tests for syphilis are negative, the serologic test should be repeated several times during the first two or three weeks and every few weeks thereafter for three months after the appearance of the lesion. If the patient's serologic test remains negative during this period of time, he can be assured that the lesion was not that of early syphilis. If, however, the patient develops a positive serologic reaction in a high or rising titer (with or without evidence of secondary manifestations), then antisyphilitic therapy should be begun. A single serologic test of low titer is not sufficient evidence for beginning antisyphilitic treatment if dark-field examinations are negative. Such tests should be confirmed several times for at least two or three weeks before treatment for syphilis is justified.

Penicillin or other spirocheticidal drugs should not be given as a therapeutic test to patients suspected of having primary syphilis. Such treatment will cause disappearance of spirochetes from the lesion and make dark-field examination useless. In addition, it may delay the appearance of a positive serologic reaction. Healing of the genital lesion following such therapeutic tests does not necessarily indicate the presence of syphilis, since nonsyphilitic lesions sometimes heal spontaneously. Biopsy of the genital lesions is often of value in the diagnosis of these patients.

Secondary Stage. The secondary stage of syphilis usually develops about six weeks after appearance of the chancre and is manifested by a generalized skin eruption and systemic symptoms. Some patients exhibit secondary lesions without ever being aware of a primary lesion, while others never develop secondary manifestations and enter the latent stage directly following the healing of the chancre.

The appearance of the *cutaneous lesions* of secondary syphilis varies considerably and may be confused with many other skin eruptions. The lesions most often found are papules, maculopapules, or follicular papules (fig. 152). Occasionally, annular (fig. 153), pustular or rupial lesions occur. Indeed, almost any type of skin eruption may appear except a vesicular one. The rash is usually widespread and frequently involves the palms, soles, and face, in addition to the trunk and extremities. The lesions are sometimes pruritic.

The *mucous membranes* of the mouth and genitalia are often involved in secondary syphilis.

Syphilitic lesions of the mouth appear as painless, superficial erosions on the buccal surfaces, on the tongue, or inside the lip. When these lesions are covered with a thin, grayish exudate, they are known as *mucous patches*. They contain



FIG. 152. Secondary syphilis. These lesions are small, conical, follicular papules arranged in clusters and widely spread over the trunk and extremities. Larger papules or papular pustules are also common. (Courtesy, Dr. Harry M. Robinson.)



FIG. 153. Secondary syphilis with annular skin lesions. Commonly found about the face in Negroes, the lesions consist of rings or arcs with hyperpigmented central areas. (Courtesy, Dr. Harry M. Robinson.)

large numbers of spirochetes, but may be very inconspicuous, and the patient may not be aware of their existence. Mucosal lesions also occur on the palate and tonsillar area and can cause a persistent *sore throat*. Erosions of the palpebral fissures, so-called *split papules*, are occasionally

seen in secondary syphilis and may be mistaken for herpes, benign fissures, or the lesions of riboflavin deficiency.

Syphilitic mucosal lesions of the genitalia or perianal regions often become hypertrophic and are called *condylomata lata*. These lesions are broad, flat, wartlike excrescences which are found on the labia majora, perineum, and anal region (fig. 154). They are highly infectious and

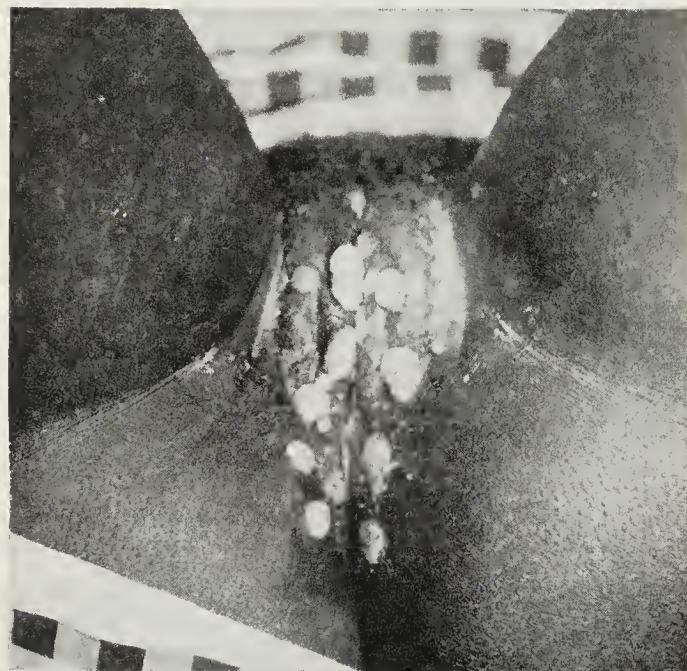


FIG. 154. Secondary syphilis with condylomata lata. These lesions are grayish, raised, moist papules frequently occurring on the genitalia. They are highly infectious, containing large numbers of *Treponema pallidum*. (Courtesy, Dr. Harry M. Robinson.)

should be differentiated from condylomata acuminata, which are nonvenereal, pedunculated lesions.

Although the clinical findings of secondary syphilis are often confined to the skin and mucous membranes, many patients will present evidence of *constitutional symptoms* and widespread spirochetal dissemination. Malaise, lassitude, headaches, fever, and myalgia are often noted. There may be a *generalized lymphadenopathy*. The lymph nodes are usually nontender and may be quite large, particularly in the Negro. Since lymph nodes in the epitrochlear and axillary areas are often enlarged in normal individuals, this finding is not so significant as enlargement of the posterior cervical and occipital nodes. Localized areas of *alopecia* also occur, causing a "moth-eaten" appearance of the scalp.

Approximately 4 per cent of patients with secondary syphilis have involvement of the eye,

usually *iritis* or *neuroretinitis*. Syphilitic iritis cannot usually be distinguished clinically from other types of iritis. The diagnosis, therefore, is based upon its association with secondary syphilis and its prompt response to antisyphilitic treatment. Neuroretinitis is characterized by blurring and hyperemia of the nerve head and retinal edema. Both iritis and optic neuritis are often relapse phenomena and are found in patients who have had inadequate treatment for early syphilis.

Skeletal lesions occasionally occur in secondary syphilis and are manifested by localized areas of swelling and tenderness. The tibia, skull, and sternoclavicular joints are most frequently affected. Roentgenographic examination usually reveals periostitis, but destructive lesions of the bone may be found. *Arthralgia* and *hydrarthrosis* also occur, but changes in the joints cannot be detected by x-ray examination. An acute *nephrosis* with marked proteinuria, edema, and hypercholesterolemia is sometimes seen in secondary syphilis. Evidence of *central nervous system involvement*, such as paralysis of the cranial nerves or meningitis, may also appear in this stage of the disease.

It is apparent from the above description that secondary syphilis may be manifested by a great variety of apparently unrelated clinical symptoms. Although isolated lesions, such as iritis or periostitis, may not in themselves suggest the diagnosis, the recognition of other symptoms, such as sore throat, lymphadenopathy, or skin lesions, in a given individual will often make the diagnosis of secondary syphilis obvious. Whenever secondary syphilis is suspected, blood should be taken for a serologic test. This will be positive in practically 100 per cent of the cases. Conversely, if the serologic test is negative (and technical errors excluded), secondary syphilis can be ruled out.

INFECTIOUSNESS AND EPIDEMIOLOGY

Syphilis is most infectious during the primary and secondary stages, when there are moist skin or mucosal lesions. The infectiousness of the early lesions depends largely upon the duration and type of lesions, the state of healing, and whether they are dry or moist. The genital condylomas and the oral mucosal lesions contain large numbers of spirochetes and are more in-

fectious than the dry skin lesions. The transmission of the disease by individuals or marital partners who deny having had open lesions is probably by way of small mucosal lesions which appear during the recurrent episodes of spirochetemia. These lesions may be small and are easily overlooked.

The infectiousness of various secretions, such as milk, tears, saliva, and semen, is probably not great and occurs only in the early stages of the disease. Some of these secretions, such as saliva and semen, are frequently in contact with infectious mucosal lesions and may thus contain *T. pallidum*. The blood of patients with early syphilis has been shown to contain spirochetes and should not be used for transfusion. The serologic test is not always an indication of the infectiousness of the blood, since transfusion syphilis can be transmitted from patients in the incubation period or in the seronegative primary stage of the disease. The danger of transmitting syphilis either by transfusion or by direct contact is greatest in the first four years of the disease and is negligible after this period of time. In pregnancy, however, the disease can apparently be transmitted to the fetus for as long as 10 years or more after the onset of the disease, although the vast majority of congenital infections are acquired during the first four years of maternal infection. The mechanism by which *T. pallidum* in patients with late syphilis is stimulated by pregnancy to produce intrauterine infection is not known.

It is important that the physician make an effort to determine the source of infection of his patients with syphilis, particularly those with primary and secondary manifestations, and should arrange to have these individuals treated. It is equally important that the individuals to whom the patient may have transmitted the infection be located. If the presence of syphilis is not immediately evident in these cases, they should be followed with physical examinations and serologic tests for several months before being dismissed.

LATENT SYPHILIS

Latent syphilis is that stage of the disease in which there are no clinical signs or symptoms of the infection, the diagnosis usually being based on a positive serologic test. The diagnosis can sometimes be made in the presence of a negative

serologic test if the patient has given birth to a syphilitic child or if there is a definite history of an inadequately treated infection. The presence of a negative spinal fluid is essential for the diagnosis of latent syphilis. Patients without signs or symptoms but with abnormal spinal fluid findings have a much more serious prognosis and are not regarded as having latent syphilis, but are classified instead as having asymptomatic neurosyphilis.

Latent syphilis is by far the most frequent type of syphilis encountered and is usually discovered as the result of the widespread use of serologic tests. Indeed, routine serologic testing is the only way in which the majority of patients with latent syphilis can be recognized, as more than one third of them either have had symptomless infections or do not recall having had the primary or secondary manifestations of the disease.

The early years of the latent period may be interrupted by repeated spirochetemia. With the development of immunity these relapses become less overt and eventually cease to occur entirely. The time required by the host to develop sufficient resistance to prevent this type of relapse varies with different individuals. Maximum tissue resistance will be acquired in most patients in two years, and in practically every patient by the end of the fourth year. The prognosis of the disease and the principles of therapy depend to some extent upon the development of this type of immunity, and four years is arbitrarily chosen as the dividing line between early and late syphilis.

In the absence of a history of lesions or previous serologic tests, it is often impossible to differentiate between early and late latent syphilis. The age of the individual, the history of sexual contacts, the existence of syphilis in the marital partner, and other data often assist in determining the duration of the disease.

Although the syphilitic infection is not clinically evident during the latent period, it may be producing serious changes in the viscera. Whether these changes become clinically apparent depends upon the resistance of the individual. Often the spirochete exists within the body throughout the entire lifetime of the host without producing any apparent effects upon health and longevity. Most of the patients with late latent syphilis develop sufficient resistance to their infection to prevent late clinical manifestations. It is believed

that approximately 75 per cent or more of these patients will remain latent even if they never receive treatment.

The diagnosis of latent syphilis is one of exclusion, and a careful history and physical examination should be made for clinical evidence of this disease. The spinal fluid must be negative and the presence of an aneurysm excluded by roentgenologic examination of the chest. Since the diagnosis of latent syphilis is dependent upon the serologic test, false positive reactions must be ruled out.

CLINICAL MANIFESTATIONS OF LATE ACQUIRED SYPHILIS

Skin and Mucous Membranes. Late syphilis of the skin may appear either as small nodular lesions or ulcerating gummas. The gumma begins as a painless, subcutaneous tumor which gradually softens and ruptures through the skin, exuding a viscous, gummy material. A chronic granulating ulcer results, which may be either a solitary lesion or a collection of several similar lesions coalescing to form one large ulceration.



FIG. 155. Late nodular syphilis of the skin with characteristic serpiginous configuration. These lesions are indolent, spreading peripherally while healing in the center. Ulceration may occur. (Courtesy, Dr. Harry M. Robinson.)

Spirochetes are seldom found in these lesions. The nodular form of late syphilis consists of slightly raised, reddish brown lesions on the skin, which often coalesce to form arciform or serpiginous configurations (fig. 155).

Gummatus lesions also occur in the mucous

membranes of the nose and throat, and may produce painful destructive lesions in the palate and nasal septum. Although the lesions of the skin and mucous membranes sometimes can be recognized by simple inspection, biopsy may be necessary to establish a definite diagnosis. If biopsy is not feasible or if histologic examination is inconclusive, the diagnosis of such lesions (as well as gumma of the viscera or skeletal system) sometimes can be made by a short therapeutic trial with iodides or bismuth and arsenicals. Gummatus involvement of the genitalia, the lymph nodes, and the juxta-articular areas may be difficult to distinguish from a host of other conditions.

Syphilis of the Skeletal System. Late osseous syphilis often presents a difficult diagnostic problem. The chief symptoms are pain, tenderness, and local warmth. The bones usually involved are the skull and tibia, although the clavicle, humerus, ribs, and nasopalatine structures are sometimes affected. Periostitis is the most common type of lesion; x-ray reveals a fine, lacy, periosteal reaction. Sclerotic thickening of the bony cortex is also frequently noted, particularly in the long bones. Osteolytic lesions also occur, usually in the skull, but may involve the entire skeletal system. A combination of all three lesions may give a complex picture.

Syphilis of the skeletal system is often confused with other types of subacute or chronic osteomyelitis, primary or secondary neoplasms, osteogenic sarcoma, or Paget's disease. The roentgenographic findings, while not pathognomonic, are often highly suggestive. The diagnosis can usually be made by close correlation of the serologic, clinical, and roentgenographic findings. In some instances biopsy may be necessary, particularly when the existence of a neoplastic disease is suspected.

Syphilis of the Joints. The most common joint manifestation occurring in late syphilis is the *Charcot joint*. This condition is not caused directly by *T. pallidum*, but develops as a consequence of destruction of the proprioceptive nerves in tabes dorsalis. It also occurs in other neurologic disorders, such as syringomyelia. The Charcot joint is usually confined to a single weight-bearing joint, such as the knee, ankle, or hip, and occasionally the spine. It begins as a painless swelling of the joint and is later manifested by hypermobility and loss of contour. The

joint surface disintegrates, so that fragments of bone and cartilage can be felt within the joint capsule. Charcot joints often appear in arrested or "burnt-out" cases of tabes dorsalis—i.e., patients with normal blood and spinal fluid findings. Antisyphilitic drugs are of little value in treatment, and orthopedic measures are usually necessary.

Syphilis of the Liver. Involvement of the liver is almost a constant finding in infants dying with early congenital syphilis, but is rare in the early stages of the acquired disease. Gumma of the liver, however, has been found at autopsy in as many as 5 per cent of patients with late syphilis. In these cases the liver may contain multiple, minute, gummatous lesions or several very large ones. On healing, these lesions produce scarring and contraction of the surface, giving the liver the appearance of having several additional lobes—hence the name *hepar lobatum*. The diagnosis of syphilis of the liver is often very difficult and it is frequently mistaken for carcinoma or cirrhosis. The patient may complain of abdominal pain, swelling, or a mass in the epigastrium. The most common finding on physical examination is a large, coarsely nodular, irregular liver. Ascites, jaundice, and splenomegaly are occasionally present. The serologic test for syphilis is almost always positive, usually in a very high titer.

The diagnosis of syphilis of the liver may be established by biopsy. Response to treatment is often dramatic, with rapid reduction in liver size and relief of symptoms. Gummatous lesions about the hilum occasionally heal with scar formation, producing jaundice and portal hypertension. This has been called a *therapeutic paradox*.

Syphilis of the Stomach and Gastrointestinal Tract. Late syphilis of the stomach may consist of either a diffuse granulomatous infiltration of the stomach wall or a localized annular constriction about the pyloric area. Secondary ulceration and obstruction may occur, so that differentiation from carcinoma by roentgenographic examination is often impossible. Syphilis of the stomach may be suspected in young individuals on the basis of the roentgenographic appearance of the lesion and a positive serologic test, but exploratory laparotomy is usually indicated, since the possibility of carcinoma of the stomach cannot definitely be excluded.

Gummas of the salivary glands and esophagus are occasionally found, but syphilitic lesions of the intestine, rectum, and pancreas or other portions of the gastrointestinal tract are extremely uncommon.

Syphilis of the Larynx and Respiratory Tract. Syphilis of the larynx produces hoarseness without pain. Laryngoscopic examination may reveal gummatous infiltration of the vocal chords with secondary ulceration. The lesions may simulate carcinoma or tuberculosis, and biopsy is necessary for differential diagnosis. Treatment of this condition should be cautious, since intensive therapy with arsenicals has been known to produce edema, stridor, and suffocation. Patients with late syphilis may also develop hoarseness without pain as a result of recurrent nerve paralysis caused by aneurysm of the aorta.

Syphilis very rarely involves the trachea, bronchi, lungs, or mediastinal lymph nodes.

Syphilis of the Kidney and Genitourinary Tract. Patients with late syphilis occasionally show evidence of a specific type of interstitial nephritis on post-mortem examination. This condition, however, does not seem to produce a characteristic clinical picture and is of histologic interest only. Gumma of the kidney is rare, but late syphilis of the bladder, testes, and penis is occasionally reported. Paroxysmal hemogloburia is sometimes caused by syphilis. It is discussed in another section (Chapter 224).

In the female, late syphilis rarely involves the internal genital organs, but gummatous lesions sometimes appear in the breast.

Involvement of the endocrine glands, such as the adrenals, thyroid, and pituitary gland, is also infrequent.

Cardiovascular Syphilis. Since cardiovascular syphilis is discussed fully elsewhere (Chapter 241), it will be mentioned only briefly at this point. Cardiovascular syphilis is one of the most important of the late lesions of syphilis and probably accounts for the majority of deaths resulting from this disease. It is much more common in men than in women and seems to be more frequent in Negroes than in whites. For obscure reasons it is very rarely found in congenital syphilis. It usually appears in the second to third decade after infection and may be associated with neurosyphilis and other late manifestations.

The fundamental lesion of cardiovascular syphilis is *aortitis*. *T. pallidum* causes destruction

of the media, fragmentation of the elastic material, and eventual dilatation of the vessel. The base of the aorta is often involved, with dilatation of the valve ring and subsequent *aortic insufficiency*. Diffuse involvement of the vessel wall may produce a slight to moderate dilatation of the aortic arch. If the weakening is localized, a saccular *aneurysm* may develop. The intima of the aorta becomes thickened and occlusion of the orifices of the coronary arteries may occur. Symptoms of chronic coronary disease may then appear. A few cases of multiple gummas of the myocardium have been reported, but the existence of a diffuse syphilitic myocarditis is a matter of controversy. While some authorities have described diffuse syphilitic inflammation of the myocardium with the presence of spirochetes, others have not been able to confirm these findings.

Syphilis of the Central Nervous System. Neurosyphilis, together with cardiovascular syphilis, accounts for about 90 per cent of deaths caused by syphilis. Invasion of the central nervous system by the spirochete occurs during the early or spirocheticemic stage of the infection in the majority of patients, but only a small number of them, 10 to 15 per cent, develop late manifestations of central nervous system syphilis. This spontaneous remission is probably the result of an immunity or resistance on the part of the host. Although all of the tissues of the central nervous system are invaded by the spirochetes, the clinical symptoms may be arbitrarily divided into meningeal, vascular, and parenchymatous. Meningeal and vascular symptoms usually develop early in the course of the disease, whereas parenchymatous involvement, as manifested by tabes dorsalis and paresis, usually does not appear until 10 to 20 years after the primary infection. Meningeal lesions are inflammatory, and for this reason are often reversible. Parenchymatous lesions, however, are likely to be degenerative with irreversible damage. In many cases of neurosyphilis there may be a combination of both inflammatory and degenerative lesions, with involvement of all three structures—the parenchyma, vessels, and meninges. The type of lesion which predominates, the structures chiefly involved, and the exact location of the lesion within the central nervous system are the three important factors which influence the prognosis and the response to treatment.

Gummas of the brain and spinal cord are occasionally observed. They produce symptoms similar to tumors of the central nervous system, and differentiation is often difficult.

ASYMPTOMATIC NEUROSYPHILIS. Asymptomatic neurosyphilis is that stage of the disease in which an abnormal spinal fluid exists without any clinical signs or symptoms to indicate that the function of the central nervous system has been affected. The diagnosis of this condition is most important, since it is the forerunner of clinical neurosyphilis and proper therapy at this time can prevent manifest damage of the nervous system. Since the prognosis, treatment, and follow-up observation in each patient with late syphilis depends upon the presence or absence of central nervous system involvement, it is imperative that asymptomatic neurosyphilis be ruled out by spinal fluid examination.

The outcome of asymptomatic neurosyphilis and the degree of the spinal fluid abnormalities appear to be definitely related, since patients exhibiting marked spinal fluid changes are more likely to develop signs and symptoms of clinical neurosyphilis. For this reason a classification of the spinal fluid findings of patients with asymptomatic neurosyphilis is a useful procedure. Those with minimal abnormalities—i.e., increased cells and/or protein with other tests negative—are usually classified as group I. Patients with maximal changes—i.e., elevation of cells and protein, a strongly positive complement-fixation or flocculation test, and a first-zone colloidal reaction—are classified as group III. Group II fluids include those of an intermediate type. Studies of patients who received various forms of treatment other than penicillin for asymptomatic neurosyphilis have shown that the probability of developing clinical neurosyphilis by the end of the tenth year of observation is approximately 8 per cent for patients with group I fluids, 16 per cent for those with group II fluids, and 21 per cent for patients with group III fluids. The probability of developing clinical progression was least among the patients receiving malarial fever therapy. These studies showed that many patients with asymptomatic neurosyphilis had had a relatively benign prognosis. Approximately one third of the patients with group II or III fluids who received what was regarded as inadequate arsenical and bismuth therapy obtained normal spinal fluid findings. The probability of these patients de-

veloping clinical neurosyphilis was minimal. The prognosis was poor, however, in the patients whose spinal fluids remained the same or became worse. In these cases the probability of clinical progression within 10 years was 36 per cent.

Some workers believe that the activity of the neurosyphilitic process is related to the spinal fluid cell count and protein level. The presence of a positive spinal fluid Wassermann reaction indicates that infection of the central nervous system has occurred; the cells and protein indicate the activity of the condition. This concept maintains that if the spinal fluid is inactive—i.e., if the cell count and protein are normal—the syphilitic infection in the central nervous system has been arrested and no further therapy is needed. Although this concept is not completely accepted, it seems to hold true in the majority of patients.

The serologic reaction of the blood does not always parallel the spinal fluid findings. Patients with previous treatment may have a negative blood test and a strongly positive spinal fluid. This combination seldom occurs in untreated cases.

If the spinal fluid is completely negative five years after the onset of the disease, it rarely if ever becomes positive again. Repeated spinal fluid examinations are not necessary in these patients and they can safely be assured that clinical neurosyphilis will not develop.

SYPHILITIC MENINGITIS. In a small number of patients, involvement of the central nervous system may be manifested by an acute meningitis. This condition usually appears within the first two years after the onset of syphilis. It nearly always occurs in patients who have previously had inadequate therapy, and may be associated with an infectious or mucocutaneous relapse. It may also occur in untreated cases.

The clinical manifestations of meningeal syphilis fall largely into three main groups and may vary from a simple headache to a severe meningitis. The first group consists of basilar meningeal signs and is manifested predominantly by cranial nerve lesions. The second group is characterized by symptoms referable to the vertex of the brain, such as convulsions, hemiplegia, delirium, and aphasia. The third group shows evidence of increased intracranial pressure with nausea and vomiting, headache, stiff neck, and papilledema. These signs are also seen in many patients of the first two groups. *Papilledema* is frequently found

in patients with syphilitic meningitis, and these cases are often diagnosed erroneously as having brain tumors.

The serologic test for syphilis and the spinal fluid Wassermann are usually strongly positive. The spinal fluid may show a marked lymphocytosis, counts as high as 2000 cells per cubic millimeter having been observed. This condition is often confused with other forms of lymphocytic meningitis, such as tuberculous or virus meningitis. These diseases frequently produce false positive spinal fluid complement-fixation tests for syphilis, and differentiation may be extremely difficult. The patient's temperature in syphilitic meningitis may be helpful in differential diagnosis, since it is almost always less than 101° F. The immediate prognosis is very good, but the ultimate prognosis is much more serious. If the patient does not receive adequate treatment, late manifestations of neurosyphilis or paresis are likely to develop.

MENINGOVASCULAR SYPHILIS. Meningovascular syphilis is usually manifested by clinical signs of thrombosis of one or more of the branches of the cerebral or spinal arteries. Since there is almost always some evidence of leptomeningitis, the term meningovascular syphilis is used to describe these cases. The vascular changes in this condition are characterized by a dense infiltration of the adventitia with lymphocytes and plasma cells. The intima becomes thickened and the vessel lumen is narrowed or obliterated. The blood supply to the parenchyma is diminished, producing infarction of the nervous tissue.

The symptoms of this condition vary considerably, depending upon the location and size of the vessels involved. Prodromal symptoms of dizziness or severe headaches may occur, and sometimes minor paresthesias or motor weakness precede the major vascular episode. Although the vessels of the motor cortex and internal capsule are the most frequently involved, any of the cerebral vessels may be occluded. Monoplegia or hemiplegia, hemianesthesia, aphasia, or hemianopsia may occur. Cranial nerve palsies are frequent and convulsions are often observed. Syphilitic endarteritis may also involve the cerebellar vessels, and symptoms of cerebellar artery occlusion are occasionally noted. Patients with meningovascular syphilis sometimes develop psychotic behavior, and differentiation from paresis is often difficult.

The diagnosis of meningovascular syphilis may be relatively easy in young individuals free of hypertension or arteriosclerosis. In older patients, however, it is often impossible to differentiate clinically between syphilitic vascular disease and a cerebral vascular accident of other etiology. In such cases the blood and spinal fluid findings provide the only means of differentiation. The blood serologic test is positive in the majority of patients with vascular neurosyphilis, and the spinal fluid usually shows a moderate increase of cells and protein with a positive Wassermann reaction. A diagnosis of meningovascular syphilis should not be made if the spinal fluid is normal.

In general, the prognosis of patients with this form of neurosyphilis is better than that of patients with similar lesions caused by arteriosclerosis and hypertension. The syphilitic patients are younger, the area of infarction is smaller, and adequate treatment will usually prevent a recurrence of the attack. The degree of return of nervous tissue function depends almost entirely upon the size and site of the vascular involvement.

The vessels and meninges of the spinal cord undergo changes identical with those in the brain. With thrombosis of the anterior spinal artery, the patient may suddenly develop signs of an acute *transverse myelitis* with paraplegia, loss of sensation, and fecal or urinary incontinence. Usually, however, meningovascular lesions of the spinal cord are insidious and produce chronic progressive paralyses and sensory disturbances. A number of neurologic syndromes result from more or less localized spinal cord lesions: syphilitic involvement of the pyramidal tract produces the so-called *Erb's spastic spinal paraplegia*; anterior horn cell degeneration causes a picture similar to *progressive muscular atrophy*; while a single localized *gumma* may simulate cord tumor.

The term "meningovascular syphilis" is also employed for a large group of patients with diverse signs and symptoms, such as *epilepsy*, *eighth nerve deafness*, other cranial nerve lesions, or chronic headaches. Pupillary abnormalities are frequently present and may consist of a variety of changes, such as miosis, dilatation, anisocoria, fixed pupils, or typical Argyll Robertson phenomena.

TABES DORSALIS (LOCOMOTOR ATAXIA). Tabes dorsalis is a form of neurosyphilis in which there

is selective degeneration in the posterior roots of the spinal nerves and the posterior columns of the spinal cord. In far advanced tabes the spinal cord may be small and atrophic. The dorsal surface of the cord may be flattened and the dorsal roots of the lumbosacral area may be reduced in caliber. A moderate degree of leptomeningitis is usually present. Microscopically the dorsal roots may appear completely demyelinated and there is marked loss of nerve fibers. The posterior columns of the spinal cord also show a loss of myelin and degeneration of the axons. Spirochetes are rarely found in these lesions. There is still considerable uncertainty as to the pathogenesis of tabes, and the exact mechanism and origin of the degenerative process have not been completely determined. In the majority of cases tabes appears 20 to 30 years after the initial infection. It is found more commonly in men than in women.

Pains and paresthesias are common symptoms of tabes and are thought to be caused by irritation of the dorsal spinal roots. Patients with tabes frequently develop severe, agonizing *shooting* or "*lightning*" pains in the legs. Attacks of lightning pains are usually of short duration but may sometimes last for several days. They are often precipitated by minor infections, cold weather, constipation, etc. Girdle pains also occur in tabetics, along with paresthesias, numbness, and tingling of the trunk, hands, or feet. Another type of severe pain occurs in attacks of *gastric crises*. About 10 per cent of tabetic patients develop severe episodes of abdominal pain associated with nausea and vomiting. These attacks may last for days, resulting in dehydration and exhaustion. Patients with gastric crises are sometimes diagnosed as having acute surgical conditions, and unnecessary operations have been performed on these individuals.

Ataxia is a major symptom in tabes and may be so severe that the patient is unable to walk or stand. Some patients develop a typical tabetic gait, which consists of slapping of the feet and walking on a broad base. The ataxia is worse in the dark and the patient may sway or fall when standing with his eyes closed (*Romberg sign*). The damage to the nerve fibers in the posterior columns not only results in ataxia, but also produces loss of position sense, and the patient does not know without visual assistance the exact position of his toes or feet. Vibratory sensation in the legs is diminished or absent. There may be

diminution of deep pain sensation to pressure on the testes or Achilles tendon, and areas of hypoesthesia may be present on the trunk or in the hands and feet. The patella and Achilles tendon reflexes are sluggish or absent. Patients with tabes often show evidence of hypotonia and hyperextensibility of the joints. Degenerative lesions, such as chronic, nonhealing lesions of the skin and *Charcot joints*, are also found. The skin lesions, known as *mal perforant* ulcers, are usually found at the base of the great toe as painless, punched-out lesions.

Involvement of the autonomic nervous system may occur in patients with tabes, and *postural hypotension* is occasionally present. Severe *paroxysmal hypertension*, associated with gastric crises, has also been observed and may simulate paroxysmal hypertension caused by pheochromocytoma.

Urinary difficulties occur in approximately 50 to 60 per cent of patients with tabes. These often appear early in the disease and consist of hesitancy or difficulty in starting micturition. Later the patient develops complete loss of bladder sensation and can retain a full bladder for long periods of time without discomfort. Eventually there is urinary incontinence. Patients with tabetic bladder sometimes develop severe pyelonephritis or hydronephrosis, and may die in uremia. Disturbance of tone and contraction of the bladder can often be detected relatively early by cystometric examination. In advanced cases the cystometrogram reveals increased bladder capacity, low intravesicular pressure, and absence of contraction waves. Patients with tabetic bladder often give no history of urinary symptoms, and catheterization for residual urine should be done in all who have evidence of tabes. *Impotence* and loss of sexual desire are frequently noted.

Paralysis of the oculomotor nerves is common in tabes, resulting in diplopia, ptosis of the lids, or ophthalmoplegia. Pupillary abnormalities are also extremely common and may be manifested by the classic *Argyll Robertson phenomena*; that is, miosis, reaction to accommodation but no reaction to light, poor response to atropine, and absence of ciliospinal reflex. This condition must be differentiated from Adie's pupil, which is usually unilateral, is larger than the normal pupil, and reacts slowly to both light and accommodation. Patients with Adie's pupils may also have absent or diminished tendon reflexes.

Atrophy of the optic nerve occurs in about 10 to 15 per cent of patients with tabes. This condition begins as a gradual diminution of vision, which slowly progresses to involve both eyes and eventually results in complete blindness. About 70 per cent of patients with untreated optic atrophy become blind in three years and 90 per cent in five years. On ophthalmoscopic examination the optic disk appears white and sharply defined. The physiologic cup is prominent and the lamina cribrosa is abnormally conspicuous. Visual field examination may reveal various types of defects and scotomas. Visual field defects and diminution of vision may be present with only slight changes in the color of the disks. To detect such cases of optic atrophy early, careful perimetry and visual acuity examinations should be made in all cases of neurosyphilis. Although improvement in vision is not to be expected in patients with optic atrophy, arrest of the atrophic process can usually be obtained by fever therapy in patients with unilateral involvement or with only slight impairment of visual acuity in the better eye.

In early cases of tabes the serologic test for syphilis is often strongly positive and the spinal fluid may show definite abnormalities, such as increased cells and protein and a positive Wassermann. In patients with long-standing tabes, however, the blood and spinal fluid findings may be misleading. Approximately one fourth of such patients have negative blood serologic tests, while as many as 20 per cent have normal spinal fluids. Tabes dorsalis must be differentiated from numerous other diseases of the spinal column, such as cord tumor, combined system disease, and syringomyelia, as well as various types of peripheral neuritis (particularly diabetic neuropathy). The response of tabes to treatment is often poor and symptoms may progress despite all forms of therapy.

PARETIC NEUROSYPHILIS (DEMENTIA PARALYTICA, PARESIS, GENERAL PARALYSIS OF THE INSANE). General paresis is a psychosis caused by extensive spirochetal invasion of the brain. *T. pallidum* produces marked inflammatory reaction in the meninges and atrophy of the brain, particularly in the frontal areas. The cerebral sulci are widened, the ventricles become dilated, and ependymitis occurs. On histologic examination the most prominent feature is degeneration of the nerve cells. The myelin sheaths and axis cylinders also show destructive changes. Peri-

vaseular infiltration and endothelial proliferation of the small vessels is seen. *T. pallidum* can be demonstrated in the cerebral cortex and other portions of the brain. The amount of blood flowing through the brain of patients with paresis and the oxygen consumption of the cerebral tissue have been found to be considerably reduced. Following adequate treatment, however, there may be a rise in both cerebral blood flow and oxygen consumption.

Paretic neurosyphilis accounts for about 10 per cent of all admissions to mental hospitals. It is more common in men than in women and usually develops between the ages of 35 and 50 years. The onset is most often insidious; prodromal symptoms consist of headache, insomnia, difficulty in concentration and easy fatigability. In the early stages the patient may be thought to have a psychoneurosis. As the disease progresses, a gradual change in personality takes place, with increased irritability, memory loss, poor judgment, lack of personal care, and deviations in character. These alterations may occur over a period of several months. Many of them are noted by the patient's family only in retrospect and elicited only by close questioning. The onset of paresis is sometimes sudden and may be ushered in by convulsions, syncope, or a cerebral vascular accident. Paretic psychoses may follow these episodes immediately or within a period of several weeks.

Five main types of psychosis may develop: (1) The simple, demented type, which is the most common. These patients show confusion, apathy, impaired memory, and defects in judgment. Memory is particularly poor for recent events. These patients may be completely disoriented as to time and place. They are often unable to concentrate on simple calculations and show little insight or concern about their illness. They are difficult to engage in logical conversation and answers to questions may be irrelevant. They have a poor fund of information and deterioration of their intellectual faculties is obvious. (2) The grandiose form, which is manifested by euphoria, overactivity, ideas of grandeur, and megalomania. The prognosis in this type of paresis is often good. Auditory and visual hallucinations are not common in these patients, but delusions of wealth and prowess are frequent. Although this type of psychosis is assumed to be frequent in paresis, it actually accounts for only 10 to 20 per

cent of the cases. (3) The paranoid type, in which there are persistent delusions of persecution with a fair retention of intellectual faculties. (4) The simple depressive type. (5) The neurasthenic type, characterized by a variety of vague complaints. The type of psychosis that prevails in a given case depends to a great extent upon the prepatetic personality of the individual. As the disease progresses, however, the symptoms of euphoria, paranoia, or mania recede and simple deterioration and dementia become the outstanding features.

The course of paresis may be interrupted by repeated vascular episodes, convulsions, or hemiplegia. Eventually the patients become completely bedridden and are unable to move and feed themselves. They become emaciated, develop bed sores, and ultimately succumb to intercurrent infections.

On neurologic examination these patients may present various motor disturbances, such as tremors of the facial muscles, tongue, and outstretched hands. The patient's handwriting is altered because of the tremors and incoordination. The speech becomes slurred and test phrases are mispronounced. Pupillary abnormalities are common and deep reflexes are usually exaggerated. Some patients with paresis also have signs and symptoms of tabes—i.e., taboparesis—and in these cases the deep reflexes may be absent. In other patients marked mental and personality changes may be present with few, if any, neurologic abnormalities.

The demented form of paresis must be differentiated from senile dementia and Alzheimer's disease. The manic and paranoid types must be distinguished from manic depressive psychoses and schizophrenia. In the early stages of paresis, differentiation from neurasthenia is sometimes difficult and spinal fluid examination may be the only means of diagnosis.

The spinal fluid in general paresis shows marked changes, with increased cells and protein, positive Wassermann test, and first zone colloidal reaction. The diagnosis of paresis should never be made in the presence of a normal spinal fluid, since a positive spinal fluid is present in 100 per cent of untreated cases. If a normal spinal fluid is obtained in patients suspected of having paresis, the test should be repeated to exclude the possibility of laboratory error. In patients who have received treatment for paresis, however, the

spinal fluid may become negative. The cell count and protein usually return to normal within the first year, but the Wassermann reaction may not become negative for as long as 5 to 10 years after treatment.

The course of untreated paresis is progressive, and death usually occurs within a few years after the onset of symptoms. The prognosis improves considerably with therapy, but the chances for complete recovery are at best about 50 to 60 per cent and depend upon the extent and duration of the disease. In the very early stages of paresis the lesions of the brain may be predominantly inflammatory in nature and hence reversible. In moderately severe cases, however, definite destruction of cortical tissue has usually taken place and complete remission of symptoms is not to be expected.

SYPHILIS IN PREGNANCY

Syphilis in pregnancy is a special problem because of the possibility of uterine transmission of the disease. The fetus becomes infected after the fifth month of pregnancy by passage of *T. pallidum* through the placenta. This usually occurs in women with early untreated syphilis, but is sometimes observed in late syphilis. Pregnancy complicated by syphilis may terminate in a spontaneous abortion, a stillborn infant, or a premature or full term infected child. The maternal infection, however, becomes attenuated as the duration of the disease increases, and the chances of the fetus being infected are less with each succeeding pregnancy. Thus, a woman with syphilis may give a history of having delivered a stillbirth, then a living syphilitic child, and finally normal healthy offspring.

Pregnancy is believed to have a beneficial influence upon the course of the syphilitic infection, and late manifestations of the disease seem to occur less frequently in multiparous women than in others. Lesions of early syphilis likewise are often suppressed in pregnant women, and the recognition of the infection in these individuals depends almost entirely upon the serologic test. The titer of the serologic tests in early syphilis is not diminished by pregnancy. A serologic test for syphilis should be taken routinely at the first prenatal visit of every pregnant woman. Syphilis is occasionally contracted in the later months of pregnancy, and for this reason the serologic test should be repeated shortly

before term. The early recognition of syphilis in pregnancy followed by adequate treatment will prevent congenital syphilis in almost every instance.

CONGENITAL SYPHILIS

Infantile congenital syphilis is often an overwhelming infection; such infants are severely ill, malnourished, and dehydrated. The most common manifestations of the disease in infants are skin lesions, anal fissures and condylomas, persistent rhinitis, tenderness over the long bones, and pseudoparalysis.

The diagnosis of syphilis in the infant is best established by dark-field demonstration of *T. pallidum* from the cutaneous or mucosal lesions. A positive serologic test in the first two months of life does not always indicate syphilis in the infant, since reacting substances may have been transferred from the maternal circulation. A very high titer of the serologic reaction or a steady rise in titer, however, is indicative of congenital syphilis. Roentgenographic examination of the long bones may show characteristic areas of bone destruction and *osteochondritis*.

Late congenital syphilis frequently manifests itself in the second decade with signs of central nervous system involvement, such as eighth nerve deafness, optic atrophy, and *juvenile paresis*. The prognosis of congenital neurosyphilis is serious; these patients commonly show little response to treatment. Cardiovascular syphilis is rare in the congenital infection.

Patients with late congenital syphilis often exhibit typical stigmas, such as hypoplasia, wide spacing and notching of the central incisors (*Hutchinson teeth*), frontal bossing, a highly arched palate, and *saber shins*. *Interstitial keratitis*, a frequent complication, usually appears in the second decade. It is characterized by pain, lacrimation, circumcorneal injection, and corneal opacity. The response to therapy is poor and serious impairment of vision often results. Occasionally hydrarthrosis of the knee joint (*Clutton's synovitis*) is associated with interstitial keratitis.

LABORATORY DIAGNOSIS OF SYPHILIS

The laboratory diagnosis of syphilis depends upon three procedures: Dark-field demonstration

of the causative agent, serologic tests of the blood and spinal fluid, and biopsy.

Dark-Field Examination. The dark-field demonstration of *T. pallidum* is most useful in the early stages of syphilis. It should be employed routinely on every genital lesion and on all cutaneous and mucosal lesions suspected of being syphilitic. Several varieties of spirochetes which may be confused with *T. pallidum* are found on the genitalia and oral mucous membranes. In the hands of a competent microscopist, however, dark-field examination is reliable and establishes without doubt the diagnosis and stage of the infection.

Serologic Tests. Serologic tests for syphilis (S.T.S.) are the most commonly used diagnostic procedures. In latent syphilis they are the only means by which the diagnosis can be made. The serologic tests are based upon the presence of an antibody-like substance (sometimes called reagin), which appears in the patient's serum soon after the onset of the disease. Syphilitic serum reacts with an antigen made from an alcoholic extract of beef heart. Various modifications of flocculation tests for syphilis have been named after their originators (Kahn, Eagle, Mazzini, Kline, and Hinton). The complement-fixation technic, or Wassermann test, employs the same type of antigen. The Kolmer and Eagle modifications of the Wassermann technic are most commonly used in this country.

Quantitative serologic tests for syphilis measure the quantity of reagin and are of value in the diagnosis and management of various stages of the disease. A sharply rising titer is usually found in recently acquired syphilis, while a stationary titer indicates an infection of some duration. Quantitative serologic tests are also useful in the detection of false positive reactions. A rapidly falling titer in the absence of therapy is evidence against the diagnosis of syphilis. The height of the quantitative titer has no bearing on the prognosis or outcome of the disease. Low titers are usually found in late cases of syphilis and high titers most often occur in early cases, but there is so much variation that a single quantitative test is of little value in differentiating between them. The quantitative tests are also important in determining the results of therapy; a continuing fall in titer indicates a satisfactory response.

Serologic tests for syphilis are not without limitations. The presence of a negative reaction does

not always exclude syphilis, nor is a positive reaction always proof of the existence of the disease. Serologic tests are negative in the incubation period of syphilis, during the early weeks of the primary stage, and in many of the late manifestations, such as cardiovascular and neurosyphilis (tabes dorsalis in particular). False negative reactions may also occur as a result of prozone phenomena. These reactions occasionally appear in serums containing large amounts of reagin and can be detected by the use of quantitative serologic tests. Both false negative and false positive reactions may result from technical errors, such as mislabeling of specimens or careless laboratory technics.

Biologic False Positive Serologic Tests for Syphilis. Positive reactions appear in a great variety of illnesses and are due presumably to the appearance in the patient's serum of substances which act like reagin and give positive flocculation and complement-fixation reactions for syphilis. These reactions are usually transient, but in some instances may be positive for as long as several months or years. False positive reactions are usually low in titer, and often the results are conflicting when several flocculation or complement-fixation technics are employed. In some patients, however, the titer may be high.

Biologic false positive reactions are frequently observed in patients with vaccinia, infectious mononucleosis, malaria, leprosy, and upper respiratory diseases, as well as in spirochetal infections, such as yaws, pinta, and relapsing fever. Other infections which are occasionally associated with false positive reactions are lymphogranuloma venereum, chancreoid, measles, chicken pox, atypical pneumonia, infectious hepatitis, rat bite fever, and disseminated lupus erythematosus. In fact, any febrile disease or immunization is a potential cause of false positive tests. The cause of a false positive reaction cannot always be determined; the patient may appear to be a healthy individual.

No patient who has recently had a febrile illness or immunization should be diagnosed as having syphilis on the basis of the serologic test alone. The presence of a false positive reaction should also be suspected in patients without history or clinical evidence of syphilis, in individuals whose marital partners have negative serologic reactions, and in cases where there is no history of sexual exposure. In all such instances it is ad-

visible to withhold treatment and to conduct further studies. A careful history should be taken as to symptoms of intercurrent infection or immunization, and a physical examination should be performed for evidence of such conditions. The blood should be examined for infectious mononucleosis and possibly for malaria. Repeated serologic tests for syphilis should be taken with different technics in different laboratories, and the quantitative titer of the reaction followed. Periodic quantitative tests will show a fall in titer if the reaction is false positive, but will rise or remain stationary if the patient has syphilis. A spinal fluid examination should also be done to exclude the possibility of neurosyphilis. The patient's parents, siblings, and sex contacts should also be tested for syphilis. Attempts to produce a rise in the serologic titer by injection of arsenicals or penicillin (the so-called provocative test) are of no value in the diagnosis of questionable reactions. The use of a highly purified and more specific antigen, called cardiolipin, and the euglobulin inhibition test devised by Neurath and his associates are often of considerable aid in the diagnosis of false positive tests. It has been shown that serums producing false positive reactions do not contain antibodies which immobilize virulent *T. pallidum*. Since these antibodies are usually present in the serums of patients with latent syphilis, tests for immobilizing antibodies may be of value in excluding the diagnosis of syphilis and in the detection of biologic false positive reactions.

If none of these procedures can establish a diagnosis and if the patient is still thought to have a false positive reaction, he should be kept under close observation for several months. In most cases, the false positive reaction will become negative within this period of time. If after six months the patient still continues to show a positive serologic test and if the adjunct procedures do not indicate a false positive reaction, antisyphilitic therapy should be instituted. If the patient becomes pregnant or is to be married, immediate treatment is indicated.

Seroresistance. In many patients with syphilis the serologic test remains positive despite prolonged, intensive therapy. These patients are called seroresistant or Wassermann-fast. It is not known whether the positive reaction in these cases represents persistent foci of spirochetes which have not been destroyed by therapy or

whether it is merely an expression of immunity remaining after the infection has been cured. In patients with early syphilis seroresistance is often an indication of a persistent or inadequately treated infection, since many of these patients will develop clinical progression or relapse. One of the aims of therapy in early syphilis (particularly during the first two years of the disease) is to procure and maintain a negative serologic reaction. In late syphilis, however, seroresistance is of little clinical importance and has no relationship to the outcome of the disease.

The interpretation of a persistently positive serologic test following treatment of early syphilis depends upon a variety of factors, such as the length of time of follow-up observation, the titer of the serologic test at the onset of therapy and at the time of last observation, and the changes in titer following treatment. In most patients with early syphilis the serologic test becomes negative within six months after beginning therapy. Occasionally the titer of the serologic reaction falls very slowly and the tests remain positive in low titer (i.e., less than 4 dilutions) for as long as one to two years. This type of seroresistance is probably not clinically significant, since the majority of such patients eventually develop negative tests without further treatment. In some patients with early syphilis there is very little serologic response to treatment and the titer remains high for six to nine months or more. This type of seroresistance is usually followed by clinical relapse and these patients should be re-treated.

In late syphilis seroresistance is extremely frequent and occurs in more than 50 per cent of the patients treated for this stage of the disease. Clinical progression or relapse is no more frequent, however, in seroresistant patients with late syphilis than in those whose serologic reactions have reversed. Patients with late clinical manifestations, however, are more likely to be seroresistant than are patients treated for late latent infection. Patients with late congenital syphilis are particularly prone to remain seroresistant, despite all forms of therapy. Neurosyphilis is frequently associated with seroresistance in both early and late cases, and the spinal fluid should be examined in every patient with a persistently positive serologic reaction.

Patients with seroresistance are often given vigorous and intensive antisyphilitic therapy in

an attempt to reverse the serologic reaction, usually without success. It must be emphasized that in late syphilis the aim of treatment should be to arrest the disease and to prevent future recurrences, not to obtain a negative serologic reaction. The seroresistant patient is often discouraged over the failure to reverse the serologic test and becomes deeply concerned for fear that the infection is not arrested. In addition, he may be embarrassed in applying for a marriage license or employment when blood tests are a part of the premarital or pre-employment examination. The physician should make every effort to reassure such patients that the outcome of the disease is not related to the persistence of a positive serologic test and should discourage the patient from taking further treatment for the purpose of reversing the serologic reaction. Whenever pre-employment blood tests are required, the physician should assist these patients in procuring or retaining their jobs by explaining the nature of the condition to the company physician. In most states having premarital legislation, marriage licenses can be obtained if the patient is not infectious for syphilis. Seroresistance should not be an obstacle to marriage.

Conflicting Serologic Reports. Occasionally, repeated specimens from the same patient or different tests on the same specimen will show conflicting results. Although these discrepancies may be due to poor laboratory technic or variations in the antibody content of the serum, they are in most instances indicative of a small but definite amount of antibody in the serum. In the presence of threshold amounts of antibody, a relatively slight difference in the sensitivity of the various tests from day to day can account for the discrepancies of serologic results. The existence of such small amounts of reagin may result from previous therapy, a long-standing infection, or a false positive reaction. For some reason which is not understood, patients with late congenital syphilis may show a persistently negative flocculation test and a positive Wassermann test.

Spinal Fluid Tests for Syphilis. The spinal fluid must be examined in every patient with syphilis. This is the only method of detecting involvement of the central nervous system in the asymptomatic stage, of determining the efficacy of treatment, and of confirming the diagnosis of symptomatic neurosyphilis. The omission of a spinal fluid examination often leads to wrong diagnosis, im-

proper therapy, and disaster for the patient. The spinal fluid examination in syphilis consists of a cell count, flocculation or complement-fixation test, quantitative protein determination, Pandy or globulin test, and colloidal reaction.

The spinal fluid cell count should be done within an hour after the fluid is withdrawn. A count of more than eight lymphocytes per cubic millimeter is usually considered abnormal. Care should be taken to avoid mistaking erythrocytes for leukocytes in the spinal fluid; a diluting fluid containing methylene blue may be used. A bloody tap should be avoided since even a small amount of blood in the spinal fluid will affect the accuracy of the various examinations. The Pandy or globulin tests are only approximate measurements of protein changes; a quantitative determination of the spinal fluid protein should be done in every case. The normal amount of protein in the spinal fluid is usually less than 50 mg. per 100 ml.

Complement-fixation tests for syphilis are generally regarded as being more sensitive than flocculation tests for examination of spinal fluid. Spinal fluid Wassermann tests should be titered to determine the response to therapy, as well as the prognosis of the condition. The spinal fluid of patients with neurosyphilis has been found to contain immobilizing antibodies for *T. pallidum*.

The spinal fluid may also show biologic false positive complement-fixation or flocculation reactions. This may be caused by a bloody tap or any condition which produces an increased protein in the spinal fluid. The presence of a brain tumor, bacterial or virus meningitis, encephalitis, or subarachnoid hemorrhage may produce a false positive test for syphilis in either syphilitic or nonsyphilitic patients. These reactions are usually transient but may be extremely confusing in the differential diagnosis of central nervous system disease.

The value of colloidal precipitation tests (gold and mastic reactions) has been overemphasized in the diagnosis of neurosyphilis. The zone of precipitation or the shape of the colloidal curve has little diagnostic significance, but is merely an indication of the relative amounts of globulin and albumin in the spinal fluid. If accurate quantitative protein determinations are not available, the colloidal precipitation reactions are useful in indicating the presence of abnormal protein levels.

Biopsy. Biopsy is a valuable diagnostic procedure, especially for cutaneous lesions. In late syphilis involving the lymph nodes, testes, or larynx, it is indispensable. In the hands of a competent pathologist, biopsy is particularly helpful in the diagnosis of genital lesions. The histologic appearance of syphilis has already been described.

TREATMENT OF SYPHILIS

The results which can be obtained with present methods of syphilitotherapy depend largely upon two somewhat related factors: the duration of the disease at the time of treatment and the extent of tissue damage. In patients with early syphilis adequate treatment can produce an absolute, or biologic, cure, with complete healing of lesions and reversal of serologic tests and spinal fluid findings. These patients become entirely well, are not infectious, and do not develop any of the late manifestations of the disease.

Treatment of late syphilis may not achieve these goals. Despite long and vigorous therapy the serologic tests in late syphilis often remain positive. Such patients may not develop late manifestations and are noninfectious. Late syphilitic lesions are often associated with permanent damage, and treatment may produce little or no return of function.

Treatment of Early Syphilis. The first drug found to be effective in healing lesions of early syphilis was mercury. Iodides were later given along with mercury, as they were thought to dissolve granulomatous tissue, thereby allowing greater penetration of the metal into the lesion. These drugs are probably not curative.

Early in the present century, arsphenamine and neoarsphenamine were discovered. These drugs are highly treponemicidal and produce rapid disappearance of spirochetes and healing of the lesions. It was soon found, however, that a very high relapse rate occurred unless multiple injections of both arsenicals and mercury were given for at least 12 to 18 months. This treatment cured syphilis in a high percentage of cases, but relatively few patients completed the entire course of therapy.

Bismuth was later found to be an effective and safe treponemicidal agent and gradually replaced mercury as an adjunct to arsenical therapy. It is still a very useful drug and is best given as the insoluble suspension of bismuth subsalicy-

late in oil. Water-soluble preparations of bismuth are also available if rapid absorption and excretion are desired.

Arsenoxide ("Mapharsen") was introduced in 1934 as an effective drug, simple to administer and less toxic than the arsphenamines. It has become the arsenical of choice. A derivative of arsenoxide, dichlorophenarsine, has also been produced. This compound is converted to arsenoxide when dissolved in water and is as effective as "Mapharsen."

The trivalent arsenicals and bismuth compounds are strongly treponemicidal, and even dilute concentrations of these drugs produce rapid immobilization of *T. pallidum* in vitro. The mechanism by which these drugs act is not completely understood, but they are believed to exert their treponemicidal effect by combining with the sulphydryl (—SH) group of the spirochete and preventing essential enzymic or metabolic activities. The addition of sulphydryl compounds, such as cysteine, glutathione and BAL (dimercaptopropanol), will abolish the antispirochetal activity of arsenic and bismuth compounds in vitro, and under certain experimental conditions may even reactivate organisms which have previously been immobilized by the action of the arsenicals.

The use of less toxic drugs, such as "Mapharsen" and bismuth, permitted rapid methods of treatment. It was found that the total curative dose of "Mapharsen" in early syphilis in man was remarkably constant, approximately 1200 to 1800 mg. This dose could be administered in five to eight days with continuous infusion of mapharsen; or in 10 to 12 weeks, using mapharsen (50 to 60 mg.) three times a week and bismuth subsalicylate (0.2 Gm.) once a week. Either of these schedules produced about 85 per cent cures in early syphilis, but the toxicity varied considerably, depending upon the duration of treatment. The fatality rate in treatment schedules of less than 10 days was about 1:200. When treatment was prolonged to 10 weeks or more, the fatality rate was 1:3000.

A third treatment schedule, adopted for a while by the armed forces, consisted of 40 injections of arsenoxide (60 mg.) and 16 of bismuth subsalicylate (0.2 Gm.) in 26 weeks. In this schedule, arsenoxide is given twice weekly for 10 weeks, omitted for 6 weeks, then given again for 10 weeks. Bismuth is given during the first and last five weeks of arsenical therapy and during

the six weeks between arsenical courses. This system was a compromise between the toxic intensive schedules and the impractical, prolonged treatment schedules. The incidence of relapse with this schedule was very low and was thought to be about 5 per cent.

In 1943, penicillin was found to be effective in early syphilis, and shortly thereafter a large-scale coöperative study was organized to investigate the value of various dosage schedules. The results indicated that the minimal effective total dosage of penicillin in early syphilis was approximately 2.4 million units. This could be given in 4, 8, or 15 days or in equally divided doses at intervals of two, three, or six hours without altering the results. Increasing the total amount of penicillin from 2.4 to 4.8 or 9.6 million units did not appear to decrease the failure rate. The concurrent use of several injections of arsenicals and/or bismuth along with penicillin also failed to decrease the number of relapses. Penicillin was found to produce better results in patients with early primary syphilis than in those with secondary syphilis. Patients who had previously failed to respond to penicillin or arsenical-bismuth therapy were more likely to develop a recurrence of the infection following re-treatment with penicillin than were patients treated for the first time. There is, however, no evidence that *T. pallidum* becomes penicillin-resistant. Crystalline penicillin-G was found to be much more effective in early syphilis than amorphous penicillin containing various penicillin fractions (X, F, G, and K). A total dosage of 2.4 or 4.8 million units of crystalline penicillin-G, given intramuscularly every three hours in equally divided doses for seven to eight days, was found to produce satisfactory results in 87 per cent of patients followed for two years. These patients developed negative serologic tests, their spinal fluids were normal, and they showed no evidence of clinical relapse.

Penicillin therapy has many distinct advantages over the older forms of treatment; it is non-toxic, easy to administer, and can be given in a very short period of time. Although usual therapeutic doses of penicillin produce complete disappearance of *T. pallidum* from early lesions in six to nine hours, high concentrations of the drug (500 units per ml.) do not immobilize the spirochete in vitro. In experimental syphilitic infection of rabbits the organisms appear to be rendered noninfectious at much lower concen-

trations of penicillin, even though their mobility is not impaired.

Administration of penicillin in aqueous solution necessitated admission of the patient to a hospital. Therapy of out-patients, however, was found to be possible with the use of absorption-delaying products, such as penicillin in oil and beeswax. This form of penicillin was given to patients with early syphilis in doses of 600,000 units daily for a total of 4.8 to 9.6 million units. Such treatment schedules were as effective as comparable doses of penicillin in aqueous solution. The use of oil and wax mixtures as a means of delaying penicillin absorption has since been discarded in favor of relatively insoluble penicillin products, such as procaine penicillin. The latter preparation produces a concentration of penicillin in the serum for a longer period than the oil and wax mixtures and has the additional advantage of causing less pain at the site of intramuscular injection.

JARISCH-HERXHEIMER REACTION. Within a few hours after the first injection of either an arsenical or penicillin, about 50 per cent of patients with early syphilis experience an acute exacerbation of symptoms and lesions. The reaction is usually manifested by fever, malaise, headache, myalgia, and a flare-up of cutaneous lesions. It is presumed to be caused by release of breakdown products of spirochetes following the injection of treponemicidal agents. The syphilitic lesions show definite histologic changes with increased congestion, edema, and inflammatory cell infiltration. In early syphilis these symptoms disappear within several hours and leave no permanent tissue damage. In late syphilis such reactions can be disastrous if the lesions are located in such areas as the ostiums of the coronary arteries, the wall of an aneurysm, or the central nervous system.

POST-TREATMENT OBSERVATIONS IN EARLY SYPHILIS. Every patient treated for syphilis should have careful post-treatment observation. After completing treatment, the patient should return every month during the first year for quantitative serologic tests and examination for relapsing lesions. The titer of the serologic test for syphilis begins to fall shortly after treatment and usually the test becomes negative about the fourth to sixth month. A continuous fall in titer following therapy is a satisfactory response, but a sharply rising titer is an indication of treatment

failure. If the patient develops a recurrence of syphilitic lesions or evidence of neurosyphilis, or if there is a birth of a syphilitic child, re-treatment is necessary. If the serologic test in patients with early syphilis shows no appreciable decrease within six months, or if the titer is elevated (arbitrarily a dilution of 1:4 or higher) one year after completion of therapy, further treatment is indicated. When the serologic test is positive in a low titer (less than 1:4) at the end of a year, additional therapy may not be required, but the patient should be followed carefully.

Serologic tests should be taken at three-month intervals during the second year after treatment and at six-month intervals during the third, fourth, and fifth years. If at the end of five years the patient has no clinical evidence of syphilis and has a normal blood and spinal fluid, he may be considered completely cured.

A spinal fluid examination should be performed six months after the completion of treatment for early syphilis. If it is normal at this time and if the patient continues to show no evidence of clinical or serologic relapse, it need not be repeated until approximately two years following treatment. Patients having positive spinal fluid tests for syphilis six months or more after treatment for early syphilis should be re-treated.

RELAPSE AND REINFECTION IN EARLY SYPHILIS. Evidence of relapse in early syphilis usually appears between four and nine months after completion of treatment, but may occur as early as four weeks or as late as two years. Infectious relapses rarely appear after the end of the second year, but repeated administration of inadequate treatment may prolong the period during which they may develop.

Serologic relapse is the most common form of relapse. It occurs when the serologic test, once negative, becomes strongly positive, or when there is a sharp rise in the quantitative titer. If allowed to go untreated, patients with serorelapse frequently develop *clinical relapse*. This type of relapse is manifested by the reappearance of infectious mucosal or cutaneous lesions, ocular manifestations, or neurosyphilitic symptoms. *Ocular relapse* may appear as an iritis or neuroretinitis. *Neurorelapse* or *neurorecurrence* is the most serious type of relapse and may be asymptomatic or may appear as an acute or subacute meningitis. It is important that a spinal fluid examination be made in every patient with re-

lapsing syphilis. Fortunately, the incidence of neurorelapse following penicillin treatment is very low.

The prognosis of relapsing syphilis is more serious than the initial infection, and re-treatment with larger doses of penicillin is advised. This may be followed by the 26-week arsenical and bismuth schedule. Many patients with recurrent syphilis actually have a new infection rather than a relapse of their original infection. Although various criteria have been set up to distinguish relapse from reinfection, differentiation is often impossible.

The frequency of reinfection seems to have increased as a result of rapid methods of therapy. When such treatment is given early in the course of the infection, it may produce a cure before the patient has developed an appreciable degree of immunity. With prolonged methods of therapy, rapid cure of the disease often was not obtained and a considerable degree of immunity to reinfection may have developed. Moreover, the prolonged administration of arsenicals and bismuth in the older treatment schedules may have acted as a prophylaxis against reinfection.

Treatment of Syphilis in Pregnancy. Congenital syphilis can be prevented by proper treatment of syphilis in pregnancy. Although women with syphilis of many years' duration and previously adequate therapy are not likely to bear syphilitic children, further treatment of such patients during pregnancy is usually recommended. Treatment is best given before the fetus is infected—i.e., before the fifth month of pregnancy. A total dosage of 2.4 to 4.8 million units of penicillin in aqueous solution in 7 to 10 days will not only protect the fetus, but will usually be adequate treatment for the mother. Penicillin is more effective in the prevention of congenital syphilis than arsenicals and bismuth. It is also of considerable value when given during the last trimester of pregnancy, a time when arsenical therapy is least useful. Less than 5 per cent of the infants born alive following penicillin treatment of prenatal syphilis have been infected. Occasionally the fetus is so severely infected at the time of penicillin therapy that a miscarriage or stillbirth occurs shortly after the beginning of treatment. The use of procaine penicillin in prenatal syphilis has not yet received as extensive clinical trial as penicillin in aqueous solution. The administration of 600,000 units of this preparation daily for

a total dosage of 6 million units should be effective, particularly if given before the fifth month of pregnancy.

All patients treated for syphilis in pregnancy should be observed very closely, and quantitative serologic tests for syphilis taken at least every month. Re-treatment during pregnancy is indicated if there is a rise in serologic titer following therapy, if a definite decrease in titer fails to occur in patients with early syphilis, or if the patient develops recurrent syphilitic lesions. A positive serologic test at the time of delivery does not necessarily indicate that treatment has been inadequate. The child born of a mother treated for syphilis should have a serologic test every two to four weeks until it is at least six months of age.

Treatment of Congenital Syphilis. Infants with congenital syphilis are often premature and malnourished. They should receive careful supportive care and adequate nutrition, in addition to antisyphilitic treatment. Penicillin is very effective; a total dosage of 100,000 units per kilogram of body weight is adequate. This should be given in equally divided amounts every three hours for 7 to 10 days. Although the incidence of relapse in infants is low following penicillin therapy, deaths during therapy or shortly thereafter are not uncommon. Most of the deaths are due to prematurity, dehydration, or intercurrent infections, such as bronchopneumonia or dysentery. Follow-up blood tests and the indications for re-treatment in early congenital syphilis are the same as in early acquired syphilis. Serologic and spinal fluid tests should be negative before these children are dismissed.

Penicillin or arsenical and bismuth therapy of late latent congenital syphilis is the same as in patients with late acquired syphilis except for differences in dosage based on weight. The response of the serologic test in these patients is similar to that in late acquired syphilis and the tests often remain positive despite vigorous therapy.

There is no satisfactory treatment for interstitial keratitis. Penicillin therapy is preferable to arsenicals and bismuth, chiefly because of its shorter duration and decreased toxicity, but it does not produce marked improvement in vision. Fever therapy should be employed in patients who do not respond to penicillin. The treatment of hydrarthrosis or Clutton's synovitis is also

unsatisfactory. This condition usually regresses very slowly, regardless of the form of therapy.

Treatment of Late Syphilis: LATENT STAGE.

The chief purpose in treating late latent syphilis is to prevent the development of gummatous lesions and cardiovascular syphilis. Patients with late latent syphilis have negative spinal fluids and rarely, if ever, develop neurosyphilis. They are not infectious and their prognosis is very good, even without treatment. Vigorous or prolonged therapy is not necessary. The only reliable method of determining the success of treatment is observation over a period of years for the possible development of late complications. The serologic test of the blood is not a reliable indication of the effectiveness of treatment, since the majority of patients with late syphilis retain persistently positive serologic reactions, regardless of the method or duration of therapy.

It has been shown that 20 arsenical injections and 20 injections of bismuth were sufficient to prevent late complications in approximately 95 per cent of patients followed for more than five years. Late manifestations seemed to develop as frequently in patients receiving more than this amount of treatment. The system of treatment also has little effect on the outcome of these patients, and irregular and intermittent courses of treatment seem to be as effective as continuous therapy. Treatment should be given in nontoxic schedules such as outlined in the 26-week arsenoxide-bismuth routine. The use of penicillin has not been evaluated in the late latent syphilis. Since this drug is effective in early syphilis, however, it is presumed to be of value in these cases, and doses of 4 to 6 million units of penicillin are recommended.

POST-TREATMENT OBSERVATIONS OF LATE LATENT SYPHILIS. Patients treated for late latent syphilis should have quantitative serologic tests every three months and follow-up physical examinations every year. Although the serologic tests may become negative in a few cases, the majority of patients will continue to have positive reactions at about the same titer as before treatment. If the serologic titer shows a significant and persistent rise (at least two or more dilutions), clinical relapse may impend and the patient should be re-treated. Failure of the serologic test to revert to negative after adequate treatment—i.e., *seroresistance*—is not necessarily a forerunner of late complications. Once the

patient with late syphilis has had adequate treatment, additional penicillin or heavy metal therapy will not contribute significantly toward reversal of the blood test.

The spirochete usually invades the central nervous system early in the course of syphilis. If such invasion has not occurred by the fifth year, as evidenced by a negative spinal fluid, it is not likely to occur at all. Examination of the spinal fluid should be made before treatment in late syphilis in order to establish the diagnosis of latency. Once the fluid has been demonstrated to be negative in late latent syphilis, repeated examinations are unnecessary.

Treatment of Gummas of the Skin, Bones, and Viscera. Gummatus lesions of the skin, mucous membranes, bones, and viscera usually respond promptly to either the 26-week arsenical-bismuth schedule or to 4 to 6 million units of penicillin. In a few instances, gummas of the skin or mucous membranes failed to heal or recurred following penicillin therapy, but responded promptly to treatment with arsenicals or bismuth. The use of iodides along with arsenicals and bismuth is thought to enhance the healing of gummatus lesions. There seems to be little need, however, for the routine administration of iodides with either penicillin or arsenical-bismuth therapy.

Treatment of Cardiovascular Syphilis. The value of antisiphilitic therapy in late cardiovascular syphilis is difficult to determine. Many syphilologists believe that treatment does not delay the ultimate development of myocardial failure or aneurysmal rupture. Treatment appears to be of some value, however, in early aortic insufficiency, uncomplicated aortitis, or small asymptomatic aneurysms, if the general condition of the patient is satisfactory. Once congestive failure has occurred, the prognosis is often grave and therapeutic efforts should be directed chiefly toward regaining cardiac compensation. The treatment of rapidly advancing aortic aneurysms is essentially symptomatic, and rest and sedatives are generally advised. Surgical intervention, such as cellophane wrapping of the aneurysmal sac, is being employed at present and may be a useful procedure in selected cases.

The use of penicillin in cardiovascular syphilis has not yet been evaluated, but it appears to be preferable to arsenicals since it is less toxic and treatment can be completed in a shorter period

of time. The risk of a serious Herxheimer reaction following initiation of penicillin treatment of these cases has been found to be minimal. Nevertheless, this possibility exists and the use of preparatory bismuth therapy seems warranted in an effort to prevent this type of reaction. Approximately eight weekly injections of bismuth salicylate in oil should be given before penicillin therapy is started. A total dosage of 6 to 9 million units of penicillin in 10 to 15 days should be sufficient. As in other types of late syphilis, the serologic test often remains positive after therapy.

Several patients have been observed in whom obvious signs of aortic insufficiency appeared shortly after they received penicillin for what was thought to be either latent syphilis or minimal cardiovascular involvement. Such cases of "therapeutic paradox" are presumably caused by rapid healing of the aortic lesions. The resultant contracture and deformity of the valve leaflets produced aortic regurgitation.

Cardiovascular syphilis can easily be prevented. The majority of patients who progress to this stage have never had what is considered to be a minimal course of treatment for syphilis. As little as 20 arsenical and 20 bismuth injections given in the late latent period will usually prevent the development of cardiovascular complications.

Treatment of Neurosyphilis. The results of treatment of neurosyphilis depend largely upon the type and duration of the neuropathologic process. If the predominant lesion of the central nervous system is degenerative, as in tabes and optic atrophy, little response to any form of treatment can be expected. If the tissue reaction is chiefly inflammatory, as in siphilitic meningitis, rapid and almost complete return of function will occur. The extent to which one type of lesion predominates is often impossible to estimate, and the prognosis in individual cases may be difficult to predict. For this reason many syphilologists regard changes in the spinal fluid as the best method of evaluating the effect of treatment. They believe that if the spinal fluid cell count and protein become and remain normal following therapy, the neurosyphilitic process has been rendered inactive and treatment can be considered effective. This concept has gained many adherents.

The value of fever therapy in the treatment

of neurosyphilis was first demonstrated in patients with paresis. It has since been shown to be effective in certain other types of neurosyphilis. Fever therapy has produced satisfactory spinal fluid results (normal cell count and protein levels) in as high as 90 per cent of patients treated for syphilis of the central nervous system. The two most popular methods of inducing fever are by inoculation with malaria parasites and by fever cabinet. Therapeutic malaria is usually produced by injection of whole blood taken from individuals with active malaria. Benign tertian malaria (*Plasmodium vivax*) is generally used, but quartan malaria (*Plasmodium malariae*) is preferable for Negroes, since they are usually resistant to vivax malaria. About 10 to 12 febrile paroxysms of malaria, or approximately 50 hours above 103° F., are usually adequate. Similar or even greater amounts of hyperpyrexia can be obtained by mechanical means, such as the fever cabinet. This form of therapy is as effective as malaria, but has the disadvantage of requiring expensive apparatus and constant attendance of trained nurses and physicians. The production of fever by the use of continuous intravenous infusion of typhoid vaccine is also effective, but has never achieved great popularity. Any method of fever therapy, however, is not without danger. Malaria may produce jaundice, severe anemia, debilitation, hypoproteinemia, rupture of the spleen, and azotemia. In patients treated in fever cabinets, vascular collapse, burns, and excessive hyperpyrexia have occurred.

The mortality rate from fever therapy depends largely upon the type of patients treated, the skill and experience of the attending physician, and the number of fever paroxysms administered. In institutions treating advanced, debilitated paretics, the average death rate is approximately 9 per cent. The mortality is less than 3 per cent, however, in general hospitals where patients are admitted in an early stage of the disease. Fever therapy should not be given to patients with chronic kidney disease, cirrhosis, myocardial insufficiency, or active tuberculosis.

The mechanism of action of fever therapy is not completely understood. Although high temperatures are known to be somewhat spirocheticidal, there is reason to believe that other factors are necessary.

Pentavalent arsenicals, such as tryparsamide,

were formerly used to a great extent in the treatment of paresis and other types of neurosyphilis. Tryparsamide has the serious disadvantage of producing toxic amblyopia and is contraindicated in patients with optic atrophy. It is not nearly so efficacious as penicillin and its use in neurosyphilis has been completely abandoned.

Penicillin is of considerable value in the treatment of neurosyphilis and is often followed by a dramatic clinical response with prompt and favorable changes in the spinal fluid. Shortly after penicillin therapy, there is a rapid reduction in the spinal fluid cell count and protein, regardless of the type of neurosyphilis. The spinal fluid Wassermann reaction, however, may not become negative for as long as five years or more, depending upon the duration of the disease and the quantitative titer of the reaction before treatment. The colloidal reaction tends to become normal as the protein content falls. Complete reversal of the spinal fluid abnormalities has been observed in 15 to 20 per cent of patients with late neurosyphilis two to four years after penicillin therapy. A completely negative spinal fluid is achieved more frequently in patients with early neurosyphilis and in those with minimal spinal fluid abnormalities before treatment. Penicillin produced normal spinal fluid cell counts in 85 to 90 per cent of patients treated for various types of neurosyphilis. The remaining 10 to 15 per cent showed abnormal spinal fluid cell counts 6 to 12 months following treatment and were considered treatment failures. These results are better than could be expected with heavy metal therapy, and penicillin has consequently replaced bismuth and trivalent and pentavalent arsenicals in the treatment of neurosyphilis.

It is generally agreed that the response of the spinal fluid tests following penicillin is as good as that obtained with fever therapy. It has not yet been established, however, whether the clinical response in late parenchymatous neurosyphilis is comparable to that seen with fever therapy. For this reason most workers advise the use of a combination of penicillin and fever therapy in the more severe forms of neurosyphilis, such as paresis, taboparesis, primary optic atrophy, and eighth nerve deafness. The use of penicillin alone is recommended for the treatment of patients with early and late asymptomatic neurosyphilis, syphilitic men-

ingitis, and meningovascular syphilis, and those with irreversible manifestations, such as fixed pupils and Charcot joints. Penicillin not only appears to be as effective as fever therapy in these cases, but also is less hazardous. The optimum dosage schedule of penicillin in these cases has not been definitely established. Although large doses of 8 to 10 million units or more of penicillin in 10 to 20 days are generally recommended, good results have been obtained with smaller doses—i.e., 4 to 6 million units in 7 to 10 days. The slowly absorbed penicillin products, such as procaine penicillin, have not yet been completely evaluated in these cases, but preliminary reports indicate that they may not be so effective as penicillin in aqueous solution.

Penicillin produces immediate relief of headache and stiff neck in patients with acute syphilitic meningitis, and cranial nerve palsies often disappear completely. In meningovascular syphilis, as in other types of neurosyphilis, the clinical improvement depends largely upon the extent of nerve cell degeneration. In most instances penicillin produces arrest of the neurosyphilitic process and prevents clinical progression.

Penicillin can also be used alone as the initial treatment of tabes dorsalis. In about half of the patients striking improvement occurs in ataxia and lightning pains, and in some instances gastric crises are relieved, paresthesias disappear, and urinary difficulties are decreased. In general, however, the results of penicillin therapy in tabes are variable and symptoms often recur. In such cases re-treatment with combined fever and penicillin is advised. In patients with severe ataxia, improvement in gait can sometimes be obtained by proper exercises and re-education in walking and standing. Lightning pains sometimes are not controlled by any form of syphilitotherapy. The use of thiamine hydrochloride has been recommended in such patients, and in the very severe cases neurosurgical procedures, such as cordotomy, may be used as a last resort. Treatment of the tabetic bladder may be very discouraging. Drugs, such as "Mecholyl Chloride" and ergotamine, have been employed to increase bladder tone and contraction, but the results are variable. In early cases the patient can be trained to micturate at regular intervals and empty the bladder by pressure on the lower

abdomen. In late cases, surgical procedures (transurethral resection of the vesical neck, suprapubic cystotomy) may be necessary. Urinary tract infection should be prevented and instrumentation avoided as much as possible. Charcot joints are rarely improved by anti-syphilitic therapy, and special orthopedic treatment is necessary. The management of patients with gastric crises is sometimes very difficult. In the acute attack the patient should be heavily sedated. Morphine should be avoided. Dehydration caused by excessive vomiting should be treated with subcutaneous and intravenous administration of fluids. Patients may have repeated attacks of gastric crises despite all forms of therapy. In such cases surgical procedures, such as vagotomy and rhizotomy, have been attempted with little success.

The outcome of optic atrophy depends upon the duration, severity, and progressiveness of the condition. In some series as many as 85 per cent of the patients have retained useful vision following malarial fever, while in other reports only 50 per cent of the cases were arrested. The use of penicillin alone in optic atrophy has not yet received an adequate clinical trial, and it is generally believed that combined fever and penicillin therapy should be employed in these cases.

The relative value of penicillin and fever therapy in paresis has not yet been determined. Penicillin alone often results in marked improvement of tremors and speech and writing defects, and has been reported to produce definite improvement in the mental status of about half the patients with paresis. Although patients with very early paresis can safely be treated with penicillin alone, combined fever and penicillin therapy should be given to patients with moderately severe or far advanced disease. Large doses of penicillin—i.e., 10 to 20 million units of penicillin over a period of 12 to 20 days—are recommended. The prognosis of paresis is, in general, poor. Fever therapy has resulted in complete remissions in 50 per cent of the patients with early paresis, in 25 per cent of patients with moderately severe psychoses, but in only 2 to 10 per cent of those with far advanced disease.

Careful neuropsychiatric and spinal fluid observations should be made following treatment on all patients with neurosyphilis. These should

be done every four months during the first year, twice during the second year, and once a year thereafter, or until the spinal fluid is completely negative and permanent regression of symptoms seems apparent. If the cell count and protein levels of the spinal fluid increase, the patient should be re-treated, regardless of the clinical status. In late neurosyphilis the spinal fluid Wassermann often remains positive for many years, despite repeated courses of chemotherapy or fever. The presence of a persistently positive spinal fluid Wassermann or flocculation reaction does not in itself indicate progression or relapse of the neurosyphilitic process. A significant increase in the titer of the spinal fluid Wassermann reaction is an indication for retreatment, particularly if associated with other spinal fluid abnormalities.

HERXHEIMER REACTIONS IN LATE SYPHILIS. Exacerbations of late syphilitic lesions are not infrequently observed following the initial administration of either arsenicals or penicillin. The mechanism of the Herxheimer reaction in these patients is probably the same as in early syphilis. The reaction may be considerably more serious, however, and may result in irreversible damage. Approximately one half of the patients treated for paresis become temporarily worse and show increased agitation and mental confusion during the first 24 hours of penicillin treatment. Other manifestations of Herxheimer reaction, such as myelitis, convulsions, and exacerbation of lightning pains, have been reported. Death occurred shortly after the institution of penicillin treatment of a patient with gumma of the brain.

Exacerbations of cardiovascular syphilis have also been noted. Rupture of aortic aneurysms and sudden death, presumably caused by aggravation of syphilitic lesions about the coronary ostiums, have been observed following the use of arsenicals. Similar reactions can be expected to occur during penicillin therapy. The use of small initial doses of penicillin does not seem to prevent Herxheimer effects, and many workers have advised giving preparatory treatment with bismuth.

Toxic Reactions to Antisyphilitic Treatment. Toxic reactions may follow the use of arsenicals, and patients receiving these drugs should be carefully observed. Nausea, vomiting, and diarrhea are the most frequent complications. These

symptoms can usually be prevented by abstinence from food several hours before treatment. Care should be taken to avoid extravasation of the solution into the subcutaneous tissues. This may be extremely painful and may result in tissue necrosis and slough. If arsenoxide is injected too slowly, however, pain in the arm caused by venous spasm will result. About nine days after the initial injection of arsenicals in early syphilis, a syndrome known as *erythema of the ninth day* may appear. This reaction is similar in many respects to serum sickness and consists of fever, erythema, myalgia, and arthralgia. The condition will usually subside spontaneously if arsenical therapy is discontinued.

One of the most serious arsenical reactions is exfoliative dermatitis. This begins as a mild pruritus early in the course of treatment, but develops into a severe, widespread dermatitis if arsenicals are continued. Arsenoxides may also cause depression of the bone marrow with thrombocytopenia, agranulocytosis, and aplastic anemia. Encephalopathy is another serious reaction to arsenicals, but is not common in the less intensive treatment schedules. Jaundice has been observed frequently during syphilitotherapy and was thought to be the result of arsenical hepatitis. Most of these cases, however, were probably serum hepatitis of virus origin transmitted by improperly sterilized syringes and needles. The severe toxic reactions can be successfully treated by BAL (see Chapter 92). This compound has a marked affinity for arsenic, as well as bismuth and mercury, and, if given early enough after heavy metal poisoning, will produce dramatic relief.

The toxic reactions following bismuth are usually mild and consist of pain and tenderness at the site of injection, discoloration of the gum margins, and gingivitis. Renal damage, or bismuth nephrosis, has been observed following the prolonged use of bismuth in patients with pre-existent kidney disease.

Penicillin therapy is relatively nontoxic. The reactions are of an allergic nature and consist chiefly of dermatitis, angioneurotic edema, and urticaria. The use of antihistamine drugs, such as "Pyribenzamine," may be of value in the treatment of the latter conditions.

Effect of Penicillin on Syphilis When Used for Other Diseases. The increasing use of penicillin for a variety of infections has created con-

fusion in the diagnosis and management of syphilis. This is particularly true when penicillin is used in the treatment of gonorrhea. Patients with gonorrhea are likely to have acquired syphilis simultaneously and may be either in the incubation period of the disease or have early inconspicuous primary manifestations. The use of penicillin therapy for gonorrhea in such patients may either suppress the lesions of syphilis or delay their appearance. For these reasons it is recommended that all patients with gonorrhea treated with penicillin should have serologic tests for syphilis at monthly intervals for at least four months. Patients with gonorrhea should be examined carefully for evidence of syphilitic lesions. Penicillin should not be administered when such lesions are present until a dark-field examination and serologic tests have excluded the possibility of a concurrent syphilitic infection. The appearance of fever several hours after the administration of penicillin for gonorrhea is suggestive of a Herxheimer reaction and the presence of syphilis.

The management of patients with positive serologic tests who have had previous penicillin therapy for other nonrelated infections is sometimes difficult. The presence of a biologic false positive serologic reaction caused by the preceding infection must first be ruled out. If syphilitic infection is thought to be present, the decision as to further therapy should be based upon the amount of penicillin already administered, the type and duration of syphilitic infection, the result of the spinal fluid examination, and the titer of the serologic test. Such patients should be re-treated if they have received less than the minimal amount of therapy suggested in the above paragraphs.

Trends in Syphilitotherapy. The discovery of penicillin has produced revolutionary changes in syphilitotherapy and has greatly simplified the treatment of this disease. There is no question that penicillin is the drug of choice in the treatment of most patients with syphilis, because of its low toxicity, therapeutic effectiveness, and ease of administration. The treatment schedules outlined in the foregoing paragraphs are those recommended at the time this section was written. Final evaluation of any form of treatment for syphilis, particularly late syphilis, requires many years of post-treatment observation. It is not known at the time of writing what the even-

tual clinical outcome will be, for example, in patients treated with penicillin for neurosyphilis or for cardiovascular involvement. It is possible that some of the treatment schedules recommended herein will prove to be inadequate. Although penicillin is generally regarded as superior to arsenoxide and bismuth in the treatment of early syphilis, only future studies will determine if it should replace fever therapy in neurosyphilis.

At present there appears to be little reason for the use of arsenicals and bismuth in the routine treatment of early syphilis. Although experiments with rabbit syphilis suggested that the heavier metals potentiated the action of penicillin, this synergism was not always demonstrable in man. Moreover, arsenical and bismuth compounds may produce serious toxic reactions, and their use in early syphilis is indicated only in patients who have previously failed to respond to penicillin alone. Increasing the total dosage of penicillin in early syphilis also seems to offer little advantage. The number of treatment failures following total doses of 2.4, 4.8, and 9.6 million units of penicillin in a single course of treatment was not significantly different. It is possible, however, that repeated courses of therapy given at intervals of several months may be more effective than a single course of treatment employing very large doses.

The production of slowly absorbable salts of penicillin, such as procaine penicillin, is another development which will influence syphilitotherapy in the coming years. These compounds are more easily administered than penicillin in oil and wax and have already supplanted the latter product. The addition of water-repellent substances, such as aluminum monostearate, has been shown to delay the absorption of penicillin and produce measurable blood levels of penicillin for as long as five days following injection. The value of such penicillin products in the treatment of syphilis has not yet been determined, but it seems probable that one or more injections of such compounds at weekly intervals will be adequate in many patients with early syphilis. New spirocheticidal substances are being developed. "Chloromycetin" and aureomycin, for example, have been found to produce healing of syphilitic lesions, but appear to be less efficacious than penicillin. It is possible that within a few years new antibiotics will be forthcoming which

will be synergistic or replace penicillin in the treatment of syphilis.

The difficulty in distinguishing reinfection from relapse often complicates the evaluation of penicillin treatment of early syphilis. It has been estimated that one half of the cases of recurrent syphilis which occur following present-day penicillin schedules are reinfections rather than relapses. Accurate evaluation of penicillin, therefore, depends to a large extent upon the promiscuity of the patients treated and the reservoir of syphilitic infection in the community. The use of penicillin and intensive methods of therapy has resulted in an increased number of cases of reinfection. Although rapid methods of treatment with penicillin may reduce the incidence of the infection, it is quite obvious that eradication of the disease cannot be produced by penicillin alone.

PROPHYLAXIS OF SYPHILIS

Syphilis and the other venereal diseases as well can be prevented in most instances by the use of proper prophylactic measures during and following sexual intercourse. Protection from contact with infectious genital lesions can be obtained to some degree by the use of a condom. The danger of infection can be reduced if, following exposure, the genitalia are washed well with soap and water and a preparation containing spirocheticidal substances is applied. Although calomel ointment has been used for this purpose for many years, soap solutions of phenyl arsenoxide have been found to be effective prophylactic agents and will probably replace the mercurial compound. Small amounts of penicillin have been shown to be effective in aborting syphilitic infection in rabbits when administered soon after inoculation of spirochetes. This suggested that penicillin could be given orally or parenterally in man as a prophylactic agent for syphilis as well as for gonorrhea. This procedure has not yet been given an adequate trial.

Some workers have recommended that penicillin also be given to individuals who show no evidence of infection but are known to have been sexually exposed to patients with primary or secondary syphilis. It is felt that such practice is justified, not only as an attempt to abort the infection in the exposed individual, but also to prevent reinfection of the original patient who often maintains sexual relations with the con-

tact, despite instructions to the contrary. This form of prophylaxis, or "abortive cure," may be dangerous in that it may not always prevent infection, but may only suppress the disease or delay the appearance of lesions for long periods of time. Similar objections obtain for the prophylactic treatment of nurses and physicians who are accidentally exposed to or inoculated with infectious material. These individuals are now advised to wash the infected site well and to use preparations such as calomel ointment locally. Following this, the individual should be carefully observed and a serologic test should be taken every two weeks for three to four months to determine if infection has occurred. The only good indication for prophylactic treatment at present is in pregnant women who are sexually exposed to infectious patients. A full course of penicillin treatment in these cases is indicated in an effort to prevent fetal infection. The entire subject of prophylaxis and abortive cure is now under investigation, and many of the present-day concepts may eventually be discarded.

PSYCHOTHERAPY OF THE SYPHILITIC PATIENT

There is still considerable stigma and psychologic trauma attached to the diagnosis of syphilis, and proper treatment requires more than the mere administration of chemotherapeutic agents. The physician must be aware of the sociologic and psychologic aspects of this disease. Patients often have a sense of shame and guilt, and some of them postpone or discontinue medical care for fear that their friends and neighbors may learn the diagnosis. Other patients develop serious anxiety states and return to the physician repeatedly for reassurance that the disease has been arrested. Some individuals develop syphiphobia as a result of having heard or read of the serious effects of the disease. The physician should make every effort to relieve these patients of their anxiety by correcting mistaken ideas regarding the infection and by emphasizing the good prognosis whenever possible. His attitude toward the patient should be free of censure. He should assist the patient to recover his self-respect and to look upon syphilis as a disease which can be treated and not a disgrace from which there is no salvation.

Upon learning the diagnosis, many patients either condemn their marital partners and

threaten divorce or separation, or else refuse to impart the information to their spouse. The physician should not enter into the moral aspects of the disease, but should make certain that the marital partners of patients with infectious syphilis are told the diagnosis and examined at regular intervals for evidence of the disease. At the same time he should attempt to prevent the breaking up of a marriage by appropriate guidance.

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Yaws

Albert Heyman

Definition
Etiology
Epidemiology
Manifestations
Diagnosis
Treatment

Definition. Yaws is an infectious tropical disease caused by the *Treponema pertenue*. It is characterized by a primary cutaneous lesion which is followed by a granulomatous skin eruption and, in some instances, by late destructive lesions of the skin and bones. The disease is also known as frambesia, pian, bouba, and parangi.

Etiology. The etiologic agent of yaws, the *T. pertenue*, is morphologically indistinguishable from *Treponema pallidum*. *T. pertenue* further resembles the spirochete of syphilis, as it produces a positive reaction with the Wassermann and flocculation tests for syphilis, and is also sus-

ceptible to arsenicals, bismuth, and penicillin. Cross immunity between the two diseases has been observed in both man and experimental animals. There has been considerable controversy as to whether the two diseases were at one time identical, but have been modified over the years by climate, race, and other factors.

Epidemiology. Yaws is confined entirely to the tropics and is prevalent in the West Indies, South Pacific islands, equatorial Africa, and South America. The disease is usually acquired before puberty and is spread by direct contact with open lesions containing the spirochete. Transmission of the disease occurs rarely by sexual contact. Certain species of flies are also thought to be vectors of this infection. The disease is more common in natives with poor personal hygiene.

Manifestations. Following an average incubation period of three to four weeks, a primary lesion, the *mother yaw*, appears at the site of inoculation. This is almost invariably extragenital and usually occurs on the legs. This lesion is a granuloma which later ulcerates and heals with scar formation. About 6 to 12 weeks after the appearance of the lesion, a generalized eruption develops, consisting of large papules or granulomas on the face, neck, extremities, and buttocks. These lesions often occur about the mucocutaneous junctions, such as the mouth, nose, and rectum, and resemble condylomas of secondary syphilis. They heal slowly, but relapses may occur months or years after the onset of the initial yaw. The lesions of yaws often appear on the soles of the feet and produce painful ulcerations, so-called "crab yaws."

After several years, late destructive lesions may appear in the skin and bones. Periostitis and osteitis are found in the bones of the hands, arms, and legs, and produce characteristic dactylitis and "saber shins." Destructive lesions appear about the nose and result in severe ulcerative areas (*gangosa*). Proliferative exostoses develop in the nasal portion of the maxillary bone; this is known as *goundou*. Juxta-articular nodules are

also seen in the late stage of the disease. Involvement of the aorta and the central nervous system has been reported, but these complications are rare.

Diagnosis. The diagnosis of yaws can often be made on the appearance of the generalized skin eruption alone, but *T. pertenue* is easily demonstrated in the lesions. The Wassermann and flocculation tests for syphilis are usually positive. The lesions of yaws may be confused with leishmaniasis, leprosy, and tuberculosis. It is often impossible to differentiate between late lesions of yaws and late gummatous syphilis.

Treatment. Trivalent arsenicals, bismuth, and penicillin produce a rapid disappearance of the lesions, although prolonged therapy similar to that required in syphilis may be necessary to prevent relapse.

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Pinta

Albert Heyman

Definition
Etiology
Manifestations
Treatment

Definition. Pinta is an infectious disease of the skin caused by *Treponema carateum*. It is characterized by an initial papular lesion of the skin, followed by depigmented areas on the extremities and hyperkeratosis on the soles and palms. The disease is also known as *mal del pinta*, *azul*, and *carate*. Pinta is found almost entirely in the Western Hemisphere and is especially prevalent in Mexico and Colombia.

Etiology. *T. carateum*, the etiologic agent of pinta, is morphologically indistinct from *Treponema pallidum*. The exact relationship of this disease to other treponematoses (syphilis, yaws, and bejel) has not been definitely determined, and there are many similarities in the clinical manifestations of these infections. Pinta is usually transmitted from person to person by direct contact. It may also be spread by an insect vector.

Manifestations. The primary lesion of pinta appears after an incubation period of 7 to 20 days as a nonulcerative papule at the site of in-

fection. This is followed 5 to 18 months later by a secondary eruption characterized by flat erythematous and hyperpigmented lesions, called pintids. Late lesions develop after several years and appear as vitiligo-like, slate blue, or variously colored patches of the skin. The hands, wrists, knees, and ankles are commonly involved, and hyperkeratoses of the palms and soles are also seen. Aortitis and spinal fluid abnormalities similar to those found in neurosyphilis have been observed in some of these patients. The Wassermann reaction of the blood and flocculation tests for syphilis are usually positive in the late stages of the disease. Eosinophilia is often present.

Treatment. In the early stages of the disease there is a response to treatment with arsenicals and bismuth, but these drugs have little effect on the depigmented areas. Penicillin has not yet had an adequate clinical trial, but should be of value in the treatment of this disease.

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Weil's Disease (Leptospirosis)

Paul B. Beeson

Definition
Etiology
Pathogenesis
Epidemiology
Manifestations
Laboratory
Differential Diagnosis
Laboratory Diagnosis
Treatment
Prognosis

Definition. Weil's disease (leptospirosis) is an acute febrile illness caused by leptospirae, characterized by fever, leukocytosis, muscle pains, and signs of acute hepatitis and nephritis.

Etiology. The causative organisms are spirochetes, delicate in structure, with characteristic configuration and motility when observed with the dark-field microscope. In America two varieties are known to infect man, *Leptospira icterohaemorrhagiae* and *Leptospira canicola*. These are pathogenic for various animals including rats, dogs, guinea pigs, and mice. In the rat, which is the principal source of infection of man, leptospirae cause a chronic nonfatal infection in the renal tubules, from which site they are excreted into the urine in large numbers. Leptospirae can

be cultivated in vitro in mediums containing serum.

Pathogenesis. The portal of entry in infections of human beings apparently is variable. Evidence indicates that leptospirae can enter the body through the digestive and respiratory tracts or through abrasions of the skin. In the earliest clinical stage of infection the organisms are present in the blood; as a consequence of this dissemination they later cause inflammatory changes in many parts of the body, including striated muscle, liver, kidney, eye, and meninges. The lesions in muscle consist of focal necrosis attended by a variable degree of cellular reaction; the majority of the cellular elements present consist of sarcolemma nuclei, while inflammatory cells are comparatively rare. The absence of vascular changes in this lesion differentiates it from similar muscle lesions which may occur in the rickettsial diseases. Similar changes are encountered in the myocardium. The liver is generally enlarged and icteric. The histologic picture is that of slight focal degenerative phenomena in the liver

cells, with some evidence of liver cell regeneration, and diffuse bile stasis in the bile canaliculi. Rare instances of extensive central and midzonal necrosis are encountered. The changes in the *kidney* consist of marked degeneration of the proximal convoluted tubules. These contain large amounts of proteinaceous material and bile casts. There is generally a striking edema of the interstitial connective tissue with occasional small foci of chronic inflammatory cell infiltration. Inflammation of the *meninges* is usually of low-grade intensity with a predominantly lymphocytic pleocytosis in the spinal fluid. In those cases which terminate fatally there is deep jaundice of all tissues, and widespread petechial hemorrhages are encountered. Leptospirae are best demonstrated in sections of kidney and liver.

Epidemiology. The principal source of infection in man is through contamination of water with rat urine. Much less commonly, human beings become infected as a result of association with dogs, possibly by way of dog urine. To some extent Weil's disease is an occupational hazard, since many of the patients are individuals who work in damp places likely to be infested by rats. Such occupations as sewer work, fish cutting, ditch digging, and coal mining involve a hazard of Weil's disease. Because of the factor of occupational exposure the disease is more common in men than in women. The disease is seldom observed in children. In Holland many of the infections have been acquired as a result of swimming or accidentally falling into the canals. Infection has also been acquired by swimming in stagnant water in the United States and other parts of the world. There are reports of Weil's disease resulting from rat bite, but the risk of such a complication is less than that of infection by *Streptobacillus moniliformis* or *Spirillum minus*.

Manifestations. After an incubation period of 8 to 12 days, the illness usually begins suddenly, often with a chill, followed by a remittent fever ranging between 102° and 104° F. Soon after the onset the patient begins to suffer from muscle pains which are most marked in the lumbar region and in the calves of the legs. Headache, anorexia, and nausea may be experienced during this period. There may also be soreness of the throat and cough. Fever usually persists for four to six days, terminating by rapid lysis. Jaundice occurs in about 70 per cent of cases, usually appearing between the third and sixth days. At this time

the liver is somewhat enlarged and moderately tender. Jaundice usually increases in intensity for two to four days after its appearance, then subsides gradually over a period of 7 to 10 days, except in those cases which terminate fatally, in which the severity of jaundice may increase steadily until death. Splenomegaly is not common. The urine output often diminishes during the latter part of the first week, and in those patients who suffer severe renal involvement there may be almost complete suppression of urine; in fatal cases this is usually an important factor. If recovery is to occur, the urine output will gradually return to normal during the second week. Marked suffusion of the conjunctiva is likely to be present and is a finding of some help in diagnosis, particularly when the underlying sclera is icteric. Cutaneous hemorrhages of varying size may occur in the severest cases, but they are not common. Scarlatiniform and morbilliform rashes have been described, but these also are uncommon. *Iridocyclitis*, manifested by photophobia and circumcorneal congestion, occurs in 5 to 10 per cent of patients. Signs of meningeal irritation, severe headache and stiffness of the neck, may be observed at any time during the first week of the disease. Rarely, the picture is that of acute meningitis, with severe headache, stiffness of the neck, Kernig and Brudzinski signs, and with little or no evidence of hepatic or renal involvement.

Recovery is gradual. Most patients are asymptomatic by the end of the second week except for a rather marked asthenia. Relapses are fairly common in Weil's disease, being reported in about 20 per cent of cases. These usually take the form of rerudescence of fever during the second week, together with muscle pain and headache. The duration of fever in relapses is usually short —i.e., two to five days. Severe hepatic or renal involvement is rare during relapses.

Laboratory. The blood leukocyte count is nearly always elevated, ranging from 12,000 to 25,000 cells per cu. mm. The platelet and prothrombin content of the blood may be reduced, though seldom is either of these so reduced as to be a likely cause of the hemorrhagic tendency. In the majority of cases the bilirubin content of the plasma is increased and bilirubin appears in the urine. The stools are seldom acholic, however. Disturbed liver function may be manifested by positive cephalin flocculation and an elevated

thymol turbidity reading. In patients who have leptospiral nephritis there may be oliguria, hematuria, proteinuria, and cylindruria, and elevation of the blood nonprotein nitrogen. Examination of the spinal fluid reveals abnormal findings in 85 to 90 per cent of cases, the commonest of these being increase in number of cells—i.e., from 10 to 250 per cu. mm., the majority being lymphocytes. Xanthochromia of the spinal fluid is usually present in those patients with clinical jaundice.

Differential Diagnosis. Weil's disease is not difficult to recognize in its full-blown form. The combination of sudden onset with fever, leukocytosis, jaundice, muscle tenderness, conjunctival suffusion, and pleocytosis in the spinal fluid comprises a fairly characteristic syndrome. Furthermore, a history of contact with water likely to be contaminated by rats is helpful. It is probable, however, that the diagnosis is overlooked in as many as one half of the cases, especially those which are of short duration and without jaundice. The statement made previously that jaundice occurs in about 70 per cent of cases should be interpreted with this in mind. Recognition of Weil's disease may be difficult in those cases with predominant meningeal or renal manifestations. In the early stages, Weil's disease may simulate such acute infectious diseases as influenza, trichinosis, typhus fever, brucellosis, and the acute bacterial meningitides. Diseases with which Weil's disease may be confused in its later manifestations include infectious hepatitis, obstructive and hemolytic jaundice, and acute glomerulonephritis. If the various manifestations of Weil's disease are known, and its possible existence is considered, there is rarely much difficulty in making at least a presumptive diagnosis.

Laboratory Diagnosis. Experienced observers often are able to find leptospirae in dark-field examination of the blood during the first five days of the disease. Inexperienced observers, however, are likely to make an erroneous diagnosis of leptospiral infection because strands of fibrin being whipped about by Brownian motion are readily mistaken for leptospirae. The organisms may be isolated from the blood by inoculation of guinea pigs, mice, or hamsters during the first few days of the disease. Leptospirae can also be isolated from the urine between the second and fourth weeks of disease by animal inoculation in about 25 per cent of cases. Good results have been ob-

tained in a few laboratories by cultural isolation of leptospirae from the blood or urine. Specific antibodies for leptospirae appear in the blood of patients with Weil's disease during the second week, and often are present in extremely high titers: agglutination with serum dilution of 1:10,000 is not uncommon, and even 1:1,000,000 has been reported. This test gives the best results when freshly prepared antigen is employed; some workers prefer to use live leptospirae. A presumptive diagnosis of Weil's disease can be made during the first few days of the disease on the basis of a muscle biopsy, since the changes found in voluntary muscle are fairly characteristic. The spinal fluid should always be examined when the possibility of Weil's disease is being considered; the finding of xanthochromia and pleocytosis is strong evidence in support of the diagnosis. Yellow discoloration of the spinal fluid does not occur in infectious hepatitis or other forms of jaundice unless the icterus is very marked, and of long duration.

Treatment. In Europe good therapeutic effect has been reported following the use of high-titer antiserum, especially when given early in the disease. Such serum is not available in the United States. It has been suggested that blood or plasma from persons convalescent from Weil's disease might be of similar value. In experimental animals, penicillin in large doses is effective in the treatment of leptospiral infection if given very early. The results obtained with penicillin in human beings have been difficult to assay, because of the great variability in severity and manifestations of the disease. Furthermore, because of the fact that patients are usually afebrile after four to six days, an effect on the fever cannot be used as a guide. Cases have progressed to fatal termination while receiving penicillin in doses as large as 1,000,000 units per day. In view of the unquestioned favorable effect of penicillin in experimental infections, it seems logical to use this agent in therapy of human beings. Possibly doses as large as 5,000,000 to 20,000,000 units per day should be given.

Aureomycin is even more potent than penicillin in experimental leptospiral infections, and may prove similarly more effective in clinical usage. It deserves a trial, in a dosage of at least 6 Gm. per day. The value of "Chloromycetin" remains to be determined.

The general care of the patient is the same as

in any acute systemic infection. It is unlikely that diet will have much influence on the course of the hepatitis. Patients with oliguria should not be waterlogged with too much parenteral fluid and salt.

Prognosis. The reported fatality rates refer only to the more severe cases of leptospiral infection. In such cases, presenting evidence of hepatitis and nephritis, the fatality rate is in the range of 5 to 10 per cent.

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Relapsing Fever

Paul B. Beeson

Definition
 Etiology
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 Manifestations
 Course of Disease
 Laboratory Findings
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Definition. Relapsing fever is an acute infectious disease, caused by spirochetes belonging to the genus *Borrelia*. The outstanding clinical characteristic is a relapsing type of fever.

Etiology. Members of the genus *Borrelia* are slender, flexible spirochetes, 10 to 20 microns in length (fig. 156). They move with a corkscrew-like action. *Borrelia* species are pathogenic for many rodents, including rats, mice, and squirrels. They can be cultured in mediums enriched with serum or blood. The strain which is encountered most commonly in North America is *Borrelia recurrentis*. In other areas *Borrelia novyi* and *Borrelia duttonii* are of clinical importance.

Epidemiology and Pathogenesis. Relapsing fever occurs in many parts of the world, including Asia, Africa, Europe, and South and North America. Wild rodents appear to be the natural reservoirs of the infection. The disease is transmitted to man by insect vectors. In some parts of the world human beings are infected by the bite of ticks (Ornithodoroi), while in other locali-

ties, as in Asia, the principal vector is the body louse. The excreta of the louse may be infectious, and disease in man may follow the crushing of a louse on the skin, especially when the area is

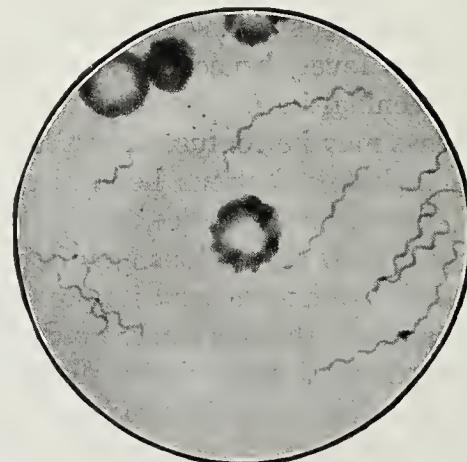


FIG. 156. *Borrelia recurrentis* from blood of a man with relapsing fever. (Kolle and Wassermann.) (Courtesy, Stitt, Clough, and Branham: "Practical Bacteriology, Hematology, and Parasitology," Philadelphia, The Blakiston Company.)

scratched. Fleas and bedbugs also have been suspected of transmitting relapsing fever. It is likely, then, that under certain circumstances an animal reservoir is not necessary for perpetuation, and, instead, that infection is transmitted from man

to vector to man. In the United States relapsing fever has been recognized only west of the Rocky Mountains and in Texas; in these areas ticks appear to be the principal vectors, with wild rodents or bats as reservoirs.

After inoculation by contact with the excreta or by the bite of an arthropod, *Borrelia* is apparently disseminated by way of the blood stream and lymphatics. The large number of spirochetes present in the blood of an infected person suggests that these organisms are capable of growing in the blood itself. They have also been demonstrated in the cerebrospinal fluid during the acute stage of relapsing fever. Autopsy in fatal cases discloses their presence in the brain, spleen, kidneys, and liver.

Manifestations. It is often impossible to determine the *incubation period* in individual cases, but there is epidemiologic evidence to suggest that 5 to 11 days is the usual time. *Symptoms* develop abruptly, with chilliness, fever, headache, muscle aching, and nonproductive cough. Nausea and vomiting are common symptoms. The patient appears acutely ill, with flushed face and injected conjunctival and pharyngeal mucous membranes. At the height of the fever there may be dizziness, mental cloudiness, or delirium. Signs of extracellular fluid deficit—dry, inelastic skin and wrinkled tongue—are often present. *Tenderness of the calf muscles* is a characteristic physical finding. *Jaundice* occurs in a small proportion of cases, usually after several days of fever. A transitory erythematous rash may be observed, especially about the neck and shoulders. In severe cases there may be *petechiae*. *Enlargement of the spleen* is observed in about half of all cases. The pattern of the temperature curve is somewhat variable. Usually there is an elevation to 103° to 105° F. The fever may be sustained or remittent.

Course of Disease. The febrile bout usually persists from 4 to 15 days and then subsides spontaneously. At the termination of fever there is usually profuse sweating and the temperature may fall to 96° or 97° F., gradually returning to normal during the succeeding day or two. A relapse is to be expected several days later, with a repetition of the same series of events. Unless specific therapy is administered it is usual for a patient to have three to five attacks of fever, after which the disease ceases spontaneously. Additional relapses may occur, but the usual end

result is complete cure of the infection. Death from relapsing fever is usually associated with hyperpyrexia, a hemorrhagic tendency, and circulatory failure.

Complications are not numerous. Nosebleed and gastrointestinal bleeding occur in severe cases. Pneumonia may be observed at the time of death. Orchitis and iridocyclitis are rare complications. In China an unusual frequency of *Salmonella enteritidis* septicemia has been observed in patients with relapsing fever.

Laboratory Findings. The leukocyte count is variable, but most commonly is between 10,000 and 15,000 per cu. mm. The spinal fluid may show increased protein content and a pleocytosis, predominantly lymphocytic.

A *specific diagnosis* nearly always can be made during febrile periods, and occasionally even during remissions, by the finding of *Borrelia* in stained smears of the peripheral blood. Giemsa or Wright's stain is satisfactory. If the organisms cannot be found by this method, mice should be inoculated intraperitoneally with the patient's blood. *Borrelia* can then be found in the blood of these animals 16 hours to 3 days later, if the patient is suffering from relapsing fever.

Because of the ease with which a specific diagnosis can be made from the blood smear, serologic diagnostic tests are not needed. It is worth noting, however, that false positive serologic tests for syphilis are obtained in about 10 per cent of patients with relapsing fever, and that nearly all patients develop agglutinins for *Proteus OXK*.

Differential Diagnosis. This disease has to be differentiated from other acute infectious diseases, particularly those which may be associated with a relapsing type of fever, such as malaria, meningococcemia, and rat bite fever. At the onset of the disease the picture simulates that of Weil's disease. Under conditions of poverty and famine, the problem of diagnosis may be increased by concurrent epidemics of typhus fever, malaria, and tuberculosis. Fortunately, a specific diagnosis of relapsing fever usually can be made simply by microscopic examination of a stained smear of blood.

Treatment. Therapy with arsenical preparations such as "Mapharsen" (arsenoxide) is usually highly effective in *Borrelia* infections. It is recommended that two injections of this drug be given intravenously, three to five days apart, the dose being 0.04 Gm. for adults. Arsenical therapy

is likely to cause a Herxheimer-like reaction 4 to 12 hours after the injection, evidenced by rise in temperature, malaise, and intensification of symptoms. This reaction can cause death of the patient when superimposed at the height of a severe febrile attack. Consequently, it is usually recommended that specific therapy be withheld in severely ill patients until a natural crisis occurs. The patient should be given supportive therapy meanwhile, in the form of parenteral fluids and electrolytes. "Mapharsen" is then administered at the onset of the next febrile period, or a day or two before it is expected. Further treatment is indicated in the event of a relapse. *Penicillin* is effective in experimentally infected animals, but large doses are necessary, and initial clinical experience with conventional doses has been disappointing. In experimental animals *aureomycin* appears to be more effective than penicillin, and clinical trial of this drug is warranted.

Prognosis. Relapsing fever is not in itself a highly fatal infectious disease. However, due to the fact that it occurs frequently under conditions of famine and extreme poverty, and therefore may be associated with other infections and malnutrition, there is usually a significant fatality rate ascribed to it. Reported fatality rates have varied from 2 to 50 per cent. Fatalities would probably be less than 5 per cent among otherwise healthy persons given proper treatment.

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Rat Bite Fever—*Spirillum minus* Infection

Paul B. Beeson

Definition
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 Laboratory Findings
 Differential Diagnosis
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Definition. Rat bite fever is an acute infectious disease caused by *Spirillum minus*, and characterized by relapsing fever, arthritis, and a skin eruption.

Etiology. The causative organism is a spirillum 2 to 5 microns in length; it has two to five broad spirals, and is propelled by flagella. The organism is easily identified in dark-field preparations by its quick, darting motility. It is found occasionally in the blood of apparently healthy rats, mice, and guinea pigs.

Epidemiology. In man infection by *S. minus* is almost always acquired through the bite of a rat. It is commonest in infants and young children, but may also occur in adults. Rats may attack sleeping persons, and will bite anyone attempting to catch or handle them.

Manifestations. The incubation period varies widely, from one to six weeks. With the onset of symptoms the site of the rat bite usually becomes swollen, tender, and purplish red in color. The regional lymph nodes also become enlarged. There is fever, which is usually relapsing in type. A chill may occur at the onset of a febrile period. Bouts of fever last two to four days, and are separated by afebrile periods also lasting two to four days. The principal symptoms during febrile episodes are malaise, headache, sweating, photo-

phobia, nausea, and vomiting. In perhaps 50 per cent of cases there is *arthritis*, with redness and swelling of one or more large joints. In a similar proportion of cases a *skin eruption* occurs, usually on the extremities. The rash is frequently asymmetric in its distribution, and most commonly consists of reddish or purplish plaques which may become large and confluent. The disease tends to run a prolonged course, usually four to eight weeks, but cases have been reported in which clinical manifestations continued for more than a year.

Laboratory Findings. The total leukocyte count may be normal, or there may be a moderate leukocytosis. In prolonged cases there is a normochromic anemia. Biologic false positive serologic tests for syphilis have been observed. The *S. minus* seldom can be found in the blood or tissues of patients suffering from this infection, and can be demonstrated only by transmission to laboratory animals. Mice or guinea pigs may be inoculated intraperitoneally with the patient's blood. The *S. minus* usually can be found in the blood of the animal by dark-field examination one to three weeks later. Since laboratory animals may be naturally infected with *S. minus*, precautions must be taken to ensure that the animals used in this test are free of infection before inoculation.

Differential Diagnosis. It is important to inquire about rat bite in all patients with a relapsing type of fever. In patients with a history of rat bite the principal problem is in differen-

tiating between *S. minus* infection and *Streptobacillus moniliformis*. This cannot be done with certainty on clinical grounds, but a prolonged incubation period and few or no manifestations of arthritis suggest a diagnosis of *S. minus* infection. Laboratory tests should be made for both organisms. The significance of a previous rat bite may not be appreciated in cases with a long incubation period, and the disease may be confused with other infections characterized by relapsing fever, such as malaria, meningococcemia, *Borrelia recurrentis* infection, and occasionally pyogenic infection.

Treatment. This infection usually responds promptly to treatment with arsenical preparations such as arsenoxide ("Mapharsen") or neoarsphenamine. Doses appropriate to the patient's age and size and equivalent to those used in the treatment of syphilis are satisfactory. The usual practice is to give two or three injections at three- or four-day intervals. The effect of penicillin in this infection has not been determined adequately.

Prognosis. In the absence of serious complicating illnesses, rat bite fever caused by *S. minus* is never fatal.

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Section 15—Rickettsial Infections

NATURE OF RICKETTSIAE

Rickettsiae are minute infectious agents, smaller than most bacteria and larger than viruses. Other properties likewise place them in a position midway between these two classes of organisms. They can be stained and are visible with the ordinary microscope as tiny pleomorphic coccobacilli. Most of them will not pass through bacterial filters. Those species pathogenic for man will multiply only in the presence of living cells,

and in fact most of them are obligate intracellular parasites.

Rickettsiae are fundamentally parasites of arthropods, but a number of species also utilize mammals as intermediary hosts. Ticks, mites, fleas, or lice may be involved in the transmission of disease to man. In the following chapters particular emphasis will be given to the rickettsial diseases of man which are indigenous to the United States.

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Murine Typhus

Edward S. Miller

Definition
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Epidemiology and Pathogenesis
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. Murine typhus fever is an acute infectious disease caused by *Rickettsia mooseri*, and characterized by sudden onset, fever of two to three weeks' duration, and a rash which is located predominantly on the trunk.

History. Typhus fever has been known since ancient times as a catastrophic epidemic disease. A series of important investigations during the present century established the fundamental facts concerning the causes and the modes of spread. Actually, there are two distinct kinds of typhus, the classic variety and the murine variety.

Classic or Old World epidemic typhus is a severe, often fatal, illness which occurs in great epidemics. It is transmitted from man to man by the human louse and there is no animal reservoir. This form of typhus has appeared in the United States from time to time, but has never become permanently established here.

The history of murine or endemic typhus can be traced back only a few decades, for until recent years cases were considered to represent

merely a mild sporadic form of classic typhus. The disease was first described in this country by Paullin in Georgia in 1913. In subsequent years it was shown to differ from classic typhus as to both etiologic agent and mode of spread.

Etiology. The causative agent of murine typhus is the *Rickettsia mooseri*. This organism is closely related to *R. prowazekii*, which is the infecting organism in classic typhus. Nevertheless, there are differences. In the guinea pig and the rat, *R. mooseri* provokes a more severe disease, attended by a marked inflammatory reaction in the tunica vaginalis. Significant differences in antigenic structure have been revealed by serologic tests and by cross-immunity experiments.

Epidemiology and Pathogenesis. The chief mammalian reservoir of murine typhus is the rat. In this animal, the naturally acquired disease is usually nonfatal, but often leads to the development of a chronic carrier state. The infection is transmitted from rat to rat by several species of rat fleas (the most important is *Xenopsylla cheopis*) and by the rat louse (*Polyplax spinulosa*). The infecting agent establishes itself in the alimentary tract of the flea, where it exists for a month or more without killing its host. This comfortable adaptation of rat, flea, and rickettsia to one another suggests that their relationship is one of long standing.

The rat louse does not feed on man, but the

flea will if given the opportunity. Although the actual flea bite is not infectious, feeding is accompanied by the excretion of rickettsia-laden feces, and the unwitting host infects himself by scratching the dejecta into the skin.

The human body louse is also capable of transmitting *R. mooseri*, and, in a population heavily infested with lice, murine typhus may assume epidemic proportions by a cycle of man-louse-man transfer, without intervention of rats or rat parasites. This has been observed to occur in Mexico, where the epidemic disease is called *tabardillo*. Under these conditions of rapid human passage, murine typhus becomes a more severe disease, and is attended by a high mortality rate.

The usual mode of human infection is considered to be by the transcutaneous route outlined above. However, evidence suggests that other portals of entry may be of clinical importance. Experimental animals can be infected via the conjunctiva as well as the respiratory and gastrointestinal tracts. Accidental infections have occurred among laboratory workers under circumstances which suggested one of these routes of entry. Furthermore, experimental infection has been produced in man by feeding suspensions of *R. mooseri*. Rickettsiae are regularly present in the excreta of infected fleas and rats, and have been shown to survive in dried flea feces for as long as 651 days. It is not difficult to visualize human infection resulting from inhalation of contaminated dust or ingestion of contaminated food. Having gained entrance to the body, the rickettsiae are disseminated widely and establish themselves in the endothelial cells lining arterioles, capillaries, and venules. There they multiply and produce characteristic histopathologic alterations with perivascular infiltrations of lymphocytes, and with thrombosis of small blood vessels.

The foregoing account of the mode of spread of murine typhus explains why it is usually a sporadic disease. It occurs especially among individuals who are occupationally exposed to rats, such as food handlers and employees of feed mills; consequently, the disease is most common in adult males. However, there are no intrinsic differences in susceptibility as regards age, sex, or color. In the United States most cases of murine typhus are seen during the months of July through November. This period coincides

with the season when rats are most heavily infested with fleas.

Murine typhus occurs throughout the southeastern portion of the United States in an area extending as far west as Texas and as far north as Ohio and Maryland. It is also found in California. The disease is endemic in many other parts of the world, particularly in warm climates.

Manifestations. The clinical features are fairly constant and distinctive. The *incubation period* is 6 to 14 days. The *onset of illness* is usually abrupt, often with a chill. Mild *premonitory symptoms* precede this sharp onset in one half of the cases, and consist of muscular aching, headache, feverishness, anorexia, and cough. After one to three days there is a rapid transition to the full-blown disease. The *symptoms* of murine typhus are those common to many acute infectious diseases. Frontal or occipital *headache* is almost invariably present, and many patients consider it the worst feature of the illness. It appears early and often lasts throughout the febrile period, varying in intensity with the rise and fall of the fever, and gradually diminishing during defervescence. *Muscular aching* is nearly as common as headache, and is noted particularly in the lumbar region, the legs, the shoulder girdle, and the back of the neck. Occasionally, there is *pain in the abdomen*, suggesting the possibility of a condition requiring surgery. Shaking *chills* occur in the majority of patients, often repeatedly, and usually during the first week of illness. Nearly all patients are *anorexic* and many experience *nausea* and *vomiting*. Other common complaints include nonproductive *cough*, *photophobia*, and *sore throat*.

Patients with murine typhus fever are acutely ill, but only rarely is there severe prostration. Varying degrees of *delirium* are not uncommon. The *skin eruption* is the most helpful physical finding leading to the diagnosis of murine typhus. It is present in 90 per cent of white patients, but, due to the difficulty in distinguishing the lesions on deeply pigmented skin, is seen in less than half of colored patients. Lesions are 3 to 10 mm. in diameter, macular or papular, discrete, and neither painful nor pruritic. At first they are pink to dull red in color and blanch on pressure. Only rarely are they hemorrhagic. As the lesions mature, they no longer disappear with pressure, but assume a brownish cast and gradually fade away. The number of lesions present on

a patient may vary from a few dozen to many hundreds. If an eruption can be seen at all, it is invariably present on the trunk, being most profuse on the chest and abdomen and less extensive over the back. It is also seen frequently on the proximal segments of the extremities, but is found only rarely on the skin of the palms, soles, or face. The rash appears between the second and eighth days of illness, begins to fade after several days, and usually is gone by the time the temperature has returned to normal.

In one third of the patients, the *spleen* is *palpable*, slightly enlarged, firm, and occasionally tender. The majority of cases show moderate *injection of the conjunctivas* and of the *pharyngeal mucous membrane*, as well as some generalized muscular tenderness. Despite the frequent occurrence of cough, physical examination of the chest reveals no significant abnormalities other than an occasional rhonchus. Chest x-rays show increased bronchial markings. Lymphadenopathy does not occur in murine typhus. There are no abnormal signs referable to the central nervous system, other than occasional delirium and, more rarely, slight *stiffness of the neck*.

The course of illness follows a predictable pattern. The symptoms persist unabated for the first 8 to 10 days, and then gradually diminish in intensity during the following week. Fever is present in the average patient for 13 to 17 days (extremes of 9 to 25 days). During the first week the temperature ranges between 103° and 105° F., then it gradually drops, and defervescence takes place over a period of two to seven days. Symptoms disappear with the fever and relapses do not occur. Complications are infrequent. Bronchopneumonia is sometimes seen, but it is not clear whether the pulmonary lesions are due to rickettsial infection or to secondary bacterial invaders.

Laboratory Findings: SEROLOGIC TESTS. The Weil-Felix reaction has long been a standard diagnostic test in this disease. This reaction is believed to depend upon the existence of an antigen common to *R. mooseri* and to certain strains of *Proteus*. Patients with murine typhus regularly develop antibodies against *Proteus vulgaris* OX19 strain, and sometimes against *P. vulgaris* OX2. Agglutinins appear between the fifth and twentieth days of illness, and a minimum titer of 1:160 generally is considered necessary for diagnosis. As with other serologic tests, it is desirable to demonstrate a rising titer of antibodies during

the course of illness. One important limitation in the value of the test lies in the fact that it is also positive in Rocky Mountain spotted fever, in classic typhus, and at times in other nonrickettsial illnesses, such as *Proteus* infections of the urinary tract.

In recent years a complement-fixation test has been developed which specifically differentiates the various rickettsial diseases. It is a particularly useful diagnostic procedure in areas where several rickettsial infections coexist. Antibodies appear in the patient's blood during the second or third week of illness, and persist in significant titer for many years. A rickettsial agglutination test has also been developed, and it appears to be as specific as the complement-fixation test.

Biopsy of a skin lesion is a simple and useful procedure which, in the hands of an experienced pathologist, can provide a diagnosis before circulating antibodies appear.

R. mooseri can be isolated from the blood of a patient by intraperitoneal inoculation of a guinea pig. However, rickettsial isolation is not a suitable procedure for routine use because it requires especially trained personnel, and because there is great danger of accidentally infecting the laboratory workers.

The white blood cell count is within normal limits in the majority of patients. During the early part of the illness leukopenia is not unusual, with a total count as low as 1500. Sometimes, especially later in the course, the leukocyte count may rise as high as 20,000. Differential counts are normal or show a moderate increase in polymorphonuclear cells. Murine typhus fever does not cause anemia.

Small amounts of albumin and a few granular casts may be found in the urine during the early period of illness. The blood sedimentation rate is moderately elevated. The spinal fluid is normal except in rare patients who show a slight pleocytosis.

Differential Diagnosis. Murine typhus must be differentiated from other varieties of rickettsial infections. *Classic typhus* is clinically similar, but is a much more severe and prostrating disease. *Brill's disease* was formerly confused with murine typhus, but they are now known to be different illnesses. Most patients give a history of having had classic typhus, and all show a specific complement-fixation reaction with *R. prowazekii*. In *Rocky Mountain spotted fever* there is frequently

a history of tick bite. The patient is severely ill and often edematous, and the rash is hemorrhagic and most profuse over the distal segments of the extremities. The Weil-Felix reaction does not differentiate these diseases, but the complement-fixation test does. *Typhoid fever* is more gradual in onset; usually it is associated with abdominal distention and tenderness, symptoms which are unusual in typhus. The rashes in the two diseases are dissimilar. The isolation of the typhoid bacillus and the development of specific antibodies aid in differentiation. *Malaria* is characterized by periodicity of fever, and parasites can be found in the blood. Murine typhus and *atypical pneumonia* may bear certain clinical resemblances at the outset. The presence of pulmonary consolidation and of cold agglutinins in atypical pneumonia, and the rash in typhus, are differential points.

Treatment. Aureomycin and "Chloromycetin" are both of established value. One or the other should be given as outlined in Chapter 156. Certain supportive measures are also useful. Most patients are dehydrated and anorexic during the acute phase of illness, and are benefited by appropriate quantities of parenterally administered dextrose and saline solutions. Codeine, meperidine hydrochloride, and ice caps give partial relief for headache and muscular aching.

Prognosis. Murine typhus is a self-limited disease whose normal course is one of short convalescence followed by complete recovery. Relapses do not occur and there is a lasting immunity. The fatality rate is 1 to 4 per cent, with deaths occurring chiefly in the aged or in patients debilitated by some coexistent disease.

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Epidemic Typhus

Edward S. Miller

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Definition. Classic or epidemic typhus fever is a severe infection of man caused by *Rickettsia prowazekii*. The principal features of the disease are headache, generalized rash, splenomegaly, and a self-limited febrile course.

Etiology. The etiologic agent is closely related to *Rickettsia mooseri*, the organism that causes murine typhus fever. Human body and head lice transmit the disease from man to man. Classic

typhus differs epidemiologically from all other rickettsioses except trench fever, in that human infections are necessary to perpetuate the disease. There are no naturally occurring animal hosts, and the louse does not convey rickettsiae to its offspring; thus man represents the only reservoir of infection.

Epidemiology and Pathogenesis. Classic typhus is one of the most devastating of human diseases. In recent decades it has been especially prevalent in Central Europe, China, and North Africa, though from time to time all the continents have received its visitations. Epidemics have occurred in the United States, but the dis-

ease never has become permanently established here. The only cases now seen in this country are those designated as Brill's disease. Zinsser showed that Brill's disease is a mild, late re-crudescence of classic typhus. It is seen primarily among immigrants from Europe who contracted their original infections many years before in their native countries.

Manifestations. Classic typhus bears a close clinical resemblance to murine typhus. The incubation period, the symptoms, the characteristics of the fever, the exanthema, and other salient features are qualitatively the same. They differ chiefly in that the louse-borne variety is a more severe and more frequently lethal disease. Patients are markedly prostrated, apathetic, and stuporous. Renal insufficiency and azotemia are not infrequent, particularly in the more gravely ill patients. Other serious manifestations include pneumonia, vascular thrombosis, and gangrenous changes in the skin or extremities. The over-all fatality rate is about 20 per cent, being lower in children and much higher in patients past the age of 50.

Laboratory Findings. Agglutinins for *Proteus* OX19 appear in the serum during the second or

third weeks of illness, as also do agglutinins and complement-fixing antibodies for homologous rickettsial antigens. Biopsy of a skin lesion also affords a ready means of diagnosis.

Prophylaxis and Treatment. Effective methods have been developed in recent years, both for prophylaxis and for treatment. The Cox type vaccine, utilizing killed suspensions of *R. prowazekii*, prevents infection or modifies it so greatly that practically all immunized persons recover. The disease responds to treatment with para-aminobenzoic acid as well as with the antibiotic agent "Chloromycetin"; aureomycin, too, probably will prove effective.

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Scrub Typhus (Tsutsugamushi Disease)

Edward S. Miller

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Definition. Scrub typhus is caused by *Rickettsia tsutsugamushi*, and is characterized by a primary eschar, an extensive rash, lymphadenopathy, and an acute febrile course of two to four weeks' duration. The disease is endemic in Japan, southeastern Asia, northern Australia, and islands in the southwest Pacific and the Indian Ocean. It has acquired a variety of regional names, such as Japanese river fever and mite-borne typhus.

Epidemiology. Rats, mice, voles, and possibly other rodents constitute the animal reservoirs of infection. Rickettsiae are transmitted from animal to animal, and from animal to man, by mites (*Trombicula akamushi*, *Trombicula deliensis*, and perhaps other species). These arthropods feed on mammals only once, and only in the larval stage of development. The cycle of infection is preserved by virtue of the hereditary transmission of rickettsiae to the mite ova.

Manifestations. The course of illness, the rash, and other clinical manifestations are similar to those of typhus except for two important features—the presence of a primary lesion and of

lymphadenopathy. The lesion or eschar, seen in 60 per cent or more of cases, develops several days before the onset of constitutional symptoms. It appears at the site of the mite bite, which may be anywhere on the body, and consists of a small, painless papule surmounted by an ulcer and covered by a dark scab. During the first week of illness, groups of superficial lymph nodes become enlarged and somewhat tender. The lymphadenopathy may be either generalized or limited to the region draining the eschar. The acute phase of illness lasts two to four weeks and is followed by a prolonged convalescence, but recovery is ultimately complete. In fatal cases, death usually supervenes within 7 to 21 days after the onset of symptoms, and may be due to circulatory failure, pneumonia, or encephalitis. Fatality rates average about 5 per cent, though they vary widely in different outbreaks.

Diagnosis. The Weil-Felix test is the most useful laboratory method of diagnosis of scrub typhus. In contrast to other typhus fevers, agglutinins appear for the *Proteus* OXK antigen,

but not for the OX2 and the OX19 strains. A complement-fixation test has been devised but has not proved so reliable as in other rickettsial diseases. The isolation and identification of *R. tsutsugamushi* is a highly technical procedure unsuitable for routine use.

Treatment. There is as yet no scrub typhus vaccine of established worth. Para-aminobenzoic acid and "Chloromyctin" are both substantially effective therapeutic agents. As of this writing, there are no reports on the use of aureomycin in human cases, but it seems likely that this antibiotic also will prove to be of value.

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Rocky Mountain Spotted Fever

Edward S. Miller

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Definition. Rocky Mountain spotted fever is a severe infectious disease, the most characteristic features of which are chills, fever, prostration, and a hemorrhagic rash. It is caused by *Rickettsia rickettsii* and is transmitted by ticks.

History. A syndrome called spotted fever was first noted during the late nineteenth century by physicians practicing in the Rocky Mountain region. Early investigators recognized its infectious

nature and suspected that it was transmitted by ticks. Ricketts, for whom the genus is named, identified the etiologic agent, reproduced the disease in experimental animals, and demonstrated that infected ticks exist in nature and can transmit spotted fever to mammalian hosts.

Etiology. The causative agent, *Rickettsia rickettsii*, is pathogenic for a wide variety of mammals, the guinea pig being among the most susceptible. Like other rickettsiae, it grows in the embryonated egg. The organism is distinctive in that it multiplies not only in the cytoplasm of tick cells, but also within nuclei.

There exist a number of related tick-borne rickettsioses, of which Rocky Mountain spotted fever is the prototype. The Brazilian disease,

called São Paulo typhus, is identical with Rocky Mountain spotted fever. Fièvre boutonneuse is found in Mediterranean countries and is caused by *Rickettsia conorii*, an organism which is serologically related to *R. rickettsii*. South African tick bite fever and Kenya fever are also members of the spotted fever group.

Epidemiology and Pathogenesis. Rocky Mountain spotted fever is largely a rural disease. It is not limited to the region for which it is named, since cases have been recognized in all of the states except Maine and Vermont. The disease occurs chiefly during the warm months of the year when ticks are active. Both sexes and all age groups are susceptible, though the illness tends to be milder in children. There are variations in the virulence of different rickettsial strains, and hence in the severity of the clinical disease in different areas. However, it is not true, as was once believed, that spotted fever as seen along the eastern seaboard is milder or significantly different from that seen in the West.

Ticks are the only known vectors, and in this country at least four species are infected in nature. These include the wood tick (*Dermacentor andersoni*), which exists in the western states; the dog tick (*Dermacentor variabilis*), found in the middle-western and eastern states; the Lone Star tick (*Amblyomma americanum*), found in the southeastern and south central states; and the rabbit tick (*Haemaphysalis leporis-palustris*), which occurs throughout the country. The tick can acquire infection by feeding on an infected animal. The organisms also pass hereditarily from the pregnant female to some of its eggs, and survive through the various developmental phases of the new generation of parasites. The agent invades the cells of the gut, the salivary glands, the generative organs, and other tissues, yet apparently does no harm to the arthropod host. The carrier rate for *R. rickettsii* in a tick population rarely exceeds 3 per 1000.

Ticks infest a wide variety of rodents as well as other wild and domesticated animals. Many of these species develop manifest disease or inapparent infections on experimental inoculation, and are believed to act as natural reservoirs of spotted fever. Dogs are of particular epidemiologic importance in regions where *D. variabilis* is abundant, for they have intimate contact with both the arthropod vector and the human host.

Rickettsiae are present in the salivary secre-

tions as well as in the feces of the tick. Illness in man is believed to result chiefly from tick bite, but may also follow contamination of the skin by a crushed tick, or by its feces. After the arachnid has found its host, the actual transmission of infection may not occur for as long as eight hours. This parasite is often slow in attaching itself, and, furthermore, it may not be infectious until it has undergone a preliminary "warming up" period. During this period the rickettsiae within the tick are "reactivated" in some remarkable but poorly understood fashion, being altered in the direction of increased virulence and perhaps increased numbers. Animals also can be infected experimentally via the respiratory or intestinal tracts, or by conjunctival implantation. Conceivably, these portals of entry may be important in the pathogenesis of human disease in regions where dogs are frequently infested with *D. variabilis*, for their coats may be contaminated with dried infectious tick feces.

The essential pathologic lesion in man consists of an endangiitis. Rickettsiae localize in the endothelial and the smooth-muscle cells of the vessel wall. The ensuing inflammatory reaction results in proliferation and swelling of endothelial cells, narrowing of vascular channels, and formation of thrombi. Lesions occur chiefly in the smaller vessels of the skin, subcutaneous tissues, testes, skeletal muscles, and brain. The eruption seen in this disease is a manifestation of such lesions in the skin.

A striking drop in plasma proteins is commonly seen. This is thought to be due principally to leakage of colloids through damaged vascular walls. Other factors which contribute to the hypoproteinemia are increased protein breakdown associated with severe infection, and possibly impaired production of protein.

Manifestations. The *incubation period* varies from 2 to 14 days, tending to be shorter in the more severe cases. Though mild *prodromata* occasionally are seen, the onset of illness is usually abrupt. The outstanding *symptoms* include rigors, fever, severe frontal or occipital headache, pains in the muscles and joints, and sensitivity of the eyes to pressure and to light. Nausea, vomiting, constipation, epistaxis, mild nonproductive cough, and alopecia are sometimes seen.

Patients usually appear severely ill and prostrated. The temperature rises rapidly to 103° to 105° F., and the heart rate increases moderately.

The conjunctivas are injected. The skin may be flushed or cyanotic, and jaundice is occasionally observed. Edema is common; it may be generalized or limited to the hands or face. The spleen is usually enlarged, and hepatomegaly is not infrequent.

A rash is the most characteristic physical finding, and is present in nearly all cases. It develops two to six days after the onset of illness, appears first and most abundantly on the wrists and ankles, and then spreads to involve all the body surfaces. Unlike typhus, the eruption commonly appears on the palms, soles, face, scalp, and sometimes on the oral mucosa. At first the lesions are circumscribed rose-colored macules which measure 1 to 5 mm. in diameter. Later they usually become hemorrhagic, and they may enlarge and coalesce. Several successive crops sometimes appear at intervals of a few days. When the cutaneous vascular changes are extensive, ecchymosis and necrosis occur, with gangrene and sloughing in such areas as the genitalia; the tips of the fingers, toes, and nose; the ear lobes; and the soft palate.

Brain lesions are manifested by a variety of neurologic abnormalities. Patients often exhibit stupor, restlessness, and insomnia. Less commonly there may be cutaneous hyperesthesia, muscular tremors, stiffness of the neck, ankle clonus, and Babinski reflexes. Coma, opisthotonus, muscular rigidity, and convulsive seizures are grave signs.

In cases of average intensity the severe symptoms, the prostration, and the pyrexia persist for two to three weeks, following which the fever diminishes by lysis and there is slow clinical improvement. Mild cases are seen in which prostration is minimal, there is little or no rash, and the total duration of illness is one or two weeks. In gravely ill patients the temperature sometimes drops to normal or subnormal levels while the pulse becomes rapid and thready. Such cases often exhibit extensive cutaneous hemorrhages and prominent neurologic abnormalities. If death is the outcome, it usually occurs during the first or the second week of illness.

The chief complications of Rocky Mountain spotted fever are pneumonia, epistaxis, hemorrhages from the gastrointestinal or urinary tracts, thrombophlebitis, iritis, and hemiplegia.

The acute phase of illness is followed by a protracted convalescence, which may take many

months. It leads usually to complete recovery, though in rare instances the cerebral lesions result in permanent neurologic sequelae. There is nearly always a lasting immunity to reinfection.

Laboratory Findings. The etiologic agent can be recovered from the blood by guinea pig inoculation, but this is a time-consuming procedure and, furthermore, it involves danger to the laboratory worker. A specific serologic diagnosis can be established by demonstrating the appearance of complement-fixing antibodies or rickettsial agglutinins during convalescence. Agglutinins appear for all three of the *Proteus* antigens, OX19, OX2 and OXK (Weil-Felix test). The titers are usually low, but not invariably so, and in an individual case the test is not a reliable method of differentiating between Rocky Mountain spotted fever and typhus fever. Characteristic histologic changes occur in the cutaneous lesions. An experienced pathologist can, therefore, provide an early diagnosis if a skin biopsy is taken soon after the onset of illness.

The leukocyte count is normal or slightly elevated, rarely exceeding 15,000. There may be a moderate increase in monocytes. The concentration of plasma proteins is often strikingly reduced; levels as low as 3.5 Gm. per 100 ml. are seen. The level of nonprotein nitrogen in the blood may be markedly elevated. The spinal fluid is usually normal, but may show slight pleocytosis.

Differential Diagnosis. *Murine typhus* and spotted fever have many characteristics in common; typhus, however, is rarely seen in the spring or early summer, and the cutaneous lesions are most numerous over the trunk and are not hemorrhagic. *Bullis fever* is accompanied by lymphadenopathy, and rash is unusual. All of the rickettsioses can be differentiated precisely by means of complement-fixation tests. *Measles* may resemble Rocky Mountain spotted fever, but is accompanied by coryza and by Koplik spots. Other diseases associated with a hemorrhagic rash must be considered. In *meningococcal infections* there is usually a purulent meningitis, and sometimes arthritis. Bacterial endocarditis is accompanied by a cardiac murmur. *Hematologic diseases causing purpura* are distinguished by appropriate studies of the blood.

Prophylaxis and Therapy. A vaccine prepared from chick embryos is available for active immunization. It is given in three injections one

week apart, after which booster doses are given each year. Application of this measure has been shown to lower the incidence of infection, and to diminish the severity of illness in those not completely protected.

Both aureomycin and "Chloromyctin" appear to be highly effective therapeutic agents. Either drug should be administered as indicated in Chapter 156. Para-aminobenzoic acid and hyperimmune rabbit serum also have proved to be moderately beneficial; nevertheless, these forms of therapy probably will not have much application in the future.

Contrary to some opinion, intravenous supportive therapy is often of great value, and is not dangerous if the agents are selected with due regard for the metabolic needs of the patient. In the presence of hypoproteinemia and edema, plasma or whole blood transfusions often result in improved renal function, diuresis, and disappearance of edema. Glucose and saline solutions then may be administered safely in quantities sufficient to restore fluid, electrolyte, and nitrogen balance.

Prognosis. Fatality rates have varied considerably in different series, but the over-all

average for the country is 20 to 25 per cent. These variations may be due to differences in the virulence of strains of *R. rickettsii*, and to differences in population group studies. The fatality rate in children and young adults is usually 12 to 15 per cent, whereas in patients over the age of 40 it is 40 per cent or higher. Now that effective therapeutic agents are available, it seems probable that the rate for the general population will not exceed 5 per cent in treated cases.

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Rickettsialpox

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Definition. Rickettsialpox is an acute, benign disease characterized by a vesicular exanthem, caused by *Rickettsia akari*, and transmitted by a mite.

History. An unusual disease appeared in 1946 among the occupants of a housing development

in New York City. In a few months it reached epidemic proportions, and so engaged the attention of public health investigators. They were able to show that the illness results from infection with a hitherto unrecognized species of rickettsia.

Etiology. The causative agent is *R. akari*. It is pathogenic for mice and for guinea pigs, and can be cultivated in the yolk sac of the embryonated egg. This microorganism appears to be related to, yet distinct from, *Rickettsia rickettsii* (Rocky Mountain spotted fever) and *Rickettsia conorii* (fièvre boutonneuse).

Epidemiology and Pathogenesis. *R. akari* is an inhabitant of the gastrointestinal tract of a species of mouse mite (*Allodermanyssus sanguineus*). This arthropod is a blood-sucking parasite of the common house mouse, and transmits the rickettsial infection to its host. The mite also feeds on man, and human infection presumably occurs as a result of the bite, though few patients can recall such an experience.

Rickettsialpox has so far been described only in New York City. However, the mouse host is world-wide in distribution and the insect vector has been found in at least five widely separated states in this country. Therefore, there is every reason to believe that the disease will make its appearance elsewhere.

Manifestations. The incubation period has not been clearly defined as yet, though in one patient it was known to be 10 days. The illness is initiated in nearly all patients by the appearance somewhere on the body of a single symptomless lesion. It is a red papule which measures 5 to 15 mm. in diameter, and is surmounted by a vesicle which ultimately breaks down to form an eschar. *Regional adenitis* frequently accompanies the primary lesion.

Despite the presence of the initial lesion, the patient continues to feel quite well for 5 to 10 days, then abruptly becomes ill with symptoms of fever, shaking chills, headache, backache, photophobia, nausea, and moderate prostration. After another one to six days the characteristic rash appears. The lesions are discrete and erythematous, and number from a few to several hundred. Like the initial eruption, they are firm maculopapules, usually crowned by a vesicle, but measure only 2 to 8 mm. in diameter. They may be found anywhere on the body excepting the palms and the soles. Occasionally the oral mucosa is involved. After two to four days the eruption becomes encrusted, and then gradually fades away during the succeeding week.

The temperature varies diurnally, rising as high as 104° F., in the afternoon. In a few pa-

tients there is splenomegaly or generalized enlargement of lymph nodes. The fever and the acute symptoms last for approximately one week, after which the temperature falls by lysis. Weakness may persist a few days longer.

There are no complications and recovery is complete. The duration of immunity is unknown.

Laboratory Findings. Specific diagnosis can best be established by demonstrating the development of complement-fixing antibodies during convalescence. There is some serologic cross reaction with Rocky Mountain spotted fever, but the titer is always higher with the homologous antigen. The Weil-Felix reaction is nearly always negative in rickettsialpox. The causative agent can be recovered from the patient's blood by guinea pig inoculation. The cutaneous lesions exhibit characteristic histopathologic changes, so a skin biopsy will often afford the earliest means of diagnosis. The white blood cell count varies from 2400 to 7500, and some patients show an increase in mononuclear cells. The blood sedimentation rate is normal or slightly elevated.

Differential Diagnosis. Rickettsialpox may be distinguished from chickenpox and from smallpox by the history of the initial lesion, by the nodular character of the rash, and by the complement-fixation test. The rash is vesicular, thus being quite different from that seen in other rickettsial diseases, and serologic tests are specific.

Treatment. Treatment in the past has been symptomatic. Though no reports have yet been published on the clinical use of aureomycin or "Chloromycetin," one or the other should certainly be administered, as outlined in Chapter 156.

Prognosis. Rickettsialpox is a mild disease attended by no sequelae and no fatalities.

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Q Fever

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Definition. Q fever is an acute, febrile illness, often accompanied by pneumonia, which results from infection with *Coxiella burnetii* (*Rickettsia burnetii*).

History. The first human cases of this disease were observed by Derrick in Australia in 1933. They originated in Queensland and the infection was named Q fever. The causative agent was shown to be a rickettsia. Shortly afterward, Davis and Cox isolated the same organism from ticks captured in Montana. Though much remains to be learned about the distribution of Q fever, it is already evident that the disease is indigenous to many parts of the world.

Etiology. The agent isolated in Australia was named *R. burnetii*, while the one isolated in America was called *Rickettsia diaporica*. There are no important differences between the two strains or in the human diseases which they produce, and the former name is now more commonly used. This organism is infectious for guinea pigs, and grows in the embryonated egg. It differs from other pathogenic rickettsiae in several respects. It passes through a Berkefeld filter of a size which retains the other species. Though the organism multiplies only in the presence of living tissue, it grows outside the cells as well as within them.

Epidemiology and Pathogenesis. Knowledge of the mode of spread of Q fever is still fragmentary. In Queensland ticks transmit *C. burnetii* to bandicoots (small marsupial mammals), to cattle, and possibly to man. The agent is established in the wood tick (*Dermacentor andersoni*) in Montana and neighboring states, and in the Lone Star tick (*Amblyomma americanum*) in Texas. Viable organisms can be found in tick feces. The infection

is transmitted hereditarily in ticks. Cattle have recently been identified as a reservoir of infection in southern California. Naturally infected cows, though exhibiting no signs of illness, shed rickettsiae in the milk. Complement-fixing antibodies have been found in cattle serums collected in many of the western states.

Human beings are highly susceptible to Q fever, as indicated by attack rates of 25 to 40 per cent among those exposed in some epidemics, and also by the large number of laboratory workers who have contracted the illness. However, the routes and the means of transmission have not been identified clearly. Animals can be infected experimentally by tick bite, by intranasal inoculation, and through the skin. It has yet to be established which portals of entry are important in man. Presumably, infection may follow the bite of the tick, yet this vector could not be incriminated in most of the outbreaks which have been studied. Direct man-to-man transmission does not occur. Possibly the disease may follow consumption of infected raw milk (pasteurization destroys the agent). It has been suggested that the chief mode of spread is by inhalation of dust contaminated with dried tick feces or other infectious material. This hypothesis best explains the pathogenesis of several epidemics in recent years.

Q fever has been seen repeatedly in Australia, where most of the patients have been individuals whose occupations exposed them to cattle. Prior to 1946 it was recognized but rarely in the United States. A few sporadic cases were seen in Montana, and complement-fixing antibodies have been found in occasional specimens of serums collected from inhabitants of a number of northwestern states. In 1946 Q fever swept through a stockyard and abattoir in Amarillo, Texas, infecting 40 per cent of the workers exposed to one lot of cattle. More recently the disease appeared among packing house workers in Chicago, and among dairymen in Los Angeles County. A number of accidental outbreaks have involved personnel at the National Institutes of

Health and at other laboratories where *C. burnetii* was being cultivated. The infection exists in other parts of the world. It is apparently endemic in Italy, Corsica, and Greece, where major epidemics occurred among American and British units during World War II. Cases have also originated in Panama and in Switzerland.

Manifestations. The incubation period varies from 12 to 26 days. There may be mild prodromal symptoms lasting a day or two. The onset of illness is usually abrupt, with symptoms which are much like those seen in other rickettsial diseases. Severe headache, retro-orbital pain, generalized muscular aching, and malaise are especially prominent. Though chilly sensations are common, shaking chills are unusual. Mild upper respiratory symptoms such as stuffiness of the nose, slight discharge, or sore throat are infrequent. There may be conjunctival injection, lacrimation, and photophobia. Most patients are anorexic, some experience nausea and vomiting, and a few have either constipation or diarrhea.

Two striking features differentiate Q fever from other rickettsioses: the absence of a characteristic rash, and the presence of pneumonia. However, pulmonary symptoms are notably mild or absent. Half of the patients experience indefinite aching discomfort in the chest, and a few have a pleuritic type of pain. Cough commonly develops after five or six days of illness, but typically it is mild and nonproductive. Occasionally there is mucoid or even blood-streaked sputum. Transitory fine rales, slight dullness to percussion, and sometimes a pleural friction rub are the only physical signs usually elicited. Nevertheless, x-ray of the chest discloses pulmonary lesions in as many as 90 per cent of cases. Typically there is an irregular, patchy infiltration in the lower or middle lung field, which may be similar in appearance to the consolidation seen in cases of primary atypical pneumonia.

Other aspects of the physical examination are often unrevealing. There may be no abnormalities other than fever and moderate prostration. Enlargement of the spleen, generalized lymphadenopathy, and cyanosis are unusual occurrences. The majority of patients are mildly or moderately ill, though Q fever may vary from a completely asymptomatic illness to one of marked severity with fatal termination. The temperature

can rise as high as 105° F.; the fever may last for 1 to 25 days (averaging one week); it drops to normal over a period of 24 to 48 hours. Pleurisy with effusion, orchitis, epididymitis, arthritis, and esophagitis have been observed as unusual complications. Convalescence proceeds rapidly except in severe cases, where there may be residual asthenia for several weeks.

Laboratory Findings. Specific diagnosis is established by demonstrating the development of complement-fixing or agglutinating antibodies during the second or third week after onset. *C. burnetii* can be recovered from the blood, and at times from sputum, pleural fluid, or urine, by guinea pig inoculation during the acute phase of illness. The leukocyte count is usually normal, but may be slightly elevated or depressed. Mild lymphocytosis has been observed during recovery. There is moderate elevation of the blood sedimentation rate. The Weil-Felix reaction is negative and cold agglutinins do not appear.

Differential Diagnosis. Q fever with pneumonitis may be confused with primary atypical pneumonia, tuberculosis, tularemic pneumonia, and psittacosis. Other diseases which must be differentiated include influenza, sinusitis, rheumatic fever, brucellosis, dengue, and other rickettsial infections.

Treatment. Aureomycin recently has been shown to be of use in treatment. It should be administered as outlined in Chapter 156.

Prognosis. Relapses are rare, but have been observed as late as two months after the initial illness. In most instances illness is followed by brief convalescence, complete recovery, and prolonged immunity. Only eight deaths have occurred among the six hundred cases reported in the literature.

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Bullis Fever

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Definition. Bullis fever is a mild, tick-borne, rickettsial disease accompanied by lymphadenopathy, leukopenia, and sometimes by a rash.

History. Bullis fever was first recognized as a clinical entity in 1942. In the spring of that year a large number of soldiers on maneuvers at Camp Bullis near San Antonio, Texas, became ill with an acute febrile disease. Clinical and laboratory studies were conducted at Brooke General Hospital, where approximately 1000 cases were seen in 1942 and 1943. They indicated that the disease is a new one, not previously described. It has not been reported from any other part of the country, nor is information available regarding its occurrence among civilian inhabitants of the area.

Etiology. Bullis fever is an infection due to a rickettsia-like agent. The organism is apparently a new species, although no name has yet been assigned to it. It produces a mild febrile illness in guinea pigs and an inapparent infection in white mice. The infecting organism differs serologically and immunologically from the agents which cause murine typhus, Rocky Mountain spotted fever, and Q fever.

Epidemiology and Pathogenesis. The agent which causes Bullis fever is a parasite of the Lone Star tick (*Amblyomma americanum*), an arthropod which infests the Camp Bullis area. The bite of an infected tick is believed to transmit the illness to man. Outbreaks of human disease begin each year in the early spring and last until fall, a periodicity which coincides precisely with the months when the Lone Star tick is active. No animal reservoir has yet been identified, though serums from a few jackrabbits and deer cap-

tured in the camp area proved to contain complement-fixing antibodies.

Manifestations. The period of incubation lasts 7 to 10 days. In a minority of patients this is followed by mild *prodromal symptoms* for one or two days. More usually the illness develops rapidly, with chills, fever, severe headache in the occipital and postorbital regions, and marked lassitude. The most striking finding on physical examination is the *lymphadenopathy*, which may involve one set of glands or may be generalized. The nodes are often tender. A rash is seen in 10 per cent of the patients, particularly in those who are severely ill. It is distributed over the trunk in the form of discrete erythematous macules and papules, and fades after a day or two. The eruption resembles that seen in murine typhus.

The acute phase of illness is characterized by fever of 102° to 105° F., and lasts for 4 to 14 days. As the temperature drops by lysis, the symptoms and signs recede and convalescence proceeds uneventfully.

Laboratory Findings. A complement-fixation test has been developed, and appears to offer the most satisfactory means of diagnosis. Serums from convalescent patients do not show a positive Weil-Felix reaction and do not react with typhus, Rocky Mountain spotted fever, or Q fever antigens.

All patients show leukopenia and neutropenia during the first few days of illness. The white blood cell count may fall as low as 2000, with 25 per cent polymorphonuclear cells. The total count then rises slowly to normal, while a relative lymphocytosis persists into convalescence. Enlarged lymph nodes have been biopsied in a few cases, and have revealed the presence of rickettsia-like bodies in the cytoplasm of mononuclear cells.

Differential Diagnosis. Bullis fever may be confused with dengue, Colorado tick fever, infectious mononucleosis, malaria, and influenza, as well as with other rickettsioses. Dengue occurs only in areas where mosquitoes are active, and

typically is characterized by a saddle-back type of fever. Colorado tick fever and Bullis fever are clinically similar, but can be differentiated by the complement-fixation test. Infectious mononucleosis may be distinguished by the presence of abnormal leukocytes and a positive Paul-Bunnell test. Parasites are found in the blood in malaria. Influenza is associated with respiratory symptoms, while lymphadenopathy and rash are absent. Other rickettsial diseases differ in their clinical manifestations and in serologic reactions.

Treatment. Aureomycin or "Chloromycetin" should be given, as described in Chapter 156.

Prognosis. There are no complications or after-effects, and the mortality rate is practically nil. The duration of active immunity is unknown.

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Treatment of Rickettsial Infections

Edward S. Miller

The course and prognosis in human rickettsioses have been altered radically by the introduction of chemical and antibiotic agents useful in treatment. *Para-aminobenzoic acid* was the first such drug shown to be effective. The results of clinical trials had hardly been published before two potent antirickettsial antibiotics were developed, namely *aureomycin* and "Chloromycetin."

Para-aminobenzoic acid is useful in the treatment of classic typhus, murine typhus, Rocky Mountain spotted fever, and probably other rickettsial infections. It is administered orally, an average initial dose for an adult being 6 to 8 Gm. The drug is excreted rapidly in the urine; therefore additional doses of 1 to 3 Gm. must be given every two hours until the temperature returns to normal. Optimum blood levels in murine and classic typhus are 10 to 20 mg. per 100 ml. of blood; levels of 40 mg. are preferable in spotted fever. Sodium bicarbonate is administered simultaneously in quantities of 2 to 4 Gm. every two hours, or enough to render the urine alkaline. The toxic effects of *para-aminobenzoic acid* include gastric irritation, delirium, and leukopenia. Positive cephalin flocculation tests and diminution in prothrombin levels have been reported.

Aureomycin is a yellow, crystalline substance derived from cultures of *Streptomyces aureofaciens*. It has proved to be highly effective in the treatment of human cases of Rocky Mountain spotted fever, murine typhus, and Q fever. The results of animal experiments indicate that the drug possesses marked therapeutic activity over the entire spectrum of rickettsioses. *Aureomycin* is given orally in doses of 1.5 to 6.0 Gm. per day, in divided doses every six hours. Administration is continued until the temperature returns to normal. The only untoward effects so far reported from oral administration in this dosage range have been occasional benign symptoms of nausea, vomiting, and looseness of the bowels.

"*Chloromycetin*" was derived originally from cultures of *Streptomyces venezuelae*, but can be produced synthetically. It has shown striking efficacy in the treatment of Rocky Mountain spotted fever, scrub typhus, murine typhus, and classic typhus. There is every reason to believe that it will also prove beneficial in the treatment of other rickettsial diseases. "*Chloromycetin*" is given orally, the daily dose ranging from 1.5 to 4.0 Gm. per day in divided doses every six hours until the patient becomes afebrile. No clinical evidences of toxicity have been observed.

The therapeutic results with both aureomycin and "Chloromycetin" have been so spectacular that they will probably render the use of paraaminobenzoic acid obsolete.

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Diagnostic Procedures in Viral and Rickettsial Infections

Glen R. Leymaster

Cold Hemagglutination
Hemagglutination and Hemagglutination Inhibition
Rickettsial Agglutination
Complement Fixation
Neutralization Tests
Isolation of Virus

Because of the similarity of the clinical manifestations of many infections to those of viral and rickettsial agents, laboratory methods are especially necessary aids for arriving at exact etiologic diagnoses. However, although an ever increasing array of diagnostic tests are available, in general they often are not suitable for performance in routine hospital and clinical laboratories because of the expense in time and money, the multiplicity of tests necessary, and the high degree of technical skill required. In addition, extensive laboratory facilities often are required because of the necessity of producing the requisite antigens and control serums, since these are not generally available commercially.

Most of the tests described below can be performed satisfactorily only in specialized laboratories. Satisfactory information will be obtained from laboratory studies only if the laboratory

specialist receives, in satisfactory condition, specimens which have been collected in the proper manner at the right time in regard to the stage of the infection. The specimens, unless the diagnostic possibilities are very limited, should be accompanied by detailed clinical, laboratory, and epidemiologic data. Under these conditions, the actual tests to be performed often may be chosen by the laboratory specialist rather than the clinician.

Blood for serologic studies should be collected aseptically from the fasting patient. If the material is to be en route to the laboratory more than 24 hours, the serum should be removed aseptically, placed in a container which will not leak (rubber-stoppered test tube or sealed glass ampule), and dispatched to the laboratory by the fastest route.

Almost without exception, at least two serums are required. One must be taken during the acute stage of the disease, the second during convalescence. Table 89 indicates the earliest date after the onset of symptoms that antibodies may be expected to appear. Since these dates are based

Table 89

Agent	Virus Isolation (Source of Specimen)	Serologic Types (Time of Earliest Appearance of Antibodies)		Other Types
		Complement Fixation	Neutralization	
VIRUS ENCEPHALITIS				
St. Louis.....	Brain and cord	4th day	7th day	..
Japanese B.....	Brain and cord	3rd-14th day	3rd-14th day	..
East. equine.....	Brain and cord	7th day	1st-7th day	..
West. equine.....	Brain and cord	7th day	1st-7th day	..
Lymphocytic choriomeningitis	Spinal fluid, blood, brain	7th-21st day	6th-10th week	..
Rabies.....	Brain, saliva	Demonstration of Negri bodies (brain) ..
Psittacosis.....	Blood, sputum, throat washings, lungs, spleen	4th to 8th day	..	
Lymphogranuloma venereum	Biopsy tissue or bubo pus	30th day	..	Frei test 7th to 40th day; elementary bodies in tissue or pus
Influenza.....	Nasopharyngeal washings	7th-10th day	7th-10th day	Agglutination inhibition 7th-10th day
Primary atypical pneumonia	Cold hemagglutination 10th-25th day; Strep. M.G. agglutination 10th-25th day
Mumps.....	Saliva, blood, spinal fluid	7th-21st day	..	Agglutination inhibition 10th-31st day
Yellow fever.....	Blood	2nd week	2nd week	Microscopic examination of liver "viscerotome"
Colorado tick fever...	..	9th-14th day
RICKETTSIAL				
Typhus, epidemic	Blood	5th-7th day	WEIL-FELIX	AGGLUTINATION
Typhus, inurine....	Blood	4th-7th day	5th-8th day OX19	5th-7th day
Typhus, scrub.....	Blood	..	5th-8th day OX19	5th-7th day
Rocky Mountain spotted fever	Blood	2nd week	2nd week OXK	..
Q fever.....	Sputum, spinal fluid, urine	7th-13th day	2nd week OX19, OX2	2nd week
			..	9th-28th day

on variable and often incomplete data, they should be used only as a guide. Ordinarily, the acute serums should be obtained on the earliest possible date and convalescent serum *later* than the latest day shown, since maximum antibody titers may be reached days or weeks after antibodies first appear in the circulating blood. In many instances, a third serum, obtained one to two months after the second, may be essential for diagnosis. This is especially true in the infections with neurotropic viruses.

It is the purpose of this chapter to describe basic principles underlying certain of the viral and rickettsial serologic tests important in the diagnosis of human disease, and to describe in

more detail certain of the most useful specific tests. This will include a discussion of (1) cold hemagglutination, (2) virus hemagglutination and hemagglutination inhibition, (3) rickettsial agglutination, (4) complement fixation, (5) virus neutralization, and (6) isolation of virus.

Cold Hemagglutination. Of interest in several fields of medicine are substances found in the blood in a variety of diseases, but especially during the later weeks in primary atypical (viral) pneumonia, which cause agglutination of erythrocytes at low temperature (0° to 4° C.) but not at 37° C. These agglutinins have no relationship to the isoagglutinins which are important in determining blood types, although they may make

blood typing and cross matching difficult or impossible unless the material is warmed. It can be demonstrated that these agglutinins are adsorbed onto the erythrocyte at low temperature and eluted into the suspending fluid at higher temperatures.

The serums of many normal persons have titers of cold hemagglutinins at levels of 1:10 or less. In primary atypical pneumonia, titers usually rise to significant levels during the second week after onset of illness, increasing to a maximum from the tenth to the twenty-fifth day, and declining rapidly thereafter. The height of the maximum titer seems to be unrelated to the time at which it is attained, but does seem to be related to the severity of the disease. While variations in the methods of performing the test influence the level of titer that can be considered significant, titers of 1:40 are usually considered suggestive, and 1:80 or higher uncommon in health, or in disease other than primary atypical pneumonia. A fourfold or greater increase in titer, even though maximum levels are not exceptionally high, may be of considerably more diagnostic aid than a single positive test.

The test requires only materials and equipment which are readily available—namely, human type O erythrocytes, fresh or preserved in Alsever's solution; normal saline; and the serum to be tested.

Certain precautions are important in order to obtain valid results. Blood on which the test is to be performed should not be refrigerated before removing serum, since this results in a loss of the hemagglutinins adsorbed onto the cold erythrocytes. Ideally, it should be kept at 37° C. until the serum is removed, although room temperature is usually considered satisfactory. The hemagglutinins gradually disappear from serum in the liquid state, rapidly at room temperatures, much more slowly at refrigerator temperatures. Since it is often desirable to repeat titrations, in order to obtain comparable readings on serums at different stages of the disease, it is essential that the serums be stored at low temperatures, and preferable that they be frozen.

Hemagglutination and Hemagglutination Inhibition. It has been demonstrated repeatedly that suspensions of certain viruses and rickettsiae (human and swine influenza, vaccinia, variola, mumps, Newcastle disease of fowls, pneumonia virus of mice, ectromelia of mice, and scrub

typhus) cause agglutination of erythrocytes. The different agents vary in their ability to agglutinate erythrocytes from different hosts, and in some, cells from individuals within the species differ in their reactivity.

It has been demonstrated that, in the case of influenza virus, the infectivity and hemagglutination activity of fresh virus preparations are closely related, although destructive agents, such as heat, can produce loss of infectivity without loss of hemagglutination titer. Also, the hemagglutination activity has been shown to be associated with the virus particle itself, unlike that of vaccinia and ectromelia, in which the hemagglutinin is apparently associated with the soluble antigens rather than with the infectious particle.

With the viruses of mumps and influenza it has been demonstrated that when the virus comes into contact with susceptible erythrocytes, adsorption takes place followed by elution of the virus into the suspending fluid. The elution is retarded or prevented by low temperatures (0° to 4° C.) and enhanced by higher temperatures (37° C.). This information has provided a simple method of producing a concentrated, relatively pure suspension of influenza virus for vaccine production and for serologic procedures.

Useful from the practical point of diagnosis of clinical disease is the fact that the hemagglutination produced by the virus is specifically inhibited by immune serum in a quantitative manner. This phenomenon provides an *in vitro* method of measuring antibodies that is accurate, inexpensive, and comparatively simple to perform.

Although many modifications of the agglutination-inhibition test have been used in the diagnosis of influenza, they are apparently equally satisfactory. One type of test utilizes a constant amount of virus (four times that concentration required to produce a standard degree of hemagglutination), serial twofold dilutions of heat-inactivated serum, and 1.5 per cent washed, pooled chicken erythrocytes. The test is read at 75 minutes, and the end point selected as the highest dilution of serum in which the concentration of cells remaining in suspension matches in density a standard tube containing one-half the concentration of cells (0.375 per cent) contained in the test proper. This method has the advantage that it can be adapted readily for reading with an electric densitometer or spectrophotometer, thus minimizing the errors due to bias and

lack of skill in reading the end point. It is preferred by some workers because it seems to give more definite end points and is less subject to minor differences in reagents and glassware.

A second type of test utilizes the same basic principles. A constant amount of virus is used with serial twofold dilutions of inactivated serum to which washed, human type O cells are added. After shaking, the cells are allowed to settle until all are deposited on the bottom of the tube, usually about 60 to 90 minutes. The agglutinated cells, on settling to the bottom, stick at the point of impact and form a thin film of cells over the rounded bottom of the test tube. The unagglutinated cells—i.e., those whose agglutination has been inhibited—instead of adhering to the glass at the point of impact, roll to the lowest part of the tube, forming there a discrete, dense “button” of cells. The end point is considered to be the highest dilution of serum which inhibits agglutination.

This procedure requires much smaller amounts of antigen, serum, and erythrocytes. Furthermore, the use of human type O cells, especially those preserved in Alsever's solution, is often a distinct advantage over the use of chicken cells. A major disadvantage is that end points are apt to be indefinite, thus introducing considerable subjective error into the determination.

In the laboratory diagnosis of influenza, two serums are always tested. One is taken early in the disease, the other 10 to 20 days later. Both serums must be tested at the same time, with the same antigens and erythrocytes. The numerical values obtained may vary considerably if the serums are retested on different days, but the relationship of the acute and convalescent values will remain fairly constant. Under usual circumstances, each serum is tested against two or three antigens, a standard influenza type A (PR-8), type B (Lee), and since 1947 a strain of influenza type A isolated in that epidemic year often is included, since there is considerable antigenic difference between that strain and the PR-8 strain. A fourfold or greater rise in the inhibition titer to any of the three strains is considered diagnostic of infection with that strain. In expert technical hands, a twofold rise may be significant, if repeatable.

The agglutination-inhibition test has had widespread application in the diagnosis of influenza. It has been used to a lesser degree, and is

apparently equally satisfactory, in the diagnosis of mumps infections. The technics applicable in mumps are essentially the same as are used in influenzal infections, and are described in detail in original sources. Similar tests, although perhaps applicable to the laboratory diagnosis of other diseases, are not at present of importance in clinical medicine.

Rickettsial Agglutination. Reactions involving agglutination of infectious particles by immune serums, similar to such tests commonly used in the study of bacterial diseases, have not been useful in viral and rickettsial study except for a few of the rickettsial agents—i.e., *epidemic and murine typhus, Q fever, and Rocky Mountain spotted fever*. While the actual test is less difficult than, and as reliable and accurate as, the complement-fixation tests, it is considerably more costly in materials, since about 10 times as much of the rather expensive antigen is required.

The test is dependent upon the availability of a concentrated, purified suspension of rickettsiae, usually prepared from the yolk sac of infected, embryonated hen's eggs. Serums from convalescent patients, under controlled conditions, cause agglutination in titers from 1:10 to over 1:200, while serums taken in the acute phase of the disease seldom yield titers over 1:10. The technics are fully described in original sources. The same principles regarding the desirability of testing at least two serums from the same patient apply as in the other tests described in this section.

Complement Fixation. Although the complement-fixation reaction has been extremely useful in the diagnosis of clinical viral and rickettsial diseases and in the laboratory study of these agents, its practical application to the routine diagnosis of disease has been severely limited by a number of factors.

The basic principles of this serologic test are the same, whether employed in the study of virus and rickettsial diseases or in the study of bacterial infections. The preparation of satisfactory antigens, however, has been accompanied by considerable difficulty because (1) the preparation of relatively concentrated suspensions of organisms involves procedures which are time consuming, expensive, and sometimes dangerous; (2) as a result of the necessary inclusion of relatively large amounts of nonviral tissues, non-specific reactions are apt to occur with normal serums, and especially serums from syphilitic

persons; (3) satisfactory antigens are often infectious and thus potentially dangerous; and (4) the antigens are often unstable and lose antigenicity or rapidly become anticomplementary. Even if available from commercial sources, satisfactory antigens are apt to be very expensive.

Thus, for the determinations of complement-fixation reactions, it is desirable to include controls not ordinarily necessary in bacterial tests. In addition to the usual complement, serum complement, antigen, antigen complement, and positive and negative serum controls, the test should include a titration identical to the test titration of the serum, using as antigen normal tissue prepared exactly as the antigen is prepared. This is necessary, since the serums may fix complement as a result of reaction with the nonviral components of the antigen.

The technic of the test varies with individual investigators. The usual method is to use constant amounts of antigen and complement and serial twofold dilutions of serum, expressing the titer as the greatest dilution of serum giving partial fixation of complement, in accordance with a predetermined standard.

It is always desirable, although not always possible, to test simultaneously at least two serums from each patient, one taken as early as possible, the second during convalescence. A definite (four-fold or greater) rise in titer is of considerably greater diagnostic value than a single determination, especially in those diseases with low maximum titers, such as the neurotropic virus group.

The technical details of performing the test should be obtained from original sources or from texts dealing with viral and rickettsial technics.

Neutralization Tests. The neutralization test is based on the ability of serum from patients convalescent or recovered from virus diseases to protect susceptible animals from infection with the etiologic agent. This reaction can be applied to the quantitative estimation of antibodies, and, as such, has yielded much information of value to clinical medicine as well as to experimental biology.

Neutralizing antibodies appear to be distinctly different in most cases from complement-fixing antibodies, in that they tend to appear at the same time or occasionally slightly later, but persist for a longer time, often for many years or for life. As such, the neutralization test is probably

a better index of past infection or acquired immunity than the *in vitro* tests. The neutralization tests have not been especially useful in the diagnosis or study of most of the rickettsial diseases.

A useful neutralization test requires a satisfactory test animal in which evidence of infection can be recognized by the appearance of specific pathologic reactions or lesions, definite *in vitro* reactions (i.e., hemagglutination, the development of complement-fixing antigens, etc.), or death. For accurate determinations, a number of animals must be used, and so it is desirable that the experimental animals be available in adequate numbers and at relatively low cost. Mice and embryonated hen's eggs are most commonly used, although frequently other species must be employed.

The principles involved in the neutralization of virus by antibodies are incompletely understood. It is apparent that antiserum does not destroy the virus, since a mixture of virus and antiserum which is noninfectious for the animal often can be rendered infectious by such procedures as dilution or enzyme digestion. In several virus-antivirus systems a third component, presumably complement, has been shown to enhance markedly the neutralizing capacity of immune serum. This finding is of practical importance, since it is usually desirable to compare antibody titers of two serums, one taken early in the illness, the second during convalescence, days or weeks later. Since complement deteriorates on storage, unless frozen at low temperatures, it is essential that such serums, to be comparable, must *both* be inactivated by heat or *both* be protected by storage at low temperatures. The first condition has the disadvantage of causing lower neutralizing titers, and thus smaller differences in the values obtained for the serums compared. The latter method requires refrigeration facilities not always available and scrupulous care in handling the serums.

In addition, in some of the neurotropic viruses at least, serum lipids have been shown to have a definite nonspecific inactivating effect on the virus. Collection of serums in the fasting state, always a desirable procedure for any serologic test, would appear to minimize this source of error.

Isolation of Virus. Isolation of virus, while one of the most useful and definitive tests for the establishment of the etiologic agent involved in

a clinical infection, should not be attempted except by persons skilled in the technics involved and acquainted with the pitfalls which await the inexperienced. These include (1) the necessity of choosing a suitable animal species for the suspected virus; (2) the difficulty of recognizing virus infection of the experimental animal; (3) the frequent isolation of latent viruses of the experimental animal; (4) the difficulty of identification of a virus, once isolated; and (5) the very real danger of infection, not only to the investigator, but also to other personnel not directly involved in the work.

The clinician should, in most cases, be content to collect the necessary material and supervise its delivery *in good condition* to the specialized laboratory. Any material that is to be utilized for virus isolation should be collected under

aseptic conditions, chilled, and, if possible, frozen and transported in dry (CO_2) ice, unless it can be delivered *immediately* to the laboratory.

Table 89 indicates the tissues or specimens which may be collected for attempted virus isolation with best possibilities of success.

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Common Respiratory Disease

A. E. Feller

Introduction
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Occurrence
Epidemiology
Classification
Clinical Manifestations
Common Cold Group
Acute Undifferentiated Respiratory Disease Group
Nonstreptococcal Exudative Tonsillitis or Pharyngitis Group
Primary Atypical Pneumonia Group
Complications of Common Respiratory Disease
Pathology
Pathogenesis
Immunity
Prevention
Prognosis
Treatment

INTRODUCTION

The acute respiratory infections, for purposes of discussion, may be considered as a spectrum of clinical conditions with gradations in severity and extent from mild or minimal involvements of the respiratory passages to prostrating illnesses with or without pulmonary infiltration. This broad spectrum encompasses certain well-known specific infections—i.e., influenza A, influenza B, beta-hemolytic streptococcal infections, and the bacterial pneumonias, which are considered in other sections of this book. But the greater part of the spectrum in terms of frequency of occurrence of cases is the large group of illnesses which are variously called the common cold, coryza, head cold, nasopharyngitis, laryngitis, catarrhal fever, flu, grippe, tracheitis, bronchitis, primary atypical pneumonia, virus pneumonia, etc. The term "common respiratory disease" is employed in this section to refer collectively to this large and heterogeneous part of the spectrum of the acute respiratory infections.

The common respiratory diseases have not been satisfactorily classified. A great deal of time and effort has been devoted to investigations of these infections, but relatively little is yet known about their interrelationships and causation. Clinical classification presents a difficult prob-

lem, both with respect to distinguishing illnesses of this group from those due to known specific viruses or bacteria, and in regard to separating, one from another, the possible entities within the group. Progress in studying the problem of the etiology of the common respiratory diseases is hampered by the lack of a susceptible laboratory animal.

The concept presented here is that the common respiratory diseases comprise a large and diverse group of infections. Chief emphasis is placed upon the general aspects of the problem, but those illnesses, or groups of illnesses, which now appear to represent definite segments of the spectrum are described. It should be emphasized, however, that such segregation is mainly for convenience in presenting the disease picture, that the segments overlap one another, and that many patients with common respiratory disease present a clinical picture which cannot be assigned clearly to any of the groups.

HISTORY

Common respiratory disease has afflicted mankind for centuries. Hippocrates (about 450 B.C.), and Galen and Celsus in the early Christian era, described illnesses which almost certainly were respiratory infections, possibly the common cold. Since then many epidemics of respiratory disease have been described, including influenza and other less specific disease entities. But then, as now, difficulty of recognition of the various entities precludes reliable disease specific interpretations in the history of common respiratory disease.

OCCURRENCE

The common respiratory diseases are worldwide in distribution, and no geographic area is known to be consistently free of them. Certain isolated communities have been without respira-

tory illness for variable lengths of time, but the resumption of intercourse with the outside world usually is followed by their reappearance. Racial immunity or predisposition has not been established. It is commonly believed that respiratory diseases are less prevalent in the warmer areas of the earth, but there are insufficient data to determine whether the presumed difference is due to an actual decrease in attack rate, to the occurrence of less severe degrees of illness, to less crowding in the tropics, or to incomplete observation.

The respiratory diseases are highly prevalent in this country and are the most common cause of acute illness. Data from industry show that they are among the leading causes of absenteeism from work. Most persons have at least two or three acute respiratory infections each year.

EPIDEMIOLOGY

The common respiratory diseases are distinctly seasonal in their occurrence and are confined largely to the cold months of the year in the temperate zones. Waves of increased prevalence occur in the fall, winter, and spring. There is, however, a residue of these infections throughout the year in any large population. The thesis has been advanced that the minor illnesses tend to occur most commonly in the fall or early winter, whereas the most severe illnesses tend to be concentrated in the late winter and spring.

Since recognition of the common respiratory diseases is dependent mainly upon clinical features, epidemiologic concepts are applicable only to the problem as a whole. Detailed epidemiologic data and the investigation of "carriers" or inapparent cases must await the acquisition of more definite information concerning the causation and interrelationships of the various illnesses in the spectrum. Nevertheless, certain epidemiologic concepts have become established and may be summarized as follows:

1. The airborne route of transmission appears to be the most important, but not necessarily the only mode of transfer.
2. Certain studies, particularly those of isolated communities, suggest that "carriers" or very mild cases are capable of transmitting the infections.
3. Highest attack rates occur in children under the age of five years. Infants under the age of one year have relatively low rates. The lowest attack rates occur in the second decade of life. The

curve rises slowly to a small peak in the ages from 25 to 35 years and then gradually declines in the older age groups.

4. Studies of segregated populations, such as military recruits or boarding school children, show that a wave of respiratory infections may sweep through the population shortly after the individuals are brought together. These outbreaks are followed by mass insusceptibility to subsequent large outbreaks which may last for several months, or possibly much longer. In the military services this phenomenon is considered part of the "seasoning" process. The explanation for "seasoning" is unknown. It is not certain that a similar process occurs in small groups, such as the family unit, or in individuals, although the observation that school children appear to have fewer respiratory infections after they have been in attendance for extended periods suggests that it does.

5. Certain studies indicate that a rigorous life or exposure to inclement weather per se are not important factors in provoking the occurrence of the common respiratory diseases in the military services.

6. An increased prevalence of the common respiratory diseases contributes in some obscure manner to the increased occurrence of the bacterial pneumonias.

CLASSIFICATION

Clinical classification of the common respiratory diseases, the only method of classification at present available, presents a difficult problem because (1) the clinical picture in individual cases often does not differ from that of several specific diseases such as influenza A, influenza B, and beta-hemolytic streptococcal infections, and (2) the illnesses within the spectrum, when studied in the mass, present smooth gradations in severity rather than sharp differences, and there is a vast array of combinations of symptoms and physical signs which so far has not been reduced to relative simplicity. One important reason for this difficulty of clinical classification is that the respiratory tract is rather limited in the manner in which it can respond to the presence of infection. Influenza A is a good example because the diagnosis can be confirmed by laboratory methods. When a population is studied during an epidemic it is found (1) that cases of influenza vary in severity from very minor to rather severe ill-

nesses and (2) that many of the cases of influenza do not differ clinically to a recognizable degree from other respiratory infections occurring during the epidemic and demonstrated by laboratory methods not to be influenza.

The most useful clinical classification employs a combination of the criteria of the site of localization of the prominent symptoms or physical signs, severity of illness, the presence of exudate in the throat, and the presence or absence of pneumonia. These criteria result in a classification which is highly artificial if they are used to "pigeonhole" all of the illnesses which are included in the common respiratory diseases. In spite of this difficulty, however, the scheme of classification has resulted in the recognition of certain groups of illnesses which have been very useful bases for studies of the epidemiology and etiology of the common respiratory diseases. These groups are the common cold, acute undifferentiated respiratory disease, exudative tonsillitis or pharyngitis, and primary atypical pneumonia.

Table 90

TRANSMISSION OF COMMON RESPIRATORY DISEASE TO HUMAN VOLUNTEERS WITH BACTERIA-FREE FILTRATES OF RESPIRATORY TRACT SECRETIONS

Donor of Respiratory Tract Secretions, Clinical Diagnosis	Results of Inoculation in Human Volunteers	
	Incubation Period	Character of Illness Produced in Volunteers
Common cold.....	18-48 hr.	Symptoms predominantly coryzal, constitutional symptoms minor
Acute undifferentiated respiratory disease	4-7 days	Prominent symptoms pharyngeal, constitutional symptoms present, illnesses mild
Primary atypical pneumonia	12-14 days	Respiratory and constitutional symptoms, pulmonary infiltration

Limited support to the division of the spectrum into these clinical groups is given by etiologic studies carried out in human volunteers. Transmission experiments, employing bacteria-free filtrates of respiratory tract secretions, show that there are at least three agents, presumably

viruses, which are capable of causing respiratory illness (table 90).

Bacteriologic and immunologic studies demonstrate that many cases of exudative tonsillitis or pharyngitis are nonstreptococcal in origin. Clinically, some of these cases of nonstreptococcal exudative pharyngitis or tonsillitis are difficult or impossible to distinguish from true beta-hemolytic streptococcal infections, but the great majority of them present a clinical picture which parallels more closely that of the common respiratory diseases. For this reason, nonstreptococcal exudative tonsillitis or pharyngitis is added to the groups of illnesses falling within the spectrum of the common respiratory diseases.

Until additional information is available, the following tentative classification will serve as the basis for presentation of the clinical manifestations.

CLASSIFICATION OF COMMON RESPIRATORY DISEASE

1. Common cold group.
2. Acute undifferentiated respiratory disease group.
3. Nonstreptococcal exudative tonsillitis or pharyngitis group.
4. Primary atypical pneumonia group.

CLINICAL MANIFESTATIONS

COMMON COLD GROUP

Definition. The common cold is an acute infection of the upper respiratory tract in which coryza is the prominent feature. Constitutional symptoms are characteristically mild and there is little or no fever. The acute symptoms usually last for only a few days. The clinical picture is quite variable.

Etiology. Transmission of the common cold to human volunteers and to chimpanzees using bacteria-free filtrates of respiratory tract secretions indicates that the disease is caused by a virus. There is no evidence that bacteria are capable of initiating the disease.

Manifestations. The onset is gradual with a sensation variously described as irritation, dryness, rawness, or tickling in the nasopharynx or the nose. Frequently, chilliness or malaise accompanies the local symptoms. During the next 24 to 48 hours the symptoms progress to the clinical picture of a "full-blown" cold (fig. 157). There is

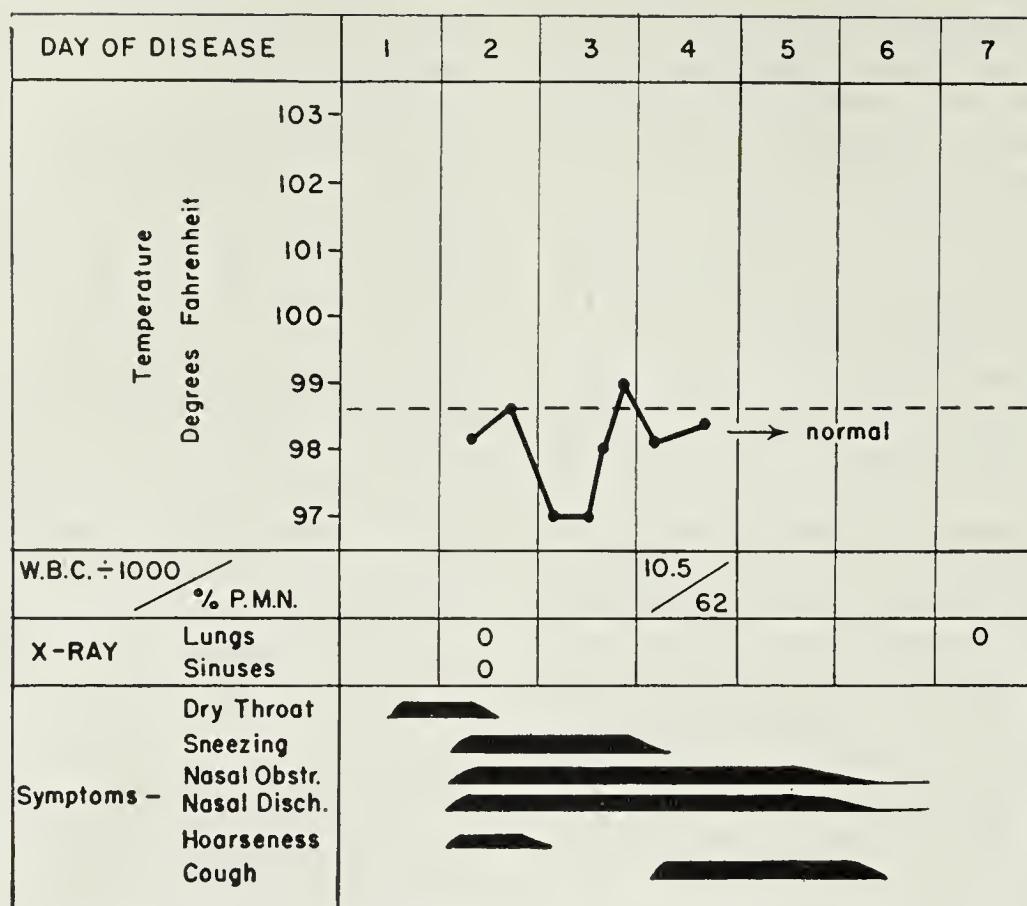


FIG. 157. Clinical chart of a patient with a common cold. (Courtesy, Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *J. Clin. Investigation*, 26:959, 1947.)

coryza, sneezing, nasal obstruction, thin nasal discharge which may be profuse, a feeling of tightness in the nose and over the paranasal sinuses, mouth breathing, and watery eyes. Malaise, lassitude, chilliness, headache, or the subjective feeling of feverishness with little or no fever add to the general discomfort and irritability of the individual, who may be described as not feeling well enough to work efficiently but not sufficiently ill to submit to bed rest. During the next two or three days these symptoms gradually subside, the nasal discharge becomes mucoid or purulent, the coryza and nasal irritation become less troublesome, nasal obstruction lessens, and the general symptoms gradually disappear. The nasal obstruction and thick discharge may persist for many days, or even for several weeks, in some individuals; the frequency with which paranasal sinusitis contributes to the prolonged nasal obstruction and discharge is not certain.

Physical signs are often quite definite. The nasal mucosa is reddened and edematous, nasal obstruction is readily demonstrable, and the nasal discharge is usually obvious. The nares may be reddened or even excoriated. There may be

slight tenderness over the maxillary and frontal sinuses. The lymph nodes of the anterior cervical triangle may be slightly tender, but enlargement and marked tenderness are unusual.

The clinical picture just noted is subject to great variation, and no two individuals will describe their "colds" in the same manner. The symptoms may progress no further than to the stage of definite nasal irritation, and then subside completely. The order in which the symptoms appear is variable. The symptoms may be quite severe, the pharynx may be involved, and the patient may develop a troublesome tracheitis or bronchitis with an early irritative cough and finally a cough productive of mucoid or purulent sputum.

Laboratory Findings. The leukocyte count, differential leukocyte count, and erythrocyte sedimentation rate are normal. Leukocytosis, if present, suggests a bacterial complication (see general section on complications). Cultures of the nasal secretion, nasopharynx, or oropharynx usually reveal only the bacteria which are common inhabitants of these areas. The urine is normal.

Differential Diagnosis. During the first 24 or 48 hours of illness one of the important differen-

tial diagnostic problems is to distinguish the common cold from the similar symptoms which precede the rash in the acute exanthemas, notably measles and chickenpox. Measles which has been attenuated or modified by the administration of immune serum may be very difficult to recognize if there is no rash, or only an evanescent rash. Coryzal symptoms or signs in a young person should suggest the possibility of the acute exanthemas, and a history of exposure should be sought.

The recognition of meningococcus infection in the early stages when there may be only symptoms of coryza is important because early institution of therapy is a paramount consideration. The presence of purpuric lesions indicative of meningococcemia, or the early signs of meningeal involvement such as stiff neck, should be investigated in all patients with coryza, particularly in young individuals.

The most frequent differential diagnostic problem is to separate the common cold from the other common respiratory diseases, especially the milder forms of acute undifferentiated respiratory disease. Since the clinical pictures of these two groups have much in common, it is often difficult or impossible to distinguish one from the other. The choice between them is often a matter of opinion and cannot be confirmed by clinical, epidemiologic, or laboratory methods.

Exudative lesions in the throat or the presence of pneumonia indicate either that the primary diagnosis is not the common cold or that a complication is occurring.

ACUTE UNDIFFERENTIATED RESPIRATORY DISEASE GROUP

Definition. Acute undifferentiated respiratory disease is an acute infection of the respiratory tract in which constitutional symptoms and fever are more prominent than respiratory symptoms. The latter are especially likely to be localized to the throat, trachea, or bronchi, and tend to be of mild or moderate severity. The respiratory illnesses in this group differ from those in the common cold group in that they are more severe, and constitutional symptoms predominate over the local or respiratory symptoms. As employed here, the term "acute undifferentiated respiratory disease" includes the illnesses commonly called "grippe" or "flu" but does not include influenza A or influenza B.

Etiology. Bacteria-free filtrates of respiratory tract secretions from a single donor selected as representative of the acute undifferentiated respiratory disease group induced similar but milder illnesses in human volunteers. The filter-passing agent is presumed to be a virus. Bacteriologic studies of the respiratory tract have indicated that bacteria are not involved in the causation of the disease.

Manifestations. The onset is gradual and the acute febrile episode is confined to a period of approximately three days, but certain of the symptoms, notably the respiratory symptoms, may persist for an additional several days. The prominent constitutional symptoms are feverishness, chilliness, and headache; in addition, malaise and anorexia are present in approximately 50 per cent of the patients. The amount of fever varies widely but averages 101° F. Sore throat, consisting of discomfort rather than actual pain on swallowing, is the earliest and most salient respiratory symptom. Hoarseness and cough often are prominent complaints and there may be discomfort in the chest which is described as substernal discomfort, soreness, or tightness. Symptoms of nasal obstruction, nasal discharge, and sneezing may occur but are usually a minor part of the clinical picture. The fever and constitutional symptoms generally subside by about the third day of illness, but the sore throat, hoarseness, and cough often persist for a few additional days and it is not uncommon for the cough, which may be productive of mucoid or purulent sputum, to persist for one or more weeks.

Physical signs are not characteristic. The pharynx and fauces may be slightly or moderately reddened and the lymphoid follicles may be conspicuous. There is no exudate in the throat. The cervical lymph nodes often are palpable and "sore" to palpation but are not acutely tender nor grossly enlarged. Physical signs in the chest are unusual but there may be tenderness or soreness to pressure over the sternum, and a few scattered coarse rales may be heard. Rales suggest the presence of pneumonia but they may occur in the absence of other physical or roentgenographic signs of pulmonary consolidation. Nasal discharge and obstruction may be present but are not as marked as in the common cold.

Acute undifferentiated respiratory disease is a more severe illness than the "typical" common

cold (fig. 158) and many patients with the disease will seek, or be willing to accept, bed rest for a few days during the acute episode. These patients are usually only mildly or moderately ill, but occasionally may be severely ill and prostrated. Complete recovery of strength and a feeling of well-being may require several days following the acute episode.

Laboratory Findings. The total leukocyte count and the differential formula are within normal limits, although occasionally a total count of 10,000 to 12,000 per cu. mm., or even higher, may be found. The erythrocyte sedimentation rate is normal or only moderately increased. Bacteriologic studies of the throat or sputums usually reveal only the organisms which are common residents of the respiratory tract.

Differential Diagnosis. The differential diagnosis includes the common cold, influenza, infectious mononucleosis, primary atypical pneumonia, bacterial pneumonia, and the acute exanthemas; in certain instances, the diagnosis may be so difficult as to present the problem of the "fevers of unknown origin."

The differential diagnosis between the acute undifferentiated respiratory disease group and the common cold group has been discussed above (see section on the Common Cold Group).

Influenza A and influenza B are difficult or impossible to differentiate from acute undifferentiated respiratory disease on clinical grounds, although the constitutional symptoms in influenza tend to be more severe, the onset may be more sudden, and the conjunctivas may be injected. During widespread influenza epidemics the diagnosis of influenza is not difficult, but in the individual case the diagnosis can be made with certainty only on the basis of laboratory studies. Sporadic cases of influenza usually cannot be recognized except by laboratory studies.

Infectious mononucleosis should be suspected when there is enlargement of the lymph nodes in the posterior cervical triangles, or elsewhere, in addition to those in the anterior cervical triangles.

The recognition of primary atypical pneumonia is dependent upon the demonstration of pulmonary infiltration (see p. 1030). The clinical

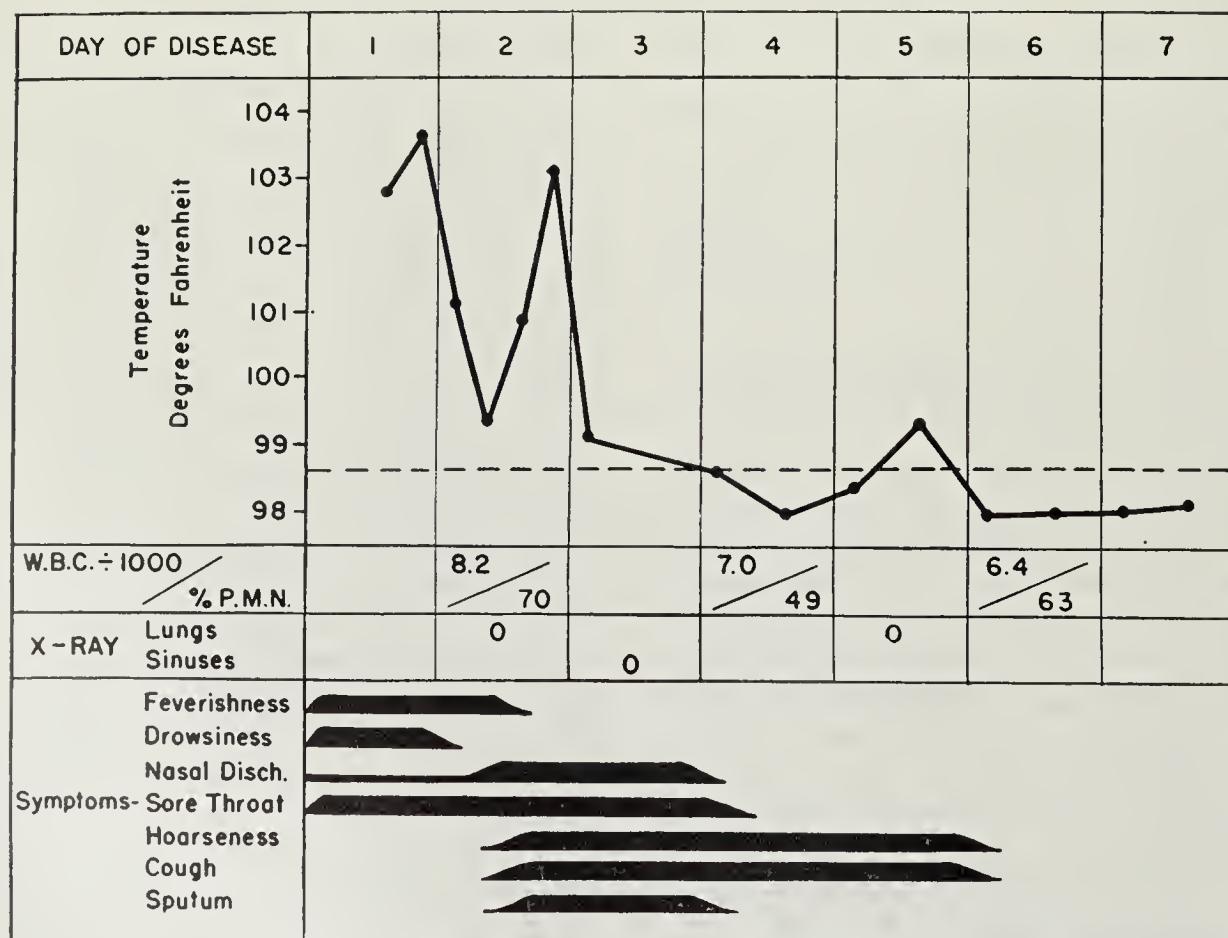


FIG. 158. Clinical chart of a patient with acute undifferentiated respiratory disease. (Courtesy, Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *J. Clin. Investigation*, 26:959, 1947.)

picture in acute undifferentiated respiratory disease may be so similar to that of primary atypical pneumonia that only a pulmonary lesion demonstrable on roentgenograms will distinguish between them.

The bacterial pneumonias occasionally may be confused with acute undifferentiated respiratory disease during the first 12 or 24 hours of illness, but the appearance of a pulmonary lesion, the more severe nature of the illness, leukocytosis, and identification of the causative agent point to the correct diagnosis.

The disease may mimic the early symptoms and signs of the acute exanthemas, and continued observations and alertness for the characteristic signs of the latter diseases are required.

Occasionally, acute undifferentiated respiratory disease may present only insignificant respiratory symptoms with a brisk fever, malaise, anorexia, and headache. In such instances, it may present the diagnostic problem of a fever of unknown origin. The appearance or intensification of respiratory symptoms may decide the issue, but not infrequently the diagnosis may be possible only in retrospect after many other conditions have been ruled out by continued observations and laboratory studies. Diagnosis by a process of exclusion is admittedly an undesirable method, but occasionally is the only method possible.

NONSTREPTOCOCCAL EXUDATIVE TONSILLITIS OR PHARYNGITIS GROUP

Definition. Nonstreptococcal exudative tonsillitis or pharyngitis is an acute respiratory disease of unknown etiology in which exudate on the tonsils or pharynx is the distinctive feature. The condition in other respects resembles acute undifferentiated respiratory disease rather closely but, in certain instances, presents symptoms and signs suggestive of beta-hemolytic streptococcal tonsillitis or pharyngitis. The "entity," in actuality, is the remainder of the common respiratory diseases presenting exudate on the tonsils or pharynx after the cases of known etiology, chiefly beta-hemolytic streptococcal infections, have been excluded.

Etiology. The etiology is unknown. The beta-hemolytic streptococcus is excluded by definition. Bacteriologic and limited serologic studies have indicated that other bacteria are not causative.

It may be a virus disease but there are no experimental data to support this view.

Manifestations. Nonstreptococcal exudative tonsillitis or pharyngitis is a mild disease of short duration (fig. 159, left). The onset is gradual as a rule. The early symptoms in most cases are referable to the throat, but constitutional symptoms may be the presenting complaint. The great majority of patients have the constitutional symptoms of feverishness and, in most cases, malaise, headache and anorexia. During the acute illness the average maximum temperature is 101° to 102° F., but the variations from patient to patient may be great. The acute febrile period usually is two or three days, but may be longer.

Sore throat is the most prominent respiratory symptom and is described as discomfort, rawness, or soreness rather than actual pain or difficulty in swallowing. The majority will complain of hoarseness, cough, discomfort in the chest, and sputum. There is a tendency for the sore throat, hoarseness, and especially the cough to persist beyond the acute febrile period. Sputum is scanty and usually mucoid, but may be purulent. Nasal symptoms are not prominent.

The chief physical signs are in the throat, where, by definition, exudate is always present. The exudate is white, yellow, or pearly gray in color and is present on the tonsils, in the tonsillar fossae, in the oropharynx, or in all of these areas. The exudate is usually small in amount and patchy in distribution. The individual areas may be only pinhead in size but are frequently larger. Confluent and extensive exudate is quite uncommon but does occur. The mucous membranes of the pharynx, tonsils, and palate are injected in the great majority of cases, but this injection is usually "streaky" and only rarely is diffuse and intense. The lymphoid follicles of the pharyngeal wall are enlarged and are usually reddened. Frequently, these swollen and reddened follicles are surmounted by small patches of exudate. Edema of the soft palate or fauces may be present but is usually only moderate in amount. The lymph nodes in the anterior triangles of the neck may be palpable and, occasionally, are definitely enlarged and tender. Scattered coarse rales in the chest may be heard in about 15 per cent of cases. Nasal obstruction, nasal discharge, and redness of the nasal mucosa may be present.

Laboratory Findings. The total leukocyte count is either normal or at the upper limits of

normal in most patients, but may be above 10,000 per cu. mm. in approximately one third. The differential count is normal. Erythrocyte sedimentation rates have not been adequately studied. Throat cultures reveal a flora which does not differ from that of the normal throat. By definition, the illness is nonstreptococcal in origin, and the presence of beta-hemolytic streptococci in the throat culture precludes the clinical diagnosis of nonstreptococcal exudative tonsillitis or pharyngitis.

Differential Diagnosis. Differential diagnosis includes acute undifferentiated respiratory disease, beta-hemolytic streptococcal tonsillitis or pharyngitis, infectious mononucleosis, Vincent's infection, and diphtheria.

By definition, the presence of exudate in the throat eliminates acute undifferentiated respiratory disease, although the two groups of illnesses often are otherwise quite similar. The occasional

presence of whitish "cheesy" material on the tonsils or in the tonsillar crypts may be confused with the presence of exudate. This "cheesy" material, however, wipes away quite readily and the signs of inflammation are generally lacking, whereas true exudate does not come away easily and signs of inflammation are present in the area immediately surrounding the lesion.

Beta-hemolytic streptococcal tonsillitis or pharyngitis is typically a more severe illness; the onset is usually sudden, the throat is diffusely red and more edematous, the exudate is more extensive and may be confluent, there is pain on swallowing, anterior cervical lymph nodes are enlarged and tender, the fever is higher, and there is definite leukocytosis. Beta-hemolytic streptococci are readily demonstrable by throat culture in the majority of cases, are usually present in large numbers, and are of Lancefield group A as a rule (fig. 159, right). These features are not al-

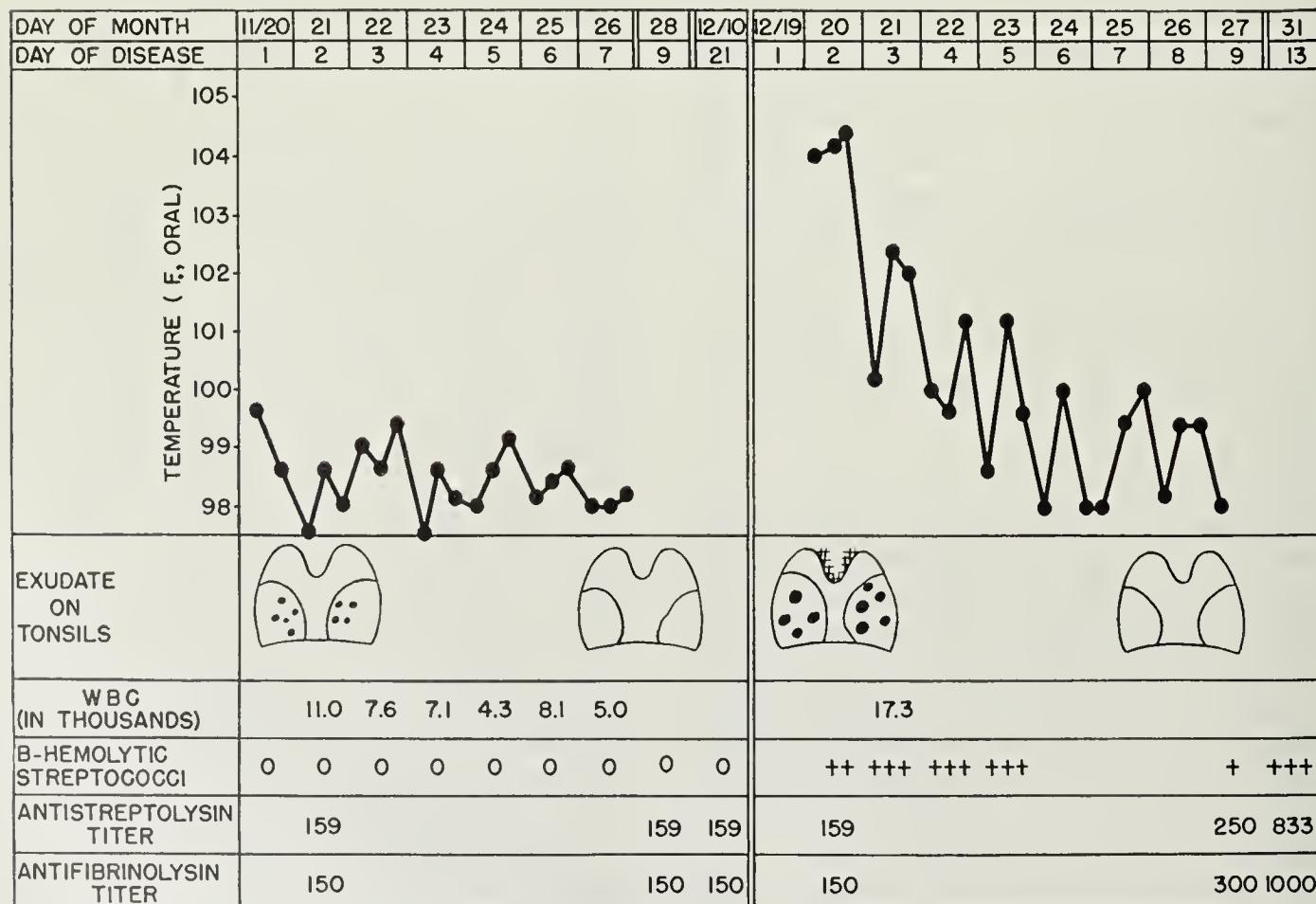


FIG. 159. Clinical and laboratory data from a patient with nonstreptococcal exudative pharyngitis and tonsillitis of average severity (*left*), and from a patient with beta-hemolytic streptococcal tonsillitis and pharyngitis (*right*). Note the absence of beta-hemolytic streptococci in repeated throat cultures in the former and their presence in large numbers in the latter; the rise in titer of antistreptolysin and antifibrinolysin (expressed in units) in convalescent phase serums in the latter; the definite leukocytosis in the latter; the differences in the amount of exudate on the tonsils; and the presence of edema of the uvula and soft palate in the latter. (Courtesy, Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *J.A.M.A.*, 133:588, 1947.)

ways present, however, and the differential diagnosis frequently cannot be made clinically; especially is this true when facilities for bacteriologic studies are not available.

On the one hand, nonstreptococcal exudative tonsillitis or pharyngitis may present many of the clinical features enumerated above except the presence of beta-hemolytic streptococci in the initial throat culture. Such cases are difficult to differentiate from streptococcal infections, but the absence of beta-hemolytic streptococci in repeated throat cultures is usually sufficient evidence to rule out streptococcal sore throat. On the other hand, beta-hemolytic streptococcal sore throat may present essentially all the clinical features regarded as typical of a nonstreptococcal infection, but the organisms are present in the throat culture, and subsequent serologic studies demonstrate that antibodies have developed.

Infectious mononucleosis with exudate in the throat may be differentiated when there are enlarged lymph nodes in the posterior cervical triangles, axillas, or inguinal areas. The exudate may be extensive or confluent. The spleen may be palpable or a skin rash may appear. In many instances the appearance of atypical lymphocytes or heterophil agglutinins in the blood will be the first indication of the correct diagnosis.

Vincent's infection, when it involves only the throat, characteristically attacks the tonsils and is unilateral or more marked on one side with regional enlargement of the cervical lymph nodes. The lesion is a necrotic ulcer which is covered with a yellowish, gray, or greenish membrane and surrounded by an edematous, dusky red area. Removal of the membrane leaves an ulcerated, bleeding surface. Constitutional symptoms and fever are usually mild but may be severe. The sore throat may be unilateral.

Diphtheria must be considered in the differential diagnosis and, occasionally, may be very difficult to exclude. The most important single factor is to think of the possibility of diphtheria and obtain smears and bacteriologic cultures. A history of recent immunization is helpful in reducing the likelihood of diphtheria. In diphtheria, the onset is insidious and the fever is not high. Sore throat is often mild. The membrane usually involves the tonsils but may spread over the palate or pharyngeal wall and is a dirty white, gray, or green color. The edges of the membrane may be curled. There may be bleeding. The sur-

rounding mucous membranes are dusky red rather than bright red as in tonsillitis, and less of the total area of the throat is involved. There may be nasal or laryngeal involvement. The appearance of paralysis, especially of the palate, or the presence of myocarditis is almost diagnostic, but either is a late manifestation of diphtheria. It is better to make the diagnosis or suspect diphtheria too often than to fail to consider it until the serious manifestations occur.

PRIMARY ATYPICAL PNEUMONIA GROUP

Definition. Primary atypical pneumonia is an acute respiratory infection characterized by pulmonary infiltration most readily demonstrated by roentgenologic examination, minimal physical findings in the chest, constitutional symptoms, cough, sputum, and prolonged convalescence.

Etiology. The disease has been transmitted to human volunteers employing bacteria-free filtrates of respiratory tract secretions. Presumably then, primary atypical pneumonia is caused by a virus. Transmission of a filtrable agent to cotton rats, hamsters, and chick embryos and the suggestion that a bacterium, streptococcus MG, may play a role as a synergist or secondary invader in the causation of the disease have been reported, but there are insufficient data to permit adequate evaluation of these possibilities. The aerobic bacterial flora of the respiratory tract in primary atypical pneumonia does not differ from that of the other common respiratory diseases or from that of well individuals. It has been suggested that primary atypical pneumonia is a severe form of a more prevalent minor respiratory disease.

Manifestations. The onset is gradual and insidious, and most patients have minor respiratory or constitutional symptoms for several days, or even a week, before they consult their physician. An acute, sudden onset is unusual but does occur.

During the early part of the acute febrile illness, constitutional symptoms are predominant. Feverishness, chilliness, headache, and malaise are the outstanding complaints. Anorexia is common. Shaking chills are very unusual. The headache is often frontal but may be occipital or generalized and may be very distressing, particularly while coughing. The most common re-

spiratory symptom is cough. It may be the presenting complaint but more often appears during the illness and then progresses in severity. The cough at first may be dry in character but later becomes productive. The cough is frequently paroxysmal and is often harassing and interferes with sleep. Sputum is mucoid or mucopurulent. Streaks of bright red blood may appear in the sputum, but grossly bloody, rusty, or "prune juice" sputum is rare. Substernal pain, soreness, or discomfort is common but pleural pain is very unusual. The throat may be slightly sore, dry, or "scratchy" but this symptom is generally minor. Coryza is unusual but moderate nasal obstruction is not uncommon.

Physical signs are not prominent, especially early in the illness. The patient appears only mildly or moderately ill and is not cyanotic nor in respiratory distress. There is fever, usually below 104° F. The pulse and respiratory rates are increased but are only moderately elevated. The throat is often slightly inflamed and, occasionally, slight coryza and nasal obstruction are demonstrable. Cervical adenopathy is slight, if present at all. Examination of the chest, especially early in the course of illness, may reveal few signs in spite of the pulmonary infiltration which is demonstrable radiographically. Rales, usually "sticky" in character, may be heard over the involved area and are the most characteristic physical signs in the chest. Often the rales may be heard only at the height of inspiration, which is typically punctuated by frequent coughing as the patient tries to coöperate by breathing deeply. Later the rales increase in quantity and are easily heard. Coarse rales or rhonchi, especially later in the illness, often appear and may be widespread. Dullness is unusual, but impairment of the percussion note may be elicited, especially with extensive pulmonary infiltration. Increased tactile fremitus, changes in the voice or breath sounds, or friction rubs are very unusual. Physical signs in the chest may be absent in 5 or 10 per cent of cases.

Roentgenographic examination of the chest is the most reliable method of detecting the pulmonary infiltration, especially early in the illness when physical signs are sparse or absent. The pulmonary shadows are not dense and typically are soft, diffuse, patchy, or nodular and poorly outlined. The earliest lesions often begin as a hilar enlargement which then "fans out" or is

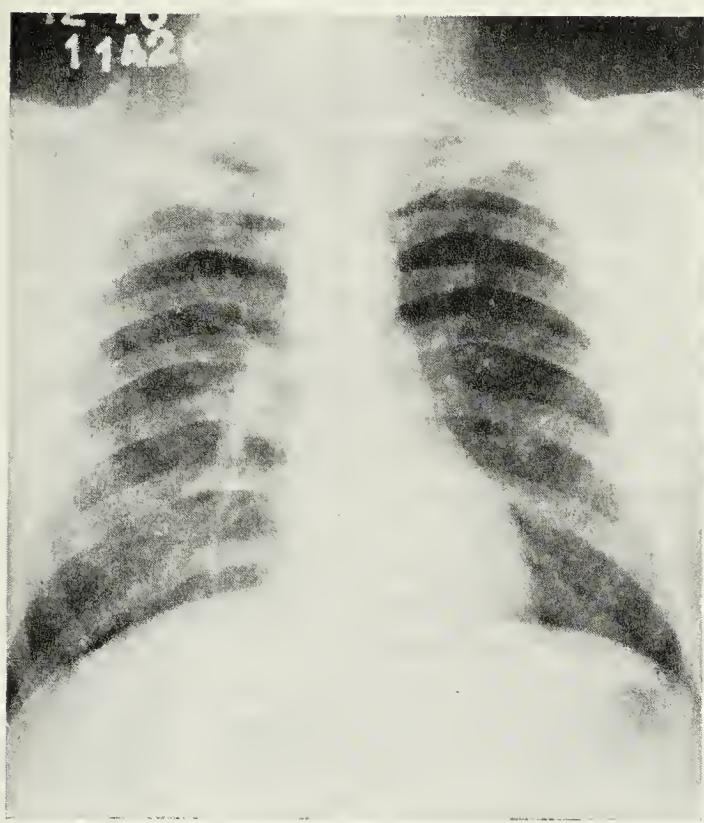
wedge-shaped. The lower lobes are involved most frequently, but any area or multiple lobes may be involved. The shadow is usually not so dense as that of pneumococcal pneumonia, tends to be less limited by anatomic structures, and is not usually lobar in extent. Variations are marked. Lesions varying from slight, stringy, peribronchial shadows to extensive infiltration may be seen. The latter may be indistinguishable from the shadow seen in pneumococcal pneumonia. Occasionally, the lesion may be demonstrable only in lateral or in oblique films. Only transient shadows may occur, but usually one to three weeks are required for resolution.

The course of illness is variable. In the average case (fig. 160) the fever and acute illness last for five to eight days. Very mild illnesses or asymptomatic infections recognized only by roentgenograms may occur. Very severe illnesses are also encountered, and such patients may be critically ill, cyanotic, and dyspneic.

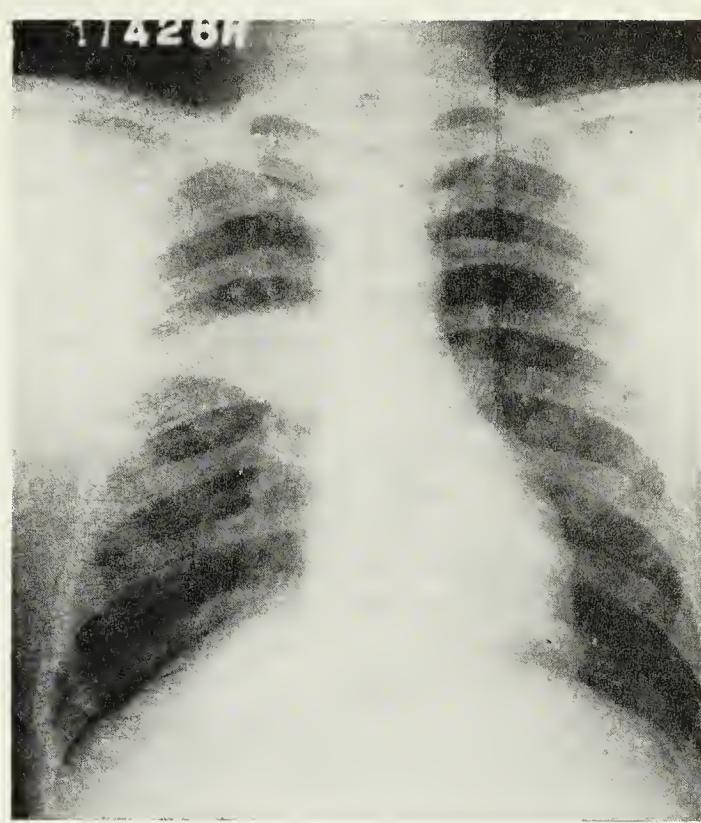
Typically, the convalescence is prolonged. There is continued cough and sputum and relatively slow return of strength and the feeling of well-being. Convalescence, particularly in robust and energetic individuals, may be rapid. Complete recovery without complications is to be expected.

Laboratory Findings. The routine laboratory findings in the average case of primary atypical pneumonia are usually within normal limits. The total leukocyte count, differential formula, and urine are normal. Leukocytosis, 10,000 to 20,000 per cu. mm., or even higher, may occur and tends to appear coincident with clinical improvement. Leukocytosis when seen early in illness suggests some other diagnosis. Slight proteinuria may be found, especially in severe cases. The erythrocyte sedimentation rate may be slightly or moderately increased, but this is not a consistent finding. The bacterial flora of the respiratory tract or sputum do not differ from that seen in other common respiratory diseases or in well persons. Plasma chloride and amino acid levels are not altered as in pneumococcal pneumonia.

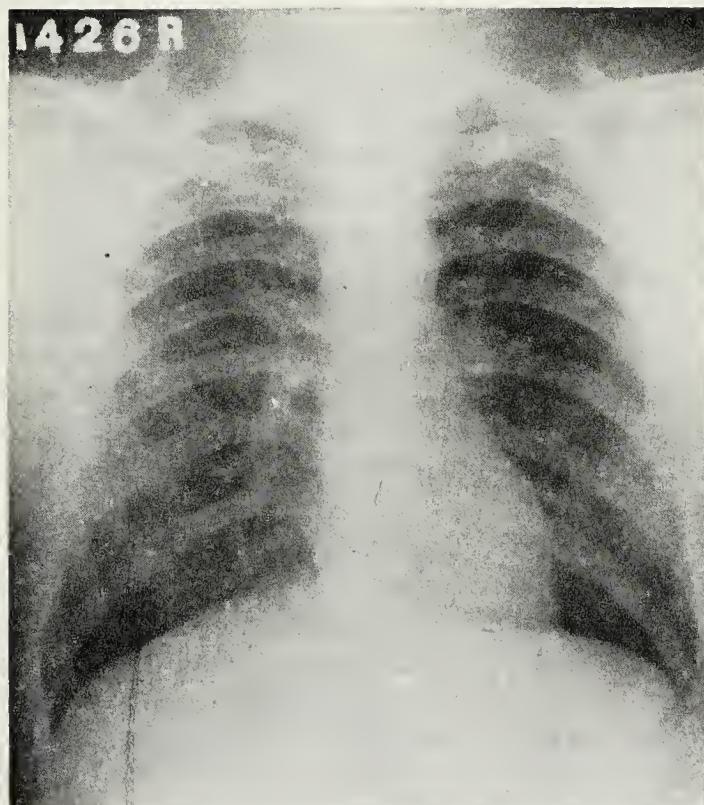
The occurrence either of cold hemagglutinins for human group O erythrocytes or of agglutinins for streptococcus MG in the blood are of value in the retrospective diagnosis of primary atypical pneumonia. These agglutinins either do not appear or, if initially present, do not increase in titer until the second or third week after onset



Day 2



Day 4



Day 9

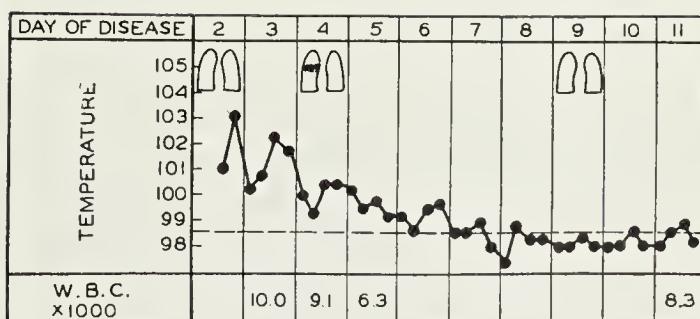


FIG. 160. X-rays and clinical chart of a patient with primary atypical pneumonia of moderate severity. (Courtesy, Dingle *et al.*: *War Medicine*, 3:223, 1943.)

and are, therefore, not useful at the time therapeutic considerations are paramount. Cold hemagglutinins are demonstrable in approximately 50 per cent of cases. The incidence of cold hemagglutinins is increased in the more severe illnesses as judged by the height and duration of fever and the number of lobes of the lung which are involved. Agglutinins for streptococcus MG are present in approximately 25 per cent of cases, but the incidence increases with the severity of illness. Cold hemagglutinins or agglutinins for streptococcus MG, when present in high titer or when they increase in titer during the course of illness, are helpful in confirming the diagnosis because these agglutinins are not often found in other conditions, especially in the United States. The two antibodies are immunologically distinct, so that one agglutinin may be present when the other is absent. It must be emphasized that the absence of either cold hemagglutinins or agglutinins for streptococcus MG, or of both agglutinins, does not exclude primary atypical pneumonia. Tests performed on acute and convalescent phase serums are much more likely to yield interpretable information than tests performed on convalescent phase serums alone.

False positive Wassermann reactions may occur in primary atypical pneumonia. The occurrence of several other serologic reactions in convalescent phase serums indicate that serologic tests in general should be interpreted with caution in this disease.

Differential Diagnosis. There are no diagnostic laboratory tests utilizing specific reactions with the causative agent. The differential diagnosis of primary atypical pneumonia is, therefore, essentially a process of excluding the known specific diseases which may present the same syndrome. As pointed out above, the detection either of cold hemagglutinins or of agglutinins for streptococcus MG is chiefly of value for retrospective diagnosis.

The diseases of known causation which must be considered include those caused by bacteria, fungi, *Rickettsia*, and viruses. Actually, however, these agents are responsible for a relatively small proportion, probably less than 5 per cent, of the patients presenting the signs, symptoms, and roentgenographic features of primary atypical pneumonia.

Primary atypical pneumonia can be differentiated from the bacterial pneumonias on clinical

grounds in most instances. However, it is not sound practice to make this differentiation in the absence of adequate bacteriologic studies of the sputum and blood. Sudden onset, a shaking chill, pleuritic pain, rusty sputum, definite signs of pulmonary consolidation, or leukocytosis suggest pneumococcal pneumonia. In approximately 10 per cent of cases seen in practice, the differentiation from pneumococcal or other bacterial pneumonias may be difficult or impossible. In certain hospitals, where severely ill patients and difficult diagnostic problems are preferentially admitted, the problem of differential diagnosis from the bacterial pneumonias may occur in 25 per cent, or even 50 per cent, of cases. This difficulty may arise even though proper bacteriologic studies have been made. Pulmonary tuberculosis, tularemia, brucellosis, beta-hemolytic streptococcal pneumonia, staphylococcal pneumonia, and pneumonia due to Friedländer's bacillus must be considered occasionally in the differential diagnosis, especially early in the illness, and observation plus laboratory studies may be required to exclude them.

Of the fungous infections, coccidioidomycosis most often simulates primary atypical pneumonia. This disease is endemic in the southwestern United States but has been seen elsewhere in servicemen who trained in the endemic area. Coccidioidomycosis can be suspected either from a history of possible exposure or from the presence of thin-walled pulmonary cavitation. Further confirmatory data may be obtained from a skin test with coccidioidin, tests for precipitins or complement-fixing antibodies in the serum, and a search for *Coccidioides immitis* in the sputum. Recent studies suggest that pulmonary histoplasmosis may be confused with primary atypical pneumonia.

Pulmonary infiltration is well known in several rickettsial infections but does not present a problem in those diseases with either a rash or a primary lesion—i.e., typhus, Rocky Mountain spotted fever, scrub typhus, or tsutsugamushi fever, and South African tick fever. Q fever, however, does not have a rash or primary lesion and may present pulmonary infiltration and certain clinical features which are indistinguishable from those of primary atypical pneumonia. Constitutional symptoms are usually more severe in Q fever, and respiratory symptoms are absent or minimal. A certain diagnosis of Q fever must be

based on isolation of *Coxiella burnetii* from the blood or the development of agglutinating or complement-fixing antibodies in serum. Q fever occurred in the Mediterranean theater in the recent war, and the significance of antibodies for Q fever in the blood of veterans from that area must be interpreted with the possibility in mind that the infection may have occurred during the war. The disease has been considered rare in the United States, but recently three outbreaks have been recognized (Texas, Illinois, California).

The most common virus diseases which require consideration are the psittacosis group and influenza A or B. Psittacosis or ornithosis may be indistinguishable from primary atypical pneumonia, and the only hint of the correct diagnosis may be a history of exposure to parrots, parakeets, other exotic birds, pigeons, or barnyard fowl. The virus may be isolated from sputum, or an increase in titer of complement-fixing antibodies may be detected when convalescent phase serum is compared with acute phase serum. Ordinarily the pneumonias associated with influenza A or B are caused by bacteria, but the virus is apparently capable of causing pulmonary infiltration. Pneumonia due to the virus alone has occurred almost exclusively during epidemics of influenza and appears not to be a diagnostic consideration of nonepidemic periods. The diagnosis depends on isolation of the virus or the demonstration of a definite rise in titer of neutralizing antibodies.

Rarely, pulmonary infarct, neoplasm, Loeffler's syndrome, bronchiectasis, or atelectasis may have to be differentiated from primary atypical pneumonia.

COMPLICATIONS OF COMMON RESPIRATORY DISEASE

Purulent paranasal sinusitis, otitis media or mastoiditis, and bacterial pneumonia are frequent and often serious complications, or sequelae, of the common respiratory diseases. Occasionally, bacterial endocarditis may follow a respiratory infection in individuals with rheumatic, congenital, or other forms of heart disease. These conditions appear to be true bacterial complications of the underlying illness. Pneumococci, staphylococci, streptococci, and occasionally other organisms, are the chief offenders. Detailed presentation of the signs and symptoms of the bacterial complications is not

within the scope of this discussion. A bacterial complication should be suspected, however, when the fever increases and leukocytosis occurs. Localized signs and symptoms of inflammation may indicate the involved area, but roentgenograms, otoscopic examination, and transillumination or aspiration of the paranasal sinuses are often required. Bacterial endocarditis is especially to be suspected when cardiac abnormalities, petechiae, hematuria, or signs of focal involvement of the central nervous system occur. Proper bacteriologic cultures should be obtained, and when bacterial endocarditis is suspected, repeated blood cultures are indicated.

Several other conditions are often considered complications of the common respiratory diseases. Several examples will be cited. Copious, thick nasal exudate, postnasal discharge, laryngitis with hoarseness or loss of voice, and tracheitis or bronchitis with chronic cough and mucoid or mucopurulent sputum are examples of conditions which occur so frequently either during the acute illness or as the acute process begins to subside that they might well be an integral part of the clinical picture. Painful involvement of the paranasal sinuses during the acute illness seems in many instances properly to be regarded as an extension of the inflammatory process. There is considerable uncertainty concerning the role of bacteria acting as "secondary invaders" in these conditions (see section on Pathogenesis).

Herpes of the lips or face is often seen in the common respiratory diseases and is particularly frequent in the common cold group. There is, however, one outstanding exception and that is in primary atypical pneumonia, where herpes is so unusual that its presence suggests the possibility of bacterial pneumonia.

Relatively little is known about the complications in nonstreptococcal exudative tonsillitis or pharyngitis. There is as yet no indication that they differ appreciably from the complications which occur in the common cold or acute undifferentiated respiratory disease groups. Rarely, the sore throat may be severe and interfere with the intake of foods or fluids. Peritonsillar abscess may occur but the etiology of this complication is not established.

Complications of primary atypical pneumonia are unusual. Pleural effusion is almost invariably small in amount, bacteriologically sterile, and

readily absorbed. Bacterial complications are rare. Bronchiectasis has been described as a common sequel. Insufficient time has elapsed since the recognition of the syndrome to determine the incidence of bronchiectasis following primary atypical pneumonia. Superimposed bacterial pneumonia is rare. Encephalitis, meningoencephalitis, or myocarditis occasionally occurs in severe cases and may lead to a fatal outcome. Hemolytic anemia may occur during the acute illness. Numerous other complications have been described but are exceedingly unusual.

PATHOLOGY

The primary site of involvement in the common cold is the upper respiratory passages, principally the nasal mucosa, and frequently the lining membranes of the paranasal sinuses. The mucous membrane is thickened and red. Histologically, there is edema, hyperemia, and moderate infiltration with mononuclear cells and granulocytes. Superficial necrosis and desquamation of epithelial cells ensues. The early nasal secretion is thin and watery, but in a few days becomes thick and mucoid or purulent. The thin secretion contains bacteria, epithelial cells, inflammatory cells which are mainly polymorphonuclear but may include a few mononuclear cells and, occasionally, moderate numbers of eosinophils. The thick secretions contain many bacteria and usually there are many inflammatory cells with an increasing proportion of mononuclear types. Red blood corpuscles may be seen.

The principal point of attack in acute undifferentiated respiratory disease appears to be the throat or the tracheobronchial tree rather than the nose. The nature and degree of morphologic change are not known. Progression from thin to mucoid or purulent secretion is not so obvious as in the common cold, but this sequence may be obscured because acute undifferentiated respiratory disease does not usually involve the nasal mucous membranes and thus permit frequent examination of the secretion. The mucoid or purulent sputum in the later stages of illness suggests that the character of the secretion may be the same as in the common cold.

The occurrence of laryngitis, tracheitis, bronchitis, or even rhinitis in nonstreptococcal exudative tonsillitis or pharyngitis indicates that the disease is more than a local one in the throat. The exudate does not wipe away easily, thus indicat-

ing that the inflammatory process is more than superficial.

The prominent morphologic changes in severe, fatal cases of primary atypical pneumonia are severe necrotizing bronchitis and bronchiolitis and interstitial pneumonia. Bronchoscopic examination during life in cases of average severity reveals diffuse inflammation of the larynx, trachea, and bronchi. The mucous membranes may be intensely reddened and edematous and there is mucoid or mucopurulent exudate. Multiple small ulcerations covered with a thin, grayish yellow membrane may be seen. The pathologic changes in primary atypical pneumonia are not distinctive and there are no features which distinguish them with certainty from the interstitial pneumonias due to other causes. Microscopic examination of the bronchi and bronchioles shows infiltration, necrosis, and ulceration of the walls. The bronchioles are often dilated, and pus, epithelial cells, cellular debris, and mucus are present in the lumens. Parenchymal involvement is most marked in the tissues surrounding the bronchi and bronchioles, where there is mononuclear infiltration and thickening of the alveolar septums. Alveolar exudate is predominantly mononuclear. Bacteria are not usually seen except in the larger bronchi. Changes other than in the respiratory system are not commonly seen. Acute myocarditis or hemorrhagic encephalitis have been described.

PATHOGENESIS

Discussion of the pathogenesis of common respiratory disease includes consideration of the causative agent (or agents), the role of bacteria, alterations in the normal physiologic processes, anatomic abnormalities, and the resistance of the host.

The causative agents, presumably viruses, have an affinity for the mucous membrane of the respiratory tract. Principal localization of the symptoms and signs to the nose in the common cold group, to the pharynx in the acute undifferentiated respiratory disease and nonstreptococcal exudative tonsillitis or pharyngitis groups, and to the lung in the primary atypical pneumonia group, suggests that the viruses of each group also possess an affinity for a particular area of the respiratory tract. Limited support to the latter concept is given by the results of transmission experiments in human volunteers wherein

the common cold agent induced illnesses with main localization of symptoms and signs to the nose; acute undifferentiated respiratory disease, to the pharynx; and primary atypical pneumonia, to the lung. The widespread involvement of the respiratory tract which occurs in each of the four groups of illnesses indicates, however, that the inflammatory process is more than a localized one.

There is a great deal of uncertainty concerning the role of bacteria in the pathogenesis of the common respiratory diseases. The weight of evidence indicates that bacteria are not primary incitants although the possibility must remain until more complete information is gained. A great deal of clinical, bacteriologic, serologic, and experimental study has been concerned with the thesis that bacteria, once the viruses have given the initial stimulus for the inflammatory process, act either alone or in concert with the viruses as "secondary invaders." The chief points in favor of the hypothesis that bacteria commonly act as "secondary invaders" are (1) reports that the total bacterial population increases as the inflammatory process proceeds, especially when the secretions become thick, and (2) that certain specific organisms are present in large numbers in the secretions. It is difficult to interpret these observations because of limitations in the accuracy of quantitative bacterial technics, and the finding that in many cases the bacteria detected in the secretions are the same that are found in the respiratory tract earlier in the illnesses, or in the normal respiratory tract; also, the presence of copious secretions or exudate might increase the likelihood of detecting the presence of bacteria both by increasing the total amount of bacteria-containing material picked up by the swab and by acting as a favorable culture medium for the bacteria normally resident in the area. The unconvincing nature of the evidence, however, does not justify the categorical statement that bacteria do not act as "secondary invaders" in the common respiratory diseases; one has only to recall the course of events which ensues when the leukocyte count is greatly reduced, for example, in agranulocytic angina. In this condition the respiratory passages, especially the pharynx, become the site of an intense and often extensive infection by the organisms that are normally present in the area and do no apparent harm. Nevertheless, the conclusion that bacteria com-

monly play an active role as "secondary invaders" is to be deprecated until evidence more substantial than the mere presence of the organisms in the respiratory tract secretions is available.

There can be little doubt that true bacterial infections by species or organisms normally resident in the respiratory tract do occur as complications of the common respiratory diseases—e.g., suppurative paranasal sinusitis, otitis media and mastoiditis, and bacterial pneumonia (see section on Complications). The infecting organisms can often be recovered in pure culture from the involved areas; leukocytosis, increased fever, and localized symptoms and signs of acute infection are usually present; and, frequently, there is prompt response to surgical drainage or therapy with the sulfonamides or antibiotics. When all of these features are present, no one would seriously question the bacterial nature of the infection. The pathogenesis of these true bacterial complications is not clear, but alterations in the normal physiologic processes and anatomic abnormalities must be considered. Interference with normal ciliary action and blocking of normal avenues of drainage by the swollen mucous membranes may be important factors in confining infected material in closed spaces. Likewise, deviations of the nasal septum, enlarged turbinates, or other anatomic alterations may contribute, in certain instances, to poor drainage from the respiratory appendages. If there be validity to the thesis that many bacterial pneumonias are initiated by the aspiration of respiratory secretions (or exudate) containing bacteria into the terminal bronchioles or alveoli, the pathogenesis of the bacterial pneumonias complicating the common respiratory diseases is not difficult to understand.

Host factors are undoubtedly important in the pathogenesis of common respiratory disease. The host is discussed in the section on Immunity.

IMMUNITY

It seems probable that both the causative agent and the host are important considerations in the determination of immunity or the lack of immunity to common respiratory disease. The agent will be considered first.

The isolation, identification, and characterization of the agents of common respiratory disease must be accomplished before we can attempt to

evaluate the role of the parasite in the immune mechanism. Repeated or successive respiratory infections in an individual do not necessarily imply lack of immunity unless it can be established that a single agent is responsible. Variations or mutations of a single agent also have to be considered as a possible explanation. Further consideration of the role of the parasite seems fruitless until the agents are identified.

Information concerning immunity in the host is more definite but still far from complete. The problem will be discussed separately for each of the four groups considered above in the section on Clinical Manifestations.

It is commonly believed that there is little or no immunity to the common cold. One's personal experience of having repeated attacks of the disease often serves to confirm this conviction. Furthermore, experiments with human volunteers show that challenge reinoculation with common cold filtrates in the early postconvalescent period may induce a second illness. It would be easy to conclude that these experimental data fit with the prevalent impression that the common cold does not lead to immunity. Attractive though it may be, such reasoning may not be valid because the doses of the agent used for challenge may be much larger than doses received in ordinary life. The observation that common respiratory disease eventually ceases to occur in isolated communities suggests the existence of host immunity and, by inference, includes the common cold. If there is lack of immunity to the common cold, one wonders how an individual succeeds in recovering from the illness. It seems reasonable to conclude, therefore, that immunity to the common cold may occur but is not a solid or lasting immunity.

Epidemiologic studies indicate that immunity to acute undifferentiated respiratory disease develops in army recruits following the wave of illness occurring shortly after they are brought together as a military organization. Second inoculation of acute undifferentiated respiratory disease filtrates in human volunteers three weeks after the first inoculation does not induce a second illness. Thus, the epidemiologic and experimental data indicate host immunity. How widely this principle may be applied to the acute undifferentiated respiratory disease group as a whole is an unsolved problem.

Host immunity in nonstreptococcal exudative

tonsillitis or pharyngitis is essentially an unexplored problem.

Numerous reports indicate that second attacks of primary atypical pneumonia occur even though only a few weeks or months have elapsed since the first attack. Evaluation of these data is not possible because information concerning the number of agents which may cause primary atypical pneumonia is lacking. Second inoculations in human volunteers with a single primary atypical pneumonia filtrate have not been made. Volunteers convalescent from the common cold or acute undifferentiated respiratory disease, or both, are not immune to primary atypical pneumonia filtrate.

Much has been said and written concerning the effects of chilling, wet feet, loss of sleep, over-work, improper diet, vitamins, etc., on man's ability to resist common respiratory disease and, specifically, the common cold. Certain epidemiologic data suggest that these factors do not lead to a respiratory illness if the infective agent is *not* present. The possibility that chilling, wet feet, etc., reduce resistance to respiratory infection when the agent *is* present has not been established, but there are data which give limited support to the concept.

The existence of local immunity in the respiratory tract has been suggested but not proved.

PREVENTION

There are no established methods, procedures, or immunizing agents which are effective for preventing common respiratory disease. Various "cold vaccines" or "cold shots" are widely employed but none has as yet been shown to be of prophylactic value when tested in controlled experiments. Since they contain various combinations and amounts of killed bacteria of the species commonly resident in the respiratory tract rather than the viral agents, one would anticipate their lack of prophylactic value. The use of such "cold vaccines" or "cold shots" is not rational. There is no sound evidence to warrant the use of vitamins, cold showers, or other forms of strenuous physical conditioning to increase resistance to respiratory infections. The sulfonamides and antibiotics are not of prophylactic value for the primary illness but are useful in treating bacterial complications (see below). In selected instances, these compounds are worth a trial for the prevention of bacterial complications—e.g., repeated

attacks of otitis media, pneumonia, etc. The use of aerosols, ultraviolet light, and the oiling of floors and clothing is being investigated and certain results are encouraging, but much more work to define their uses, dangers, and limitations is required before they can be recommended.

Adequate rest, a nutritious diet, sensible avoidance of undue exposure to cold or wet, and avoidance of exposure to those with respiratory infections seem reasonable and advisable but cannot be relied upon to prevent the common respiratory diseases.

PROGNOSIS

In the absence of complications, the prognosis for life is uniformly good with but few exceptions. Common respiratory disease, especially primary atypical pneumonia in the debilitated or in patients with chronic disease—e.g., cardiac disease, asthma, etc.—may be serious or fatal. Severe cases of primary atypical pneumonia with extensive pulmonary involvement, cyanosis, and dyspnea indicate a guarded prognosis, although it is often surprising how desperately ill some of these patients may be and still recover. Fatalities in young adults occur in approximately one in a thousand cases of primary atypical pneumonia; the fatality rate in the young and in the aged is not well established but is probably less favorable.

The occurrence of chronic paranasal sinusitis or chronic tracheitis or bronchitis is frequently responsible for prolongation of symptoms and lack of well-being. More important from the standpoint of prognosis for life is the appearance of the bacterial complications. Pneumonia, otitis media, mastoiditis, paranasal sinusitis, or endocarditis may alter an otherwise excellent prognosis if the complication is not promptly recognized and treated.

TREATMENT

There is no specific treatment for common respiratory disease; the sulfonamides and antibiotics at present available are not of value for the treatment of the primary illness and should not be used routinely for this purpose. These compounds are of value, however, in certain circumstances, as will be pointed out below.

General measures include bed rest when there is fever. Adequate fluid intake and a light diet should be promoted. Isolation is usually not practical. The avoidance of chilling is desirable.

Humidification of the air is comforting. Temporary discontinuation of smoking is advisable. Mild sedation to insure rest and sleep should be provided.

Symptomatic therapy is advisable but is often overdone. Aspirin is as good as any of the various compounds employed for the relief of feverishness, headache, and malaise. Codeine and papaverine and the currently popular "antihistamine" drugs offer no decided advantage over aspirin. The use of aspirin when the temperature is markedly elevated may result in a precipitous fall in temperature and undesirable drenching perspiration. Symptomatic therapy of cough may be difficult. Any of several cough syrups, particularly those containing codeine, or codeine alone, are useful for the control of cough. Codeine, however, may lead to loss of appetite, nausea, headache, or somnolence. The temporary use of morphine may be required in refractory cough. Cold compresses and throat irrigations with warm saline may be used for sore throat. Nasal obstruction must often be relieved to provide sleep, and the drainage which results is believed to be desirable for the prevention of paranasal sinusitis. A great variety of effective compounds is available for this purpose. The frequent and continued use of any of these agents is to be avoided since the nasal mucosa often becomes edematous, pale, and boggy, and the reverse of the desired effect is the result. The use of oily preparations should be avoided because of the danger of lipoid pneumonia; compounds containing sulfonamides serve no useful purpose and may lead to sensitization to the drug. The chief disadvantage of the volatile vasoconstrictors is their simplicity, hence they tend to be used too frequently and may produce nasal obstruction rather than relieve it.

Routine use of the sulfonamides or antibiotics for the prophylaxis of the bacterial "secondary invaders" is to be condemned. Use of these substances in therapeutic doses, however, is justified when the bacterial complications are present, particularly pneumonia, otitis media, or mastoiditis. "Immune serums," x-ray therapy, diathermy, etc., are not of value.

Several aspects of the therapy of primary atypical pneumonia require special comment. Early in the illness the differential diagnosis from bacterial pneumonia may be difficult or impossible and, under the circumstances, the trial of sul-

fonamides or antibiotics in therapeutic doses for 24 to 48 hours should be considered. Patients with severe primary atypical pneumonia may be dyspneic or cyanotic, and the use of oxygen is very helpful and, occasionally, appears to be life-saving. Convalescence in this disease is frequently slow and may be prolonged. In general, bed rest for five to seven days after the temperature is normal is advisable. Complete resolution of the pulmonary process does not appear to be necessary, however, before the patient is allowed out of bed. The temperature curve, the general appearance of the patient, and his tolerance to activity are better guides. The resumption of activity should be graded upward slowly.

Recent reports suggest that aureomycin is of value in the treatment of primary atypical pneumonia. Aureomycin appears to have been of striking benefit in many instances, but the course of illness in the disease is often unpredictable. In some instances the drug has not altered the clinical course of the disease, and it is possible that such failures may be of more importance in the final evaluation of aureomycin in primary atypical pneumonia than the apparent successes. Further data are required.

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Influenza

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Definition
 History
 Etiology
 Pathogenesis
 Epidemiology
 Manifestations
 Laboratory Findings
 Differential Diagnosis
 Treatment
 Prognosis

Definition. Influenza is an acute infectious disease of viral etiology, characterized by sudden onset, fever, headache, muscular aches, chilliness, cough, and periodic appearance in epidemics.

History. Influenza has been recognized as one of the great epidemic diseases since the earliest times. Although major outbreaks occurring at irregular intervals have been traced back as far as 1173, the disease appeared in its most disastrous form in the pandemic of 1918. It was not until 1933, however, that the etiology of influenza was established by the isolation of a virus from patients ill with influenza during a typical epidemic in England. This virus is now known as influenza A. In 1940 a second etiologic type of influenza virus, which is referred to as influenza B virus, was isolated. The discovery of the causative agents permitted a rapid development of laboratory methods for studying the disease, and in recent years an extensive and more accurate knowledge of influenza has been acquired. Epidemics have been identified in some part of the world each year, and the outbreaks since 1918 have been characterized by a relatively mild clinical disease with a low fatality rate.

Etiology. Two influenza viruses, known as type A and type B, have been identified as the causative agents of the epidemics studied since 1933. Although they are distinct antigenically and differ in some of their fundamental properties, the clinical diseases produced by them are indistinguishable. Numerous strains of virus differing in antigenic structure within each type have been demonstrated, a fact which has an important bearing on the preparation of vaccine for prophylaxis against influenza.

We can only speculate as to the cause of the

epidemics of influenza which occurred prior to the discovery of the viruses responsible for influenza in recent years. In spite of the large amount of experimental work done during the 1889 and 1918 pandemics, no etiologic agent was demonstrated conclusively. A number of bacteria, including *Hemophilus influenzae*, pneumococci, streptococci, and staphylococci, frequently were found in the lungs of fatal cases. It seems apparent now that the bacteria were secondary invaders and that the primary infection was due to an unidentified virus. The virus responsible for the 1918 epidemic was probably an unusual strain (or strains) of influenza virus which was highly pathogenic and invasive.

Pathogenesis. Little is known about the pathogenesis of influenza virus infection in man, since the uncomplicated disease is rarely fatal. Presumably the virus infects the epithelial cells of the pharynx and larynx. In more severe infection, the virus also invades the lung. The autopsy findings in a few cases uncomplicated by bacterial infection, from which influenza type A was demonstrated in the lungs, have been reported. The lungs in these cases showed edema, alveolar hemorrhages, fibrin, infiltration of the walls of the bronchioles with cells of various types, marked edema of the septums, and extensive formation of a hyaline membrane. There was no evidence of epithelial necrosis, as was so commonly seen in cases of the 1918 epidemic. It has been suggested that the epithelial necrosis is due to the secondary bacterial infection. Influenza virus infection in experimental animals has been extensively studied. In the ferret, necrosis of the epithelium of the nasopharynx, trachea, and bronchi is observed. After adaptation of the virus a fatal disease with pulmonary consolidation is produced in ferrets and mice. The pulmonary changes produced depend on the dose and virulence of the virus. They consist of edema, peribronchial round cell infiltration, and thickened alveolar walls with relatively little exudate in the alveolar spaces.

Epidemiology. The virus is transmitted from person to person by way of droplets of the secretion of the respiratory tract. It may be airborne over short distances. One of the striking characteristics of influenza is its explosive appearance in a population, usually in the winter or early spring. The epidemic usually reaches its peak in two to three weeks and gradually subsides within four to eight weeks. It should be emphasized that the epidemics vary considerably in extent and severity. Influenza A epidemics in this country have been shown to occur at intervals of two to three years, and influenza B epidemics at intervals of four to six years. It appears, therefore, that the immunity resulting from natural infection is of relatively short duration. The factors responsible for this periodicity of influenza epidemics are not fully understood at the present time. During an epidemic a large proportion of the susceptible population develops immunity as a result of either manifest illness or subclinical infection. The level of immunity reaches its maximum in about two to three weeks, after which it begins slowly to decline. In addition, sporadic cases of influenza have been shown to occur at all seasons of the year. Thus, it seems that influenza virus is constantly present in the human population, and that various factors, such as virus mutation and the general level of immunity in the population, play an important role in the complex mechanism which initiates an epidemic.

Manifestations. The onset of illness is usually quite sudden, following an incubation period varying from one to three days. Headache, drowsiness, fatigue, and chilliness, together with backache and muscular pains, are the usual initial complaints. There may be anorexia, nausea, and even vomiting, but diarrhea is uncommon. The clinical picture of gastroenteritis, commonly referred to as "intestinal flu," is not caused by the influenza virus. The patient is usually irritable and dislikes being disturbed. The temperature rises within 12 to 24 hours after onset, usually to 100° to 102° F., but may reach levels of 104° F. or higher. Symptoms referable to the respiratory tract are those of a mild tracheobronchitis, laryngitis, and pharyngitis, usually a cough which may become intense, and a feeling of dryness and irritation of the throat. Rhinitis is not uncommon, but is usually mild and is not a striking feature of the disease.

On physical examination the patient appears

flushed and acutely ill. There may be cyanosis. The nasopharynx is usually only slightly reddened or may appear entirely normal. The lungs are usually clear, but a few scattered rales may be heard. Other findings include muscular tenderness, pain on ocular pressure, and injection of the conjunctivas. There is no enlargement of lymph nodes or spleen.

The fever and symptoms usually subside within two to four days, although convalescence may be prolonged an additional week or two. The severity and course of the illness, however, vary considerably. Subclinical cases are observed in each outbreak, and occasionally a fulminating disease with pulmonary involvement terminating in death is observed. The pulmonary involvement may be due to the virus alone or may be complicated by secondary bacterial infection. It should be recognized that none of the signs or symptoms described above are pathognomonic of the disease, and laboratory aids are necessary to establish the diagnosis. Nevertheless, the clinical findings as a whole, particularly in an explosive outbreak involving the population in epidemic proportions, strongly point to the diagnosis of influenza.

Laboratory Findings. A number of laboratory methods are now available for establishing the diagnosis of influenza. In general, these include (1) the isolation and identification of the causative virus, and (2) the demonstration of a rise in titer of specific antibody in the circulating blood. Influenza virus may be recovered from throat washings of patients during the acute illness by inoculation of the washings into ferrets or into embryonated hen's eggs. After primary isolation, the virus can be adapted to mice by repeated passage, producing lung lesions and death. In addition, specific antibodies can be elicited in monkeys, hedgehogs, rats, guinea pigs, and hamsters following intranasal inoculation of influenza virus. Influenza virus has the curious property of agglutinating the red blood corpuscles of certain species, particularly human, chicken, and guinea pig red corpuscles, and this reaction is widely used in laboratory methods for diagnosis. A more practical method for the diagnosis of influenza, however, is the demonstration of a rise in antibody titer against influenza A or B virus in the serum of the patient. It is essential to obtain a blood sample during the acute phase of the disease (during first week of illness), because in-

fluenza virus antibodies occur in varying titer in normal subjects, presumably the result of previous infection with the virus. A second sample of serum is obtained after two weeks, and a rise in the antibody titer is diagnostic of influenza. The serum antibodies can be measured by the specific inhibition of the red corpuscle agglutination reaction, by the complement-fixation test, or by means of the neutralization test in mice or chick embryos.

The leukocyte count and differential is usually within normal limits. A leukopenia of moderate degree, however, may be found in some patients. The sedimentation rate is usually increased.

Differential Diagnosis. The variability in the clinical manifestations of influenza and the lack of pathognomonic features often make the diagnosis of influenza virus infection difficult without laboratory assistance. The large group of diseases of the respiratory tract which have not as yet been differentiated may present clinical findings indistinguishable from influenza. These diseases are referred to by a variety of terms, such as *grippe*, *febrile catarrh*, *bronchitis*, *laryngitis*, *nasopharyngitis*, etc. The *common cold* usually presents a more severe rhinitis with a profuse nasal discharge, little or no fever, and minimal systemic symptoms. *Acute pharyngitis* and *tonsillitis* can be differentiated from influenza by the local findings and throat cultures. Influenza virus infection of the lungs may produce the picture of atypical pneumonia, and usually can be differentiated only by laboratory studies. *Neurotropic virus infections*, particularly poliomyelitis and lymphocytic choriomeningitis, may resemble influenza during the initial stages.

Treatment. There is no specific treatment of influenza virus infection at the present time. Symptomatic treatment includes bed rest, adequate fluid intake, salicylates, codeine if the cough is intense, and occasionally barbiturates to ensure adequate rest. If secondary bacterial infection occurs, the specific chemotherapeutic and antibiotic agents should be used promptly. Isolation and quarantine measures are ineffective.

During the last few years, considerable attention has been devoted to the development of a vaccine for the prevention of influenza. The vaccine consists of a concentrated suspension of influenza A and influenza B viruses prepared from the allantoic fluid of developing chick embryos. A single injection of 1.0 ml. of the vaccine is given

subcutaneously. Approximately 5 to 10 per cent of individuals receiving the vaccine exhibit reactions not unlike those observed following typhoid vaccination, consisting of an inflammatory reaction at the site of injection, fever, and chilly sensations. Children under two years of age seem to be particularly susceptible to reactions, and it is advisable not to give the vaccine subcutaneously to this group. There is evidence that intradermal injection of 0.1 ml. of the vaccine elicits an antibody response comparable to that following subcutaneous inoculation. This may prove to be the method of choice. In addition, the usual precautions against allergic reactions must be taken, since the vaccine contains egg protein. Definite evidence of the effectiveness of the vaccine in reducing the incidence of influenza was obtained in this country in the influenza A epidemic of 1943 and the influenza B epidemic of 1945. However, the vaccine was not effective in reducing the incidence of influenza in the 1947 influenza A epidemic. The failure in the latter epidemic has been attributed to an unusual strain of virus causing the epidemic. In general, it appears that the strain or strains of virus used in the vaccine is an important factor, and that the immunity produced is not of long duration. The vaccine is, therefore, still in the experimental stage of development and further investigation is required.

Prognosis. Influenza as seen in recent years has a low fatality rate (less than 1 per cent), and recovery within three to five days without complications is usually observed. The prognosis is less favorable in the chronically ill and elderly patient. In the epidemic of 1918-19 the fatality rates were much higher, but, as previously stated, bacterial pneumonia undoubtedly contributed greatly to the seriousness of the disease. The chemotherapeutic and antibiotic agents which are now available should reduce markedly the fatalities from this complication.

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Psittacosis (Ornithosis)

William F. Friedewald

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Etiology
Pathogenesis
Manifestations
Laboratory Aids
Differential Diagnosis
Treatment
Prognosis

Definition. Psittacosis is a naturally occurring viral disease of birds. It is occasionally transmitted to man, producing an acute illness characterized by fever, chilly sensations, headache, anorexia, malaise, and a patchy pneumonia.

History. Psittacosis was recognized as a clinical entity during the latter part of the nineteenth century. Ritter (1880) and Wagner (1884) referred to it as "pseudotyphus." An outbreak of 51 cases with 16 deaths occurred in Paris in 1892. In 1929-30 the disease appeared in 12 different countries, involving approximately 750 to 800 persons. This episode stimulated investigation of the disease, and it was soon demonstrated that parrots, particularly those from South America, were the main source of the infection. As far back as 1930, however, it was apparent that a variety of other avian species were susceptible to the virus of psittacosis. The elementary bodies found within reticuloendothelial cells, and in body fluids of infected birds and human beings, were described independently by Leventhal, Cole, and Lillie in 1930, and have since been called "L. C. L. bodies."

Etiology. The elementary bodies, which undoubtedly represent the virus particles themselves, can be seen readily with the ordinary microscope when stained by either the Macchiavello or Castañeda methods for the demon-

stration of rickettsiae. The bodies appear as tiny spherical or ovoid cocci in the cytoplasm of mononuclear cells or free in the tissue spaces. The size of the elementary bodies as determined by ultrafiltration has been reported to be 200 to 300 millimicrons in diameter, but electron photomicrographs reveal the bodies to be spherical particles with a mean diameter of 455 millimicrons. Psittacosis virus can be stored at -76° C. but is apparently not stable in glycerin. It is rendered noninfectious when heated at 70° C. for 15 minutes. The virus is related in certain of its properties to the viruses of lymphogranuloma venereum, meningopneumonitis, mouse pneumonitis, feline pneumonitis, inclusion blenorhea, and trachoma. It has been suggested that these infective agents be grouped and differentiated from the true viruses and rickettsiae. They are the largest known viruses and approach the size of rickettsiae.

A wide variety of birds, including parrots, parakeets, canaries, rice birds, finches, sparrows, pigeons, doves, and ducks, are susceptible to infection with psittacosis virus. Infections of man and birds with viruses of nonpsittacine origin are often referred to as "ornithosis," reserving "psittacosis" to designate those infections definitely proved to be of parrot origin. The mouse and the chick embryo are highly susceptible to psittacosis virus infection and are usually used in diagnostic and experimental studies. Other animals, such as guinea pigs, rabbits, and rhesus monkeys, exhibit varying degrees of susceptibility.

Pathogenesis. The virus of psittacosis is present in the blood, tissues, and discharges of dis-

eased birds and mice. Of great importance is the fact that apparently healthy birds may also harbor and disseminate the virus. It is transmitted from birds to man by handling of sick or dead birds, rarely through bites, and most often by inhalation of virus from the air, which is readily contaminated with dried infectious particles stirred up by the beating of the birds' wings. There is considerable evidence to indicate that the virus also may be spread from a patient to other persons. The upper respiratory tract is the principal portal of entry. The virus is then disseminated to the lungs and other tissues. There is no evidence of any natural immunity to psittacosis. Individuals who have recovered from an attack are usually resistant to reinfection, but a few second attacks have been reported.

Manifestations. The incubation period varies from 7 to 14 days. The onset is usually sudden, with chilly sensations, fever, anorexia, malaise, severe headache, photophobia, sore throat, and nonproductive cough. In occasional instances the onset is gradual and insidious. The temperature rises to 103° to 105° F., remains high for 7 to 10 days, and then declines by lysis during the second or third week. At the height of infection there may be delirium, insomnia, extreme restlessness, abdominal distention, and epistaxis. The pulse tends to be slow in relation to the temperature. Involvement of the lungs occurs within a few days after onset. Although there may be extensive pneumonia, the cough is often insignificant or absent. If sputum is produced it is scanty and tenacious, but not blood-tinged. Physical examination of the chest usually fails to reveal the extent of pulmonary disease. X-ray examination shows patchy areas of consolidation in one or both lungs. The appearance is difficult to distinguish from that in primary atypical pneumonia. There is usually little or no pleural reaction. The spleen occasionally is palpable, and either constipation or diarrhea may occur. In fatal cases the pulse and respiration become rapid and cyanosis may be marked.

Relapses are seen occasionally. The symptoms are similar to those of the original onset, but are considerably milder, and the temperature returns to normal within a few days. *Thrombophlebitis* appears to be the most common complication and may cause death by pulmonary embolism.

Laboratory Aids. The virus can be isolated by inoculating the sputum or blood of patients into

white mice or other susceptible animals. Infected mice die within 4 to 20 days, depending upon the amount and virulence of the virus. The livers of such mice show focal areas of necrosis, which grossly appear as white or yellow areas surrounded by a red margin. The spleen is usually enlarged. Elementary bodies are readily demonstrable in the spleen and in the peritoneal exudate.

Antibodies can be demonstrated in the serum of patients during convalescence by means of the complement-fixation test. It is impossible at present, however, to differentiate between psittacosis and lymphogranuloma venereum by serologic tests. Cold agglutinins usually are not demonstrable in the serum. The leukocyte count is either normal or subnormal.

Differential Diagnosis. Psittacosis is most often confused with influenza, typhoid fever, and atypical pneumonia. A history of association with birds may be helpful, but a definite diagnosis of psittacosis is dependent on the specific virus tests described above. Influenza can be differentiated by demonstration of the virus or the development of specific serum antibodies (see p. 1040). The diagnosis of typhoid fever depends on the isolation of *Salmonella typhosa* or on a positive Widal test. Diagnosis of primary atypical pneumonia is largely an exclusion diagnosis, which is strengthened by significant rise in titer of cold agglutinins or agglutinins for the streptococcus MG. *Q fever* may also strongly resemble psittacosis. The diagnosis of *Q* fever requires the isolation of the etiologic agent or the demonstration of specific serum antibodies during convalescence. *Bacterial pneumonias*, particularly those due to staphylococci and *Klebsiella pneumoniae*, and *coccidioidomycosis* must be considered in the differential diagnosis. Acute *tuberculous pneumonia* may occasionally mimic psittacosis.

Treatment. The patient should be strictly isolated during the febrile stage. All discharges must be disinfected and the room thoroughly decontaminated on discharge of the patient. The source of the infection should be investigated and appropriate measures taken to control the spread of the disease.

Sulfadiazine and penicillin are being widely used in the treatment of psittacosis. It is difficult to assess the efficacy of these agents at present, and further studies are required. Sulfadiazine has been reported to be effective against certain

strains of psittacosis virus. Experimental psittacosis responds to treatment with penicillin, and successful penicillin treatment of human psittacosis has been reported. It is advisable, therefore, to use both agents in therapy. "Chloromycetin" has been shown to possess considerable therapeutic activity in embryonated eggs and mice infected with psittacosis virus. If thrombophlebitis occurs, dicumarol or venous ligation should be considered.

Prognosis. The fatality rate in various outbreaks has varied from 20 to 40 per cent. In recent years the rate has dropped to about 10 per

cent, probably because of the increased recognition of mild infection and the use of chemotherapy. Most of the deaths occur in persons above the age of 40.

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Section 17—Exanthematous Viral Infections

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Measles (Roseola)

William F. Friedewald

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Pathogenesis
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Laboratory Findings
Differential Diagnosis
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Definition. Measles is an acute, infectious, and highly communicable disease characterized by fever, coryza, cough, conjunctivitis, Koplik spots, and a typical rash.

History. In 1675 Sydenham recognized measles as a distinct clinical entity and differentiated it from other exanthemas. Koplik, in 1896, stressed the pathognomonic significance of the spots which appear on the buccal mucous membranes in the early stage of the disease. The nature of the etiologic agent was first demonstrated in 1905 by Hektoen, who transmitted the disease to human volunteers by inoculating blood from measles patients, and later by Goldberger and Anderson (1910) by transmission of the disease to monkeys. In 1918 Chapin, Nicolle, and Coneille established the value of convalescent serum for the prophylaxis and attenuation of the disease.

Etiology. Although measles is undoubtedly caused by a virus, progress in studying the infectious agent has been greatly handicapped by the lack of a suitable experimental animal. Rhesus monkeys have been shown to develop an illness characterized by fever and an erythema following the inoculation of blood and throat washings from measles patients. There have been several reports indicating that the virus can be propagated by serial passage in the chick embryo. However, it can be demonstrated only on inoculation into monkeys or susceptible human volunteers. Recently the disease was transmitted back to man in a modified form after 66 serial passages on the chorioallantoic membrane of chick embryos.

Pathogenesis. Measles virus is readily transmitted by direct contact and by droplets of the secretions of the respiratory tract. It is probably airborne over short distances. The virus concentration in the secretions appears to be greatest during the pre-eruptive stage. The virus enters the susceptible individual by way of the nose or mouth and attacks primarily the mucous membranes of the nasopharynx, trachea, and bronchi. It is then disseminated throughout the body by way of the circulating blood. Virus has been recovered from the brain of a child who died of encephalitis complicating measles nine days from the onset of the disease. It is not clear, however, whether the encephalitis is due simply to invasion of the central nervous system by the virus or whether other factors such as immune mechanisms play a role. The characteristic lesions observed on the skin and mucous membranes of the eyes and nasopharynx consist of a proliferation and exudative reaction involving the capillaries. There is moderate edema, hyperemia, and an accumulation of lymphocytes around the blood vessels. Similar lesions also may occur in the lungs, which on x-ray examination have a miliary-like distribution.

The virus can be transmitted from the infected mother to the fetus by way of the placenta, as indicated by the occurrence of measles in the newborn. Ordinarily, infants under six months of age are protected by the passive transfer of antibodies, unless the mother has not had the disease. After 6 to 12 months, nearly all individuals are susceptible to measles. The disease is endemic in urban communities and usually undergoes epidemic cycles at two-year intervals as new crops of susceptible individuals appear. More than 95 per cent of adults in urban populations have had the disease. The disease tends to be sporadic in rural areas. In large cities it is seen almost entirely in young children. The greatest prevalence

occurs in the winter and spring months, with the peak incidence from April to June. The disease confers a permanent immunity. Although second attacks have been reported, they are extremely rare and some doubt is usually raised as to the correctness of the diagnosis.

Manifestations. The onset of illness follows an incubation period of 8 to 12 days. The initial manifestations of the disease are those of an acute upper respiratory infection. General malaise, fever (100° to 104° F.), nasal discharge, sneezing, cough, lacrimation, and photophobia are commonly observed at this stage. The mucous membranes of the conjunctivas and nasopharynx usually are injected and edematous. A *prodromal rash* which is transient and scarlatinal in type is seen in some patients at this time. Within 24 to 48 hours after the onset of illness, the pathognomonic *Koplik spots* appear on the buccal mucosa; these are bluish white specks, like grains of salt, surrounded by a red areola. They are usually seen opposite the first molar teeth and inside the lower lip.

The *rash* appears two to four days after the onset of fever, rarely as late as the seventh day. It appears as minute, red, macular lesions which rapidly increase in size and become maculopapular. They are first noted about the head and neck, particularly in the hairline, behind the ears, over the forehead, and on the neck. The rash spreads downward, involving the entire body within two to four days, gradually assuming a deeper red color. By the fifth or sixth day a brownish discoloration is apparent and is followed by desquamation. With the onset of the eruption the patient appears acutely ill and the temperature may be as high as 104° to 105° F. The eyes are swollen and there is considerable photophobia. The nasal discharge becomes purulent and the cough is more pronounced, but usually nonproductive. The symptoms rapidly subside as the rash reaches its peak. The eruption fades in the order of its appearance and is followed by desquamation and pigmentation which is usually completed in 5 to 10 days.

A severe, highly fatal form of the disease known as *hemorrhagic* or *black measles* is rarely seen. The rash becomes purpuric and there may be bleeding from the mucous membranes of the nasopharynx and the intestinal tract. There is associated prostration, a high fever, delirium, and coma.

The most common complication of measles is acute *otitis media* and, less frequently, *mastoiditis*. Secondary bacterial infection of the lungs producing *pneumonia* is not common, but accounts for about 90 per cent of the fatalities. *Encephalitis* occurs in about 1 in 1000 to 1500 cases of measles. It usually appears two to three days after the appearance of the rash, but may occur before or as late as 11 days after the rash. There is usually a sudden rise in temperature (102° to 104° F.), headache, drowsiness or coma, delirium, irritability, and often convulsions. Stiffness of the neck and positive Brudzinski, Kernig, and Babinski signs are almost always present. There may be twitchings of muscles, hyperactive reflexes, general muscular spasticity, and bulbar signs with dysphagia and respiratory irregularity. The neurologic signs are often bizarre, varying from day to day. The illness usually subsides within a week. In more severe cases the neurologic signs may persist for weeks. Sequelae are commonly observed following encephalitis. These consist chiefly of personality disorders, irritability, impairment of intelligence, headache, tremors, and depression of the deep reflexes.

Laboratory Findings. There are no specific laboratory tests to establish the diagnosis of measles. It is not practical to use monkeys for isolation of the virus. Furthermore, the clinical manifestations of measles are usually so characteristic that little difficulty is encountered in diagnosis. The *white blood count* in uncomplicated measles is normal or shows a mild leukopenia. In encephalitis the white count varies from 5500 to 25,000. The spinal fluid is clear and under slightly increased pressure. The protein is usually increased and the number of cells, which are predominantly lymphocytes, varies from less than 10 to 500.

Differential Diagnosis. During the prodromal symptoms, before the appearance of the rash, the illness is similar to other acute upper respiratory infections. A careful search for Koplik spots is the most important diagnostic procedure at this stage. The conditions most commonly encountered in differential diagnosis are rubella, scarlet fever, and serum sickness. In *rubella* the symptoms are milder and of shorter duration, the rash more macular and smaller, and lymphadenopathy, particularly of the postauricular and postcervical glands, is present. *Scarlet fever* is differentiated by the acute streptococcal pharyngi-

tis and the character and distribution of the rash, which is essentially erythematous and more punctate. In *serum sickness* urticarial wheals or hives, possibly arthritis, intense itching, and a history of serum administration can be obtained.

Treatment. The treatment is entirely symptomatic. During the acute illness this consists of bed rest, adequate fluids, a liquid or soft diet, and salicylates if fever is excessive. Due to the photophobia, the patient is more comfortable in a room with subdued light. Sulfadiazine and penicillin are used only in complications due to secondary bacterial infection. If itching of the skin is excessive, calamine lotion may be applied.

Measles is one of the few diseases in which immune serum is of definite value in preventing or modifying the disease after exposure to the virus. Protective antibodies against measles virus are present in most individuals who have had the disease. It is possible, therefore, to use normal or convalescent serum, placental extracts, or gamma-globulin from pooled plasma which has been concentrated about 25 times. In general, a dose of 0.1 ml. of gamma-globulin per pound of body weight will provide complete protection, while 0.02 to 0.03 ml. per pound will modify the disease in most cases, if given within six days of initial exposure. Between the sixth and ninth days following exposure, a larger dose will often modify the disease. It is of little or no value after the ninth day. Prevention of the disease is indicated in children under three years of age, in the debilitated, and in the presence of other illness at the time of exposure. Ideally, the disease should be modified by the use of appropriate amounts of antibody so that a mild illness inducing permanent immunity results. Permanent

immunity, however, does not invariably follow modified measles.

There is no method of active immunization available at the present time. Recent experimental studies, however, have shown that measles virus cultivated on the chorioallantoic membrane of the chick embryo will produce a modified type of disease in the majority of inoculated children. Following recovery, these children were found to be immune to measles.

Prognosis. Measles is a serious disease in infants and children under three years of age. The disease also may be very severe in adults. The most desirable time to have measles, therefore, is during adolescence. Uncomplicated measles rarely results in a fatal disease. The most serious complications are pneumonia and encephalitis. Over 90 per cent of deaths are attributable to pneumonia. The fatality rate in encephalitis is about 15 per cent, and sequelae have been reported in as high as 70 per cent of patients.

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German Measles (Rubella)

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Definition
History
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Pathogenesis
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. German measles (rubella) is a mild, contagious disease of viral etiology, characterized by catarrhal symptoms, lymphadenitis, and a rash.

History. Accurate clinical descriptions of rubella were first recorded in the eighteenth century by Hoffman, de Bergen, and Orlow. In 1829 Wagner differentiated the disease from other acute exanthemas. In recent years the relationship of this disease in the mother to the occurrence of congenital deformities in infants has received considerable attention. Gregg in 1941 and Swan *et al.* in 1943 reported various congenital defects in infants born of mothers who had German measles during the first trimester of pregnancy.

Etiology. Very little is known about the etiologic agent of rubella. There is no doubt, however, that the disease is caused by a filtrable agent and that it is distinct from that which causes measles. The disease has been transmitted to children by the use of bacteria-free nasal washings. In 1942 Habel reported the transmission of the disease to monkeys by injection of blood and filtered nasal washings from infected human beings.

Pathogenesis. The virus is apparently transmitted by way of droplets of the nasopharyngeal secretions of patients. The infection is communicable for one to two days before the appearance of the rash and for about two days thereafter. Rubella occurs in epidemic form in urban communities and is most commonly seen in the spring of the year. It is principally a disease of children between the ages of 3 and 12 years. Infants under six months of age are usually protected by passive transfer of immunity from the mother. Young adults, particularly from rural areas, who have not had the disease in childhood are

susceptible, and sizable epidemics have occurred in military groups.

Manifestations. The incubation period varies from 10 to 21 days, most cases occurring between the fourteenth and eighteenth days. Prodromal symptoms include malaise, headache, slight rise in temperature, mild coryza, and some stiffness or soreness of the neck due to inflamed lymph nodes in the posterior triangle. These symptoms may occur one to four days before the rash, but often the rash is the first manifestation of the illness. The rash is first observed on the face and neck, spreads rapidly over the entire body, and fades from above downward. It is macular and discrete in character in the beginning, but later may have a scarlatiniform appearance, particularly on the trunk. The rash may be very transient or may persist for two to three days. The acute illness is usually very mild with relatively slight constitutional signs. The temperature remains normal or may be raised to 100° to 101° F. for about 24 hours. The pharynx is only slightly injected. Koplik spots are not seen.

~~A generalized lymphadenitis~~ is a prominent feature of the disease. The glands most commonly affected are the postauricular, suboccipital, and postcervical, but the preauricular, clavicular, axillary, epitrochlear, and inguinal glands also are frequently involved. The inflamed glands are slightly enlarged (about 1 cm. in diameter) and are firm, discrete, and tender. The swelling subsides in one to three weeks. The entire illness usually lasts not more than two to three days, with only mild discomfort to the patient. The disease is more severe in adults and in the very young.

An attack of German measles almost always confers lasting *immunity*. However, it is not uncommon for individuals to report having had several attacks of the disease. The mildness of the illness and the lack of specific diagnostic tests make it difficult to refute such statements, although it is well known that a variety of other conditions may simulate the clinical picture of the disease.

Complications are rare in children. Otitis media, pneumonia, neuritis, and a mild form of meningoencephalitis occasionally are encountered. More important, however, is the amply confirmed observation that in the early months of pregnancy the fetus is susceptible to infection with the virus, leading to the occurrence of congenital defects. The most common abnormalities reported in the fetus are microcephaly, cataracts, deaf-mutism, and malformation of the heart.

Laboratory Findings. A leukopenia is usually observed during the acute illness. By the tenth day the leukocyte count rises to the upper limit of normal. There is no practical method at present for specific identification of the virus.

Differential Diagnosis. German measles is most frequently confused with scarlet fever and a mild attack of measles. The characteristic adenitis of rubella is most helpful in differential diagnosis. In scarlet fever there is an acute streptococcal pharyngitis, desquamation, and leukocytosis.

In measles the maculopapular rash, Koplik spots, and more severe constitutional and upper respiratory symptoms aid in differentiation. Occasionally the exanthemas of infectious mononucleosis and various hypersensitivity states (serum, drugs, foods) may be confused with rubella.

Treatment. The disease is usually so mild that no treatment is required. Every effort should be

made to protect pregnant women, particularly in the early months of pregnancy, from contact with the disease. If exposure occurs, or if the disease is contracted, human immune globulin may be tried in an attempt to prevent or modify it. However, limited experience indicates that the only effect of such treatment is to prolong greatly the incubation period. It is highly desirable for all girls to have the disease before they reach the child-bearing period.

Prognosis. Except for the effect on the fetus, the prognosis in rubella is excellent. Australian workers estimate that rubella in the first three months of pregnancy results in congenital fetal malformations in 90 per cent or more of cases. American figures indicate a rate of about 50 per cent. Further large-scale studies are required to establish the incidence of this serious complication.

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Chickenpox (Varicella)

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Definition
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Differential Diagnosis
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Definition. Chickenpox is an acute, highly contagious viral disease, characterized by mild constitutional symptoms and an eruption of papules and vesicles which make their appearance in successive crops.

History. The first clinical description of vari-

cella appeared in the sixteenth century. It was not until the nineteenth century, however, that it was clearly differentiated from smallpox. In 1917 Paschen described the elementary bodies found in fluid from chickenpox lesions, and in 1933 Amies demonstrated that these bodies were

specifically agglutinated by the serum of patients convalescent from the disease.

Etiology. Chickenpox vesicle fluid contains elementary bodies in large numbers. Electron microscopy reveals that these bodies are brick-shaped with an average size of 210 by 243 millimicrons. The vesicle fluid is infectious and has produced varicella when inoculated experimentally in susceptible children. There is no conclusive evidence that the virus multiplies in any host other than man.

Clinical observations of many years have suggested some relationship between chickenpox and herpes zoster. For example, the two diseases may occur simultaneously in a family or at the same time in one child. Furthermore, numerous outbreaks of varicella in children have been attributed to exposure to a case of herpes zoster. The two diseases are caused by viruses of about the same size and shape, and it has been reported that convalescent serums from either varicella or herpes zoster patients will agglutinate both viruses. Cross immunity is not produced with regularity, however, as numerous cases of herpes zoster have now been reported in children and adults who previously had chickenpox. It is possible that the two viruses are distinct entities, but possess certain antigenic components in common.

Pathogenesis. The virus is found in the vesicle fluid of lesions on the skin and mucous membranes of the mouth. It is readily transmitted from an infected individual to susceptible persons by contact or by dissemination through the air. It presumably enters the body through the respiratory tract, multiplies, and is widely distributed throughout the tissues of the body. Death seldom occurs except in infants. In the few autopsies of such cases which have been reported, characteristic lesions may be found in the liver, pancreas, adrenal gland, esophagus, renal pelvis, ureter, and bladder.

Chickenpox is extremely contagious and occurs almost exclusively in children, although occasional cases occur in adults from rural communities. An attack usually produces a lasting immunity which may be transmitted passively by a mother to her infant, protecting it during the first months of life. On the other hand, chickenpox has been observed at birth and during the first few days thereafter in babies of non-immune mothers.

Manifestations. The incubation period is usually from 14 to 16 days, but may vary from 10 to 20 days. In older children and adults mild constitutional symptoms, including headache, malaise, anorexia, and fever (100° to 102° F.), frequently precede the exanthema by 24 to 36 hours. A slight transitory eruption, scarlatiniform or macular in type, may accompany these symptoms. In young children, prodromal symptoms are frequently absent and the first sign of illness is the appearance of the exanthema. The rash usually appears first on the body and later on the face, neck, and extremities. Occasionally lesions are seen on the mucous membranes of the mouth before they are found on the skin. The eruption begins as pinpoint red macules, which in the course of a few hours become papular. The papules rapidly change to vesicles, enlarge, and may be surrounded by an irregularly shaped area of erythema. Often the red areola is lacking and the pocks appear as drops of water on the skin ("tear drop" vesicles). The vesicles are usually unilocular and discrete, and have a thin covering which is easily broken. Some of the macules, however, do not progress to vesicle formation.

The eruption is usually most abundant on the trunk. Successive crops of lesions appear, so that various stages of papules, vesicles, and crusts are seen simultaneously in a given area. New lesions appear during a three- or four-day period. After about seven days most of the pocks have dried up and are covered by hard, brown crusts. During the next two to four days the crusts become detached, leaving slightly indented, superficial scars which soon disappear.

Secondary infection of the pocks by scratching is the most common complication. Staphylococci and streptococci are the usual offending organisms. The vesicles become pustular, and, if extensive, may suggest smallpox. Scarring frequently results from such secondarily infected lesions. Chickenpox lesions may be especially numerous and confluent on areas of preexisting skin inflammation. *Encephalitis*, similar to that following vaccination, measles, and mumps, is occasionally observed, but is seldom fatal. Pneumonia, otitis media, and erysipelas are rare complications.

Laboratory Aids. There is no practical method at present for specific identification of varicella virus. The blood picture shows no significant change in uncomplicated chickenpox.

Differential Diagnosis. The vast majority of cases of chickenpox present no problem in differential diagnosis. Occasionally the differentiation from mild smallpox (see discussion of smallpox, p. 1053) is difficult and requires tests for the specific identification of smallpox virus. Chickenpox and *herpes zoster* may be indistinguishable in exceptional instances. In general, the vesicles of herpes zoster are larger, tend to be confluent, and are grouped along the line of the affected nerve or nerves, and there is severe nerve root pain. In contrast, chickenpox lesions are usually widely distributed. They are pruritic but not painful. Various skin lesions, including impetigo, scabies, eczema, and syphilis, must occasionally be considered in differential diagnosis.

Treatment. The treatment is symptomatic. The lesions should be kept clean and free from irritation. The fingernails should be trimmed very short, and in young children, if itching is severe, gloves or splints should be kept on the patient's hands to prevent scratching. Pruritus may be relieved by calamine lotion containing 1 per cent phenol or by anesthetic ointments. If

secondary infection occurs, antibiotic or chemotherapeutic agents are indicated. Isolation and quarantine are of little value in controlling the spread of the disease, since the virus is readily transmitted before the eruption appears. The patient should be kept at home, however, during the contagious period, and isolated from children who have not had chickenpox.

Prognosis. Death from chickenpox is extremely rare. The disease is usually more severe in infants and adults. Occasionally secondary bacterial infection with bacteremia may be fatal.

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Smallpox and Vaccinia

William F. Friedewald

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SMALLPOX

Definition. Smallpox is an acute, highly contagious, viral disease, with an abrupt onset and intense early symptoms, followed by a papular eruption which becomes vesicular and finally pustular.

History. Epidemics of smallpox occurred in China as early as the twelfth century B. C., and

since ancient times it has been known in India and Central Africa. It was prevalent in Europe during the early Middle Ages, apparently due to dissemination by the Crusades. The first authentic description of smallpox was written by an Arabian physician (Rhazes) in the tenth century. The disease was introduced into the Western Hemisphere during the sixteenth cen-

tury, probably by Negro slaves brought from Africa. The elementary bodies in fluid from smallpox lesions were first described by Buist in 1887, and later by Paschen in 1906.

Etiology. The elementary bodies are spherical structures having a diameter of 200 millimicros. They can be stained by certain aniline dyes or by the silver technic of Morosow. It is now generally believed that the elementary body represents the virus responsible for smallpox. The virus survives in desquamated crusts for long periods of time. It can be preserved in the frozen state, in 50 per cent glycerin, or by lyophilization. It is destroyed by heating at 55° C. for 30 minutes. In addition to man, the virus is pathogenic for the monkey, producing a local reaction with moderate constitutional symptoms. A local inflammatory lesion can be elicited on the skin of the rabbit, and characteristic pocks are produced on the chorioallantois of the chick embryo.

Pathogenesis. The virus is present in the skin eruption at all stages, and also is found in the lesions of the mucous membranes and in the blood. It is transmitted readily from a patient to other persons by contact, by clothing, or by other contaminated objects. It is found in dust and may be airborne over short distances. The virus does not appear to penetrate the intact skin, but usually enters by way of the respiratory tract. It then multiplies and is distributed widely throughout the tissues of the body, but clinical manifestations do not develop until about 12 days after infection. Human beings are universally susceptible to the virus unless immune from previous smallpox or from vaccination. The disease is more common during the winter months and occurs in all regions and climates.

Manifestations. The incubation period is usually 12 days, rarely as short as 8 days or as long as 21 days. In the typical unmodified case the patient suddenly becomes acutely ill with chills, headache, nausea, vomiting, prostration, severe backache, and fever (102° to 104° F.). These symptoms continue for three or four days. Occasionally there is a transitory prodromal rash which varies in character from erythematous to hemorrhagic. The characteristic skin eruption appears on about the fourth day of illness and, simultaneously, the patient feels better and the temperature falls. Ordinarily the eruption begins on the face, then spreads to the upper extremities, particularly the distal portions, the trunk,

and lastly the lower extremities, with most of the lesions below the knee. The palms and soles are almost invariably involved. The spread of the eruption is completed in about two days. The lesions are of nearly the same age and do not appear in successive crops as in chickenpox. The eruption begins as small red macules, which rapidly become papular and have a shotty feel. By about the sixth day the papules become vesicular. At this time the vesicles are extremely firm with a central depression (umbilication). The pock fluid is walled off in several separate compartments, producing the characteristic multilocular appearance. By the eighth or ninth day the contents of the pocks become turbid and pustular. During this stage there is a secondary rise in temperature with increased constitutional reaction. Considerable pain, burning, and itching are experienced at the site of the most extensive eruption. The eruption also involves the mucous membranes of the nose, cheek, tongue, pharynx, larynx, conjunctivas, and genitalia. Extensive ulceration may occur and there may be considerable difficulty in swallowing.

Regression of the lesions, with drying and crusting, occurs during the next 10 days, and the fever subsides. The pustules frequently rupture, yielding a sticky, yellowish material with a foul odor. Within a month the crusts separate, and some desquamation occurs, leaving the familiar pitted scars which are the mark of the disease. Bronchopneumonia and bacterial infections are the most common complications in smallpox and are present in practically all cases which end fatally.

A number of varieties of smallpox have been described. The most common form is that in which the pocks remain *discrete*, with the number of lesions varying from a few small pustules to many covering the entire body. In a more severe form of the disease, the lesions are so numerous that they become *confluent*. Hemorrhages into the pocks and from the mucous membranes are seen in the form known as *hemorrhagic smallpox*. The most malignant form of the disease is *purpuric smallpox*. Petechiae and purpura followed by hemorrhages from the mucous membranes appear on the second or third day of illness, and death usually occurs before the sixth day. *Alastrim* or *variola minor* is a form of smallpox, usually with a prolonged incubation period and a sparse eruption which does not become pustular.

It is due apparently to a less virulent strain of the virus.

Modified smallpox or *varioloid* is the term used to designate a mild form of smallpox which occurs in partially immune individuals who have had a previous vaccination. There is considerable variation in the severity of the illness, depending on the level of immunity present. In general, the prodromal symptoms are much less severe and the eruption is discrete and often scanty. The lesions go on to the pustular stage, but no secondary rise in temperature occurs. The severe constitutional reaction is absent and the course of illness is shortened. It is particularly important to recognize this form of smallpox because of the widespread use of vaccination at the present time. Often the disease is so mild as to be overlooked, but cases of this type may serve as a means of spreading the infection to unvaccinated individuals.

Laboratory Aids. The laboratory tests available for the specific diagnosis of smallpox fall into two general groups: (1) the isolation and identification of the virus by inoculation of animals or embryonated hen's eggs, and (2) serologic techniques designed to demonstrate the virus or its specific antigens directly in fluid from the lesions. Virus may be isolated by inoculating fluid from the lesions onto the chorioallantoic membrane of embryonated hen's eggs. Characteristic pocks are produced in two or three days. The identity of the virus is then confirmed by complement-fixation or neutralization tests, using an extract of the infected membranes and specific antiserum. Another method of demonstrating the virus is to scarify the cornea of a rabbit with a needle dipped in the fluid from a pock. Small vesicles or shallow ulcers appear within two to three days if the virus is present. Histologic sections of the cornea reveal the pathognomonic Guarnieri bodies in the cytoplasm of some of the cells. A more rapid diagnostic method is to perform complement-fixation or flocculation tests with antigen prepared from vesicles or pustules and specific rabbit antiserum. During convalescence, specific antibodies can be demonstrated in the serum of patients by complement-fixation or flocculation tests.

Differential Diagnosis. During the initial stage, smallpox is difficult to differentiate from the prodromal phase of a variety of other acute infectious diseases, such as influenza, measles,

typhus, scarlet fever, and malaria. Epidemiologic evidence is often helpful at this stage. *Chickenpox* usually is easily distinguished from smallpox, but experience in recent epidemics has emphasized the fact that at times the differentiation between mild smallpox and chickenpox may be very difficult. The lesions in chickenpox are more shallow, are usually unilocular, vary greatly in size, and appear in successive crops. In some patients the differentiation cannot be made without resort to virus tests. In contrast to smallpox, fluid from the lesions of chickenpox does not produce lesions on the rabbit cornea or on the chorioallantois of embryonated eggs. The pustular lesions occasionally observed in *syphilis* are not umbilicated, rarely involve the palms and soles, and run a more chronic course. Serologic tests and the dark-field demonstration of spirochetes establish the diagnosis of syphilis. *Skin lesions*, such as impetigo, erythema multiforme bullosa, and *drug eruptions* seldom need be confused with smallpox if the course of illness and characteristics of smallpox are kept in mind.

Treatment. The patient with smallpox must be isolated in a hospital properly equipped to handle such cases. The isolation technic must be carried out rigidly to prevent contact, or airborne infection. All contacts and hospital attendants should be vaccinated. No specific therapy for smallpox is available and, in general, treatment is symptomatic. Penicillin and sulfonamides are helpful in preventing and treating secondary bacterial infections. Sedatives are usually necessary to make the patient comfortable. A variety of topical applications have been used in the treatment of the skin lesions. They have little effect on the course of the lesions, but anesthetic ointments provide relief from pain and itching. Adequate nutrition and fluid and salt balance must be maintained during the severe and prolonged illness. Immunization for control of smallpox will be considered under *Vaccinia*.

Prognosis. The fatality rate varies greatly in different epidemics of smallpox, ranging from less than 1 per cent to 30 per cent or more. Confluent and hemorrhagic or purpuric smallpox carries a grave prognosis. Smallpox is usually more severe in infancy and old age. Previous vaccination, even though done years before, usually modifies the disease and greatly improves the prognosis. Antibiotic and chemotherapeutic agents should greatly reduce the fatality rate from secondary

infections, which are the most common complications arising in smallpox.

VACCINIA

Definition. Vaccinia or cowpox is a naturally occurring disease of cattle, caused by a virus which is closely related to smallpox virus. The disease occurs in man as an occupational hazard, particularly in milkers who handle infected cattle, or as a result of purposeful inoculation with cowpox virus (vaccination). The disease is characterized by one or more nodules, vesicles, or pustules, mild constitutional symptoms, and the development of immunity to smallpox.

History. In 1798 Jenner published a treatise entitled "An Inquiry into the Causes and Effects of the Variolae Vaccinae," which established the effectiveness of vaccination with cowpox virus for protection against smallpox. Following this report the method was adopted widely in many civilized countries of the world. It was introduced into the United States in 1800.

Etiology. The elementary bodies of vaccinia are spherical particles about 225 millimicrons in diameter, and can be seen by the ordinary microscope or better by dark-field microscopy. Electron microscopy reveals the bodies to be bricklike structures with six rectangular surfaces and an internal structure not unlike that seen in bacteria and rickettsiae. The precise relationship of vaccinia virus and smallpox virus has not been settled. Immunologic and serologic studies indicate that vaccinia virus is actually a modified form of smallpox virus. Vaccinia virus is indigenous to cattle, causing a mild disease in its natural host and in man. It can be preserved for long periods of time in the frozen state (-10° C. or lower) or in glycerin. It is inactivated by ultraviolet light, x-ray radiation, and a number of antiseptics.

Manifestations. Naturally acquired cowpox of man is characterized by one or more lesions, usually on the hands or lower arms. They begin as nodules and progress to vesicles and pustules. Constitutional symptoms are mild. Occasionally a generalized eruption appears, but usually it is not extensive and heals rapidly without scarring.

Vaccination against smallpox is accomplished by producing a localized skin lesion with living vaccine virus. The virus usually is obtained from the pocks of calves previously inoculated on the abdominal wall. The technic of producing the

vaccine is carefully standardized and controlled to ensure potency of the preparation and the absence of contaminating pathogenic bacteria.

The site of vaccination of human beings is usually on the arm about an inch above the insertion of the deltoid muscle. The outer aspect of the thigh is sometimes chosen for the site of vaccination in girls for aesthetic reasons, but this is not advocated because the present method of vaccination rarely results in an unsightly scar, and secondary infection can more easily be prevented on the arm. The skin is cleaned carefully with soap and water and allowed to dry thoroughly. A drop of the virus is then placed on the skin, and inoculation is made through the drop, usually by the multiple pressure method. This consists of gently pressing the side of the point of a needle into the skin through the drop 10 to 15 times over an area not more than 2 mm. in diameter. After 5 or 10 minutes the excess vaccine is gently wiped away. Intradermal vaccination with vaccine prepared from tissue culture or the chick embryo has also been tested on a limited scale. Such a vaccine has certain advantages in preparation and control of sterility, but the results obtained thus far have not been encouraging.

The course of events following vaccination varies according to the level of immunity of the individual. *Primary vaccinia* is observed when little or no immunity to the virus is present. The reaction does not occur until the third to fifth day. It begins as a small, reddish papule which soon becomes vesicular. By the seventh day the vesicle is multilocular and has enlarged to about 1 cm. in diameter, with a red area of induration surrounding it. The vesicle and the area of induration continue to increase in size, reaching the maximum diameter in 8 to 12 days. Regression of the lesion usually begins by the twelfth day, with fading of the inflammatory reaction and the formation of a brownish crust or scab. The scab becomes detached on about the eighteenth day, leaving a red, well-demarcated scar which gradually becomes less obvious. *Secondary vaccinia* or *accelerated reactions* are observed in partially immune individuals who have been vaccinated previously. The papule appears on the second or third day and the lesion is fully developed between the fourth and eighth days after vaccination. The lesion and the area of induration are smaller than in primary vaccinia. *Immune reactions* are seen in individuals who re-

tain a high degree of immunity from a previous vaccination. A small area of redness or a papule appears within 24 to 48 hours after vaccination. A vesicle does not form and there is usually no induration. The lesion disappears in a day or two without scarring. There is some difficulty in interpreting this early type of reaction. It does not indicate immunity to smallpox unless the vaccine is of known potency, as proved by the production of primary or secondary reactions in other individuals. Occasionally *no reaction* is observed following vaccination. This is usually due to faulty technic or to the use of inactive virus. *If no reaction occurs, the vaccination must be repeated at intervals until successful.*

Symptoms of vaccinia vary considerably in different individuals. Itching and pain at the site of inoculation usually occur in primary and secondary vaccinia. At the height of the reaction there may be loss of appetite, fever, chills, and general malaise. *Generalized vaccinia* is a rare condition which occurs several days following primary vaccination. It may occur in children with various types of skin lesions, such as impetigo and eczema. The eruption resembles varioloid, and pitted scars are not produced. *Autovaccination* may occur by transferring virus from the original pustule to another skin site by scratching. *Postvaccinal encephalitis* is a rare complication. In 1947, following an outbreak of smallpox in New York City, 6,350,000 people were vaccinated. Postvaccinal encephalitis was considered probable in 46 cases and, of these, eight died. Examination of the brain tissues of the fatal cases, however, failed to show the characteristic lesions of postvaccinal encephalitis. Two of the deaths were caused by tuberculous meningitis, one by brain tumor, one by coronary sclerosis, and four "probably by cerebral lesions." There was, therefore, no proof of any death due to postvaccinal encephalitis in this large number of vaccinated individuals. Symptoms of encephalitis usually occur 11 to 14 days following vaccination. Headache, vomiting, fever of about 104° F., varying degrees of stupor, and convulsions are the usual symptoms. The spinal fluid is usually under slightly increased pressure and contains up to 300 cells which are predominantly lymphocytes. The cause of the encephalitis is not fully understood, but it has been attributed to a hypersensitivity reaction of the central nervous system to the virus. Death is re-

ported to occur in about 40 per cent of the cases, usually within a week after the onset of symptoms. In patients who recover, residual disturbances are unusual. *Secondary infection* of the lesion with a variety of organisms may occur. This is seen usually where the pustule is broken by trauma. Cellulitis, lymphadenitis, and erysipelas have been recorded. Tetanus also has been described in the past, but careful control of the vaccine and the abandonment of the use of shields or protective dressings has eliminated this danger.

There is abundant evidence that a high degree of immunity ordinarily results from vaccination. It must be noted, however, that the immunity in occasional instances is not complete. Recent experiences with military personnel in epidemic areas has shown that epidemics may occur in individuals who have been vaccinated. Most of these cases are of the modified type, but occasional deaths occur. It is apparent that successful vaccination does not necessarily confer lifelong immunity. Furthermore, considerable difficulty arises in interpreting the "immune" type of reaction. In many instances these should be recorded as "no take," and the vaccination should be repeated.

Vaccination should be carried out as a routine procedure in children, preferably within the first six months. It should be repeated before entering school and every 5 to 10 years thereafter. All individuals exposed to the disease should be vaccinated immediately. Careful observation of the vaccination reaction is required to ensure a "take." If no reaction occurs, it should be repeated at intervals of one to three months until successful.

Treatment. Treatment is symptomatic. If secondary infection occurs, chemotherapeutic or antibiotic agents may be indicated, depending on the infecting organism. Certain precautions should be followed to avoid complications. Shields and tight protective dressings should not be used, since they increase the chance of secondary infection. Vaccination should not be performed when inflammatory lesions of the skin are present, to avoid the danger of generalized vaccinia. It is also advisable not to vaccinate during pregnancy, particularly during the early months. Even though no effect of vaccinia virus on the fetus has been proved, this precaution seems to be warranted at present, in view of the evidence

of the relationship between rubella virus and congenital defects in the fetus.

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Dengue

L. T. Coggesshall

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Definition. Dengue is an acute viral febrile disease characterized by extreme muscular soreness (from which it derives the name "breakbone fever"), a short course of 7 days' duration, and protracted convalescence. There is an initial and a terminal rise in fever. The disease is transmitted by *Aëdes aegypti* mosquitoes, and it occurs in many tropical and subtropical countries.

Dengue was first reported as an epidemic in Cairo and Java in 1779, although the disease was first described by Rush in Philadelphia in 1780. In 1903 Graham showed that it was transmitted by mosquitoes, and in 1907 Ashburn and Craig transmitted the disease through the medium of filtered blood. The cycle of transmission was demonstrated by Siler, Hall, and Hitchens in Manila in 1924. Sabin and Schlesinger in 1945 apparently were successful in producing a vaccine.

Etiology. The virus is filtrable and circulates in the blood the first 3 or 4 days of the illness, after which it can no longer be isolated as it has been neutralized by antibodies. It remains viable for many months when it is preserved in the frozen desiccated state. The virus is transmitted by *Aëdes aegypti* mosquitoes that have become infected after biting a patient within the first three days of the fever. After an interval of eight days, the mosquito is able to transmit the disease, and

virus may be recovered from the mosquito throughout its lifetime. An attack of the disease produces a fair degree of immunity probably lasting five to seven years, and, when there are reinfections, there is a tendency toward milder infections. Convalescent serum is not useful for the treatment of the disease. Sabin and Schlesinger in 1945 successfully transferred virus from a human patient and, by serial passage through mice brains for approximately 16 generations, were able to modify the virus so that it would produce an attenuated disease in man. Thus the possibility of a successful immunizing agent for dengue is now good.

Pathogenesis. Dengue fever is not a fatal disease; hence there are few descriptive reports of the pathologic picture in man. It is known, however, that the gastrointestinal tract will show petechial hemorrhages, which probably are coincident with the rash. There are some mild inflammatory changes in the myocardial and skeletal muscles, and the kidneys may show a glomerulitis. There is enlargement of the lymph nodes and spleen. The blood picture is one of mild to marked leukopenia followed by a leukocytosis at the termination of the febrile attack.

Manifestations. The incubation period is from 3 to 15 days. The first signs appear abruptly with extreme headaches, postorbital pain, generalized muscle aches, and prostration. There may be rigors and convulsions in the more severe cases. Characteristically, the pain is so severe that the patients prefer not to walk but, if they do, they

assume a very rigid protective gait to shield themselves against sudden jars, often walking on the balls of their feet—hence the name dengue or "dandy" fever.

~~X~~ The fever is quite typical, rising to a range of from 104° to 106° F. in the first few hours, at which time it may subside to normal. There is a secondary rise to approximately the same level on the fifth to sixth day, furnishing a saddle-back type of curve. The temperature usually returns to normal on or about the seventh day. The pulse is usually very rapid early in the course of the infection, but characteristically it falls before the temperature. Occasionally, it may slow to a rate as low as 40 per minute.

There are commonly two types of ~~rashes~~—a primary one, diffuse and erythematous in appearance, occurring at the outset on the neck, face, shoulders, and trunk. This reaction rapidly subsides and on about the fifth day a macular or scarlatiniform rash appears on the hands, arms, and legs, but rarely on the face. Desquamation occurs frequently.

The above symptoms are those of a typical case. However, in many cases there is a wide divergence of symptoms. The fever may be more or less continuous or there may be only the initial abrupt rise. There may be only a terminal rash or none at all. There is, however, a tendency for individuals in an epidemic to show a rather constant pattern. In some, muscular pain is a predominant feature, while in others arthralgia may predominate. The complications encountered are not numerous but there may be hemorrhages

(particularly epistaxis), diarrhea, orchitis, and proteinuria.

Laboratory Findings. The blood shows an early leukopenia, 2000 to 5000, with 20 to 50 per cent polymorphonuclear cells, many of which show toxic or degenerative changes. There is usually a leukocytosis late in the disease. The urine is scanty and there is a mild proteinuria.

Differential Diagnosis. In the differential diagnosis, one has to think of malaria, influenza, measles, and sandfly fever. Sandfly fever, or papataci fever, with which dengue is very closely related, must be excluded as a possibility. With sandfly fever, there is usually only an initial rise in temperature, with a leukopenia followed by leukocytosis. There is flushing of the face but a rash is exceptional.

Treatment. The treatment is entirely symptomatic and largely centered upon the relief of pain, aspirin and codeine being very beneficial. The patient should be kept as cool as possible with sponges or packs, and fluids should be forced. The prognosis is very good in that there is practically no mortality. The chief difficulty with dengue is the prolonged convalescence, in which the patient may be mildly prostrated for weeks, and does not return to a state of well-being for as long as six months or more.

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Pretibial Fever

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Definition. Pretibial fever is an acute infectious disease, probably of virus etiology, characterized by fever, malaise, frontal headache, a palpable

spleen, and an erythematous eruption over the shins. It is also known as Fort Bragg fever or Brushy Creek fever.

History. The disease was first described by Bowdoin, who studied an outbreak of 35 cases at Wrens, Georgia, in 1940. Daniels and Grennan described a similar disease among soldiers stationed at Fort Bragg, North Carolina, in 1942. It recurred at Fort Bragg in 1943 and 1944. In 1947 Tatlock isolated the etiologic agent by inoculating guinea pigs with blood from a patient.

Etiology. Tatlock reported that guinea pigs inoculated intraperitoneally with freshly drawn blood from a patient developed temperatures of 105° to 106° F. four to eight days after inoculation, but showed no other evidence of illness. Serial passage in guinea pigs was maintained by intraperitoneal or intracerebral inoculation of blood taken on the first day of fever. Rabbits also developed fever without apparent illness. Intracerebral inoculation in hamsters, however, produced death in 7 to 16 days. The etiologic agent can be propagated in chick embryos inoculated intravenously, and produces death of the embryos in about seven days. The disease was reproduced in human volunteers with infectious material obtained after numerous passages in guinea pigs and chick embryos.

Further studies are necessary to characterize this agent. It can be preserved in 20 per cent suspension of infected embryo tissue in sterile skimmed milk at -70° C. Filtration studies indicated that it passed a Corning UF fretted glass filter which retained *Staphylococcus albus*, but did not pass a Seitz pad.

Pathogenesis. Little is known regarding the pathogenesis of pretibial fever. It is interesting to note that all of the cases from Fort Bragg occurred in a localized segment of the reservation which was located near a small stream. In addition, all patients from the outbreak in Georgia had gone swimming in Brushy Creek (hence the original name of the disease, Brushy Creek fever). The significance of these observations is not clear at present.

Manifestations. The incubation period appears to be 10 to 15 days or longer. The onset is usually sudden with frontal headache, muscle pains, backache, postorbital pain, chills or chilliness, and fever. About one third of the patients have a transitory sore throat and cough. There may be nausea, vomiting, and bradycardia. The fever is spiking in nature, often reaching two peaks a day with recurrent chills. It ranges between 100° and

105° F. and persists for four to eight days. An unusual eruption appears on about the fourth day of illness in most of the patients. The lesions consist of erythematous blotches with irregular margins which are raised, warm, and slightly tender to touch. The rash characteristically involves the pretibial regions, but in about 20 per cent of cases a few scattered lesions also occur elsewhere. Occasionally, the rash is diffusely distributed over the entire body. The eruption usually persists for only 24 to 48 hours. In a small proportion of cases, perhaps 15 per cent, it is absent. The spleen is almost always palpable early in the disease, but there is no generalized lymphadenopathy. The illness subsides after 7 to 10 days, and no complications have been reported.

Laboratory Aids. Isolation of the etiologic agent may be attempted early in the course of the disease by inoculation of freshly drawn whole blood into guinea pigs, hamsters, or embryonated eggs. Neutralization tests may be performed in hamsters with acute and convalescent serums from patients and the hamster-adapted virus. A mild leukopenia is a feature of the disease, usually appearing between the third and fifth days of illness. The differential count shows no significant change. The spinal fluid in three patients with stiffness of the neck was normal.

Differential Diagnosis. Prior to the appearance of the rash, the illness may be confused with a variety of acute infectious diseases. The combination of fever, bradycardia, palpable spleen, and leukopenia strongly suggests malaria and typhoid fever. The clinical course and characteristic distribution of the rash in pretibial fever, together with negative blood smears and bacteriologic findings, provide the chief distinguishing features. The diagnosis can be confirmed by neutralization tests.

Treatment. Treatment is symptomatic.

Prognosis. The disease is self-limited, and no fatalities or residual effects have been recorded.

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Lymphocytic Choriomeningitis

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Definition. Lymphocytic choriomeningitis is an acute, rarely fatal viral disease of man, characterized by inflammation of the meninges and choroid plexuses usually accompanied by signs of systemic and respiratory tract infection.

History. In 1925 Wallgren first described the clinical entity of benign "aseptic meningitis" for which no etiologic agent could be demonstrated. Subsequently, Armstrong and Lillie (1934), while studying St. Louis encephalitis, isolated from a monkey brain a virus that they called the "virus of lymphocytic choriomeningitis." This virus was shown to be enzootic in mice and subsequently (Scott and Rivers) to be the cause of some, but not all, cases of human "aseptic meningitis." An excellent general review is that of Farmer and Janeway (1942).

Etiology. The virus is relatively small, measuring 33 to 60 microns, by filtration or centrifugation. It is infectious for the mouse, guinea pig and monkey, and can be propagated in the chick embryo or in tissue culture.

Epidemiology. Most infections occur in adults between the ages of 20 and 40 years. There is no sex difference. The disease occurs in all parts of the world. One epidemic has been proved due to this virus, but case-to-case infection is extremely rare. Since the virus usually is not transmitted from man to man, one must look elsewhere for the reservoir of infection, and the mouse is suspect. Several surveys of trapped wild mice indicate that up to 20 per cent harbor the virus and excrete it in their urine. Many laboratory workers have detected the virus in mice caught in a

house where lymphocytic choriomeningitis has developed.

Pathogenesis. Laboratory accidents suggest that the portal of entry may be the conjunctiva, the upper respiratory tract, or the skin. The virus may be recovered from the blood during the early stages of the disease, or from cerebrospinal fluid during the period of meningeal signs, and it has been recovered a few times from the nasopharynx and urine of human patients.

The few fatal human cases revealed pathologic changes similar to those in laboratory animals—namely, extensive round cell infiltration of the meninges and choroid plexuses as well as of the liver, spleen, and lung. Rarely, the brain shows perivascular lymphocytic cuffing, hemorrhages, gliosis, and degeneration of nerve cells.

Manifestations. Usually the onset of meningeal signs is preceded by one to three weeks of prodromal symptoms simulating grippe or influenza. Fever (which may be remitting), chills, sore throat, cough, and bronchitis are most common and may abate for a short interval before the onset of headache, vomiting, stiff neck, and photophobia. Meningeal signs may be slight and the patient often does not appear so acutely ill as in bacterial meningitis. The course is usually short and complications are rare, but sometimes symptoms recur one or more times after a period of apparent recovery. Encephalomyelitis may occur with diplopia mental changes, and a variety of neurologic signs. The disease may simulate influenza with no signs referable to the central nervous system. Subclinical infections probably occur, as shown by the development of virus-neutralizing antibodies in the absence of clinical disease.

Laboratory Findings. Leukopenia is common in the prodromal period and in the fatal cases observed, but is not a reliable diagnostic aid. The cerebrospinal fluid pressure is frequently normal

or slightly increased and contains 100 to 3000 cells, mostly lymphocytes. In the early stages of illness, the spinal fluid may contain predominantly polymorphonuclear leukocytes. The sugar and chlorides are normal but the protein usually is slightly elevated.

Differential Diagnosis. Other forms of viral meningoencephalitis, bacterial meningitis, influenza, or virus pneumonia may present a differential diagnostic problem. The sporadic occurrence in a patient who has not been exposed to a known communicable disease, the sudden onset of meningeal symptoms, the absence of bacteria and presence of a mononuclear pleocytosis in the cerebrospinal fluid, the benign course, and the absence of parameningeal foci of infection should suggest the diagnosis. A positive diagnosis can be made only by laboratory studies such as isolation of the virus from blood or cerebrospinal fluid, or demonstration of a rise in complement-fixing antibodies after the second week, or in virus-neutralizing antibodies after six to eight weeks.

In the eastern seaboard region of the United States, lymphocytic choriomeningitis is responsible for 5 to 10 per cent of *sporadic "aseptic meningitis"*; mumps virus causes approximately 20 per cent; and the remainder of cases are usually undiagnosed by laboratory tests now available, although occasional cases may be due to

measles, varicella, herpes zoster, herpes simplex, lymphogranuloma, infectious mononucleosis, hepatitis, or meningovascular syphilis.

Treatment. No specific treatment is available. Lumbar puncture may relieve severe headache.

Prognosis. Recovery is usually complete within two to three weeks after the onset of meningeal signs. Residual neurologic damage may persist after the rare encephalomyelitic form.

Cases of fatal progressive arachnoiditis and of fulminating interstitial pneumonia have been described.

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Viral Encephalitides

Lewis L. Coriell

Epidemic Viral Encephalitis
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EPIDEMIC VIRAL ENCEPHALITIS

Introduction. The epidemic viral encephalitides comprise a large group of arthropod-borne neurotropic virus diseases frequently occurring in epi-

demic form, and characterized by sharply delineated seasonal and geographic distribution. In this group are St. Louis encephalitis, Japanese B encephalitis, Eastern, Western, and Venezuelan

equine encephalitis, and Russian Far Eastern encephalitis. Because the diseases caused by these viruses are indistinguishable except by means of special tests, they will be discussed together, noting the individual differences which have been observed.

Louping ill of sheep is related to this group of viruses, but only a few cases of *laboratory* infection have been recorded in man (Rivers and Schwentker, 1934). Several recently isolated viruses cause encephalitis in experimentally inoculated animals, but their role as human pathogens is not known. These include West Nile and Bwamba fever, isolated from mild febrile diseases in man; the virus of encephalomyocarditis, isolated from a fatal infection of a gibbon; and Semliki Forest, Bunyamivera, Hammon-Reeves, and Ilheus viruses, isolated from mosquitoes. These viruses are of interest because specific neutralizing antibodies have been found in the serum of human beings, and some are antigenically related to a known encephalitis virus. Encephalitis lethargica of von Economo is discussed separately, since nothing is known of the virus or its mode of transmission.

History. All of the epidemic viral encephalitides, with the exception of von Economo's encephalitis, have been recognized only within the last 25 years, coincident with the development and widespread distribution of the disciplines of virology. It is probable that at least some of them occurred sporadically in the past, when laboratory diagnostic aids were not available. The dates of the first epidemic, geographic location and seasonal incidence are shown in table 91. A more comprehensive historical review of each disease is included in the References at the end of this chapter.

Etiology. The agents which cause epidemic encephalitis are among the smaller viruses, and range in size from 15 to 40 millimicrons in diameter when measured by filtration through graded collodion membranes, and hence are readily filtrable through ordinary bacteriologic filters. They can be grown in the chick embryo or in tissue culture, or transmitted to a number of experimental animals, of which the Swiss albino mouse is the animal of choice, owing to its availability. The host range varies, and this fact provides one of the laboratory methods used in distinguishing various members of the group. For example, the virus of St. Louis encephalitis is not

pathogenic for guinea pigs or rabbits, as are the viruses of equine encephalitis. In so far as tests have been carried out, none of these viruses is affected by penicillin, streptomycin, or sulfonamides. Differentiation of the viruses listed in table 91 is based entirely on laboratory procedures —i.e., complement fixation, neutralization, and animal protection tests.

Epidemiology. St. Louis and Western equine types are most common in people over 45 and under 1 year, and the observed epidemic of Eastern equine disease was mostly in children under 10 (75 per cent). The sex incidence shows a slightly increased liability to infection in men, especially in the Russian Far Eastern disease. All occur in the spring, summer, or autumn. In epidemics, most cases occur in suburban or rural areas where there is greater opportunity for contact with the insect vectors than is found in crowded urban areas; e.g., most epidemics of Russian Far Eastern encephalitis have occurred in woodcutters exposed to tick bites. Most outbreaks of equine encephalitis in man have been associated with epizootics in horses. The viruses have been isolated from naturally infected arthropods (table 91) in endemic areas, and from wild and domestic mammals and birds. Inapparent infection with viremia for several days has been demonstrated in domestic fowls, wild birds, and some mammals, following experimental infection by mosquitoes which had previously bitten an infected animal. In St. Louis encephalitis, the virus survives the winter in the chicken mite, and is passed to its progeny through the ova. The epidemiologic data, therefore, strongly suggest that these viruses are primarily pathogens of lower mammals, birds, and arthropods, where a well-balanced host-parasite relationship exists, and that infection of man is more or less accidental. The occurrence of epidemics then probably indicates that a large number of people have been bitten by the insect vectors, rather than that a direct man-to-man, or man-mosquito-man, transmission has occurred. Venezuelan equine encephalitis may be an exception, since the virus has been recovered from the nasopharynx of infected laboratory workers who contracted this disease under conditions which suggested the respiratory portal of entry.

Pathogenesis. While man is usually infected through the bite of a blood-sucking arthropod, a stage of viremia seems to be fleeting or absent in

Table 91
EPIDEMIC VIRAL ENCEPHALITIS

Disease	First Epidemic	Virus Isolated	Geographic Location	Prognosis		Size	Vector	Suspected Reservoir	Animal Disease
				Seasonal Incidence	Mortality				
Von Economo's (encephalitis lethargica)	1915	No	World-wide	Winter Early spring	30%	20%	?	?	?
St. Louis	1933	1933	Central and western U. S.	Spring Early summer	5-30%	10-40% infants 5% adults	20-30 m μ	Mosquitoes	Chicken mite
Japanese B (Russian autumn) (Australian X Disease?)	1924	1936	Japan, Java, Philippines, Australia, Korea, Manchuria, Eastern Siberia, Indo-China	Summer Autumn	50-80%	Infrequent (3%)	15-20 m μ	Mosquitoes	Horse? Chickens? ?
Western Equine (WEE)	1930	1930	Central and Western U. S., Canada, Argentina	Summer	8-15%	Rare	25-40 m μ	Mosquitoes	Chicken mite Wild bird nites
Eastern Equine (EEE)	1933	1933	Eastern U. S. and Canada, Mexico, Cuba, Panama, Brazil	Summer	65%	60%	25-40	Mosquitoes	Chicken mite
Venezuelan	1938	1938	Northern South America and Panama	?	Low?	Rare	?	Mosquitoes (droplet)	?
Russian Far Eastern (spring-summer)	1937	1937	Far Eastern provinces of U.S.S.R.	Late spring Summer	30%	20%	15-25 m μ	<i>Ixodes persulcatus</i> (wood tick)	Wood ticks Woodland mammals and birds

most diseases, and the virus quickly localizes in the central nervous system where it attacks the meninges, the gray and white matter of the brain, and the spinal cord in varying degree (meningoencephalomyelitis). The pathologic lesions in fatal cases are so similar that the etiology cannot be determined by microscopic study alone. The meninges may be hyperemic and infiltrated with small mononuclear cells. Small hemorrhages may be seen in the cerebrum, basal ganglia, midbrain, pons, or spinal cord. Perivascular infiltration with small mononuclear leukocytes may completely fill the Virchow-Robin spaces. Degeneration and necrosis of neurons with neuronophagia may be marked, and in Japanese B encephalitis striking destruction of the Purkinje cells of the cerebellum is observed. Endarteritis and small areas of encephalomalacia may be present. Focal areas of demyelination are prominent in some cases, but are not confined to perivascular areas as is the case in postvaccinal encephalitis. Pulmonary congestion and visceral edema have been noted in fatal cases of Eastern equine encephalitis.

Clinical Manifestations. The clinical picture of the viral encephalitides is extremely variable, and is not sufficiently distinctive to permit an etiologic diagnosis. The several clinical types described may be caused by each virus, i.e.: (1) meningoencephalomyelitis of severe to mild degree; (2) systemic type; (3) abortive type; and (4) clinically inapparent infection. Greater mortality and residual damage have been observed in infants and children than in adults, and the age factor may be of more importance in determining the severity than the particular virus involved. In general terms, the clinical picture is one of an acute infectious disease with death or recovery within two to three weeks, following which the sequelae are fixed and do not progress, in contradistinction to encephalitis lethargica of von Economo, where chronicity and progression of sequelae are common.

MENINGOENCEPHALOMYELITIC TYPE. The incubation period varies from 4 to 21 days, and the onset may be gradual or sudden with fever up to 104° F., headache, nausea, chills and sore throat, or conjunctivitis which persists for one to four days. Nervousness, tremors, or convulsions may be present from the first or may develop after several days of prodromal symptoms. In America, tremor, twitchings, and convulsions are more fre-

quent in infection due to the Eastern equine virus; however, this may simply reflect the greater incidence among infants in the one epidemic of Eastern equine type so far studied. Apathy, mental confusion or disorientation, lethargy, and coma occur, and in fatal cases the coma becomes progressively deeper. The rising temperature may be accompanied by nuchal and spinal rigidity, Kernig's sign, trismus, difficulties with speech, nystagmus, spasticity of the legs, and pareses or paralyses. Some degree of paralysis of the shoulder girdle is said to occur in 75 per cent of cases of Russian Far Eastern encephalitis. The spinal fluid pressure may be normal or only slightly increased. Involvement of the spinal column may show altered deep and cutaneous reflexes, tabetic ataxia, or pain-temperature dissociation. Ocular paralyses are not commonly seen. The acute phase lasts from a few days to three weeks or longer, depending upon the severity of the attack. From one outbreak to another, the mortality varies widely, as do the number with sequelae (see table 91). Protracted coma is rarely seen. Mental deficiency, spasticity, and paralyses or pareses are the most serious sequelae. Personality changes, insomnia, irritability, headache, and apparent psychoneurotic complaints occur in older persons after severe illness, but typical Parkinsonism and chronic progression of symptoms do not occur.

OTHER TYPES. The systemic type is characterized by fever, headache, malaise, gastrointestinal disturbances, chills, sore throat, and conjunctivitis for 4 to 10 days, followed by recovery with no definite signs of central nervous system involvement. Venezuelan equine encephalitis frequently causes this type of disease in man. In the Eastern equine disease a diphasic course was frequent, with a temporary remission of symptoms for one or two days, after which the fever returned, together with signs of meningoencephalomyelitis. Those cases which show only fever and headache of short duration are designated the abortive type. In addition to the manifest clinical disease, inapparent infection occurs, as shown by serologic studies on healthy persons in endemic areas.

Laboratory Findings. The total leukocyte count is usually between 10,000 and 20,000 per cu. mm., with a slight increase in polymorphonuclear leukocytes. However, in Eastern equine encephalitis, total counts up to 66,000 with 90 per

cent polymorphonuclears, have been recorded. The spinal fluid may be clear and under no increase in pressure, but usually the pressure is moderately elevated. Pleocytosis of from 10 to 300 cells is the rule, with lymphocytes predominating. Early in the disease, polymorphonuclear leukocytes may predominate in the spinal fluid, especially in Eastern equine encephalitis, where the total cell count may reach 1000 per cu. mm.

The etiologic diagnosis can be established only by isolation of the virus or by the demonstration of a significant rise in neutralizing or complement-fixing antibodies in the patient's serum during convalescence. Virus has been isolated from the blood and spinal fluid in human cases of Venezuelan equine, Russian Far Eastern, and Japanese B encephalitis; however, this is not possible in a routine hospital laboratory, and, for reasons of expense, equipment, trained personnel, and safety, should not be attempted except in special cases and by trained workers. However, it is only through such studies that knowledge of encephalitis will be advanced. Specimens for virus isolation should be collected aseptically, and kept frozen with carbon dioxide snow or in 50 per cent neutral glycerin at 4° C. until delivered to the virus laboratory. For serologic diagnosis, blood should be drawn very early in the disease, and a second specimen three weeks later. The serum should be separated as soon as the clot has retracted, and kept frozen until both serums can be tested together. If the serum is stored unfrozen at 4° C., a considerable drop in neutralizing antibody titer may occur.

Differential Diagnosis. Etiologic diagnosis of encephalitis is not an easy matter. Epidemic viral encephalitis may simulate, and must be differentiated from, lymphocytic choriomeningitis, which occurs chiefly in the colder months; poliomyelitis, which attacks mostly children and young adults; and brain abscess or tumor, which usually develops gradually and presents localizing signs. Bacterial meningitis, influenza, lead poisoning, diphtheritic polyneuritis, and tuberculous meningitis usually can be diagnosed by means of the clinical history, spinal puncture, the Wassermann test, and x-ray examination.

The presence of an epidemic, the season of the year, geographic location within an endemic area, occupational hazard or known exposure to arthropod vectors, the age of the patient, or the

presence of an epidemic among animals, may give a lead as to the most probable diagnosis. Endemic areas may overlap; i.e., St. Louis and Western equine encephalitis may exist in the same community or, indeed, in the same patient, and epidemic poliomyelitis may coincide with an outbreak of any of the above encephalitides. For these reasons, an etiologic diagnosis frequently is not established in spite of all available diagnostic tests. Furthermore, the epidemic arthropod-borne viruses discussed above rarely cause *sporadic* cases of encephalitis, which are numerically much more frequent than the epidemic types and, incidentally, even more difficult to diagnose. Mumps and lymphocytic choriomeningitis are the most frequent causes of sporadic encephalitis, and a few cases may be caused by varicella, measles, herpes zoster and simplex, German measles, lymphogranuloma, meningo-vascular syphilis, and infectious mononucleosis. It should be emphasized that most cases of sporadic encephalitis cannot be identified with any known virus.

Treatment. There is no specific treatment for any of these diseases after symptoms develop. None of the antibiotics or chemotherapeutic agents at present available are of benefit. Supportive therapy, control of convulsions, maintenance of adequate nutrition, symptomatic treatment, and good nursing care are essential. Physical therapy, muscle training, and psychotherapy may be valuable in the treatment of sequelae. Hyperimmune and convalescent serums have not been beneficial.

Prophylaxis. Formalized vaccines have been prepared for many of these diseases from infected brain, tissue culture, or embryonated eggs, and protection has been demonstrated in animals. Vaccination of horses and mules has proved successful in this country, and woodcutters have been protected by a mouse brain vaccine in Russia. Laboratory workers and others exposed to special hazards should be vaccinated.

Prognosis. The rates of mortality and of sequelae are shown in table 91.

SPORADIC VIRAL ENCEPHALITIS

Sporadic cases of "aseptic" meningoencephalitis, though uncommon, occur in all communities throughout all seasons of the year and, in aggregate, comprise a much larger group than the arthropod-borne epidemic encephalitides. The

etiology of these sporadic cases is largely obscure. Five to 10 per cent are caused by the virus of lymphocytic choriomeningitis, and 10 to 25 per cent by the mumps virus. A few cases are caused by viruses not ordinarily associated with infection of the brain, but these are relatively rare. The remaining 60 to 80 per cent of sporadic infections are not diagnosed by any of the known laboratory procedures available, as shown in table 92.

Table 92

FINAL DIAGNOSIS IN PATIENTS WITH ACUTE NEUROLOGIC MANIFESTATIONS SUGGESTING VIRUS INFECTION OF THE CENTRAL NERVOUS SYSTEM*

Results of a Virus Diagnostic Laboratory over a 2-Year Period

Total Cases Studied	Mumps	Lymphocytic Choriomeningitis	Bacterial and Other	Epidemic Poliomyelitis	Etiology Unknown
277	47	9	33	58	130

* Courtesy, M. Michael Sigel, Virus Diagnostic Research Laboratory, The Children's Hospital of Philadelphia. No cases of Eastern, Western, or St. Louis encephalomyelitis were encountered. Most specimens submitted were from children, and this may account for the high incidence of mumps meningoencephalitis.

Mumps Meningoencephalitis. This is an acute infection of the brain and its coverings by the mumps virus. It may occur in the absence of parotitis, or may precede or follow swelling of the salivary glands. It is most common in childhood, and apparently much more frequent in males than in females. The onset is usually sudden, with headache, fever, nausea or vomiting, and excitement or drowsiness. In children, convulsions may be the first intimation that the child is ill. The neck may be slightly stiff and the deep reflexes hyperactive. The course is usually benign, with complete recovery within 7 to 10 days, although severe encephalitis may occur. Sequelae are more common in adults, with unilateral deafness the most frequent. Meningoradiculitis of cranial nerves may cause temporary ocular or facial paralysis, or blindness. The spinal fluid is usually clear, and under a slightly increased pressure, with elevation of the protein and a pleocytosis of 200 to 400 lymphocytes, range 50 to

3000. The virus can be isolated from the spinal fluid and is excreted in the saliva, even though there is no detectable salivary gland involvement. By means of the complement-fixation test (Henle, Harris, and Henle), a serologic diagnosis frequently can be made during the first days of illness.

Postinfectious Encephalitis. One type of encephalitis is a rare complication of, and comes on during convalescence from, various viral and bacterial diseases. It is commonly called postinfectious encephalitis. It has been observed most frequently following rabies vaccination, smallpox, vaccinia, measles, varicella, herpes zoster, influenza, and pertussis. The pathogenesis and etiology are obscure, although there is some reason to suspect autoimmunization to components of nervous tissue and subsequent local anaphylactic reaction in the central nervous system. The chief lesion is a perivascular demyelination. Frequently the infectious agent cannot be demonstrated in the brain tissue. The onset is usually sudden in the second week of the antecedent illness, and, while the symptoms are variable, headache, vomiting, fever, and drowsiness are common. Paralysis is usually of the spastic type, and somnolence and convulsions frequently precede death. Meningeal symptoms may be prominent or entirely absent. The average case mortality rate is about 40 per cent in postvaccinal encephalitis, and 10 to 30 per cent for all cases of postinfectious encephalitis. Recovery is usually complete, but a small percentage incur permanent damage to the central nervous system.

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Encephalitis Lethargica

(von Economo's Encephalitis, Sleeping Sickness)

Lewis L. Coriell

History
Clinical Manifestations
Laboratory Findings
Diagnosis and Treatment

History. Von Economo's encephalitis, or sleeping sickness, was the first pandemic encephalitis to be recognized clinically. Although a virus agent has never been identified, this is suspected, since adequate bacteriologic studies were negative and the clinical and pathologic findings were characteristic of virus infections. The disease appeared in epidemic form in Europe in 1915, and outbreaks first appeared in the United States in 1918. Sporadic outbreaks continued throughout the world until 1926, but epidemics have not been observed in recent years. Pandemic influenza occurred during this same period.

Most cases of von Economo's encephalitis occurred in people between the ages of puberty and 45 years, and both sexes were affected equally. All epidemics occurred in the winter or early spring. While a number of cases occurred in some communities, contact cases were very rarely observed, and for this reason quarantine was abandoned after a time.

Clinical Manifestations. The clinical manifestations were similar to those described for viral encephalitis in general, with the important ex-

ception that many patients showed *progressive* disease for many months. The over-all mortality was 30 to 40 per cent, being higher in the very young and in the aged. A febrile course was completely absent in some cases, diagnosis becoming evident upon the gradual development of Parkinsonism, athetosis, salivation, mental changes, etc. Two syndromes were seen most frequently: first, the somnolent-ophthalmoplegic type characterized by paralysis of the extraocular and other muscles innervated by cranial nerves, and by oculogyric crises, failure of convergence, apathy, lethargy, stupor, or coma, which persisted for days, weeks, or even months; and second, the irritative complex, characterized by hyperkinetic reflexes, irritability, and exaggerated choreiform or myoclonic movements. Sequelae were common, and the symptoms were frequently progressive long after the acute illness. The most frequent sequelae were pseudopsychoneurosis (i.e., headache, irritability, insomnia, dizziness, fatigue, loss of mental power, etc.), muscle weakness, salivation, athetosis, spasticity, paralysis, or Parkinsonism.

Laboratory Findings. Inflammation of the meninges was not a prominent pathologic finding, and the spinal fluid pressure was usually

normal or slightly increased with a slight pleocytosis of mononuclear cells. The brain at autopsy usually appeared grossly normal or slightly edematous and hyperemic, with minute hemorrhages particularly in the basal ganglia, midbrain, and pons. Histologic sections showed perivascular mononuclear infiltration, neurorrhagia, focal encephalomalacia, and demyelination. Bacterial cultures were uniformly sterile, and sporadic attempts to propagate a virus were disappointing. For a time the virus of herpes simplex was implicated as the etiologic agent, but this was not borne out by later work.

Diagnosis and Treatment. The differential diagnosis was made entirely on the epidemiologic and clinical findings, and treatment was symptomatic. It seems quite clear that this disease does not occur in epidemic form today, but it is by no

means certain that it does not occur sporadically in a modified form, since most cases of sporadic encephalitis are not identified etiologically. It is of interest that present knowledge of the functional relationships of the basal ganglia sprang from studies of Parkinsonism.

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Poliomyelitis

William F. Friedewald

Definition
History
Etiology
Pathogenesis
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. Poliomyelitis is an acute viral disease which, in its most characteristic form, involves various parts of the central nervous system, particularly the motor neurons of the spinal cord, producing varying degrees of weakness and paralysis of voluntary muscles. In the majority of patients, however, the illness is mild and is limited to upper respiratory or gastrointestinal symptoms without signs of central nervous system involvement. A striking feature of the disease is the presence of the virus in the alimentary tract of patients with or without apparent involvement of the central nervous system.

History. Although accurate clinical descriptions of poliomyelitis were not recorded until 1840 by Heine and later, in 1891, by Medin, there seems to be little doubt that the disease occurred in antiquity. Experimental transmission of the disease to monkeys was accomplished in 1909 by Landsteiner and Popper. Flexner and his group demonstrated that the pathogenic agent was a virus. Poliomyelitis is world-wide in its distribution, but large seasonal epidemics are limited to certain countries—namely, the United States, Scandinavia, Holland, Australia, and New Zealand. Recent studies have brought out the interesting finding that the epidemics in these countries have arisen within the last 70 years.

Etiology. The virus of poliomyelitis is one of the smallest known viruses, with determination of its size ranging from 8 to 30 millimicrons in diameter. Recent evidence indicates that there are at least several strains of the virus, differing in their immunologic properties. The virus is

quite resistant, and remains viable in water or in sewage under the proper conditions for as long as four months. Ether, "Merthiolate," and low concentrations of phenol have little effect on the virus. The virus is destroyed by heat, mercuric chloride, oxidizing agents, and ultraviolet light. Free chlorine in concentration of 0.05 part per million will inactivate the virus in 10 minutes. Most strains of human poliomyelitis virus are pathogenic only for the monkey and the chimpanzee. This property helps to distinguish it from other neurotropic viruses, which are usually pathogenic for certain laboratory animals, such as mice, guinea pigs, and rabbits. Certain strains, such as the Lansing, YSK, and MEFL, are characterized by their ability to produce paralysis in rodents as well as in primates. Mouse encephalomyelitis and Teschen disease of swine are naturally occurring viral diseases of animals that have many features of resemblance to human poliomyelitis. The causative viruses, however, are distinct antigenically from human poliomyelitis virus.

Pathogenesis. Poliomyelitis virus is found chiefly in the alimentary tract and in the central nervous system. The significance of the presence of virus in the alimentary tract is not fully understood at present, but it would appear to be an important factor in the pathogenesis of the disease. The available evidence indicates that the virus enters the host by way of the mouth and passes into the gastrointestinal tract, where it may establish itself and multiply. Although the virus may be recovered from the tongue, the pharyngeal wall, and the large and small intestines, the greatest quantity of virus is found in the small intestine. The virus is only rarely found in the nose, and the characteristic lesions of poliomyelitis are not seen in the olfactory bulbs in human poliomyelitis. These findings indicate that the nose is not an important portal of entry of the virus to the central nervous system.

In a small proportion of individuals the virus, for some unknown reason, passes beyond the alimentary tract by way of the nerves and travels eentrinely up the axons to the central nervous system. The cranial nerves, V, VII, and IX (oropharynx), and X (intestinal tract), as well as the sympathetic or visceral afferents to the cord, appear to be the usual pathways to the central nervous system. The virus then spreads along other nerve cells, damaging the anterior horn cells

of the cord and, in some instances, various parts of the brain, including the pons and medulla, mesencephalon, diencephalon, and motor cortex. The lesions produced (varying degrees of nerve cell necrosis, edema, perivascular cellular infiltrations, and neuronophagia) are not pathognomonic of poliomyelitis, but the distribution of the lesions in the central nervous system is quite characteristic.

There is no general agreement as to the manner in which the virus is spread through a population. The available evidence indicates that poliomyelitis is essentially a contagious disease. The epidemiologic pattern is consistent with the passage of virus from person to person as a result of intimate contact, chiefly in the home. Apparently the virus is as widely distributed as that of measles during epidemic periods. Subclinical cases of measles, however, appear to be rare in contrast to poliomyelitis, in which the great majority of infections are subclinical or abortive. Poliomyelitis virus has been recovered from feces up to 19 days prior to the onset of illness, and persists in the feces for a few weeks to several months thereafter. Another possible method of disseminating the virus is by coughing or sneezing, since the virus may be present in the pharynx. Although poliomyelitis virus has been demonstrated in feces, sewage, water, flies, and food, the importance of these possible modes of spread has not been determined.

Various other factors are involved in the pathogenesis of poliomyelitis. The highest incidence of the disease occurs during the summer months. Negroes are less susceptible than whites. Fatigue, chilling, and pregnancy appear to be predisposing factors. It has been demonstrated in experimental infection in monkeys that physical exhaustion or chilling during the incubation period increases the incidence and severity of paralysis. The more serious bulbar type of the disease may follow operative procedures about the nose and mouth. There seems to be little doubt that tonsillectomy performed during an epidemic period enhances the susceptibility to bulbar poliomyelitis.

Manifestations. In considering the manifestations of acute poliomyelitis, it must be emphasized that the disease is primarily systemic in nature, and involvement of the central nervous system, although its most characteristic feature, occurs in only a small percentage of patients.

Although the severity and extent of the acute illness shows great irregularity, the sequence of events in most cases follows a fairly consistent pattern. The incubation period is generally believed to be from 7 to 14 days, with 3 to 21 days as outside limits. The onset is similar to that of many acute illnesses: malaise, headache, low-grade fever, a mild soreness of the throat, nausea, and occasionally vomiting. After one to three days the fever and symptoms subside, to be followed in one to seven days by a more severe illness, with an exacerbation of the initial symptoms, and by signs of the central nervous system involvement. This gives rise to the characteristic biphasic fever curve. It should be pointed out, however, that this biphasic illness is recorded in only about one fifth of the cases, probably because the initial illness is so mild and nonspecific that it is overlooked by the patient. Furthermore, there seems to be little doubt that in a large number of patients the disease does not progress beyond the initial mild illness, without any signs of central nervous system involvement, and with negative spinal fluid findings. This frequently is referred to as *abortive poliomyelitis*.

In the second phase of the febrile disease, the patient appears acutely ill, is apprehensive and hyperirritable, sweats profusely, and wishes to be left alone. Headache is a prominent symptom, particularly in adults, and frequently is associated with vomiting. The temperature is usually 101° to 103° F., but may be higher in the bulbar or encephalitic type of the disease. Varying degrees of spasm and pain in the muscles of the neck, back, and posterior thighs are observed, with stiffness of the neck and back. Attempted flexion of the neck or back is painful. The Kernig test is usually positive. Here again, the disease may terminate. This is referred to as *nonparalytic* or *preparalytic poliomyelitis*.

Spasm, weakness, or paralysis of other muscles depends on the distribution and severity of the lesions in the central nervous system, and occurs usually from the second to the fifth day of the febrile illness. It is characteristic of poliomyelitis that the muscle involvement is patchy in its distribution, affecting a group of muscles, an individual muscle, or a portion of a particular muscle. The lower extremities are most commonly involved, although any of the muscles of the thorax, abdomen, and extremities may be affected. *Muscle spasm* can be felt by palpation

and can be emphasized by gentle stretching. The actual mechanism of the spasm has not been demonstrated. The clinical picture is that of overactivity of the anterior horn cells. Recently it has been suggested that involvement of the internuncial neurons may be a factor in this process. The *paralysis* is flaccid in type, and its distribution does not coincide with the areas of spasm or sensitivity. It has the characteristics of a lower motor neuron paralysis and is most variable in its extent and distribution. The abdominal and deep reflexes are variable, but frequently are depressed or absent. *Deformities* may be observed in the extremities, back, and pelvis when muscles are not balanced in strength as a result of spasm or paralysis. When the paralysis is total, the part adopts a flail position.

Clinical manifestations referable to involvement of the medulla and the base of the brain occur in only a small proportion of patients. This condition, referred to as *bulbar poliomyelitis*, presents the gravest manifestations of the disease. One or more of the motor cranial nerves may be affected, causing lid lag, strabismus, facial palsy, and paralysis of the palate, pharynx, tongue, or larynx. More serious, however, is involvement of the respiratory center and the circulatory center. Involvement of the respiratory center is manifested by anxiety, restlessness, increasing pulse rate, and variations in the rate and depth of respirations with prolonged intervals between inspirations. As failure of the center progresses, there is confusion, delirium, and coma with increasing periods of apnea and Cheyne-Stokes respiration. Atelectasis, pulmonary congestion, and cyanosis are common at this stage. It must be remembered, however, that respiratory difficulty also results from weakness or tightness of the muscles of respiration, particularly the intercostals and the diaphragm; from pharyngeal paralysis with accumulation of mucus; from paralysis of the vocal cords, producing obstruction; and from paralysis of the abdominal muscles, which interferes with coughing and the removal of secretions from the throat. Patients with involvement of the circulatory center present a dusky red appearance, a rapid pulse rate (150 to 200) which is irregular and thready, and a pulse pressure which may be as low as 10 mm. Hg. As circulatory failure progresses, the blood pressure drops to shock levels, the pulse is imperceptible, and the skin is

cold and clammy. Delirium, coma, and hyperthermia are seen in the terminal stage. A more diffuse involvement of the brain gives rise to the *encephalitic* form of poliomyelitis in which anxiety, hyperexcitability, muscular tremors and twitching, delirium, coma, and occasionally convulsions are the principal symptoms.

The acute febrile illness in the various forms of poliomyelitis usually does not last longer than four to seven days, and during this time the muscle paralysis reaches its maximal extent. Muscle spasm and pain may continue, however, for another week or two after the fever has subsided.

Laboratory Findings. At the present time there is no specific test available for the diagnosis of poliomyelitis. The need for such a test is indeed great when it is realized that most cases are of the abortive or nonparalytic types and are difficult to differentiate from other infectious diseases. *Virus* may be isolated from the stools of patients by inoculation of monkeys, but this procedure is expensive and time-consuming, and requires laboratories with special skills and experience. *Neutralization tests* with mouse-adapted strains of the poliomyelitis virus have been studied extensively. A large proportion of individuals (up to 80 per cent) have antibodies in their serum against these viruses. The relation of these antibodies to immunity is not clear, since there is no apparent correlation between the antibodies and susceptibility to a paralytic infection. These tests have not proved to be of any value in the diagnosis of poliomyelitis. In fatal cases of poliomyelitis, careful examination of many sections of the brain and cord usually reveals changes sufficiently characteristic to establish the diagnosis. Certain other neurotropic viral infections (lymphocytic choriomeningitis, equine encephalomyelitis, St. Louis and Japanese B encephalitis, and mumps meningoencephalitis) can be ruled out by serologic methods and by isolation of the specific virus.

Routine tests of the blood and spinal fluid are of some value in providing supporting evidence for the diagnosis of poliomyelitis. The spinal fluid is usually clear or only slightly hazy, and under normal or slightly increased pressure. The cell count in both paralytic and nonparalytic infections ranges from 10 to 500 per ml., but is usually less than 200 cells per ml. The predominant cells are small lymphocytes and the percentage of polymorphonuclear cells, although

variable, particularly early in the illness, rarely exceeds 50 per cent of the total. The proteins are increased, but usually not higher than 60 to 125 mg. %, and may not reach maximum levels until the second or third week of illness. The spinal fluid sugar and chlorides are within normal limits. Examination of the blood usually reveals a mild leukocytosis with a slight shift to the left, although normal counts, particularly in adults, are not unusual. The sedimentation rate remains normal.

Differential Diagnosis. Poliomyelitis frequently gives rise to considerable difficulty in diagnosis because of the systemic nature of the disease, the similarity of the manifestations of the initial illness to other infections, and the lack of specific diagnostic criteria. Such diverse conditions as scurvy, fractures, meningismus, influenza and other upper respiratory infections, acute rheumatic fever, osteomyelitis, bacterial meningitis, syphilis, acute otitis media, transverse myelitis, cord tumors, and hysteria may be encountered in differential diagnosis. The clinician must rely on a careful evaluation of the course of the illness, the physical findings, and the available laboratory aids. In some instances it is an exclusion diagnosis.

A presumptive diagnosis of abortive poliomyelitis usually is justified only when an unexplained febrile illness of the sort already described occurs in siblings of children who have manifest poliomyelitis. The diagnosis is more definite in patients who, in addition to the initial symptoms, develop a stiff neck and back and abnormal spinal fluid findings, particularly during an epidemic of the disease. The differentiation between poliomyelitis and various neurotropic viral infections, however, may be possible only after detailed virus studies. In general, the diagnosis of poliomyelitis should be questioned if the following are found: a febrile illness continuing longer than a week to 10 days; convulsions, unless due to anoxia resulting from respiratory failure; a loss of sensation; a spinal fluid cell count of 500 to 1500 cells, which, if predominantly lymphocytes, suggests mumps virus or lymphocytic choriomeningitis infection; a high spinal fluid protein (above 150 mg. %), which raises the question of Guillain-Barré syndrome or other forms of polyneuritis; a diffuse progressive weakness; and acute localized tenderness as seen in bursitis, arthritis, or acute osteomyelitis.

Treatment. There is no specific therapeutic agent against the virus itself. Treatment during the acute stage is symptomatic and supportive, aimed at saving life, relieving symptoms, and preventing deformity. The patient is isolated according to the regulations of the local health authorities. It must be appreciated, however, that the large number of nonparalytic cases and so-called healthy carriers of poliomyelitis virus during an epidemic period make the isolation of the relatively few manifest cases an ineffective method of controlling the disease. Since the virus is found in the stools of patients for two to three weeks or longer, special precautions such as those used in handling stools from patients with typhoid fever should be followed.

Muscle tenderness and pain are relieved by proper positioning, together with hot wool compresses and gentle passive motion. In general, sedatives and analgesics are contraindicated because of possible respiratory failure, although aspirin can be used if desired. Curare and neostigmine have been used to relax spasm, but they are not advocated for general use at present. Although hypertonic solutions of glucose have been used in the hope of relieving cerebral edema, there is no evidence that such an effect is produced. Furthermore, one of the basic principles of treatment during the acute stage is that the patient should be disturbed as little as possible. The indications for the administration of parenteral fluids, therefore, are the same as those in any type of illness—namely, to maintain adequate fluid and salt balance.

The treatment of bulbar poliomyelitis presents special problems which require careful observation to determine the indications for immediate therapy. Most of the deaths are due to failure of the respiratory or cardiac centers. Oxygen is given, usually by nasal catheter, since oxygen tents and masks make it difficult to keep the pharynx clear of mucus. It is extremely important to keep the throat clear of secretions by postural drainage and suction. Tracheotomy is rarely indicated, but should be performed in patients with obstruction of the airway that cannot be relieved by the usual procedures. In the presence of pharyngeal paralysis, penicillin and possibly streptomycin should be used prophylactically. No food or liquids are given by mouth. During the first few days, parenteral fluids are given. When the patient's condition improves,

tube feeding is instituted and continued until adequate amounts can be taken by mouth. Moist heat is used to relieve tight muscles of the back, thorax, and abdomen, which may be interfering with respiration. The respirator may be of great aid to patients with certain types of respiratory difficulty, but it should be emphasized that considerable experience and judgment is required for its proper use. The respirator is most helpful in those cases with paralysis of the intercostal muscles and the diaphragm, due to damage of the anterior horn cells of the cord.

After the acute illness has subsided, treatment is directed to restoring the patient's functional capacity to its maximum. This requires an intelligent program of rehabilitation and muscle re-education, in which the specialized training and equipment of the physiotherapist play a most important role. Mechanical support may be required for a weak extremity, back, or abdomen. Reconstruction operations usually are not considered until at least two years have elapsed after the onset of illness.

Prognosis. Most of the fatalities occur in patients with the bulbar type of poliomyelitis, the fatality rate in some outbreaks being as high as 60 to 80 per cent. Fortunately, bulbar poliomyelitis occurs in only a very small proportion of patients infected with the virus. Those who survive usually show complete recovery from the symptoms and signs of bulbar origin. The spinal form of poliomyelitis is rarely fatal, except for occasional patients with cervicothoracic involvement. The recovery of muscle function is dependent upon the severity of the injury to the anterior horn cells and the number of cells injured. If enough of the cells supplying a muscle are destroyed, there can be no recovery. Usually, however, the anterior horn cells are injured but not killed, and show a remarkable degree of recovery. In such cases muscle function slowly returns, although it may be greatly hindered by deformity and stretching. Return of muscle function may occur over a two-year period, but the greatest degree of recovery is observed within the first 6 to 12 months.

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Rabies

T. F. Sellers

Definition
History
Etiology
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Laboratory Findings
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Treatment
Local
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Prognosis

Definition. Rabies is an acute viral infection of the central nervous system. All warm-blooded animals, including man, are susceptible, but the canine species is the natural reservoir of the disease. Transmission is by the saliva of the infected animal.

History. A disease of great antiquity, rabies was described by Democritus as early as the fifth century B. C., and later by Galen and Aristotle. Celsus, about 100 B. C., wrote of cauterizing the bites of rabid animals. During the first decade of the nineteenth century 200 human deaths were reported in central Europe annually. By 1819, this rose to 350. Control measures were then instituted and this disease in dogs and man declined sharply, especially in England.

In North America, the disease in dogs and foxes was first reported near Boston in 1786. By 1900 it had invaded all populous sections of the continent. In recent years, rabies in vampire bats has become an economic problem of livestock production in Central and South American countries. No country or continent except Australia has been entirely exempt (Johnson).

Etiology. The etiologic agent of rabies is a filtrable virus which can be demonstrated readily

throughout the central nervous system, and in the salivary glands and saliva. Occasionally, it may be found in the lacrimal, mammary, and adrenal glands, but not in their secretions or in the blood or other tissues of the body.

Pathogenesis. Transmission occurs in nature only by the inoculation of the infectious saliva through the skin. Infection does not occur by contact with the unbroken skin or by ingestion. From the point of entry, the virus travels along afferent nerves to the brain and thence by way of efferent nerves to the salivary glands (Harris). With very rare exceptions, man is infected only by the bite of an animal (usually the dog) in the acute stage of rabies. The virus is not present in the saliva of the animal in the incubation period earlier than two or three days prior to the prodromal clinical onset.

Manifestations. The incubation period ranges in nature from 10 to 90 days or more, averaging three weeks, but is somewhat longer in man. While the symptoms in different animals vary according to the species, those in the dog are most important in that this animal is the principal reservoir and source of danger to man.

The premonitory signs in the dog are change of disposition, increasing restlessness, and congestion of the mucosa of the eyes and nose. Within 10 to 24 hours the period of excitability sets in, including increasing viciousness, loss of appetite, excessive barking, and howling. If at large, the animal tends to fight other animals, or attack moving objects in range of vision. The eyes appear glassy and glary, due to dilatation of the pupils. At

this time or later, the classic dropping or sagging of the jaw may be noted. Increased salivation and paralysis of the throat causes the "foaming at the mouth." Inability to swallow, not fear of water, accounts for the idea of "hydrophobia." Death invariably follows within two to ten days following clinical onset, the average duration of the disease being from three to four days.

In man the earliest subjective signs of onset of the disease are mental depression and a feeling of apprehension. At this time or later, the victim may complain of headaches, sore throat, and of radiating pain and tingling in the region of the site of exposure. If the site is in the hand, pain may involve the entire arm and shoulder. This has diagnostic importance, occurring in about 80 per cent of cases. Another early manifestation is a general hyperesthesia of the skin and sensitivity to drafts and noise. There is apt to be a moderate rise in temperature, as well as pupillary disturbances, especially dilatation.

In two to three days the period of excitation sets in, and in man this usually predominates up to death. There is increasing nervousness and sensitivity to physical stimuli. The patient cannot sit still and, if not restrained, moves about aimlessly. His speech is disconnected and excited, shifting from one topic to another. If put to bed, he tosses about constantly, searching futilely for a comfortable position. The attitude and facies of intense apprehension increase. The eyes are bright and rapidly shifting, but, despite the fear and anxiety, there are no tears. Although there are periods of apparent delirium of increasing frequency, mental orientation is usually good. Viciousness, such as attempts to bite or fight attendants, is rarely manifested.

The most specific and constant symptom is difficulty in swallowing. This is not a simple paralysis of the deglutition muscles, but is due to the reflex irritability of the center of deglutition, causing spasms of the larynx at the very thought of swallowing, not water alone, but any fluid or food. These spasms are reflected to the respiratory center, causing choking and apnea so severe in some cases as to cause death.

As the disease progresses, all cerebral centers become so involved that no muscular system escapes. Generalized tremors and convulsions occur with increasing frequency. Death may occur suddenly during a convulsive seizure, or from cardiac

or respiratory failure, usually within three to five days after onset.

Occasionally, if prolonged, the excitation stage subsides and gives way to paralysis, first of the muscle groups and finally of respiration, and the patient expires quietly.

Laboratory Findings. During the course of the disease, the laboratory findings are not significant. The erythrocyte count is not altered, except at times increased due to general dehydration. The leukocyte count may be increased to 20,000 or more. No significant change occurs in the urine or spinal fluid.

The gross pathology findings at autopsy are not specific. Microscopic findings likewise are of little diagnostic value, except the Negri or inclusion bodies. These, when found, are definitely pathognomonic. While they are most apt to be found in the cytoplasm of the large pyramidal cells of the Ammon's horn or hippocampus, Negri bodies usually are demonstrable in the cortex, the Purkinje cells of the cerebellum. They vary in size from 1 to 30 microns or more in diameter, and in shape from spheroid to oval and elongated. When properly stained, they are sharply defined, and are easily distinguishable from inclusion bodies of other diseases. Failure to find Negri bodies even after long and thorough search does not exclude rabies. When they are not found, one should resort to intracerebral inoculation of suspected brain tissue into white mice. This procedure is very reliable and, if positive, is conclusively diagnostic.

Differential Diagnosis. Clinical diagnosis of rabies in man is not difficult if there is available a history of definite exposure in the form of a bite by a rabid dog. In the absence of such history, however, difficulty may be encountered in atypical cases.

If the patient has previously received anti-rabic vaccine, treatment paralysis must be considered. This may resemble the rarer forms of paralytic rabies, but the excitation phase so common to human rabies does not occur in treatment paralysis. Bulbar and spinal types of poliomyelitis may be confused with rabies. The trismus of the jaw and the constant muscular spasticity so typical of tetanus should not be confused with rabies.

Treatment. Once the disease sets in, there is no specific therapy yet known other than palliative measures in the attempt to keep the patient as

quiet and comfortable as possible. Recent experimental development of highly potent antiserums may offer some hope for the future, but no authentic instance of recovery in man has been established. Large doses of barbiturates—e.g., "Amytal" (7.5 gr., intravenously) may reduce the spasms but must be repeated often. Opiates and anesthetics are of little value. Glucose and fluids administered by vein may prolong life by counteracting dehydration.

LOCAL. Bites or scratches made by any animal should be cleaned thoroughly and instilled with strong soap solution, prolonged for 10 or 15 minutes. Cauterization with nitric acid or other corrosive chemicals is no longer advocated.

PREVENTIVE. Antirabic vaccine for human use is a finely divided suspension of the brain tissue of rabbits sacrificed in the terminal paralytic stage of fixed virus rabies. The suspension is subjected to chemical or physical treatment sufficient to kill or attenuate further the rabies virus. While there are several methods of preparing the vaccine, the most widely used procedure in the United States consists of a 5 per cent suspension of rabbit brain tissue in 1 per cent phenol solution. This is killed or inactivated by incubation at 37° C. for several days, and administered to the patient by daily injections of 2 ml. given subcutaneously for 14 days.

Brain tissue, like all animal tissues, is a combination of a great variety of complex protein substances. Some, if not all, of these protein substances may stimulate the formation of more or less specific sensitizing antibodies, when repeatedly injected into man or animals. It is to be expected, therefore, that repeated injections of antirabic vaccine may bring about varying combinations of local and systemic reactions, ranging from immediate circumscribed erythema and swelling at the site of injection to immediate or delayed urticarial rashes, often accompanied by fever, malaise, and swelling of the joints. As a rule, reactions of this nature are not dangerous and do not contraindicate the completion of the prescribed series of injections. However, there is another type of reaction which specifically affects the nervous system and manifests itself in several ways, ranging from a simple neuritis to a profound encephalomyelitis and paralysis. This serious and often fatal complication, known as treatment paralysis, while rare, occurs more frequently than does rabies in persons not actually

bitten by the teeth of rabid animals. Therefore, each case must be individualized and the decision as to the use of the vaccine should rest, first, on the evidence of rabies in the biting animal, and, second, on the nature of the exposure.

The animal is potentially infectious:

1. If clinically rabid—with or without laboratory confirmation.
2. If its brain shows Negri bodies—with or without clinical evidence.
3. If it disappears, or is killed before clinical or laboratory confirmation can be obtained. *It is very important, therefore, that the animal be kept alive under close observation for a week or ten days.*

For persons exposed to a potentially rabid animal *antirabic vaccine is indicated:*

1. For visible wounds, known or suspected to have been made by the teeth of the animal.
2. For fresh, open, preexistent abrasions suspected to be contaminated by saliva of the animal.
3. For small children who may have been in intimate contact with the animal, but who are too young to give reliable testimony.

To avoid the risk of treatment paralysis or sensitization to future treatment, *antirabic vaccine is contraindicated:*

1. For contact of saliva with unbroken skin or with old, partly healed abrasions.
2. For bites through un torn clothing.
3. For any indirect exposure, such as petting the animal, handling objects contaminated with saliva, or drinking the milk of rabid cows.
4. For any bites inflicted one week or more before the animal began to show symptoms of rabies.
5. Since treatment paralysis appears to be an allergic reaction, extreme caution should be taken in re-treating persons previously treated.

Prognosis. So far, rabies in man has been invariably fatal, but the possibility of a mistake in diagnosis warrants the diligent practice of every available therapeutic device to the very end.

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Herpes Zoster

Lewis L. Coriell

Definition
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Definition. Herpes zoster, also called shingles or zona, is an acute infectious disease of man, caused by a virus and characterized by unilateral, segmental inflammation of the posterior root ganglions or extramedullary ganglions of cranial nerves, and by a herpetic eruption of the skin along the peripheral distribution of the involved nerve.

History. The disease was called *zona* (a girdle) by the Greeks, because of the bandlike distribution of the eruption about the trunk. Bärensprung (1863) pointed out the inflammatory reaction in the dorsal root ganglion, and Landouzy (1884), on purely clinical grounds, called attention to the infectious nature of the disease. Bokay (1888) suggested a possible etiologic relationship between zoster and varicella. Head and Campbell (1900) described fully the lesions of the central nervous system, and Lipschütz (1921) defined the specific histopathology of the skin lesions. Successful transfer by inoculation of vesicle fluid into human subjects was first reported by Kundratitz (1925).

Etiology. The virus of herpes zoster is a relatively large virus (204 by 240 m μ). It is a strict parasite of man. Electron micrographs of vesicle fluid have shown the virus to be similar in size and shape to the virus of varicella. The virus

may be plentiful in early vesicles, but is typically scanty after 24 hours. The elementary bodies are just visible by the light microscope, and Amies has demonstrated microscopic agglutination by convalescent zoster serum as well as by convalescent varicella serum. The absence of a susceptible laboratory animal has hindered immunologic studies. However, Goodpasture demonstrated the presence of typical inclusion bodies in pieces of human epidermis grafted upon the chick chorioallantoic membrane, and subsequently inoculated with zoster vesicle fluid. This work has been confirmed by Blank (1948), and further improvements in the technic may yield a suitable method for laboratory cultivation of the virus.

Epidemiology. Infection is less common in children than in adults, occurs at all seasons of the year, and is slightly more frequent in males than in females. In the United States the majority of, but not all, patients with herpes zoster give a history of a previous attack of varicella in childhood. Epidemics have occurred in schools and barracks, but are not common. Outbreaks of herpes zoster have occurred in contacts of a patient with varicella, and vice versa. The grouping of these secondary infections suggests that zoster is infectious only during the first two or three days after appearance of the eruption. Secondary zoster following trauma such as spinal puncture, administration of arsenic or bismuth, spinal cord tumor, tabes, and lymphatic leukemia have suggested the possibility that the virus may remain dormant in the tissues over long periods of time. On the basis of the evidence

available, the viruses of herpes zoster and varicella are closely related, if not identical, and it is tempting to explain the various clinical manifestations by postulating one virus which causes different diseases in the susceptible and the partially immune subject. Final solutions of this problem must await the development of new laboratory technics.

Pathogenesis. Whether the virus enters the skin and travels up the sensory nerve or extends peripherally is purely a matter for conjecture at the present time. The virus has been demonstrated only in the skin lesions, although an inflammatory reaction is a constant finding in the segmental nerve, its sensory ganglion, and the posterior horn of the spinal column (posterior poliomyelitis). The regional lymph nodes show an acute inflammatory reaction. The anterior horn, the meninges, and the brain may be involved. The histologic central nervous system lesions are: infiltration with small round cells, hemorrhage, destruction of ganglionic nerve cells, and secondary gliosis.

The skin vesicle is confined to the epidermis, while the corium is congested and infiltrated with inflammatory cells. In the margin of the vesicle are epithelial cells undergoing ballooning degeneration, some of which contain eosinophilic intranuclear inclusion bodies which displace the basichromatin to the periphery of the enlarged nucleus. Multinucleated giant cells may be present, each nucleus containing an inclusion body. Within two or three days, inflammatory cells fill the vesicle, and healing progresses from below, frequently with slight scarring.

Manifestations. The incubation period varies from 7 to 21 days. A preeruptive and posteruptive stage are distinguished. The preeruptive stage consists of fever and constitutional symptoms, with pain or hyperesthesia over the segmental distribution of the involved nerve for two to four days. Following this, an erythematous dermatitis appears which quickly becomes papular and vesiculates, with large or small grouped vesicles on an erythematous base. The vesicles, at first clear, become cloudy within two to three days, then crust and dry after five to ten days. The eruption may appear first near the spinal column, with successive crops over the distal distribution of the nerve. Headache and meningismus are not uncommon. Pain is frequently slight or absent in young children, but

may be intense and refractory to treatment in older people.

The disease is almost invariably unilateral. The regional lymph nodes are enlarged and tender. Over 75 per cent of cases occur between the second dorsal and second lumbar vertebrae, and rarely below the elbow or knee. Involvement of the fifth cranial nerve is next in frequency, and when the vasociliary branch is involved, the cornea, sclera, or ciliary body may be permanently damaged; the first branch of the fifth nerve is affected more frequently than the second or third. Disease of the geniculate ganglion may lead to zoster of the concha of the ear or the external auditory canal, and loss of taste (Hunt syndrome); this is often accompanied by paralysis of the seventh nerve. Paralysis is not uncommon in cephalic and cervical zoster, but is rare in zoster of the trunk. Second attacks are exceedingly rare, and should suggest an alternate diagnosis of localized herpes simplex. In some patients, a generalized vesicular eruption simulating varicella appears shortly after the appearance of the localized lesion (zoster generalisata).

Laboratory Findings. The vesicle fluid is sterile bacteriologically. The spinal fluid pressure may be increased, and a pleocytosis of up to 300 mononuclear cells has been observed.

Differential Diagnosis. In the preeruptive stage, the diagnosis is difficult and is usually confused with many other more common causes of pain. After the unilateral eruption appears, the clinical features are so characteristic that diagnosis is simple. Occasionally, localized herpes simplex along the distribution of a segmental nerve may simulate zoster, including the localized pain and tenderness; that this is herpes simplex can be confirmed in the laboratory.

Treatment. Treatment is directed at increasing the patient's comfort and preventing secondary infection. The severe postherpetic pain in elderly persons may be difficult to manage and may be refractory to all types of therapy. Sedatives and analgesics may be needed, but local anesthetic ointments are not very effective; intramuscular thiamine has been recommended; nerve block or section of the posterior root, and deep roentgenotherapy over the affected ganglia, are not always successful but should be considered in patients with protracted pain. There are reports of dramatic and permanent

relief of pain in herpes zoster following paravertebral sympathetic nerve block with procaine. To prevent bacterial infection, antibiotic therapy and painting unruptured vesicles with collodion are recommended; when weeping, crusting, and secondary infection are severe, wet dressings are indicated. Local treatment of corneal lesions should be supervised by an ophthalmologist, and in these cases, Gundersen has reported good results with early transfusions of whole blood from persons who have recently recovered from herpes zoster.

Prognosis. It is very unusual for serious complications to follow inflammation of the spinal ganglia. Partial paralysis of the third, fourth, sixth, and seventh cranial nerves, or hypesthesia, may persist for some time. Significant impairment of vision occurs in 80 per cent of zoster ophthalmicus.

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Mumps

William F. Friedewald

Definition
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Definition. Mumps is an acute, contagious disease of virus etiology, usually involving the parotid gland and, less frequently, the other salivary glands, the testes, ovaries, pancreas, breast, and the central nervous system.

History. Mumps has been recognized as a distinct clinical entity for many centuries. The disease was clearly described by Hippocrates in the fifth century B.C. The nature of the etiologic agent was not conclusively demonstrated, however, until 1934 when typical parotitis was produced in rhesus monkeys by inoculating them with saliva from patients. Further studies re-

vealed that the transmissible agent was a virus. The discovery in 1945 that the virus would multiply in embryonated hen's eggs has provided a simple method for obtaining the virus in quantity, and has led to a rapid advance in knowledge concerning its properties.

Etiology. The mumps virus appears to be approximately 100 millimicrons in diameter. There is some evidence to indicate that there is more than one strain of the virus, as demonstrated by immunologic studies. The virus can be preserved in the frozen or dried state. It is readily inactivated by formaldehyde solution, ultraviolet light, or by heating at 55° C. for 20 minutes. Mumps virus, like influenza and certain other viruses, has the capacity to agglutinate the red blood corpuscles of various animal species, and this property has been used in tests for detecting the virus and specific serum antibodies. In addition to man and certain species of monkeys, the chick em-

bryo is highly susceptible to infection with the virus.

Pathogenesis. The virus is transmitted by way of droplets from the secretions of the mouth. It may be airborne over short distances. The infected individual can transmit the virus from 24 to 48 hours before to at least 6 days after the onset of salivary gland enlargement. The virus presumably gains entrance to the salivary glands by way of the ducts, and there it causes the characteristic inflammation and swelling. Involvement of other glandular structures, such as the testes, ovaries, and pancreas, must be due to blood stream dissemination of the virus. This may occur with or without parotitis. The virus also may invade the central nervous system, producing a meningoencephalitis.

The highest incidence of mumps occurs in the winter and early spring, although it occurs as an endemic disease throughout the year in urban populations. The disease is most prevalent in the 5- to 15-year age group, and by the age of 17 the large majority of an urban population has been infected. The incidence is lower in rural groups. Recent work based on immunologic tests has emphasized the fact that subclinical infections occur in about one third of cases. In adult populations it appears that 60 per cent have had manifest mumps, 30 per cent have had inapparent infections, and 10 per cent are still susceptible to the disease. A manifest or subclinical infection apparently induces a lifelong immunity to the disease.

Manifestations. The incubation period varies from 12 to 35 days, with an average of 18. The onset is usually moderately acute with malaise, headache, anorexia, chilliness, and fever, together with pain and swelling of one or more of the salivary glands. The parotid glands most commonly are affected, with bilateral involvement occurring in about 70 per cent of cases. Combined parotid and submaxillary involvement is observed in about 12 per cent of patients. Usually only one gland is involved at the onset of illness, and swelling and pain of the other glands may not be manifest until one to three days later. The glandular swelling varies considerably in extent and it has a doughy or elastic consistency. The skin over the gland is tense, but not reddened, and pain is increased by movements of the jaw. The orifice of Stensen's duct is red and edematous, and no discharge can be obtained

from the duct. Edema and redness of the orifice of the duct often appears before there is manifest involvement of the parotid gland. The glandular swelling reaches its maximum within 48 hours and persists for 7 to 10 days. The temperature varies from 100° to 104° F. and the pulse rate tends to be slow. Duration of fever is usually two to four days.

The other manifestations of mumps are more likely to occur in persons past the age of puberty. These manifestations may occur with or without salivary gland involvement. In the male ~~Xepididymo-orchitis~~ occurs in as high as 30 per cent of the cases. It is most commonly observed from one to eight days after the onset of illness, often accompanied by a chill, fever of 102° to 104° F., severe pain, vomiting, and often prostration. Symptoms last about one week. Atrophy of the involved testis occurs in about 50 per cent of cases. Fortunately, bilateral involvement occurs in only 15 per cent of the patients with testicular infection. ~~XProstatitis and bartholinitis~~ occasionally are observed. *Oophoritis* occurs in about 5 per cent of adults. Occasionally acute *pancreatitis* and *mastitis* in both men and women are observed. Rare cases of diabetes seem to have followed pancreatitis of mumps.

~~XMeningoencephalitis~~ occurs in both children and adults. Symptoms referable to the central nervous system usually appear four to seven days after the onset of salivary gland swelling. The symptoms vary in severity and include fever, severe headache, drowsiness or coma, nausea and vomiting, stiff neck, and occasionally facial twitching. It must be remembered that the signs of central nervous system involvement may be minimal or even absent. ~~X~~A pleocytosis can be demonstrated in about 40 per cent of mumps patients, but ~~X~~definite signs of central nervous system involvement occur in only about 5 to 10 per cent of cases. The outcome is rarely fatal and the patient recovers completely in a few days to two weeks. *Deafness* may occur during the acute illness or during convalescence, and is often complete and permanent. *Neuritis* of the facial, trigeminal, and optic nerves may occur. ~~X~~*Presternal edema* is observed in about 1 per cent of patients, usually associated with submaxillary glandular involvement. There is a painless, pitting edema of the soft tissues overlying the sternum, which usually occurs five to six days after the appearance of the glandular swelling

and persists for five days on the average. The edema appears to be due to obstruction to lymphatic drainage by the swollen salivary glands. Other manifestations of mumps virus infection which occasionally occur are involvement of the thymus and of the thyroid. A variety of *ophthalmic lesions* have been reported in association with mumps. These include conjunctivitis, dacryocystitis, keratitis, retinitis, scleritis, uveitis, iritis, and optic neuritis, as well as ocular palsies.

Laboratory Findings. Mumps virus may be recovered from patients by inoculation of saliva or spinal fluid into the parotid duct of monkeys or into the amniotic sac of developing chick embryos. In monkeys a typical parotitis is produced. Chick embryos usually are inoculated on the eighth or ninth day of incubation, and after four or five days the amniotic fluid is removed. Virus can be demonstrated in the fluid by the red corpuscle agglutination test, by the complement-fixation test, or by infectivity tests in monkeys.

During convalescence, specific antibodies against the virus appear in the circulating blood. These antibodies will fix complement in mixture with mumps virus antigen in extracts of monkey parotid glands or in the fluids of infected chick embryos. The antibodies may be demonstrated also by inhibition of the red corpuscle agglutination reaction or by neutralization of the infectivity of the virus in chick embryos. It is essential in all of these methods to compare a serum sample taken during the acute illness (within four to five days) with a sample taken during convalescence (10 days to three weeks). A rise in titer is diagnostic of mumps virus infection. After four to six weeks the concentration of antibodies begins to fall, and usually after six months no antibody can be detected or only relatively low levels are present. A skin test has been developed recently using an intradermal injection of a dilute suspension of infected monkey parotid or chick embryo fluid. A negative reaction indicates susceptibility to infection, whereas a local hypersensitivity reaction measuring 11 mm. or greater, consisting of erythema and slight induration within 24 to 48 hours following injection, indicates previous infection with the virus and probable immunity.

The total leukocyte count is usually within normal limits in uncomplicated mumps. The differential count may show a relative increase in

lymphocytes. In epididymo-orchitis and meningoencephalitis 25 to 30 per cent of cases have counts from 10,000 to 20,000. In some instances a lymphocytosis and an increase in the monocytes may be observed. The serum amylase is usually elevated during the first week of illness as a result of the parotitis. Involvement of the pancreas also causes an elevated serum amylase and, in addition, an elevated blood sugar. The spinal fluid in cases of meningoencephalitis is usually under increased pressure and contains from 150 to 1500 cells per cu. mm., and the total protein is slightly increased. The cells are predominantly lymphocytes and the number present in the spinal fluid is not correlated with the severity of the illness.

Differential Diagnosis. The clinical manifestations of mumps with salivary gland involvement are so characteristic that diagnosis usually is not difficult. In *suppurative parotitis*, pus may be expressed from the duct and there is greater pain and tenderness of the gland, together with signs of a more acute inflammatory process and abscess formation. *Cervical lymphadenitis* and *furunculosis* of the external auditory meatus with cellulitis of the surrounding tissues may be confused with mumps.

The greatest difficulty, however, is encountered in the recognition of subclinical infections and those cases of mumps with orchitis, oöphoritis, pancreatitis, or meningoencephalitis without involvement of the salivary glands. An etiologic diagnosis in these instances usually is not possible without the laboratory aids already described. The occurrence of these manifestations during an epidemic of mumps or the finding of an aseptic type of meningitis with more than 300 lymphocytes per ml. in the spinal fluid should suggest the possibility of mumps virus infection.

Treatment. The patient is isolated until all swelling of affected glands has subsided. There is no antibiotic or chemotherapeutic agent that is effective in the treatment of mumps virus infection. Symptomatic treatment includes aspirin for relief of pain, the application of heat or cold to the involved glands, adequate fluid intake, and bed rest, particularly in adults. Convalescent serum and gamma-globulin obtained from normal plasma pools have no effect on the course of the disease. There is limited evidence, however, to indicate that the administration of a large amount of gamma-globulin prepared from mumps

convalescent serum reduces the incidence of orchitis. In patients with orchitis, the testes are supported and an ice bag is applied gently. In severe orchitis, incision of the tunica albuginea has been advocated to prevent pressure necrosis. Pain usually is relieved promptly and the fever subsides. This procedure appears to reduce the incidence of testicular atrophy.

There is considerable promise that an effective vaccine for inducing immunity against mumps will be developed. Recent studies on a small scale have shown that the subcutaneous injection of a formalinized suspension of infected monkey parotid glands will induce immunity against experimental infection in both man and monkeys. The chick embryo would provide a more convenient source of virus for the production of a vaccine, but no clinical trials with such a vaccine have as yet been reported. Another method of immunization under investigation is the oral inoculation of living virus which has been attenuated by repeated passage in the chick embryo.

Prognosis. In children the prognosis is excellent, and complete recovery is the rule. In adults the more serious manifestations of the disease are more frequently encountered, with sterility and deafness being the most commonly observed sequelae. Accurate figures on the fatality rate in proved cases of mumps are not available, but it is undoubtedly very low.

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Viral Hepatitis

Richard B. Capps

Definition
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Etiology
Incidence
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Prophylaxis

Definition. The term viral hepatitis is used to describe a closely related group of diseases caused by a filtrable virus and characterized by parenchymal lesions of the liver. On the basis of immunologic and epidemiologic differences, two distinct forms are presently recognized—namely, homologous serum hepatitis and infectious hepatitis. Because of confusion in terminology it is often impossible to determine which form is indicated, but, in general, the terms postvaccinal jaundice, serum jaundice, and transfusion jaundice are used synonymously with homologous serum hepatitis, while infective hepatitis, epidemic hepatitis, catarrhal jaundice, and cholangitis are used as synonyms of infectious hepatitis. Probably most cases of so-called arsenical hepatitis seen in syphilis clinics are also due to one of these virus strains. In addition, fatal and near-fatal cases of viral hepatitis have often been described under the diagnosis of acute or subacute yellow atrophy of the liver.

History. The disease has been recognized and described in the literature for many years under a variety of names which, until recently, were looked upon as separate entities. The epidemic form has been particularly prevalent in armies in the field, and epidemics have been recorded during most of the major wars of the last 100 years.

Fatal cases were undoubtedly described by Rokitansky in 1842 under the name of acute yellow atrophy, but the relationship to the milder forms was not recognized. The term catarrhal

jaundice was first proposed by Virchow in 1865 for the transitory jaundice of young people. He suggested that the jaundice was due to a mucous plug in the common duct resulting from a catarrhal inflammation of the biliary tract. This explanation was generally accepted in spite of occasional evidence to the contrary, until the liver biopsy studies of Roholm and Iversen in 1939 demonstrated that the primary pathology was a parenchymal hepatitis.

During World War II the disease again became epidemic in the armed forces of the major combatants as well as in many civilian populations. Over 170,000 cases were reported in the United States Army alone. Studies were initiated which led to the recognition of the etiologic agent and the mode of transmission, and clarified the clinical picture and course of the disease.

Etiology. It is now reasonably well established that the causative agent is a filtrable virus. Successful attempts to infect animals or to grow the virus in the laboratory have been reported but have not, as yet, been confirmed. However, the disease is readily transmitted to humans by the administration of bacteria-free filtrates of infected material obtained from human sources. Homologous serum hepatitis has been produced solely by the parenteral injection of infected blood or blood products, whereas infectious hepatitis can also be produced by the oral ingestion of infected feces. Evidence of respiratory tract transmission is unconvincing.

The existence of two distinct viruses or two strains of the same virus is further supported by an absence of cross immunity, by variations in the length of the incubation period, and by differences in the clinical picture at onset of symptoms. Immunity to the homologous strain has been demonstrated and may be of long duration. In spite of the above evidence, the relationship of homologous serum hepatitis to infectious hepa-

titis cannot be considered as finally settled. Some workers believe that both diseases are caused by the same virus which, in the case of homologous serum hepatitis, has been modified by exposure to antibody before being introduced into the recipient, or perhaps that the route of infection plays a role.

The virus is unusually hardy. It is not killed by heating to 56° C. for at least 30 minutes, or by freezing, desiccation, or various preservatives. It is able to withstand the concentrations of chlorine ordinarily employed to purify drinking water.

Incidence. Accurate data regarding incidence among civilians are not available in the United States. There is evidence, however, that both strains of the virus are extremely widespread and that sooner or later a significant percentage of the population contracts the disease. For example, it is generally stated that about 5 per cent of adults give a history of having had "catarrhal jaundice." Since subicteric and nonicteric cases are probably at least as common as those with jaundice, this figure is much too low. Scattered epidemiologic studies suggest a similar incidence of homologous serum hepatitis.

The disease is most common among children and young adults, although it may occur at any age. There is no significant sex or race predisposition.

Pathogenesis. The virus is present in the blood stream during the latter part of the prodromal period and during the first few weeks of the acute stage in both forms of the disease. It is probable that in certain cases the virus may persist in the blood for months and perhaps years, producing what may be considered a carrier state. In contradistinction to the homologous serum strain, the virus of infectious hepatitis is found in the feces as well as in the blood.

Transmission. Homologous serum hepatitis apparently is transmitted solely by the parenteral introduction of virus. As there is no known insect vector, it must be assumed that the surprisingly wide distribution of the disease is due to the extensive use, during the last several decades, of parenteral medication as well as of capillary and venous puncture. Since only 0.01 ml. of infected serum is necessary, and since the virus is unusually hardy, transmission may be accomplished not only by the injection of human blood, plasma, or serum as medication but also by the inadvertent contamination of lancets,

needles, or syringes. Unrecognized acute cases and carriers serve as the source of infection. The chances of producing the disease are markedly increased by the common practice of pooling plasma or serum, because one infected donor can contaminate the entire pool. Transmission may result from inadequate sterilization of equipment employed for injections and for capillary puncture as well as of syringes used for the withdrawal of venous blood, because of the frequent occurrence of regurgitation. Finally, it may occur when a single large syringe containing multiple doses of medication is used for injections into a series of patients. Infected serum may be aspirated when the plunger is routinely drawn back.

Although infectious hepatitis can be transmitted in a similar manner, it can also be produced by the oral ingestion of fecally contaminated material. The naturally occurring autumnal epidemics seen especially in the Mediterranean basin, most of the large army epidemics of the past, and certain well-documented civilian epidemics are probably of this nature. Contaminated water probably plays a major role, although food infected by the use of human feces as fertilizer, by flies, by food handlers, and by infected eating utensils may also transmit the virus.

Pathology. The major pathologic lesion occurs in the liver, although inflammatory changes are often present in the lymphatic glands, pancreas, and bowel as well as other organs. No pathologic distinctions have been recognized between the two forms of the disease. The parenchymal liver cells are injured in proportion to the severity of the infection. In severe cases extensive and sometimes almost complete necrosis occurs. In mild and in early cases the findings may be limited to inflammatory exudates, especially in the portal areas. Jaundice, when present, is the result of hepatitis and is not due to extrahepatic obstruction. Catarrh of the common duct with edema and mucus is rarely if ever present in significant degree. Symptoms and findings are almost entirely due to a disturbance of the various functions of the liver. When liver cell necrosis is sufficiently extensive, liver failure and death ensue.

Complete histologic recovery usually does not take place until at least two months from the onset of illness. In certain cases inflammatory

lesions persist for many months or longer, and occasionally fibrosis appears. This may develop into one of several forms of cirrhosis, with the possibility of a fatal outcome.

Manifestations. The average incubation period of homologous serum hepatitis is between 80 and 120 days, while that of infectious hepatitis is between three and six weeks. In the first instance the onset is insidious and afebrile and characterized by lassitude, anorexia, looseness of the stools, headache, and right upper quadrant and right lumbar ache. Urticaria, arthralgia, and a vesicular eruption, primarily of the palms, are occasionally present. After a prodromal period of a few days to several weeks, jaundice, light stools, and dark urine appear.

In contradistinction, the onset of infectious hepatitis is usually acute and febrile and not associated with urticaria, arthralgia, or specific eruptions. The fever, which lasts for two to three days, may range as high as 104° F. Shaking chills are rare. Headache and nausea are prominent, and almost invariably there are a few loose stools. The febrile onset is usually followed by an afebrile period varying in duration from a few days to two weeks, which culminates in a mild recrudescence of fever and the appearance of jaundice. The symptoms during this period are similar to those of the preicteric stage of homologous serum hepatitis. Except for the onset, the clinical picture and course of the two forms of the disease are indistinguishable.

The appearance of jaundice, the acute stage of the disease, is associated with an increase in the severity of symptoms, especially nausea and vomiting, and often a mild fever. Severe abdominal pain simulating an acute abdominal emergency is seen occasionally. The icterus increases rapidly for a period of 2 to 10 days and then, accompanied by an abrupt abatement in symptoms, begins to decrease slowly. The duration of jaundice is extremely variable, ranging from a few days to several months or more, but is usually about three weeks. Convalescence is prolonged, averaging seven or eight weeks from the onset of symptoms.

Physical findings consist of mild generalized adenopathy and especially enlargement of the inferior cervical glands, splenomegaly in 20 per cent of cases, jaundice, and abnormality of the liver. The liver is almost always tender to both palpation and fist percussion, and usually en-

larged. The pain produced by fist percussion characteristically appears after a short latent period of perhaps five seconds, and persists for some minutes or hours. A small, well-localized area of tenderness in the right costovertebral angle is frequently present. The degree of tenderness and enlargement of the liver as well as the severity of symptoms, especially "liver ache," is directly related to the fact of whether the patient has been in bed or up and exercising. This effect of exercise characteristically persists for several days or longer, even after the patient is put to bed, and constitutes a true exacerbation of the disease. This relationship possesses diagnostic importance as well as therapeutic implications.

Mild forms of the disease, without clinical jaundice or with only very transitory scleral icterus, are probably more common than the better-known icteric form. The proportion of such cases varies in different groups from 35 to 90 per cent. Symptoms and findings are identical but less marked than in the more severe icteric cases, and the course is shorter, providing the diagnosis is made early and proper treatment promptly instituted.

Liver failure and death may occur within 3 to 10 days of the onset or at a later time. The first group represent cases of massive liver necrosis apparently resulting from an overwhelming infection. Cases that die at a later period show areas of regeneration in the liver, and in this group other factors, such as improper treatment or secondary infections, often play a role. Liver failure is ushered in by disorientation, restlessness, and finally coma. Severe liver injury may be complicated by purpura, which is occasionally intracerebral, due to a deficiency in prothrombin, and by marked hypoglycemia.

The duration of illness is quite variable. Approximately 10 per cent of cases require more than three months for clinical recovery, and about 3 per cent are still sick at the end of one year. The term chronic hepatitis has been applied to these groups. This condition, usually without jaundice, is characterized by exacerbations and remissions which may continue over a period of years. Symptoms consist of severe lassitude and easy fatigue, right upper quadrant and right lumbar ache, looseness of the stool, increased flatus, fat dyspepsia, and headaches. Temperature is usually absent. The liver is tender and generally enlarged. Exacerbations tend to be

produced by excessive physical exertion, intercurrent diarrhea, secondary infections, and various liver toxins such as alcohol.

A relatively uncommon group of cases which appear to represent a variant of the usual clinical picture has been called cholangiolitic hepatitis. It is seen particularly in syphilitics receiving arsenicals. In this form, jaundice is severe and prolonged often for many months. Clay-colored stools may persist for as long as six weeks, and pruritus is present as in extrahepatic obstruction.

Laboratory Findings. In general, the significant laboratory findings are the result either of a systemic reaction to infection or of disturbances in liver function. Thus, a leukopenia is usually found as in other viral infections. Atypical lymphocytes similar to those of infectious mononucleosis are present in the blood smear, but the number is rarely over 10 or 15 per cent. The erythrocyte count is normal. The erythrocyte sedimentation rate is usually normal during jaundice, but may be elevated in either the preicteric or the posticteric period.

Laboratory evidence of liver disturbance is varied. Bilirubinuria and bilirubinemia, especially involving the prompt direct-reacting bilirubin using the van den Bergh procedure, are particularly important findings. The stools may be acholic for periods up to a week or more. Urobilinogen is increased in the urine, providing there is ample bile in the stools. Other early evidence of parenchymal liver disease is provided by the thymol turbidity test, the cephalin-cholesterol flocculation test, and the serum alkaline phosphatase level.

During the icteric stage, in severe cases, the prothrombin level falls and the proportion of nonprotein nitrogen represented by urea decreases. Hypoglycemia may develop. A variety of liver function tests show functional impairment.

In convalescence and in chronic cases the bromsulfalein dye retention test is of great value. Chronic elevation of the indirect type of serum bilirubin is frequently seen. Other liver function tests may or may not be positive, and it is often necessary to employ a variety of procedures.

The laboratory findings in acute cholangiolitic hepatitis are similar to those in extrahepatic obstructive jaundice. The flocculation tests are negative and the serum alkaline phosphatase is very high. Bilirubinemia is persistent and of the prompt direct-reacting type.

Differential Diagnosis. Since specific bacteriologic or serologic tests are lacking, the diagnosis of viral hepatitis must be based on the demonstration of liver disease by either physical or laboratory examination in association with a suitable clinical picture. In doubtful cases liver biopsy may be valuable. Other causes of liver injury must always be considered and ruled out, since the liver reacts in a similar fashion to a variety of noxious agents.

In general, the stage of the disease and the presence or absence of jaundice determine the differential conditions that need be considered. Hepatitis associated with infectious mononucleosis, acute brucellosis, and viral pneumonia may, however, present an almost identical clinical picture throughout and may run a course similar to that of infectious hepatitis. Likewise, toxic hepatitis secondary to various chemicals may simulate homologous serum hepatitis. Leptospiral infection, malaria, and secondary syphilitic hepatitis are also occasionally confusing.

The diagnosis of viral hepatitis in the prodromal stage and in the acute nonicteric form is made with difficulty. The persistence of evidence of liver disease for at least 10 to 14 days is most significant and serves to rule out the mild transitory liver involvement secondary to many acute infections. During the acute stage with jaundice, bilirubinuria, and the elevated prompt direct serum bilirubin indicate that the jaundice is not hemolytic in origin. If acholic stools occur, it is necessary to consider extrahepatic obstruction. This distinction may be difficult, but the presence or absence of pain, the duration of clay-colored stools, the past history, and laboratory evidence of parenchymal liver injury are valuable. It is frequently impossible to distinguish the acute cholangiolitic form. Occasionally primary or secondary involvement of the liver with malignancy causes confusion, but in such cases anemia is usually present.

In chronic viral hepatitis various forms of chronic liver disease must be considered. Amebiasis with amebic hepatitis should always be ruled out. The gallbladder may fail to visualize because of poor liver function and so may lead to an erroneous diagnosis of chronic cholecystitis. Liver biopsy is indicated in all cases with marked symptoms or where liver injury is apparently severe.

Treatment. The cardinal principles of treatment are bed rest, diet, and the avoidance of

additional liver trauma. Proper treatment effectively reduces the duration and severity of the disease as well as the incidence of residual liver damage. All cases, even though apparently mild, should be treated rigidly because at the onset of illness it is impossible to predict accurately either the eventual severity of the acute liver injury or the danger of serious residual effects. Furthermore, the effectiveness of treatment is directly related to how early it is instituted.

By far the most important single therapeutic measure is strict bed rest. This must be continued until symptoms and liver tenderness have disappeared and until the liver size and laboratory findings approach normal. A recurrence of symptoms or abnormal findings when the patient becomes ambulatory indicates the need of further bed rest.

The question of diet in the average well-nourished civilian patient is still not entirely clear. It appears desirable, if compatible with the patient's comfort, to employ a high-calorie diet with high carbohydrates (300 Gm.), moderately high proteins (100 to 125 Gm.), and enough fat to make the food palatable. Meat fats are not well tolerated. If such a food intake can be achieved, there is no evidence to indicate that nutritional supplements such as choline or methionine are of value in acute hepatitis unless malnutrition is present. When vomiting is severe and persistent, glucose and protein in the form of amino acids, human serum albumin, or plasma must be provided intravenously. In all cases it is desirable to maintain a fluid intake of at least 3000 ml. daily until convalescence sets in. This results in a marked amelioration of symptoms, especially nausea and vomiting. Parenteral salt solution must be avoided except when vomiting is severe, and dietary salt restricted because of the tendency toward water retention and the danger of producing anasarca.

Hepatotoxic drugs, anesthetics, surgical procedures and secondary infections are to be strictly avoided as far as possible. Only a small amount of additional liver injury may produce a fatal outcome, especially in the early stages of the disease.

Prognosis. The mortality rate is variable, averaging about 0.3 per cent, but in special groups reaching as high as 20 per cent. In general the severity of the disease increases with age and with a history of previous liver trauma. Malnutrition at time of onset and the presence of other

independent infections indicate a more serious prognosis. Although some workers believe that homologous serum hepatitis has a higher mortality than infectious hepatitis, this is not established.

The incidence of residual liver disease is not accurately known. Active or symptomatic chronic hepatitis is present in approximately 10 per cent of cases after three months and in about 3 per cent after one year. Permanent liver damage, probably nonprogressive in nature and often of little clinical significance, is demonstrable in about 25 per cent of cases, according to available data. The incidence of high-grade cirrhosis also is not known, but probably is not high.

Prophylaxis. Parenteral transmission of viral hepatitis can be reduced by proper precautions. All syringes and needles, whether used for injections or for aspiration, should be sterilized between patients by autoclaving or by 20 minutes of boiling. This also applies to needles, knives, or stylets employed for capillary puncture. Multiple doses of medicaments must not be given from a single syringe. Whole blood transfusions and especially unsterilized pooled serum and plasma must be used only when the indications justify the risk of producing hepatitis. Fortunately it now appears that ultraviolet irradiation will sterilize plasma and serum. Blood donors should not be accepted if they have a history of jaundice.

Infectious hepatitis can be prevented effectively by the administration of immune globulin more than a week preceding the expected onset of symptoms or approximately within two weeks after exposure. The effectiveness of immune globulin in the prophylaxis of homologous serum hepatitis has not been well established.

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Yellow Fever

W. Elizabeth Gambrell

Definition
 Etiology
 History and Epidemiology
 Pathogenesis and Pathology
 Symptoms
 Laboratory Findings
 Treatment
 Prevention

Definition. Yellow fever is an acute infectious disease caused by a virus, transmitted to man by the bite of an infected mosquito. Its chief characteristics are fever, bradycardia, proteinuria, and a hemorrhagic tendency. Jaundice is slight and often may be absent.

Etiology. The virus of yellow fever is small, its size being estimated at 17 to 28 millimicrons. It can be inactivated easily by heat and ordinary antiseptics but can be preserved for months in 50 per cent glycerin and for years in the desiccated refrigerated state. Two general types in regard to tissue affinity are recognized: the viscerotropic, which involves the liver, kidneys, and heart; and the neurotropic, which attacks nerve tissue. In nature the virus possesses both viscerotropism and neurotropism, and is said to be pantropic. Strains which are predominantly neurotropic grow readily in tissue culture, while viscerotropic strains require minced mouse embryo brain medium and chick embryo tissue medium containing nerve tissue. The virus can be maintained in the developing chick embryo and by inoculation into the testes of mice. Strains which undergo serial intracerebral passages in mice acquire a heightened neurotropism. The various strains isolated in different parts of the world appear to be antigenically identical.

History and Epidemiology. Yellow fever at present occurs in large areas of South America and Africa. Much circumstantial evidence points to Africa as the source, although the first described epidemic occurred in Yucatan in 1648. From that time until the twentieth century, many outbreaks occurred in the Caribbean islands and the coastal regions of North, Central, and South America. The disease was confined to the trade routes of the Atlantic and showed a

seasonal incidence, being common during the warmer weather and subsiding with cold weather. From the coastal regions yellow fever was introduced along the trade routes of the Amazon and the Mississippi Rivers.

Little was known of the method of transmission, but in 1881 Carlos Finley of Cuba incriminated the mosquito now known as *Aedes aegypti* as the vector. Because of the high incidence among American troops during the Spanish-American War, the Yellow Fever Commission was established under the direction of Major Walter Reed. In 1900 and 1901, through experiments on human volunteers in Cuba, Reed, Carroll, Agramonte, and Lazear proved that the disease was transmitted from man to man by the bite of the *Aedes* mosquito and that the causative agent could pass through a Berkefeld filter. They also demonstrated that the blood of patients was infective during the first three days of fever, and that mosquitoes, after an interval of 12 days following a blood meal, were infective. Control and suppression of yellow fever followed mosquito eradication.

In 1928 Stokes, Bauer, and Hudson, working in West Africa, demonstrated the susceptibility of rhesus monkeys to the virus. With the acquisition of an experimental animal, it was possible to show that monkeys of Africa and South America were susceptible to yellow fever and that other mosquitoes besides *Aedes aegypti* were able to transmit the infection. This led to a re-evaluation of the whole epidemiologic problem, as until this time West Africa was thought to be the only remaining focus of infection. Under the auspices of the Rockefeller Foundation, surveys employing serologic tests and post-mortem biopsy studies (viscerotomy service) showed that the disease was far more widespread than had been recognized. Besides the classic urban type of yellow fever carried by *Aedes aegypti*, another type exists involving wild animals and "forest-loving" mosquitoes. This type is known as jungle yellow fever. The disease is now endemic in large areas

of South America and Africa, and it is evident that eradication of infection by means of anti-mosquito measures alone is no longer feasible.

Pathogenesis and Pathology. The mode of spread and multiplication of the virus has been studied in rhesus monkeys, and presumably follows the same course in man, although the virus has been isolated only once from a patient after death from yellow fever. In monkeys it is primarily an infection of the hemopoietic system, and secondarily invades other organs. When inoculated intradermally, the virus spreads immediately to the local lymph nodes and multiplies. After a few days it enters the blood stream and invades the liver, spleen, kidneys, bone marrow, and other lymph nodes, where it can be demonstrated several days after the blood stream no longer contains it.

The pathologic lesions can be explained on the basis of infection and multiplication of the virus. The organs which show the chief signs of degeneration are the liver, kidneys, and heart. Hemorrhages and jaundice are present in the skin and mucous membranes. The liver is normal in size or slightly enlarged, and appears yellow and fatty when sectioned. The kidneys are swollen and tense and also have a yellow, fatty appearance. The heart shows few gross abnormalities, but cloudy swelling and patchy fatty degeneration are demonstrable on section. The stomach usually shows erosion and punctate hemorrhages in the mucosa of the pylorus.

Microscopic changes are most apparent in the liver. The liver cells show marked midzone necrosis with cloudy and fatty degeneration. In severe cases, the entire lobule may show necrosis. The Kupffer cells are enlarged and granular and the sinusoids are engorged. The architecture remains intact and normal cells may be found about the central vein and the periphery of the lobule. There is complete absence of inflammatory reaction.

The lesions in the kidney are most evident in the tubules, chiefly the convoluted portion, where cloudy and fatty degeneration is present. In the spleen, as in the liver, inflammatory reaction is absent. Degenerative changes are present throughout the heart.

Symptoms. The incubation period is three to six days. The onset is usually sudden and acute, sometimes with a chill, but it may be insidious. During the first two days of illness the chief

symptoms are fever, headache, and backache. Temperature rises moderately on the first or second day. Active congestion follows, characterized by flushed face and injected conjunctivas and scleras. Nausea and vomiting are common.

As the fever reaches a peak, the pulse slows. Jaundice and evidence of hemorrhage occur on the fourth or fifth day of illness. Jaundice, even in severe cases, is not intense. Subcutaneous hemorrhages may occur as petechiae or patchy ecchymoses, and gingival bleeding is common. Hemorrhages may occur in the stomach and intestine, giving rise to "black vomit" and melena. After three or four days of illness, the temperature may fall and a remission of symptoms take place for a short time, to be followed by a recurrence of fever. Proteinuria occurs early in the disease, and the volume of urine tends to decrease. Recovery begins about the seventh day; it is rapid and usually without complications.

There is wide variation in the severity of the disease, from mild or subclinical infections to fulminating fatal cases with hemorrhages and jaundice. The over-all mortality is estimated at 5 per cent. Most deaths occur on the sixth or seventh day. The characteristic signs, whether in mild or severe cases, are the rise and remission of fever, the slow pulse in relation to the temperature (Faget's sign), and leukopenia.

Laboratory Findings. Proteinuria is marked in severe cases, but is often absent in mild infections. A terminal anuria may occur. The leukocyte count falls steadily from the onset of infection, leukopenia being most marked on the fifth or sixth day. There is a decrease in both polymorphonuclear leukocytes and lymphocytes. Since the liver is the organ most extensively damaged by the virus, this is reflected in the liver function tests.

Three laboratory procedures are available to establish a positive diagnosis: isolation of the virus, serologic tests which demonstrate development of specific antibodies during an infection, and histologic examination of biopsies of the liver both before and after death. Isolation of the virus is possible by intracerebral inoculation of mice with serum from patients up to the fifth day of the disease. The inoculated mice develop signs of encephalitis, and the agent isolated must then be identified. This is usually done by neutralization tests with specific immune serum against

yellow fever. Serum from patients may show positive protection tests in mice. Two specimens are necessary, one obtained as soon as possible after onset, and a second obtained during convalescence. Since antibodies develop very rapidly, both specimens of serum must be titrated for their neutralizing property. If the antibody content of the serum is higher during convalescence, this indicates that the infection is probably yellow fever. If the antibody content is the same in both specimens, the patient probably has had a previous infection of yellow fever.

Liver sections may be obtained by biopsy or, in fatal cases in countries where the disease is endemic, by the viscerotome. This is a simple instrument which permits removal of small specimens of liver after death. In South American countries where jungle yellow fever occurs over a large area, the study of liver sections of any fatal febrile case of less than ten days' duration is a very important part of the Yellow Fever Service.

Treatment. No specific treatment is available. Bed rest, good nursing care, and supportive therapy consisting of soft diet, adequate fluids, and saline and glucose infusions are the general therapeutic measures usually employed. Persistent vomiting may be alleviated by the administration of cracked ice by mouth, or by injections of codeine sulfate. For high fever and headache, tepid sponges and ice caps are recommended.

Prevention. Prophylactic measures consist of vaccination and the eradication of *Aedes aegypti* mosquitoes. Two strains of attenuated yellow fever virus are available for the preparation of vaccines: the French neurotropic and the 17 D strain. The yellow fever vaccine prepared from the 17 D strain consists of macerated chick embryos which have been inoculated with the virus

and allowed to harbor it for four days. The chick embryo juice is desiccated and sealed in ampules while in the frozen state. For use, the virus is reconstituted by the addition of sterile physiological saline solution. Only one subcutaneous injection of 0.5 ml. is necessary to produce immunity in man. The French neurotropic vaccine is made of dried mouse brain infected with the French neurotropic strain of virus. Vaccination consists of applying a gum arabic solution of the vaccine to the scarified skin.

Before methods of vaccination were developed, epidemics were controlled and eliminated whenever the *Aedes* mosquitoes and other vectors were eradicated. Breeding of mosquitoes was controlled in and near dwellings by pouring oil into the containers where larvae were found. The use of DDT spray on the walls of houses is now an effective preventive. At present no method is available for eradicating jungle yellow fever.

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Herpes Simplex

Lewis L. Coriell

Definition
History
Etiology
Epidemiology
Pathogenesis
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. Herpes simplex is an infectious disease, caused by a virus. Classically, it appears on the skin as clusters of grouped vesicles on an erythematous base, having a predilection for the face, lips, and mucocutaneous junctions. Although herpes is commonly regarded as a mild, local lesion, more serious or even fatal manifestations occur, such as infection of the central nervous system, the eye, the skin in eczematous patients, and the mouth and throat in primary gingivostomatitis.

History. Grüter, in 1914, first transferred infection from the cornea of a patient to the cornea of a rabbit and, subsequently, back to the cornea of a blind man reproducing a typical dendritic ulceration of the cornea. Löwenstein confirmed this work and also obtained the virus from herpes febrilis. In the early 1920's it was believed for a time that the virus of herpes simplex might be the cause of encephalitis lethargica of von Economo; however, subsequent studies have shown this to be incorrect. In 1938 Dodd, Buddingh, and Johnson isolated herpes simplex virus from the mouths of a group of children suffering with a febrile ulcerative stomatitis (acute herpetic gingivostomatitis). Burnet (1939) found no neutralizing antibodies in the acute serum from similar patients, but antibodies developed during convalescence, establishing the primary nature of this infection. Scott (1941) and others elucidated the epidemiology, and advanced the present concepts of infection with this interesting virus. In 1941 a serious complication of eczema, Kaposi's

varicelliform eruption, was shown to be caused by secondary infection of the abnormal skin with the virus of herpes simplex (*eczema herpeticum*).

Etiology. The virus of herpes simplex is a medium-sized virus which passes ordinary bacterial filters quite readily. By ultrafiltration and centrifugation it measures 125 to 150 millimicrons in diameter. It is present in early vesicles, but may be scanty after the fluid becomes purulent. Herpes simplex may be propagated on the cornea or in the brain of several laboratory animals, or on the chorioallantoic membrane of embryonated eggs.

Epidemiology. The serum of most adults (70 to 90 per cent) contains neutralizing antibodies against herpes simplex, and these persons experience recurrent manifestations of disease under suitable stimuli, which are usually the same for an individual but may vary widely for various people. For example, fever, whether due to infectious diseases or artificially induced ("fever blister"), and the common cold ("cold sore") are probably the most frequent precipitants of recurrent herpes, while emotional disturbance, physical fatigue, sunburn, menstruation, and food allergy are less common. In these persons, the virus remains latent in the tissues between attacks, but is sufficiently active to maintain a high antibody titer in the patient's serum. Virus has occasionally been found in the saliva when there was no clinical evidence of disease. Adults who have never been infected may contract a *primary* infection, if suitably exposed. Newborn infants are immune by virtue of transplacental transfer of antibodies, which they gradually lose after the first few months of life. However, in the five-year age group, the percentage with specific neutralizing antibodies approaches that observed in adults, indicating a high infection rate during infancy. The clinical syndromes recognized as *primary* infection are rare even in this age group,

and on statistical evaluation can account for less than 1 per cent of the infections. Herpes simplex has evolved an unusually successful host-parasite relationship with man. Most people harbor the virus from infancy to old age with little inconvenience to themselves, and even the primary contact in infancy is usually not accompanied by manifest clinical disease.

Pathogenesis. It appears probable that during latent periods the virus lives *within* the cells, since the body fluids contain sufficient neutralizing antibody to inactivate the virus. The various precipitating factors which induce recurrent disease may have a common denominator in altered physiology of the host cell which permits the virus to multiply, but little specific information is available on this point. Skin biopsies taken during the early vesicular stage show congestion of the dermis, with swelling and ballooning degeneration of prickle cells and basement cells of the epidermis. In some of these, the nuclear basichromatin is collected at the periphery, and the entire central area of the enlarged nucleus is filled with a homogeneous mass which in some stages of development stains red with hematoxylin and eosin. This is the type A inclusion body, and is found wherever there is active herpes simplex infection —i.e., in the skin, mucous membrane, mucocutaneous junction, cornea, brain, or in experimentally infected embryonated eggs or animal tissues. Multinucleated giant cells, with each nucleus containing an inclusion body, are frequently seen in biopsies of infected human skin.

The intraepidermal vesicle does not extend below the basement membrane, and hence does not cause scarring, although depigmentation may persist for some time in dark-skinned people. In the healing phase, the vesicle and corium are densely infiltrated with inflammatory cells.

Manifestations: RECURRENT HERPES SIMPLEX is a circumscribed eruption, consisting of closely grouped, thin-walled vesicles on an erythematous base, which tends to recur repeatedly in the same area of the skin, particularly at mucocutaneous junctions. It begins as a mild itching or burning, which rapidly becomes papular and vesiculates, and then passes successively through crusting, scab formation and desiccation, the whole process taking from 3 to 14 days. It is typically not accompanied by fever, regional lymphadenopathy, or other signs of systemic illness. The disease is self-limited, and is commonly identified with its

geographic location—herpes facialis, labialis, nasalis, progenitalis, or vulvovaginalis.

HERPETIC KERATOCONJUNCTIVITIS is characterized usually by swelling and congestion of the conjunctiva, with superficial opacities in the cornea and a palpable preauricular lymph node. Bacterial cultures are sterile; hysteresia is a prominent sign. The presence of typical herpetic vesicles on the eyelids may aid in the diagnosis; however, the recurrent manifestations are frequently confined to the cornea in the form of dendritic ulcers or, less often, as punctate, marginate, or disciform ulcers. The corneal ulcerations may persist for several weeks and respond poorly to local therapy; they are superficial and rarely lead to scarring unless secondarily infected. This may sometimes be difficult to distinguish clinically from epidemic keratoconjunctivitis, which is highly contagious and produces a more acute inflammatory response. Some laboratory studies suggest that the two viruses are related antigenically, but they differ in size and in other respects.

TRAUMATIC HERPES designates those cases where the primary infection occurs at the site of a skin abrasion on the hand, elbow, finger, or other skin area not commonly associated with the disease. Repeated recurrences have been observed to occur at the same site over a period of many years.

ACUTE HERPETIC GINGIVOSTOMATITIS is the commonest form of *primary* infection, and is seen most frequently in children from one to four years of age, less often in adults. It is characterized by gradual or sudden onset with fever, malaise, sore mouth and throat, and extreme irritability, sometimes alternating with lethargy. The fever may reach 104° F., but is usually 101 to 103° F. Physical examination reveals multiple shallow aphthous ulcers on a red base scattered over the buccal mucous membranes, tongue, and oropharynx. The gums are swollen, bleed easily on manipulation, and are typically most inflamed at the gingival margin. Fever and pain usually persist for six to eight days, followed by gradual healing of the ulcers during the following week. The ulcers may be confined to or appear first in the pharynx (herpetic pharyngitis), and in such cases the diagnosis is commonly missed.

ECZEMA HERPETICUM (Kaposi's varicelliform eruption) is a rarer manifestation of *primary* infection which occurs in persons with eczema or

neurodermatitis. Large areas of abnormal skin are involved, the grouped vesicles usually appearing in crops over a period of several days, hence the similarity to varicella. The fever may reach 106° F., and marked prostration is not uncommon. The fever subsides during the second week, coincident with the crusting and healing of the skin lesions.

MENGOENCEPHALITIS is a rare form of primary herpes in man, although common in artificially infected laboratory animals. It is accompanied by fever, headache, gastrointestinal symptoms, and signs of meningeal irritation and encephalitis. Most reported cases where the diagnosis has been definitely established have ended fatally.

In addition to the syndromes described above, herpes simplex has been known to occur in segmental nerve distribution simulating herpes zoster. The occurrence of repeated attacks in the same area is suggestive.

Laboratory Findings. The total leukocyte count is usually normal or only slightly increased, with a normal differential index. The diagnosis can be confirmed in the laboratory by: (1) isolation and identification of the virus; (2) demonstration of typical eosinophilic intranuclear inclusions in a biopsy specimen or in the brain at autopsy, or (3) in primary infections, a rising titer of specific neutralizing antibodies during convalescence. The acute phase serum should be collected before the fifth day of illness, as antibodies appear early. In central nervous system infection, the spinal fluid pressure and protein are slightly increased and a pleocytosis up to 500 cells is observed, with many polymorphonuclear leukocytes early, changing later to lymphocytes.

Differential Diagnosis. The history and clinical appearance of the recurrent skin and eye manifestations are usually sufficient to establish the diagnosis.

The laboratory tests enumerated above are confirmatory in doubtful cases, and are essential for absolute diagnosis in the primary manifestations. Many abrasions to mucous membranes take on a similar appearance due to maceration. The condition is often confused with trench mouth, and since organisms of the Plaut-Vincent type may be found concomitantly, their presence in a gingival smear cannot be considered diagnostic. Trench mouth and stomatitis due to

other Gram-positive bacteria respond dramatically to parenteral penicillin, which does not alter the course of herpetic infections. Recurrent solitary aphthous ulcers in the mouth are not caused by herpes simplex.

Eczema herpeticum may be easily confused with secondary bacterial infection of eczema. Extensive weeping and crusting may obscure the grouped vesicular nature of the lesion before the crusts are removed by wet dressings. Eczema vaccinatum usually presents larger vesicles with a central indentation, but this characteristic is not constant. Herpetic meningoencephalitis must be differentiated from bacterial and viral encephalitides, particularly epidemic viral encephalitis, poliomyelitis, lymphocytic choriomeningitis, and postinfectious encephalitis. Most cases have been diagnosed only at autopsy. Isolation of the virus from spinal fluid during life is always subject to question because of the ubiquity of the virus and the possibility of accidental contamination.

Treatment. No specific treatment is available. Repeated vaccination with calf lymph vaccinia virus is currently in vogue, but the apparent successes can probably be explained by the erratic natural history of recurrent herpes. Laboratory studies reveal no cross protection or interference between these two viruses. It is desirable to have the local treatment of eye lesions supervised by an ophthalmologist.

Penicillin and other antibiotics may be helpful in preventing or controlling secondary bacterial infection. In acute gingivostomatitis, the maintenance of adequate hydration and nutrition are aided by the local application, before meals, of surface-acting anesthetics such as 1 per cent "Pontocaine." A detergent mouth wash such as 1:1000 "Zephran" helps to maintain oral hygiene and inhibit bacterial proliferation. In eczema herpeticum, supportive therapy, fluid replacement, blood transfusions, and appropriate antibacterial measures are indicated. Convalescent serum and gamma-globulin have not been beneficial.

Prognosis. Except for complications following infection of the cornea, recurrent herpes has high nuisance value but few sequelae. The primary manifestations run a self-limited course except for meningoencephalitis, which is usually fatal, and eczema herpeticum, where the mortality rate may be 20 per cent.

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Phlebotomus Fever

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Definition
Etiology
Epidemiology
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment

Definition. Phlebotomus fever, often referred to as sandfly, pappataci, or three-day fever, is a benign, self-limited, viral infection characterized by fever, severe headache, conjunctivitis, general malaise, and leukopenia, and transmitted by the sandfly *Phlebotomus papatasii*.

Etiology. The virus has been obtained by passing infectious human serum through gradacol membranes. Its size is estimated at between 40 and 60 millimicrons. Its infectivity for human beings has been maintained for four years in frozen human serum stored in solid carbon dioxide. Several strains of the virus have been isolated and appear to be immunologically different, as evidenced by lack of cross immunity in inoculated volunteers.

Epidemiology. The disease occurs in tropical and subtropical countries. It is limited geographically to areas where the vector, *Phlebotomus papatasii*, propagates, particularly in parts of Europe, Africa, and Asia between 20 and 45 degrees north latitude (North Mediterranean area, Egypt, Asia Minor). Outbreaks usually occur among individuals who move into endemic areas, and never among the native population.

Manifestations. After an incubation period of two to six days, there is a sudden onset of malaise, giddiness, pains in the joints, back, and extremities, severe headache (usually frontal), and burning sensation or pain in the eyes. Fever is always present and may last from two to four days. The temperature may rise to 104.5° F., usually within the first 24 hours, then gradually subsides. The pulse rate is fast at first but returns to normal more rapidly than the temperature, and a bradycardia often occurs during convalescence. An erythema occurs on the face and exposed parts of the neck and chest, but a true rash does not develop. The conjunctivas are injected, and the eyeballs are tender. Convalescence is characterized by prostration and occasionally by marked mental depression.

Laboratory Findings. A leukopenia with a predominance of neutrophilic leukocytes, many of which are immature, is present, and there is a decrease in lymphocytes. The greatest drop in the leukocyte count occurs at the end of the febrile period. The urine is normal and there is no laboratory evidence of liver damage.

Differential Diagnosis. The diagnosis usually is made on clinical and epidemiologic grounds. Phlebotomus fever is generally suspected when fever of short duration occurs during the hot dry season in countries known to harbor the vector. It is sometimes confused with dengue, influenza,

infectious hepatitis, and malaria. It differs from dengue in the short duration of fever and in the absence of rash and lymphadenopathy. The absence of catarrhal symptoms and the occurrence in hot seasons differentiates it from influenza, and the absence of jaundice from infectious hepatitis. Cases are often misdiagnosed as malaria, but no chills occur and blood films are negative for parasites.

Treatment. No specific therapy is known. Control measures consist of eradicating the vector within 100 to 200 meters of living quarters. DDT

residual spray is successful in killing *Phlebotomus papatasii* at their breeding sites and within habitations.

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Foot-and-Mouth Disease

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Foot-and-mouth disease is a highly contagious viral disease of animals, especially cattle, pigs, sheep, and goats, which is occasionally transmitted to human beings. The virus has been estimated to be 10 to 12 millimicrons in diameter, and three immunologically distinct strains of the virus have been described. Man can become infected by direct contact with diseased animals or by way of contaminated food, particularly milk or milk products obtained from diseased animals.

The incubation period in man is usually from 2 to 5 days, but may be as long as 18 days. The patient is usually acutely ill, with headache, fever, and hypersalivation. Within 24 to 48 hours vesicles appear in the mucous membranes of the mouth, pharynx, tongue, and lips, and often in the skin of the hands and feet, particularly the soles, palms, and interdigital areas. The vesicles are usually small and contain clear fluid. They rupture within a few days, leaving irregular ulcers

surrounded by red areolas. Healing of the ulcers occurs within two weeks without scar formation. The pharynx is often acutely inflamed and ulcerated, and swallowing is painful. The tongue and lips may be swollen and painful. In general, the illness in man is mild and complete recovery occurs within one to two weeks.

A specific diagnosis can be made by transmitting the disease to guinea pigs, by inoculating the vesicle fluid into the food pads. Complement-fixing and neutralizing antibodies can be demonstrated in the serum of patients during convalescence. There is no specific treatment.

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Lymphogranuloma Venereum

Albert Heyman

Definition
Etiology
Incidence
Pathogenesis
Clinical Manifestations
Diagnosis
Treatment

Definition. Lymphogranuloma venereum is a virus disease usually transmitted by sexual contact and characterized by a small primary lesion, regional lymphadenitis, and constitutional symptoms. The disease is known by a variety of names, such as lymphogranuloma inguinale, lymphopathia venereum, and climatic bubo, but the name generally preferred is lymphogranuloma venereum. This disease should not be confused with granuloma inguinale, an ulcerative infection of the skin caused by the Donovan body.

Etiology. The etiologic agent of lymphogranuloma venereum is a comparatively large, filtrable virus. When stained by special methods, the organism can be seen with the ordinary microscope as small spherical granules or elementary bodies. The virus is also distinctive in that it is susceptible to sulfonamide therapy. It produces meningoencephalitis in mice and monkeys, and can be cultured in the yolk sac of the chick embryo. Infected yolk sac tissues are used as diagnostic antigens for intradermal (Frei) tests and complement-fixation reactions. There are serologic cross reactions, however, with psittacosis and certain other viruses (meningopneumonitis, feline pneumonitis).

Incidence. Lymphogranuloma venereum exists in almost every part of the world, but is especially prevalent in tropical and subtropical countries. It is frequently seen in the southeastern portion of the United States, particularly among Negroes. There is no accurate information regarding the incidence of the disease. Only 2700 new cases were reported in the United States in 1947, but it is likely that the incidence is much higher. Studies of the prevalence of the disease in the southern part of the United States, based upon skin tests and complement-fixation reac-

tions, have shown that 20 to 40 per cent of the adult Negroes and 2 to 10 per cent of whites have evidence of infection. The majority of those patients, however, give no history of the disease and present no other sign of it.

Pathogenesis. Lymphogranuloma venereum is nearly always transmitted by sexual contact. The incubation period varies from 2 to 30 days. A small evanescent lesion may appear at the site of inoculation, but more often the first sign of the infection is inflammation and suppuration of the inguinal lymph nodes. The virus is apparently disseminated throughout the body by way of the blood stream; it has been isolated from the primary lesion, the regional lymph nodes, the blood, and the spinal fluid. Fever, malaise, and headache are frequently present during the early acute phase of infection. Severe systemic manifestations, such as meningoencephalitis, keratitis, cutaneous lesions, and arthritis may also occur. Specific evidence of immunity to the virus, including skin sensitivity of the tuberculin type, and complement-fixing humoral antibodies, can be demonstrated in almost every patient shortly after the onset of the disease. Positive skin and complement-fixation reactions persist for at least several years. Patients with lymphogranuloma venereum frequently have an increase in the globulin fraction of the blood. Following the initial infection, the patient may remain asymptomatic for a long period of time, but may eventually develop late manifestations of the disease, such as rectal strictures or elephantiasis of the genitalia.

The early histologic lesion of lymphogranuloma venereum consists of a granuloma forming about a small blood vessel and composed of large mononuclear cells. The vessel is eventually compressed and obliterated, and necrosis occurs in the center of the granuloma. Polymorphonuclear leukocytes enter the area and an abscess develops. The "stellate" abscesses which are thus formed are characteristic of the fully developed acute lesions of this disease.

Clinical Manifestations. The initial lesion of lymphogranuloma venereum is seldom noted, since it is transitory and inconspicuous. Those which are observed consist of single small shallow ulcerations on the external genitalia. Shortly after the appearance of the initial lesion there is enlargement and suppuration of the regional lymph nodes. The usual site is the inguinal or femoral region, and this lymphadenitis is called the *bubo*. The typical lymphogranuloma bubo develops slowly, is bilateral, and forms an ill-defined, lobulated mass. Suppuration usually follows, producing multilocular areas of fluctuation which may rupture spontaneously, forming one or more draining fistulas.

The majority of patients with buboes show constitutional reactions: headache, malaise, fever, and anorexia. The systemic symptoms and buboes may subside spontaneously and may be the only clinical manifestations of the disease. Occasionally the virus causes inflammation of distant areas, and lymphocytic meningitis, pericarditis, and conjunctivitis have been observed. Generalized skin eruptions and arthritis have also been described; these apparently have been provoked occasionally by the performance of skin tests for the disease.

Many years after the onset of the infection, the patient may develop a proctitis associated with rectal bleeding and a purulent discharge. Eventually there is scar formation and a complete fibrous ring may develop, producing a *rectal stricture*, which may necessitate colostomy. Rectal lesions are found predominantly in women and are the result of the lymphatic drainage from the posterior part of the vulva and the vagina into the perirectal and retroperitoneal lymph nodes. In the male the lymph vessels drain from the penis to the inguinal area and thence to the deep iliac nodes. Rectal involvement in the male is often due to direct infection of the anorectal area.

Another late complication of lymphogranuloma venereum is elephantiasis of the external genitalia. This is known as *esthiomene*, and is caused by interference with lymphatic drainage. Ulceration is frequent, and secondary infection may cause marked destruction of the genitalia.

Diagnosis. Isolation of the virus is the most accurate means of diagnosis of lymphogranuloma

venereum, but it is too laborious for general use. The diagnosis is usually based upon the clinical findings, together with a positive intradermal test and complement-fixation reaction. Commercial antigens are available for these. A positive skin (Frei) test is of limited value, as it merely indicates that the patient has been infected with the virus at some previous time. In a recently acquired infection, the complement-fixation test will usually be positive in a high titer (1:80 to 1:640). Furthermore, a change in the titer of circulating antibodies may be found in successive tests. Biopsy of the primary lesion or of a lymph node should be done whenever feasible, since the histologic picture is sufficiently characteristic to permit a diagnosis and to differentiate this disease from other venereal infections.

Treatment. Sulfonamide therapy has been until recently the standard treatment of the early manifestations of lymphogranuloma venereum. Sulfadiazine, in doses of 4 Gm. a day, usually resulted in a disappearance of symptoms and lesions within one to two weeks. The use of aureomycin, however, has been reported to produce rapid healing of buboes and early proctitis. There is evidence to suggest that sulfonamide therapy may not destroy the virus completely and it may persist in the body after the acute infection has subsided. The late manifestations of the disease, such as rectal stricture and elephantiasis, do not usually respond to any form of medication, and treatment is chiefly surgical.

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Colorado Tick Fever

Paul B. Beeson

Definition
Etiology
Epidemiology
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. A benign, acute, infectious disease caused by a filtrable virus and transmitted to man by the bite of a tick.

Etiology. The causative agent has been identified as a filtrable virus which has a comparatively small particle size. It is pathogenic for hamsters, and can be adapted to mice and the chick embryo.

Epidemiology. The disease has been recognized only in the western part of the United States: Colorado, Oregon, Utah, Idaho, and Wyoming. Affected persons usually give a history of having been in a tick-infested area several days prior to the onset of symptoms; in many instances the patients can recall having found ticks on themselves. The tick which appears to be the principal vector is *Dermacentor andersoni*. The virus has been demonstrated in this insect.

Manifestations. The incubation period is usually four or five days. The onset of the disease is sudden, with malaise, headache, photophobia, muscular aching, and rapid rise in temperature to 102° to 104° F. These symptoms continue for one or two days and then subside, with the temperature falling to normal. After an interval of one or two days there is usually a second bout of fever accompanied by the same symptoms. Convalescence is usually well established by the end of 7

to 10 days, and there are no important sequelae or complications.

Laboratory Findings. The white blood cell count is helpful in diagnosis, as there is a leukopenia which is most marked during the second febrile period. Total leukocyte counts of 2000 to 3000 are common. There is a marked decrease in the number of polymorphonuclear leukocytes and a lesser decrease in lymphocytes. The virus can be recovered from the blood during the early stages of the disease, and the infection established in laboratory animals. Complement-fixing and neutralizing antibodies can be demonstrated in the serum of convalescent patients after the tenth day.

Differential Diagnosis. The disease was originally thought to be a mild variety of Rocky Mountain spotted fever, although the two illnesses are not very similar. The initial manifestations are not distinctive; in fact they are common to many viral infections such as psittacosis, influenza, and neurotropic virus diseases. The symptoms, course of fever, and leukopenia resemble those of dengue, but the geographic distribution of the two diseases does not seem to overlap.

Treatment. There is no specific treatment aside from measures to relieve the symptoms.

Prognosis. The disease follows a benign course, with complete recovery.

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Amebiasis

Max Michael, Jr.

Definition
Etiology
Pathogenesis and Pathology
Epidemiology
Clinical Features
Diagnosis
Differential Diagnosis
Treatment
Hepatic Involvement
Pleuropulmonary Involvement
Other Manifestations

Definition. The term amebiasis denotes infestation by the protozoan *Endamoeba histolytica*. The primary effect of this parasite is on the large bowel, but it may also invade the liver and lungs and, less commonly, the ileum, skin, brain, and pericardium.

Etiology. *E. histolytica* is a parasite of the intestinal tract of man and of some species of monkeys, rats, cats, dogs, and hogs. Two forms are recognized: the motile (vegetative) or trophozoite, and the encysted or cyst. When infective cysts are ingested by the host, they pass through the stomach unchanged, but, upon reaching the lower small bowel, find conditions that are favorable for excystment. Division then occurs, each cyst ultimately yielding eight new trophozoites capable of invading the colonic mucosa. In the wall of the intestinal tract reproduction takes place by binary fission with liberation of trophozoites. These may then invade the host tissue or may pass in the feces unchanged, or may develop into precysts which, in turn, develop into mature cysts on meeting conditions outside of the host unfavorable for the parasite.

Pathogenesis and Pathology. The trophozoites invade the mucosa, extend through the muscularis into the submucosa, and produce small, flask-shaped ulcers which contain yellowish brown necrotic material. Elaboration of cytolytic enzymes, and perhaps of hyaluronidase, probably aids in this tissue destruction. There is little or no cellular reaction around the ulcers unless they are secondarily infected by intestinal bacteria.

The entire colon is often involved in the process. The order of frequency of lesions is cecum, ascending colon, rectum, sigmoid, and appendix.

A delicate host-parasite relationship determines whether or not symptoms occur. In an early experiment, 20 volunteers were fed cysts of *E. histolytica*. Eighteen became parasitized and began passing amebas in the stools. Of the entire group, however, only four developed dysenteric symptoms. It has been estimated that nearly 90 per cent of persons infested do not have striking symptoms. In these, the size of the ulcers remains microscopic. Small ulcers may coalesce, however, to form larger ones, resulting in any of the diarrheal symptom complexes. Amebas which have invaded the colonic mucosa may have any of the following fates: (1) be completely eradicated; (2) maintain an asymptomatic carrier state by virtue of the minute ulcers; (3) produce larger ulcers, which are symptomatic; (4) pass through radicles of the portal veins, lodge in the liver, and produce hepatitis and/or abscess formation; (5) travel via the blood stream or by direct extension to other locations, inducing less common disease entities.

Epidemiology. Amebiasis is world-wide in distribution, with the highest incidence of the disease in tropical and subtropical regions. It is more prevalent in the southern than in the northern parts of the United States. It has been estimated that the over-all infestation rate in the United States is in the neighborhood of 10 per cent, but the true incidence in various locales has not been determined. The Chicago epidemic of 1933, attributable to a defective plumbing system in one of the larger hotels, attests to the fact that urban areas are by no means immune.

Amebiasis is transmitted from man to man; there are no intermediate hosts. In areas with good sanitation, the principal source of infection is the food handler who passes cysts in his ex-

creta. In more primitive areas, where human fecal material is used for fertilization of vegetables, the latter, improperly cooked, are a large factor in perpetuating amebiasis. Since the trophozoites die rapidly upon exposure to changes in temperature, active cases of amebic dysentery are not a menace. Upon convalescence and with the beginning of passage of cysts, which are much more resistant to external environs, these persons then join with the chronic cyst carriers as potential spreaders of the disease. Contaminated water supplies and flies may spread the infection.

Modes of prevention are concerned with improvement of sanitation, with recognition of carriers and their removal from food handling, and with education of the general public as to the potential dangers of amebiasis, so that milder degrees of amebiasis can be recognized, treated, and the carrier state prevented.

Clinical Features: DYSENTERY. As mentioned previously, the majority of persons infected by *E. histolytica* are asymptomatic. The commonest clinical syndromes noted are varying degrees of diarrhea.

In the usual case, amebic dysentery is insidious in onset. Vague lower abdominal cramping sensations, with one or more loose stools a day, are often the first symptoms noted. The stools are usually foul smelling and often contain bits of bright red blood and some mucus. Vague indigestion, a sense of being unwell, a low-grade fever, and alternating periods of constipation and diarrhea are often accompanying symptoms. It is not unusual to find that such symptoms have been present intermittently for months or even years before a definite diagnosis is made. There is little to note on physical examination, except for slight tenderness along the course of the colon and some evidence of weight loss.

ACUTE AMEBIC DYSENTERY. A less commonly observed variant is acute amebic dysentery. Patients so affected have a sudden onset of acute bloody dysentery with frequent stools, tenesmus, severe abdominal pain, and, at times, vomiting. The temperature is elevated, at times as high as 105° F. During combat conditions of World War II, it was noted that this picture frequently accompanied acute bacillary dysentery. It is possible that in such a situation the bacterial infection activates acute amebiasis in a person who, otherwise, is a relatively asymptomatic carrier.

ASYMPTOMATIC CASES. In the so-called asymptomatic cyst passer, it is often found on careful anamnesis that vague digestive complaints and an occasional mild diarrhea have been noted by the patient.

AMEBIC GRANULOMAS. Amebic granulomas, the so-called amebomas, which are single or multiple, may be located in any region of the large bowel. They usually develop in long-standing cases of amebic dysentery. It is important that they be recognized and differentiated from carcinoma, which they may simulate. Surgical intervention before antiamebic therapy is administered is attended by a high mortality.

Diagnosis. Amebic dysentery should be considered in every case of diarrhea. The character of the stool is often of considerable aid in the diagnosis. In the usual type of amebic dysentery, it is soft or even loose and watery. Flecks of mucus and bright blood frequently cling to the outside of the stool. Microscopic examination must be performed on a fresh, warm stool. The cellular exudate in the feces is predominantly mononuclear, in contradistinction to the polymorphonuclear exudate of bacillary dysentery. Several examinations may be necessary to find the parasites. Care in choosing flecks of bloody mucus for study is rewarding. In such bits of exudate, motile amebas, often with ingested red blood corpuscles, will be seen. The amebas move actively about the stage by thrusting out pseudopodia of clear cytoplasm into which may flow red corpuscles and other particulate matter. The motile forms of *Endamoeba coli*, a nonpathogenic inhabitant of the bowel, may be confused with *E. histolytica*. The former are only sluggishly motile, do not throw out clear pseudopodia, and never contain ingested red corpuscles. Motile forms, not previously evident, may appear in stools following a magnesium sulfate purge. If parasites are not found, cyst forms should be looked for in a stool concentrated with zinc sulfate and stained by appropriate methods. *E. histolytica* may be cultured from stools by use of special mediums. In the hands of qualified workers, this method increases the chances of obtaining positive results, and is especially efficacious for recognition of the cyst passer.

The proctoscopic examination yields valuable information. In the early stages of the disease, small shallow ulcers, often covered with mucous flecks, will be seen. Punctate hemorrhage and

hyperemia may be noted. The intervening mucosa usually appears normal. As the disease progresses, the ulcers become deeper and develop slightly raised edges, giving the appearance of bomb craters. They may be multiple and small or single and large. Material obtained from one of the ulcers, either by cotton swab or by aspiration, is usually swarming with motile trophozoites. Lesions will not be seen in all cases, since involvement of the right side of the colon may constitute the sole lesion.

A complement-fixation test may be of some aid in diagnosis, but few laboratories are equipped to perform it. A mild normocytic anemia is noted in chronic cases. The white blood count is slightly elevated in mild cases, and may be as high as 30,000 in the cases of the acute type.

Differential Diagnosis. All causes of diarrhea enter into the differential diagnosis. The simple diarrheas, whether caused by *Salmonella*, viruses, or enterotoxins, or whether of functional or unknown causes, may simulate the milder forms of the disease. Moreover, acute amebic dysentery can simulate acute bacillary dysentery in onset and in course. In this respect, it should be mentioned that large mononuclear cells which appear in the fecal exudate in bacillary dysentery may be confused with amebas. Ulcerative colitis offers the chief difficulty in differential diagnosis from the usual type of amebic dysentery; however, its chronicity, proctoscopic and radiologic appearance, and lack of response to antiamebic therapy are aids in the differentiation. Mucous colitis, regional enteritis, and carcinoma of the large bowel are other entities requiring consideration. In all cases in question, careful and repeated stool examinations, adequate proctologic examination, and response to therapy will usually establish or exclude the diagnosis of amebic dysentery.

Treatment. A variety of drugs, each with a definite role, is available for the treatment of amebic dysentery. Emetine hydrochloride, which is administered subcutaneously in a dose of 0.065 Gm. per day, is used in active cases with moderately severe dysenteric symptoms. It should be given for a few days only, to control acute symptoms. Since emetine is effective against trophozoites only, supplemental therapy with iodine or arsenical amebicides is necessary. The iodine-containing compounds include "Vioform" (0.25 Gm. t.i.d.), chiniofon (1 Gm. t.i.d.), and "Dio-

doquin" (0.25 Gm. t.i.d.). The best arsenical compound is carbarsone (0.25 Gm. t.i.d.). All of these oral preparations are given for 10 days. There are many regimens for the treatment of amebic dysentery; the "cure rate" increases with each additional course. A popular schedule consists of emetine hydrochloride for six to nine days, given concomitantly with one of the iodide compounds. If stools are not negative for amebas at the end of this schedule, then a course of carbarsone, followed by another course of iodides, is given. Retention enemas of carbarsone or of one of the iodides, given once daily for 10 days, are advocated for the more resistant cases. In cases with only mild diarrheal symptoms, it is permissible to omit emetine; however, if liver involvement is thought to be present (see p. 1100), emetine must be given no matter how mild the diarrhea. In the vast majority of cases, diarrhea ceases and symptomatic improvement is striking after the first two or three days of therapy. It must be emphasized, however, that lack of symptoms does not constitute cure and that the goal in therapy is complete eradication of amebas from the body. Careful follow-up studies of stool concentrates over a long period of time are desirable. In spite of the most rigid follow-up studies, relapses may occur even years after apparent cure. Courses of therapy may be repeated as indicated after a 10-day period of rest.

The antiamebic drugs are not without toxicity. Chiniofon may cause mild diarrhea which can make evaluation of symptom response rather difficult. Emetine is a protoplasmic poison and may, rarely, produce myocarditis, circulatory collapse, or peripheral neuritis. Blood pressure should be checked daily and pulse recorded every four hours in patients receiving this drug. Electrocardiograms should be taken before and after one week of emetine. The drug is contraindicated in patients with myocardial disease. Bed rest usually is prescribed for patients receiving emetine, but recent wartime experience would suggest that this is unnecessary. Any of the iodides may occasionally cause rash. Carbarsone, which contains arsenic, may, rarely, produce exfoliative dermatitis or liver damage.

Preliminary studies have indicated that aureomycin may be effective in amebic dysentery. Its ultimate place in therapy will have to be determined in extensive clinical trials.

Hepatic Involvement. At any time in the course of infestation of the colon, amebas may be carried to the liver. In many instances, they are destroyed there; but, in approximately 5 per cent of cases of amebic dysentery, disease is manifest in the liver, with hepatitis or abscess. No clear-cut distinction between the two is warranted, as they differ only in degree.

The amebas gain access to the liver through the portal circulation, and localize principally in the right lobe. Rarely, invasion occurs by way of lymphatics or by direct extension. The pathologic lesions are characterized by necrosis and degeneration of liver parenchyma, with an absence of inflammatory response unless secondary infection with enteric bacteria has occurred. With healing, small fibrotic lesions which do not impair liver function result. Calcification is rare.

Clinical evidence of liver involvement may be apparent without bowel symptoms. Only 25 per cent of patients have diarrhea at the time of the liver disease. A history suggestive of amebic dysentery, weeks or years in the past, is obtained in about half of the cases. Amebas are found in the stools in somewhat less than half of the cases. The essential point to be remembered is that amebic liver disease can occur without any preexisting or coexisting manifest bowel disease.

The clinical states that ensue vary from an acute fulminating hepatitis to a mild, indolent abscess. In some instances, there is sudden onset with chills, sweats, severe abdominal pain tending to localize in the right upper quadrant, nausea, vomiting, and spasm of abdominal muscles. Fever may be as high as 104° F., and the leukocyte count over 25,000. The differential count is frequently normal. Any of the acute abdominal emergencies, such as cholecystitis, ruptured viscus, and acute pancreatitis, may be simulated, but a few facts suggest diffuse amebic hepatitis. Tenderness is marked over the liver, and localized areas of tenderness may be noted. Abscess formation is suggested by pain referred to the shoulder and splinting of the diaphragm. In most cases, the onset is more insidious, with dull, dragging right upper quadrant pain, referred to the shoulder, some hepatic enlargement, low-grade fever, weight loss, and tenderness over the liver. A nonproductive cough may be noted. Point tenderness in one of the intercostal spaces over the right lobe suggests abscess formation.

Jaundice and other evidences of impaired liver function are unusual. (Abscess may exist with a normal white cell count.) Certain roentgenologic features aid in the diagnosis of abscess formation. Elevation of the right dome of the diaphragm, and obliteration of the cardiophrenic angle and of the anterior costophrenic angle on lateral view, are suggestive of abscess formation. Aspiration of the contents of an abscess yields a thick, chocolate-colored material which has been likened to anchovy paste. It is rare to find amebas in the pus, since they are principally in the wall of the abscess.

TREATMENT. The response to treatment of amebic liver disease serves as an important diagnostic tool. Since "emetine is highly effective against trophozoites and is probably concentrated in the liver, it is the drug of choice. It is given for a nine-day period and, at the same time, administration of one of the oral preparations is commenced in order to attack the parasites which may be present in any bowel lesion. After a rest period of one week, emetine is administered again for six days. Within three days after the beginning of treatment with emetine, dramatic changes are noted. The temperature returns to normal, leukocytosis subsides, pain and tenderness decrease remarkably, the liver size decreases, and a sense of well-being returns. In those cases with hepatitis and little or no abscess formation, the chemotherapeutic schedule just outlined usually suffices. In those cases with abscess formation, the contents must be evacuated. This is done two or three days after emetine therapy has begun, the aspiration being performed with an 18-gauge needle no longer than 19 cm. Aspiration should be done at the point of maximum tenderness over the liver. It is unnecessary to inject emetine into the cavity. Usually one aspiration suffices, but continuing pain and localizing signs are indications for another attempt. At times it is difficult to decide whether to aspirate, since the presence of abscess cannot be definitely established; however, it is a good general rule to aspirate when in doubt. Open drainage, once popular in the management of amebic abscess of the liver, is now used only in those cases which become secondarily infected, and it is possible that antibacterial chemotherapy may make this procedure obsolete. Preliminary studies have shown that chloroquine is effective against *E. histolytica* and that it is concentrated

in the liver. Good results have been reported with its use in cases of abscess and of hepatitis.

If abscesses are not treated properly, the patient may become cachectic and die of infection. On the other hand, the abscess may rupture into the lungs, producing any of the pulmonary syndromes.

Pleuropulmonary Involvement. Direct extension into the pulmonary tract occurs in approximately 15 per cent of cases of amebic liver disease. The right lung and pleural cavity are the areas involved. Rarely, the lesions may be metastatic without any detectable evidence of pre-existing liver disease. When the process of extension is a gradual one and the pleural surfaces have adhered to each other, the abscess penetrates either directly into the lung, causing an abscess, or directly into a large bronchus, producing a hepatic-bronchial fistula. If the process is more acute, extension into the pleural cavity with empyema results. These three conditions occur with about equal frequency.

The signs and symptoms of pleuropulmonary amebiasis are similar to those of suppurative disease in these areas. In some cases, the first indication of the amebic nature of the disease is the expectoration of copious amounts of a dark chocolate brown pus which may taste like liver. As indicated, most of the patients have accompanying liver involvement, and in them pulmonary invasion is manifested by cough, septic fever, and localized chest pain. Roentgenologic

demonstration of elevation of the right dome of the diaphragm, with overlying pulmonary infiltration, is highly suggestive of amebiasis. In the lateral view, a triangular area of pulmonary infiltration overlying a bulging diaphragm is helpful in diagnosis.

Management of pleuropulmonary amebiasis is similar to that for amebic liver abscess. Frequent bronchoscopic drainage may be indicated for localized lung abscesses. With secondary infection, antibacterial chemotherapy should be instituted.

Other Manifestations. *E. histolytica* may involve any region of the body. Other rarer manifestations include pericarditis resulting from direct extension from the liver, peritonitis secondary to rupture of liver abscess, urethritis, vaginitis, and brain abscesses which are metastatic. Cutaneous lesions resulting from draining sinuses infected with amebas are exceedingly painful and destructive. Their response to therapy is satisfactory.

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Malaria

L. T. Coggesshall

Definition
History
Epidemiology
Etiology
Parasite
Mosquito
Manifestations
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Quartan Malaria
Falciparum Malaria
Complications
Blackwater Fever
Laboratory Findings and Diagnosis
Differential Diagnosis
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Quinine
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Newer Drugs
Prognosis

DEFINITION

Malaria is an infectious febrile disease produced by four species of protozoa belonging to a single genus, *Plasmodium*. It is characterized by intermittent fever, splenic enlargement, debility, and anemia, and has a tendency to run a chronic course. The acute clinical attacks and relapses respond readily to specific medication. The clinical attack has a characteristic pattern consisting of chills, high fever, and profuse sweating, alternating with periods of comparative well-being. Malaria paroxysms can occur daily, on alternate days, or on every fourth day. The disease is transmitted naturally only by the bites of infected *Anopheles* mosquitoes.

HISTORY

Because of the characteristic fever pattern, malaria was one of the first differentiated clinical illnesses. Great confusion attended attempts to discover the etiologic agent, but in general it was recognized that the disease was associated with humid, marshy areas, and the word malaria itself originally probably signified "bad air." That the mosquito had something to do with the disease was known early, as is indicated by observations that the ancient Egyptians used head nets in the malarious areas. It was not until 1880, however, that Laveran, French army surgeon, saw under the microscope pigmented forms in unstained blood preparations obtained from patients with

this disease, and correctly assumed that they were the true etiologic agent. Ten years later, his assumption was confirmed following the introduction of suitable stains and the improved microscope. At this time it was recognized that the malaria parasite assumed many diverse forms, and the scientific workers turned their attention to the discovery of the method of transmission. The possibility that an insect was the vector probably came from the studies of Theobald Smith, who was the first to prove the arthropod transmission of disease when the tick was demonstrated to be an essential intermediate host in the transmission of Texas cattle fever.

In 1897, Manson and Ross, two Englishmen, showed that *Culex* mosquitoes could carry natural malaria infection of sparrows, and definitely recognized the specific parasites in the body of the mosquito. MacCallum, at Johns Hopkins University, recognized the sexual forms of the malaria parasite in the blood stream of man and accurately described the process of fertilization, and in 1897 the Italian workers, Bignami, Grassi, and Bastianelli, demonstrated the developmental cycle in man and in the anopheline mosquito. The crucial experiment, proving beyond doubt that anopheline mosquitoes were necessary vectors for man, was conducted by Manson in 1900, when infected mosquitoes were transported from Italy to a malaria-free locality in England, and the disease was produced in volunteers after they had been bitten by these mosquitoes. For the next two decades most of the work was confined to the control of the disease. Raffaele, in 1936, and James, in 1938, described the existence of exoerythrocytic forms in avian malaria. Huff, in 1943, demonstrated the development of these forms in some of the fixed tissues in canaries, and called them cryptozoites. Cryptozoites are now believed to be the precursors of the malaria relapse, as they have been extremely resistant to all forms of therapy. In 1948 Shortt, in England, reported the existence of these forms in monkey malaria, and in man

after the introduction of enormous numbers of sporozoites by syringe and mosquito bite.

EPIDEMIOLOGY

Although there has been a considerable regression in the incidence of malaria in many areas, it is still the most prevalent infectious disease when considered on a world-wide basis. Unfortunately, vital statistics are lacking in areas where malaria is most common, but there have been a sufficient number of accurate surveys to indicate that there are probably in excess of 17 million persons suffering from this malady.

In the United States, malaria is largely confined to the southeastern states, although at one time it was extremely prevalent as far north as the Canadian border. The principal vector, *Anopheles quadrimaculatus*, still exists in the United States and southern Canada, although the lack of suitable human carriers, improved drainage, screening, etc., have probably been the chief factors responsible for the decline of the disease. At present there are probably less than 300 deaths in the United States annually, attributable to malaria.

ETIOLOGY

The organism responsible for malaria is a protozoan of the class Sporozoa, order Haemosporidia, and genus *Plasmodium*. There are several species that occur naturally in monkeys, birds, and reptiles, although none of the human species of parasites produces an infection in any of the lower animals. There are only four known species that infect man: *Plasmodium vivax* causes vivax malaria (tertian, benign tertian); *Plasmodium malariae* causes quartan malaria; *Plasmodium falciparum* causes falciparum malaria (malignant tertian, estivo-autumnal); *Plasmodium ovale* causes ovale malaria, a mild variety similar to vivax malaria. There is definite evidence that there are multiple strains of each of these species.

Parasite. The parasites of all the four species follow a characteristic pattern of development, first recognized as a small ring with a chromatin dot in the red corpuscle. They grow into ameboid forms with several divisions of the nucleus or chromatin dot, until 8 to 32 daughter cells or merozoites are formed, according to the species. During their growth, the hemoglobin of the cell is absorbed and hematin pigment is deposited.

The merozoites are released into the blood stream and most of them are quickly destroyed, but a few attack fresh red corpuscles. This asexual cycle is repeated at regular intervals: 48 hours for *P. vivax*, 72 hours for *P. malariae*, and approximately 36 hours for *P. falciparum*. After about 10 days, sexual forms, known as gametocytes, appear in the blood stream. When fully developed, they fill the entire cell but do not cause it to rupture. The details of this general developmental cycle differ somewhat in the different species.

Mosquito. The parasite completes its development with the mosquito as soon as the latter ingests blood containing the gametocytes or sexual forms. These produce no symptoms and never undergo fertilization in the human blood stream. As soon as they find themselves in the stomach of a mosquito, the male gametocytes exflagellate—a process of forming and releasing 10 to 12 spermlike flagella, which break loose rapidly and become free-moving. They make their way to the female, hovering about until one gametocyte eventually penetrates, and fertilization occurs. At this instant, the unsuccessful ones immediately seek a new mate. The fertilized form, or oökinete, passes between the cells of the mosquito's stomach wall and encysts on its outer surface. Here the sporozoites develop in countless numbers, and upon maturity the cysts rupture and the sporozoites are released in the body cavity of the mosquito. From here they migrate to the salivary gland and await the opportunity to continue their development in the human host following the bite of the infected mosquito. The female mosquito liberates the sporozoites in the blood stream of a susceptible host. The first ring forms appear in red blood corpuscles 10 to 14 days later in vivax and falciparum malaria. In quartan malaria, the incubation is delayed 18 to 25 days.

MANIFESTATIONS

The clinical manifestations of malaria vary according to the parasite responsible for the infection. The predominant symptoms are chills, fever, sweats, with severe aching pains in the legs and back, and uncontrollable headache. The severity of the symptoms also varies greatly in relation to host immunity or tolerance and resistance. For example, in highly endemic areas, infections may be more or less continuously pres-

ent with only moderate fever and general lassitude. This is particularly true in the native populations. In the highly susceptible, the initial attack is very severe and the relapses are likewise attended by severe symptoms. There is also evidence that strains of the same species of parasites may possess different degrees of virulence.

There are certain manifestations encountered during an ordinary attack that are common to all three types of malaria. The spleen enlarges during the acute attack and is usually tender to palpation. Between attacks, its size tends to decrease but, as reinfections occur, there is a gradual enlargement which, in children, frequently reaches the crest of the ileum. Occasionally the spleen will rupture spontaneously. The liver may be tender and enlarged; headaches are very frequent, not only during the acute attacks but also during latent periods. A survey in 5000 chronic cases following the last war revealed that 40 per cent had these intractable headaches. Pains in the calves of the legs, thighs, and the back are also very common. An icteric tint of the skin may be noted and herpes labialis is usually the rule. Urticaria may be encountered on occasion.

Vivax Malaria. This is the most common type of malaria. There is usually a prodromal period of two to three days with low-grade intermittent fever, headaches, backaches, muscle soreness, and chilly sensations. The classic paroxysms make their appearance on about the fourteenth day following the bite of the mosquito. Frequently the paroxysms occur daily as the result of two broods of parasites sporulating on alternate days. After a week or less these broods usually synchronize, and then the paroxysms occur every other day. The typical paroxysm, usually called chill, is composed of "cold," "hot," and "sweating" stages.

COLD STAGE. The patient becomes chilly, with a gradual increase in intensity until there is an uncontrollable shaking. The teeth chatter, the skin is cold and blue, the pulse may be weak and rapid, and often there is nausea and vomiting. This stage lasts about 45 minutes, and it is difficult to keep the patient warm with blankets and artificial heat.

HOT STAGE. The rigor disappears gradually as the patient becomes warmer and the temperature rises rapidly to 104° to 107° F. The skin and tongue are hot and dry. Frequently there is

delirium, and occasionally convulsions. This stage lasts one to two hours.

SWEATING STAGE. The sweating begins abruptly and in a few minutes the patient is drenched. The temperature drops to normal within a few hours, and a period of sleep follows. Upon awakening, the patient is weak and listless, but the following day is one of relative well-being.

Quartan Malaria. The first symptoms of quartan malaria usually do not appear until 18 or more days, occasionally as many as 40, after the bite of an infected mosquito. The paroxysms cannot be differentiated clinically from those caused by other species of parasite. There are two days of well-being between chills, although if more than one brood of parasites is present, there may be two successive days of chills followed by normal temperature for one day; then the cycle is repeated. Rarely is a daily chill encountered. The quartan paroxysm is usually shorter than that of vivax malaria.

Falciparum Malaria. The characteristic pattern of vivax and quartan malaria is less common with this more virulent type of malaria. There is usually a chilliness which is followed by a sustained fever. The periods of remittance are relatively short, and the patient is constantly ill without intervening days of well-being. Temperature rises and falls less abruptly than with other varieties. The irregular appearance of paroxysms is due to the fact that falciparum parasites tend to mature over a relatively long period, while most of the "ripe" segmenters of vivax and quartan malaria rupture and are released during a relatively short time. The paroxysms are also irregular in their behavior.

Complications. Special types of clinical symptoms or complications may be encountered, particularly in falciparum malaria, which result from the localization of parasites in certain organs of the body. For example, a large percentage of patients show early signs similar to those found in influenza, with cough and a watery exudate which arise from pulmonary irritation due to the parasites. A localization of the parasites in the brain produces a blockage of the cerebral capillaries, which quickly leads to coma and delirium, a hyperpyrexia occasionally as high as 110° F., and rapid death unless prompt treatment is instituted. A localization of parasites in the intestinal tract also produces capillary blockage, with sloughing of the mucosa and bloody

diarrhea without pus. Although relatively rare, spontaneous rupture of the spleen can occur, and the possibility should be kept in mind constantly in cases with malaria splenomegaly.

Blackwater Fever. Blackwater fever may be considered a complication or special manifestation of malaria, characterized by hemoglobinuria. It always occurs in highly endemic areas, and is usually associated with the falciparum type. There seems to be a predilection for this complication to occur in the white immigrant, and it seldom occurs before the individual has experienced four or more attacks.

Its exact etiology is unknown, although cold, fatigue, alcohol, and exhaustion seem to be precipitating factors. Pathologically, there is extreme hemolysis, with large, dark kidneys showing necrosis and blocked tubules. There is central necrosis in the liver. The urine is scanty, varying in color from light red to dark brown, and in fatal cases there usually is complete anuria. The patient is extremely ill and prostrated, and the hemoglobinuria is the chief diagnostic symptom, as parasites may be absent from the blood.

The patient should be maintained at absolute rest, all antimalarial therapy withdrawn, and the blood count maintained above 2 million red corpuscles by transfusion, although no attempt should be made to keep the count normal, as this may result in congestive heart failure. The urine should be kept alkaline. There are many variations of this generalized treatment, although the mortality rates are very high (20 to 50 per cent) regardless of the type of therapy. The prognosis becomes progressively worse with each successive attack.

LABORATORY FINDINGS AND DIAGNOSIS

The most important diagnostic aid is the detection of the malaria parasite in a thin or thick blood smear. The thin blood smear should be made on a clean glass slide, with blood taken from the fingertip or earlobe, and stained with Giemsa's, Wright's, or Hastings' stain. For the inexperienced, the thin smear is preferable because there are less confusing artifacts encountered as compared to the thick smear. It is the exception to encounter a patient who has clinical symptoms and fever with negative blood smears, and the diligent worker will be rewarded by prolonged search.

The most frequent difficulty encountered will result from a poorly made smear. The blood on the slide should never cover the entire slide, in order that the end of the film may have separated red corpuscles that stain well. Extracellular parasites are not found. Parasitized red corpuscles are most frequently encountered on the edges of the smear. The thick film should be about the size of a dime, and has as its advantage the concentration of the blood. It should be thoroughly dried and then stained with Giemsa's or Field's stain. To stain with Giemsa, one drop of the stain should be added to 1 ml. of distilled water, and this should be overlaid on the dried drop of blood for at least 45 minutes. Approximately 2 ml. of stain should be added to the slide. Field's stain has the advantage in that it requires a relatively short time for the procedure and there seem to be fewer artifacts.

P. vivax infections can be recognized by the following characteristics: enlarged red corpuscle, diminished amount of hemoglobin, Schüffner's dots in erythrocyte substance, and a tendency toward a selectivity for reticulocytes. The parasite itself is very ameboid and the mature segmented form contains 15 to 20 merozoites. The pigment is fine and light brown. The gametocytes are infrequent but, when present, fill the entire red corpuscle. In *P. malariae* the infected red corpuscle is usually smaller in size than normal. The hemoglobin is concentrated and the mature form contains less than 12 merozoites. Frequently, the parasite assumes a band form across the surface of the red corpuscle. The gametocyte is usually much smaller than in *P. vivax*. In falciparum malaria the ring forms are very small and there may be more than one ring in each red corpuscle. There may be two chromatin dots in the ring stage. In the ordinary smear only the ring forms and gametocytes are seen. The gametocytes are quite distinct, assuming a crescent shape. The blood picture is not diagnostic, with the exception that there is a tendency to leukopenia. *P. ovale* is difficult to distinguish from *P. vivax* except that in the former the parasite is found in oval erythrocytes.

Splenic puncture is unnecessary and dangerous, and sternal bone marrow punctures offer no appreciable advantage over the ordinary blood smear. The use of epinephrine to dislodge parasites from the spleen has been, in the author's experience, of little value. There is a complement-

fixation test which affords positive results in some instances. The antigen used is that of monkey or avian malaria parasites, but the large number of negative tests in known positive cases rules out this procedure as a routine method.

Other points to be considered in the diagnosis include: (1) history (residence in malarious areas, previous attacks, recent blood transfusions, addiction to narcotics); (2) fever (usually assumes a classic form as described above); and (3) spleen (practically always enlarged, although one must consider the possibility of other febrile diseases producing the same condition).

Differential Diagnosis. In the differential diagnosis of malaria, one must consider typhoid fever, although the temperature reaction of malaria and the demonstration of the parasite are sufficient to establish the correct diagnosis. Many of the viral diseases have an onset not too dissimilar to malaria; however, leukopenia is usually much more marked in the former. Influenza, in particular, will frequently be confused with malaria. The chief difficulty arises with falciparum malaria, where the symptoms are related to the specific localization of parasites. If they agglutinate in the capillaries of the brain, one finds coma frequently in the absence of peripheral blood parasites. In this instance, brain tumors, encephalitis of various types, diabetic coma, and morphine poisoning must be considered. The localization of parasites in the lungs frequently will simulate a picture of early pneumonia, influenza, or upper respiratory infection. An agglutination of the parasites in the gastrointestinal tract frequently will lead to symptoms of acute bloody diarrhea similar to that seen in acute dysenteries.

TREATMENT

The treatment of malaria must be considered at this time, both from the standpoint of the pre-war regimes with quinine or quinacrine and also from the standpoint of the recent discoveries which resulted from an enormous investigative program conducted during World War II.

Quinine. Quinine has long been the standard remedy, and should be given orally whenever the patient is able to swallow the drug. Only coma or uncontrolled vomiting necessitates its parenteral administration. There are many therapeutic routines, but the author prefers 1 Gm. of quinine sulfate three times a day for two days, to be followed by 0.6 Gm. daily for five to seven days. In

any event, the patient should be kept under quinine therapy until he has had five days free from parasites and fever; and it does no harm to give 0.6 Gm. daily for two weeks thereafter. The patient should be advised that quinine does not result in complete cure for more than a few individuals, and that a relapse at a later date is imminent, but that a relapse is treated just as easily as the initial attack.

For those patients unable to tolerate quinine by mouth, it should be given intravenously, since the intramuscular method may produce a sloughing at the site of the injection. The soluble quinine dihydrochloride should be used, in a dosage of 0.3 Gm. in a minimum of 10 ml. of sterile distilled water. This dosage should be repeated every four hours until there is a decrease in the fever or parasite count. Then the drug should be given by mouth in accordance with the above regime, since too frequent intravenous injections may lead to thrombosis. Tinnitus, dizziness, and slight deafness encountered during quinine therapy should not be considered as symptoms necessitating the discontinuance of the quinine. The true and dangerous idiosyncrasies are those of immediate urticarial rashes, dyspnea, and cyanosis.

Quinacrine. Quinacrine ("Atabrine") is a synthetic drug and is highly efficient for the treatment of the acute initial attack or of a relapse. A course of treatment consists of 0.2 Gm. every six hours for five doses, to be followed by 0.1 Gm. three times a day for six days. Like quinine, it should be administered orally. As a rule, parasites disappear a little more slowly with this drug, but the difference is not appreciable.

If the physician prefers quinacrine and oral administration is not feasible, it can be given in 0.2 Gm. doses, using the dihydrochloride salt, but it should be given intramuscularly as collapse may follow intravenous administration. Like quinine, quinacrine should be given every 6 hours until the patient can tolerate the drug by mouth.

Since quinacrine is a dye, practically all patients develop a yellow tint of the skin, which is the result of the accumulation of the drug in the skin, and not jaundice due to liver damage. Occasionally, mental derangements have been noted with quinacrine, but these are exceedingly rare. Aside from discoloration, the most common complaint is gastric irritation, which frequently may lead to vomiting.

Newer Drugs. The newer drugs discovered or intensively investigated for the first time during World War II seem destined to replace the older remedies in the future of chemotherapy in malaria. They are more effective when used as suppressive agents, and one of the compounds appears to be a curative in chronic vivax malaria. Although several useful remedies have been found, only those promising ones which have undergone intensive trials will be presented in this chapter.

CHLOROQUINE. Chloroquine (7-chloro-4-(4-diethylamino-1-methylbutyl-amino)-quinoline) is one of a series of synthetic quinoline compounds which possess considerable antimalarial activity. Chloroquine is almost completely absorbed from the gastrointestinal tract, and its toxicity has not been found to be of concern when given within the recommended dosages. It does not produce discoloration of the skin, and appears to be much more potent than either quinine or quinacrine. Its activity for vivax malaria is confined to suppression and treatment of the acute attack. However, it will not completely eliminate the infection, even when given in the maximum tolerated doses. In falciparum malaria, it abolishes the acute attack and will also effect a cure.

The recommended dosage for suppression is 2 tablets, each containing 0.25 Gm. of chloroquine diphosphate (equivalent of 0.15 Gm. of base), taken on the same day of each week. For the acute attack the initial dose is 1.0 Gm. (4 tablets), to be followed by 0.5 Gm. (2 tablets) after 6 hours. On the second and third days 0.5 Gm. (2 tablets) is given, making a total of 2.5 Gm. (10 tablets) in three days. Although not usually necessary, 2 tablets can be given daily thereafter, for five successive days.

PENTAQUINE. A highly successful treatment for chronic vivax (tertian) malaria has been found in pentaquine, an 8-amino-quinoline compound. In volunteers infected with the tenacious Southwest Pacific vivax malaria, a high percentage of cures was obtained, even when the patients were treated before they had had an opportunity to

acquire any specific immunity. The author has treated approximately 200 ex-servicemen who had experienced an unusually refractory type of malaria as far as therapy was concerned, and all but ten were found to be cured following their initial trial with pentaquine. Some have remained free of symptoms for as long as two years, although previous to pentaquine therapy they were experiencing relapses every four to seven weeks.

In order to effect a cure, pentaquine must be given with quinine, as there seems to be a synergistic action. Pentaquine alone, or given with the other known synthetic antimalarial compounds, is not nearly so effective.

The toxicity of pentaquine is not too severe when it is administered in the recommended dosages. Occasionally, in the dark-skinned races, it has caused a hemolytic type of anemia. There may be some methemoglobinemia and postural hypotension. In the series of ex-servicemen treated, there were none whose treatment had to be terminated because of untoward reactions. All were treated as ambulatory cases.

The recommended dosage of pentaquine is 10 mg. (1 tablet) taken simultaneously with 0.6 Gm. of quinine sulfate three times daily for 14 days.

PROGNOSIS

The prognosis of all types of malaria is very good if proper treatment is instituted promptly. Actually, falciparum is the only type that is fatal if treatment is withheld or insufficient in amount. Most malaria deaths are due to intercurrent infections or debilitation from other causes. A person who has repeated attacks in hyperendemic areas, and who shows poor response to treatment, should be removed from that area if possible.

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Leishmaniasis

Edward S. Miller

Etiology
Epidemiology
Manifestations
Diagnosis
Treatment

Etiology. Protozoa of the genus *Leishmania* cause several different diseases which are referred to collectively as leishmaniasis. One takes the form of a generalized systemic infection, commonly called kala-azar, the etiologic agent of which is *Leishmania donovani*. In addition, there are two types of cutaneous leishmaniasis, the oriental variety, caused by *Leishmania tropica*, and the South American variety, caused by *Leishmania brasiliensis*.

Epidemiology. The parasites exist in mammalian hosts as nonflagellated oval organisms (Leishman-Donovan bodies) 2 to 3 microns in diameter, and exhibit certain intracellular structures. In human tissues they are found within cells of the reticuloendothelial system. The several members of this genus are indistinguishable morphologically and culturally, though the diseases to which they give rise are distinctive. Recovery from one type of infection is followed by a considerable degree of immunity to the homologous organism but not to the other species of *Leishmania*.

Leishmaniasis is transmitted by various species of sandfly vectors, and is, therefore, endemic only in tropical and semitropical regions, where sandflies are found. Oriental sore and South American leishmaniasis can also be transmitted by contact. Human cases serve as the major reservoir of disease, although, in certain Mediterranean areas and in China, dogs are also of importance in transmitting the disease.

Manifestations. The clinical course of kala-azar evolves slowly over a period of months. Irregular bouts of fever eventually are followed by loss of flesh and strength, hyperpigmentation of the skin, hepatomegaly, splenomegaly, and sometimes lymphadenopathy. The bone marrow is hyperplastic and its function is disturbed. This results in neutropenia with reduction of the total

leukocyte count to less than 4000, a moderate or severe normocytic and normochromic anemia, and some diminution in the platelet count. Liver function tests frequently reveal diminished hepatic activity in cases of more than three months' duration. The serum albumin is decreased while the globulin content rises sharply. Elevations of the serum globulin can be demonstrated readily by means of the formol-gel and antimony tests. Unless treated, kala-azar ends with death in the large majority of cases. Patients who recover sometimes develop unusual dermal lesions after a lapse of a year or more. These often take the form of nonulcerating, hypopigmented macules or nodules, which may appear anywhere on the body.

Oriental sore is manifested by a localized granulomatous ulceration of the skin and is not accompanied by pain or by constitutional symptoms. Lesions may be single or numerous, and occur chiefly on the exposed surfaces of the body. A typical sore begins as a pruritic, erythematous papule, gradually enlarges to a diameter of 4 to 8 cm., ulcerates in the center, and then often becomes secondarily infected with pyogenic organisms. The crater becomes filled with a discharge or a scab and is surrounded by a red indurated rim. It heals after several months to a year, leaving a disfiguring scar.

South American leishmaniasis is characterized by a cutaneous granuloma similar to that of oriental sore. However, in as many as one fifth of patients, serious mucous membrane manifestations appear in the form of eroding granulomatous lesions in the nose, mouth, pharynx, and larynx. The latter first develop after 6 to 18 months and progress slowly to death or to eventual healing with cicatrization.

Diagnosis. Specific diagnosis in leishmaniasis is established most readily by identifying the parasites in stained smears. In kala-azar they are most likely to be found in material aspirated from bone marrow or spleen. In the other types of disease the organisms are present only within

the local lesions or the lymphatic structures which drain them.

Treatment. Visceral leishmaniasis responds very favorably to treatment with pentavalent antimony compounds, "Neostibosan" being perhaps the most widely used member of this group. An average course of treatment for an adult consists of 0.2 Gm. intravenously, followed by 0.3 Gm. every 24 to 48 hours for a total of 12 injections. A group of drugs known as aromatic diamidines (including stilbamidine and pentamidine) have also been shown to possess potent therapeutic properties. Because of their toxicity, they are used only in cases resistant to antimony. Dosage schedules for the diamidines are as yet not well standardized.

Therapy of oriental sore is somewhat less effective, though healing eventually occurs spontaneously even in the absence of treatment. If the lesions are few in number they may be treated locally by periodic infiltration of 1 per cent

bcrberine sulfate, by curettage, or by the application of carbon dioxide snow. If the sores are numerous, the patient should be given "Neostibosan" or "Fuadin." The latter drug is administered intramuscularly every other day for a total of 8 to 10 injections. The initial dose is 1.5 ml. of a 6.3 per cent solution; subsequent doses are gradually increased to a maximum of 5 ml.

The treatment of mucocutaneous leishmaniasis is similar to that of oriental sore.

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Toxoplasmosis

Edward S. Miller

Definition
History
Etiology
Epidemiology and Pathogenesis
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. Toxoplasmosis is a systemic disease caused by an intracellular protozoan parasite. The most prominent clinical manifestations are encephalomyelitis, chorioretinitis, and pneumonia.

History. Toxoplasmosis was identified as a disease of certain animals in the early part of the twentieth century. Illness in man was first reported in 1923, and since that time rare sporadic cases have been recognized in this country as well as in many other parts of the world.

Etiology. The causative agent is generally classified as a protozoan belonging to the genus *Toxoplasma*. A number of strains have been isolated from different animal hosts and thus have acquired different specific names. It is probable, however, that all known strains are immunologically homogeneous and actually belong to the same species. The organism measures approximately 3 microns by 6 microns in size and is typically crescentic in shape, although it may be round or oval. It contains a well-defined nucleus within the cytoplasm, and is nonmotile. It is an obligate intracellular parasite, and will multiply in tissue culture or in the embryonated hen's egg, but not in artificial mediums.

Epidemiology and Pathogenesis. There are still great gaps in our knowledge of the occurrence and the means of spread of this disease. Overt

illness has been recognized but rarely in man; only a few score well-authenticated cases have been reported. Most of the patients have been young infants, who acquired the infection in utero. A few cases of acquired infection have been seen in older children and in adults. Nevertheless, inapparent or healed infections are probably more common than is generally realized.

Neutralizing antibodies are found in a significant fraction of apparently normal individuals, in most of the mothers who give birth to infants with toxoplasmosis, and in some patients who have macular chorioretinitis or cerebral calcification of unknown etiology.

Overt and latent infections occur in a wide variety of animals, including primates, dogs, cats, sheep, many rodents, birds, and reptiles. Possibly these animals represent a reservoir from which humans can be infected.

Animals can be infected experimentally by oral, intranasal, and parenteral inoculation. However, the natural routes and means by which infection is conveyed to animals and to humans are entirely unknown. It has been suggested that ticks or other arthropods may act as vectors, but this has not been proved.

Following infection the protozoa are distributed throughout the body by the blood, and become established in the cells of various organs. A typical lesion consists of a small focal area of necrosis surrounded by a zone of inflammation containing lymphocytes, plasma cells, and mononuclear cells. Within the lesion the parasites can be seen lying free, or growing within phagocytic or parenchymal cells. An invaded cell may be distended with many organisms. In congenital cases the outstanding lesions are in the brain and cord, and since the inflammatory process often extends to the ependyma, ventricular block and hydrocephalus are common. If the patient lives long enough, many of the lesions become calcified. Similar necrotic foci develop in the retina and the choroid. At autopsy granulomatous lesions can be found in many organs and tissues of the body, though often they are not numerous. In the acquired form of the disease interstitial pneumonia is usually a prominent feature, while neurologic involvement may be minimal.

Manifestations. Toxoplasma infection may be initiated during fetal life, or may be acquired at a later time. XIn the congenital form of the disease signs of illness are present at birth, or ap-

pear within a few weeks to months. Fever is common, but the temperature fluctuates, and may drop to subnormal levels. Cough, vomiting, and diarrhea are common symptoms. The predominant signs are those of a diffuse encephalomyelitis, including stiffness of the neck, ophthalmoplegia, transverse myelitis, muscular twitching, spastic paralysis, and convulsive seizures. Most infants develop internal hydrocephalus with rapid enlargement of the head. A very characteristic finding is chorioretinitis, which is usually bilateral and macular in distribution. Jaundice is seen in one third of patients. Some exhibit purpura and other hemorrhagic tendencies, while a few have a maculopapular eruption. The spleen and liver sometimes are enlarged.

XOnly a few cases of the acquired form of the disease are on record, and they fall into two clinical categories. One syndrome is characterized by delirium, coma, convulsions, and other encephalitic manifestations. In the other group the outstanding feature is pneumonia, with cough, dyspnea, and cyanosis, while neurologic signs are minimal or absent. A maculopapular rash has accompanied the pneumonia in several instances.

XThe course of disease in most of the recognized cases has been one of rapid progression, usually leading to death in a few days to a few months.

XInfants who have survived congenital infection have been left with serious sequelae such as chorioretinitis, diminished vision, nystagmus, microphthalmus, cerebral calcification and atrophy, epilepsy, mental deficiency, and chronic hydrocephalus or microcephaly. On the other hand, several children with the acquired form of encephalitis have made complete recoveries.

Laboratory Findings. Illness frequently is accompanied by a moderate leukocytosis, with a relative increase in lymphocytes and mononuclear cells. Infants are often anemic and may have circulating nucleated erythrocytes. XStriking spinal fluid changes accompany encephalomyelitis. The fluid is usually xanthochromic, the total protein is elevated, and the sugar is normal or slightly diminished. The leukocyte count may be as high as 2000 per cu. mm., most of the cells being lymphocytes; numerous erythrocytes also may be present. *Toxoplasma* organisms can sometimes be found in smears of the sediment.

One of the most characteristic findings in congenital toxoplasmosis is diffuse cerebral calcification, which can be shown by x-ray.

The best diagnostic evidence is provided by demonstration of the etiologic agent either in exudates or in tissues. Characteristic parasites often can be demonstrated in smears or in tissue sections. If a skin rash is present, a biopsy may help to establish a diagnosis. The disease may be reproduced in mice or guinea pigs by inoculation with infectious material.

~~X~~ Neutralizing antibodies appear in the blood of patients and persist for many years in those who recover. Complement-fixing antibodies likewise develop, but disappear during convalescence.

Differential Diagnosis. The congenital type of toxoplasmosis must be differentiated from bacterial meningitis, from birth injury, from congenital defects in the development of the central nervous system, and from erythroblastosis foetalis. Children who survive present neurologic abnormalities which may suggest tuberous sclerosis, cerebral angiomas, or brain tumor. The acquired form of the disease may be confused with atypical pneumonia, typhoid fever, typhus, or Rocky Mountain spotted fever.

Treatment. There is no established specific treatment. Sulfathiazole is of some benefit in experimental infections, and should certainly be tried in man. In the congenital type of disease there is such extensive destruction of the brain that no form of therapy is likely to produce a good end result.

Prognosis. The large majority of reported cases of toxoplasmosis have ended fatally. However, accumulating serologic evidence suggests that instances of cure are not rare, and that benign subclinical infections are common.

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Granuloma Inguinale

Albert Heyman

Definition
 Etiology
 Incidence
 Pathogenesis
 Clinical Manifestations
 Diagnosis
 Treatment

Definition. Granuloma inguinale is a chronic, ulcerative granulomatous disease, usually confined to the skin and mucous membranes of the genitoinguinal area, but occasionally appearing in other portions of the body.

Etiology. The etiologic agent of this disease is the Donovan body. This organism was thought for many years to be a protozoan, but recently it has been shown to be a nonmotile, Gram-negative bacillus. In stained smears of the lesions the organisms appear as encapsulated, bipolar bodies

situated within large mononuclear cells (fig. 161). In chick embryo cultures, the morphology of the organism is variable, and may consist of bipolar forms, curved rods, chains, or unencapsulated bodies. The organism is not pathogenic for laboratory animals, and can be cultivated only in artificial mediums containing yolk material.

Incidence. Granuloma inguinale was once regarded as occurring only in tropical or subtropical areas, but it has been shown to exist in almost every country and climate. The majority of the cases in the United States are found in the southeastern section, particularly among the Negroes. Approximately 2500 cases are reported in this country each year; the true incidence is probably considerably higher.

Pathogenesis. Granuloma inguinale is generally believed to be acquired by sexual intercourse. The disease is apparently not highly infectious, however, since it is frequently not transmitted to sexual partners. The factors predisposing to invasion of the organism are not

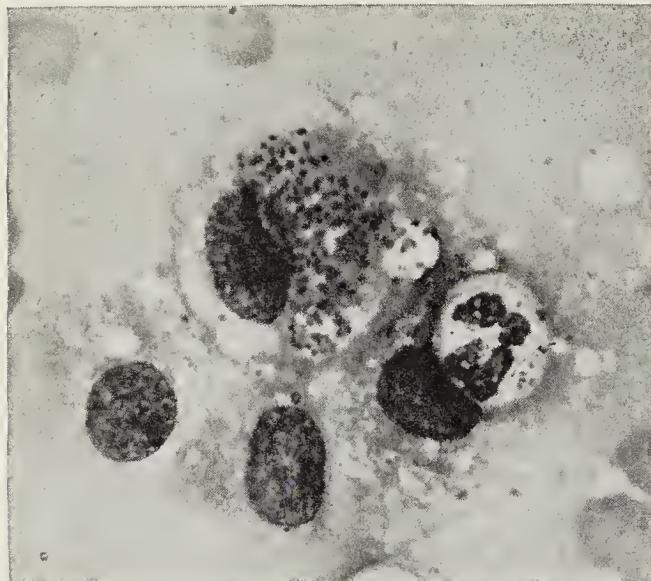


FIG. 161. Impression smear taken from a lesion of granuloma inguinale. A large mononuclear cell is filled with numerous typical Donovan bodies. Wright's stain. ($\times 1000$.)

definitely known, but the disease is found most frequently among sexually promiscuous individuals, and in association with other venereal diseases. The incubation period varies from 3 to 40 days. Experimental inoculation of infected material into volunteers produces a nodule at the site of inoculation, which later breaks down to become a typical granulomatous ulceration of the skin. Although the majority of infections appear on or near the external genitalia, lesions about the face, hands, and neck are not uncommon (fig. 162). Systemic complications of granuloma inguinale (such as invasion of the bones, joints, and viscera) have also been noted, suggesting that the infecting agent can spread throughout the body by way of the blood stream.

Clinical Manifestations. The lesion of granuloma inguinale usually is a nonpainful, sharply demarcated ulcer having an exuberant, red, granulating base which bleeds easily on trauma. The disease is very chronic and the ulcers slowly enlarge and coalesce. Secondary infection frequently is present and produces a foul-smelling, seropurulent discharge. Interference with lymphatic drainage may occur, leading to swelling and elephantiasis of the genitalia. The hyper-

trophy of the genitalia is similar to that caused by lymphogranuloma venereum. When healing occurs, further scarring and deformity of the genitalia may appear. Lesions of the cervix of the uterus are frequent and sometimes are mistaken for carcinoma.

The disease occasionally produces widespread manifestations such as arthritis and osteomyelitis. In such instances there may be general debility, anemia, and malnutrition; occasionally, these have resulted in death.

Diagnosis. The diagnosis of granuloma inguinale is based upon demonstration of the presence of Donovan bodies. Impression smears of early lesions stained by Wright's method usually will show Donovan bodies lying within the cytoplasm of large mononuclear cells. The smear is of less value in chronic cases. The diagnosis can also be made by histologic examination of fixed tissues. The microscopic appearance of granuloma inguinale is essentially that of a richly vascularized granulation tissue with marked inflammatory cell infiltration. Polymorphonuclear leuko-



FIG. 162. Exogenous granuloma inguinale. This patient also had genital lesions of many years' duration.

cytes are scattered throughout the tissue and form small microabscesses. Numerous large mononuclear cells are also present and show finely reticulated or vacuolated cytoplasm. Phagocytosis of polymorphonuclear leukocytes and other cellular debris by these cells is common. Intra-

cellular or extracellular Donovan bodies are readily seen in tissue sections, particularly in acute cases. In chronic cases they may be found only after considerable search, but the histologic pattern is sufficiently characteristic to permit a tentative diagnosis, even when organisms are not found. Specific serologic tests (complement fixation) and skin tests have been developed, but their diagnostic value is yet to be determined.

Treatment. Streptomycin is highly effective in the treatment of this infection. A dose of 4 Gm. a day for 7 to 14 days is usually sufficient to produce rapid and complete healing. Aureomycin and "Chloromycetin" have also been shown to be of considerable value in the treatment of this condition, and have the advantage in that they can be given orally. It has not yet been established which of these drugs is the treatment

of choice. The various preparations of antimony previously employed in the treatment of this disease are generally considered to be less satisfactory.

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Introduction to Diseases Caused by Helminths

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General aspects of the helminthic diseases of man deserve discussion before each disease is considered in detail. Helminths were recognized and accepted as agents of disease long before bacteria were so incriminated. *Dracunculus medinensis*, the Guinea worm, represents the most striking example, having been described in Biblical times. The life cycle of the much smaller *Trichinella spiralis* has been known for over 100 years. At some stage in their life cycle most helminths are macroscopic in size, and their recognition in the viscera or the bodily discharges is not difficult. Many aspects of the helminthic diseases of man have long been understood, but only recently have their immunologic aspects been investigated.

These diseases are world-wide in distribution but are much more important as causes of morbidity than of mortality, even in tropical areas where they are most prevalent. The magnitude of the problem they pose has been well described. It has been estimated that there are over 2200 million helminth infections in the current world population of somewhat less than 2200 million. The direction which control should take is emphasized by the observation that man has acquired over four fifths of these infections because of "ineffective insulation from his own excretory products" (Stoll).

Attention is focused on the helminthic diseases of man when, because of war or other circumstances, intercourse between nonendemic and endemic, usually tropical, areas is increased. There is concern because of the hazards to which troops stationed in endemic areas are exposed, and because of the danger of having new or more virulent forms of disease returned by servicemen to nonendemic areas. In American Army personnel during World War II, there were reported 2151 hospital admissions for filariasis and 1636 for schistosomiasis, primarily japonica, but the num-

ber of infections was undoubtedly considerably greater. The number of military personnel contracting hookworm infections in some endemic areas was large but difficult to estimate. Because of the presence in the United States of appropriate mosquito hosts, the possibility exists that filariasis may again be established here. A species of *Tropicoris* capable of acting as intermediate host for *Schistosoma mansoni* has been encountered in Louisiana. More likely is the establishment of *Ancylostoma duodenale* in the southern United States by those returning from the Pacific and Asiatic areas of combat.

The prevalence of helminthic disease in tropical areas is dependent in varying degree upon the following factors: (1) The presence of appropriate vertebrate and invertebrate hosts; (2) the higher temperature and humidity; (3) poor personal hygiene; (4) poor environmental hygiene; and (5) particular racial food habits. Some of these infections, as they are observed in adult residents of endemic areas, are usually mild and often asymptomatic. This differs from the clinical picture produced in the initially exposed, in whom the infections are more often mild to severe. The immunologic basis for these differences can only be inferred from experimental studies. What is apparent is the greater significance which a positive laboratory finding (a helminth at some stage of its life cycle) has in relation to clinical findings in initially exposed individuals. In reference to clinical findings per se, in few of these diseases are they such as to lead to a specific diagnosis. By themselves, the clinical findings may suggest a presumptive diagnosis, but the definitive diagnosis must invariably be made in the laboratory. However, even with a positive report from the laboratory, the clinician must be cautious in evaluating the role of the parasite in the clinical picture presented. For example, the presence of hookworm eggs in the feces does not make the

diagnosis "hookworm disease." A distinction must be made between asymptomatic infection and symptomatic infection or "disease." Nor does a negative stool examination rule out disease caused by blood or intestinal helminths. When direct microscopic examinations of selected portions of entire stool specimens are negative, appropriate concentration methods should be applied. Only after thorough laboratory study, occasionally requiring the examination of material obtained by proctoscope, as in suspected schistosomiasis, or duodenal drainage in suspected *Fasciola hepatica* or *Clonorchis sinensis* infection, is a final decision possible. The proper investigation of suspected helminth infections requires of the clinician a general knowledge not only of clinical manifestations, but also of epidemiology, helminthic life cycles, and laboratory

procedures. With such knowledge, taking intestinal infections as an example, it may be possible to determine whether efforts are to be directed toward search for eggs, for larvae, or for proglottids in the feces.

Brief mention should be made of the manner in which helminthic infections differ from and resemble those produced by bacterial and other microbial agents. As adults, helminths do not multiply in the human host. In this form, their presence is usually made known by effects which are primarily mechanical. The lumen of a hollow viscus or a duct system may be occluded (e.g., ascariasis, fascioliasis), penetration of the intestinal wall to obtain a blood meal may lead to extensive blood loss (e.g., hookworm), or residence in the wall of a hollow viscus intra- or extravascularly may lead to ulceration and blood loss

	Disease	Causal Agent	Stage and Habitat in Man
Nematheleminthes Class Nematoda	Hookworm	<i>Necator americanus</i>	Adults in intestine
	Creeping Eruption	<i>Ancylostoma duodenale</i>	Adults in intestine
	Strongyloidiasis	<i>Ancylostoma braziliense</i>	Larvae in skin
	Trichostrongyliasis	<i>Uncinaria stenocephala</i>	Larvae in skin
	Ascariasis	<i>Strongyloides stercoralis</i>	Adults in intestine
	Trichuriasis	<i>Trichostrongylus</i> spp.	Adults in intestine
	Enterobiasis	<i>Ascaris lumbricoides</i>	Adults in intestine
	Trichinosis	<i>Trichuris trichiura</i>	Adults in intestine
		<i>Enterobius vermicularis</i>	Adults in intestine
		<i>Trichinella spiralis</i>	Early: Adults in intestine Late: Larvae in muscles
Platyhelminthes Class Trematoda	Filariasis bancrofti	<i>Wuchereria bancrofti</i>	Adults in lymphatics
	Filariasis malayi	<i>Wuchereria malayi</i>	Larvae in blood
	Onchocerciasis	<i>Onchocerca volvulus</i>	Adults in lymphatics
	Loiasis	<i>Loa loa</i>	Larvae in blood
	Dracunculiasis	<i>Dracunculus medinensis</i>	Adults and larvae in skin, subcutaneous and other tissues
	Schistosomiasis mansoni	<i>Schistosoma mansoni</i>	Adults migrate in subcutaneous tissues; larvae in blood
	Schistosomiasis japonica	<i>Schistosoma japonicum</i>	Adults in skin and subcutaneous tissue
	Schistosomiasis haematobia	<i>Schistosoma haematobium</i>	Adults in portal and intestinal veins
	Schistosome dermatitis	Nonhuman schistosomes	Adults in portal and intestinal veins
	Fascioliasis	<i>Fasciola hepatica</i>	Adults in veins of the urinary bladder
Platyhelminthes Class Cestoda	Clonorchiasis	<i>Clonorchis sinensis</i>	Larvae in skin
	Opisthorchiasis	<i>Opisthorchis felineus</i>	Adults in bile ducts
	Paragonimiasis	<i>Paragonimus westermanii</i>	Adults in bile and pancreatic ducts
	Fasciolopsiasis	<i>Fasciolopsis buski</i>	Adults in lungs
	Diphyllobothriasis	<i>Diphyllobothrium latum</i>	Adults in intestine
	Taeniasis saginata	<i>Taenia saginata</i>	Adults in intestine
	Taeniasis solium	<i>Taenia solium</i>	Adults in intestine; occasionally cysticerci in tissues
	Echinococciasis	<i>Echinococcus granulosus</i>	Larval form in liver, lungs, and other organs
	Hymenolepiasis	<i>Hymenolepis nana</i>	Adults in intestine
	Dipylidiasis	<i>Dipylidium caninum</i>	Adults in intestine
	Sparganosis	Migrating larvae of some species of <i>Diphyllobothrium</i>	Larvae in subcutaneous tissues

(strongyloidiasis, schistosomiasis). As larvae, some helminths produce symptoms during penetration of the skin and migration to their site of definitive development. There is a similarity between helminthic and microbial infections with reference to the immunologic response of the host. In both, precipitins, complement-fixing, skin-sensitizing, and neutralizing antibodies have been demonstrated. Tests for immunologic response have diagnostic value in trichinosis, echinococcus disease, filariasis, and schistosomiasis.

The important helminths are members of the phyla Platyhelminthes and Nemathelminthes. The diseases they produce and their habitats in the human host are tabulated on page 1116.

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Hookworm Disease

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Definition
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Definition. Hookworm disease is a symptomatic infection caused by *Ancylostoma duodenale* and/or *Necator americanus*. Asymptomatic infection may be simply termed "hookworm infection," and the individual with such infection a "carrier."

Etiology. *Ancylostoma duodenale*, also known as the "Old World" hookworm, possesses four prominent hooklike teeth in its adult stage. The male measures about 1 cm. in length and presents

a characteristic copulatory bursa. The female is slightly longer and has a pointed posterior extremity. The adults inhabit the upper small intestine of man. They attach to the mucosa by means of the mouth parts, and suck blood. Each adult daily extracts about 0.5 ml. of blood. The adults migrate within the small intestine, and each site of attachment persists temporarily as a bleeding point. Following fertilization, the female liberates about 10,000 eggs per day. They measure about 40 microns by 60 microns, and are usually in the two- to four-celled stage when discharged in the feces. (See figure 168, p. 1136.)

Necator americanus, the "New World" hookworm, has a buccal capsule containing dorsal and ventral plates rather than teeth. The male bursa differs from that of *A. duodenale* in that it is rela-

tively longer and possesses a bipartite rather than a tripartite dorsal ray. The length of the adults is slightly shorter than that of *A. duodenale*, but the eggs are somewhat larger. (See figure 168, p. 1136.)

The life cycles of these hookworms are similar. In an appropriate environment the ova develop into the rhabditiform larval stage in one to two days. In the course of about three days, development into the filariform or infective stage has occurred. In this stage, in a cool moist environment they may survive for several weeks. Upon contact with the skin of the appropriate host, the larvae actively penetrate through the skin to enter vessels which carry them to the lungs. The cutaneous reaction to the penetration by the larva is more pronounced in *N. americanus* infection. The larvae leave the alveolar capillaries and enter the alveoli. They ascend the respiratory tree, enter the pharynx, and are swallowed. They reach the intestine about one week after penetration of the skin, and three or four weeks later are mature. The adults have been known to survive in the human intestine for five years.

Epidemiology and Distribution. Considered on a global basis, hookworm disease is the most important helminthic disease of man. Environmental conditions conducive to the development of the hookworm egg into the infective filariform larval stage are found in tropical and semi-tropical regions in which adequate rainfall occurs. The eggs and younger larvae are particularly susceptible to desiccation. Suitable conditions for development are also found in deep mines and tunnels. The significance of the hookworm as a pathogen for man was established in 1879, by investigation of the severe anemia developing in workers constructing the St. Gotthard tunnel through the Alps. Given the stated environmental conditions, hookworm infection will occur where there is opportunity for contact of the skin with contaminated soil. In tropical and semi-tropical agricultural areas hookworm infection can be regarded as an occupational disease, especially where bananas, sugar, coffee, and tea are raised. Infection can be acquired by ingestion of filariform larvae, but this mode of transmission is of little importance. That development of hookworm eggs into the filariform larval stage can occur in contaminated bedclothes has been shown, and also that fomite-borne hookworm infection may be of importance.

The white race is more susceptible to symptomatic infection than the Negro, the latter still constituting, however, an important reservoir of infection. Probably because of greater exposure, males show a higher incidence of infection than females.

Regarding the relative importance of the two hookworms, it has been stated that "*Ancylostoma* presents a greater public health problem than *Necator americanus*, the species now established in the southern United States, because it is more harmful to the host, is less amenable to treatment, and its free-living stages are more resistant to climatic conditions" (McCoy).

N. americanus infection predominates in the Western Hemisphere and Africa, and *A. duodenale* in northern India, China, and Japan. Both forms are found in the other Western Pacific islands; in most of China, and India, and the Mediterranean area; and in some parts of South America.

Pathogenesis and Clinical Manifestations. The nature and severity of the clinical manifestations are determined by the stage and intensity of the infection. During the invasion of the exposed skin by the larvae, the affected parts become erythematous and edematous, and there is severe pruritus. These manifestations are more marked in *N. americanus* infection than in *A. duodenale* infection. The lesions are commonest about the feet, particularly between the toes, and have been termed "ground itch."

During passage of the larvae through the lungs, cough and, in severe infections, fever are observed. The pulmonary symptoms were particularly troublesome to soldiers engaged in close combat in the Asiatic campaign in World War II.

Epigastric pain, abdominal tenderness, and occasionally vomiting and diarrhea can be prominent symptoms during the establishment and migration of the hookworms in the small intestine. Roentgenographic studies at this stage may reveal a "cogwheel" pattern of the upper small intestine, presumably produced by the mucosal involvement. As hookworm disease was observed in American troops in northern India and Burma, where *A. duodenale* infection predominates, it was during this phase of the disease that medical aid was sought. Eosinophilic leukocytosis was present but anemia was not a presenting manifestation, nor did it develop, presumably because of the short duration of the infection and

early treatment. Judging from the number of adult hookworms collected from post-treatment fecal specimens, these were relatively light infections. They were predominantly *A. duodenale* infections, which are generally accepted as being more severe than those caused by *N. americanus*.

The clinical picture which has been described as classic occurs in residents of endemic areas, and differs from the above in that anemia with symptoms and visceral changes incident to the anemia are dominant. The severity of the disease and the prognosis are dependent upon such factors as the age of the patient, the magnitude of the worm burden, the duration of the disease, and diet. Young children more often manifest the extreme anemia with cardiac insufficiency and anasarca. The anemia usually develops slowly and results from loss of blood—that which the hookworm sucks and ingests, and that which oozes into the intestinal lumen after the hookworm has left the site of mucosal attachment. Patients may have a depraved appetite with a desire to eat coarse or gritty materials. Those who survive to puberty show a retarded physical, mental, and sexual development. Milder degrees of the disease, as seen in older children and adults, are characterized by lassitude, dyspnea, palpitation, tachycardia, and constipation, in addition to the pallor of the skin and mucous membranes. In most areas in which hookworm disease is common, dietary deficiencies are also common. Poor diet influences unfavorably the course of hookworm disease. Study of hookworm infection in the dog has shown that host control of infection depends largely upon the development of immunity, and that immunity does not develop or may be lost in the presence of malnutrition, avitaminosis, and anemia. In man, considerable clinical improvement can result from institution of a proper diet, and in the treatment of severe infection it is essential that the utmost improvement from proper diet be attained before drug therapy is begun. One might well expect that the severe grades of hookworm disease would occur much less frequently in endemic areas if proper nutrition could be maintained, since immunity and host control of infection and reinfection in man may not develop in the presence of poor nutrition.

Asymptomatic infection, or the carrier state, is common in endemic areas, where asymptomatic outnumber symptomatic infections, considering

all age groups, 20 to 40 times. The worm burden is small, and in these areas the carrier state is probably indicative of some degree of acquired host resistance.

Laboratory Findings. In symptomatic infection, hookworm eggs are usually numerous enough to be detected by microscopic examination of a direct fecal smear. For survey studies particularly, methods employing a concentration of feces are required. It must be borne in mind that abdominal symptoms and pulmonary symptoms appear before eggs are discharged, although a presumptive diagnosis may be made on the basis of the clinical history and the eosinophilic leukocytosis.

In surveys, when it is feasible to determine the worm burden, Stoll's quantitative method is used. The method may also be used in testing the efficacy of treatment.

The feces are seldom grossly bloody in hookworm disease, although usually positive for occult blood. Charcot-Leyden crystals are found in the feces in one half to two thirds of the cases.

Rarely, only male adults will be present in the intestine, the diagnosis then being made by the detection of the adults in the feces following treatment.

Trichostrongylus eggs must be distinguished from hookworm eggs. The former are larger and in a later stage of maturation when observed in a fresh fecal specimen.

Generally, the leukocyte count is normal or slightly elevated, and the percentage of eosinophils increased to 15 or 30 per cent. However, in some early cases, the leukocytosis may be marked and the eosinophil percentage as high as 70 or 80 per cent. In such cases, a diagnosis of eosinophilic leukemia has been entertained. In general, the more marked the anemia, the lower the percentage of eosinophils. The hemoglobin and hematocrit values are more depressed than the erythrocyte count. The anemia is characteristically of the hypochromic, microcytic variety, with blood indices in the following ranges: mean corpuscular volume = 50 to 80 cubic microns; mean corpuscular hemoglobin = 15 to 20 micro-micrograms; mean corpuscular hemoglobin concentration = 22 to 25 per cent.

Differential Diagnosis. Since hookworm disease occurs in areas in which beriberi and malaria in their cachexial form are also more common, these diseases must be differentiated from hook-

worm disease, or their coexistence established. Chronic glomerulonephritis, arteriolar nephrosclerosis, and nephrosis have some clinical features in common with hookworm disease, but the differentiation can be made readily in the laboratory.

Treatment. Specific therapy and that directed toward improvement of the nutrition and anemia should be considered simultaneously. In the usual case it is safe to administer the anthelmintic and then add iron, occasionally liver, and required supplements to the diet.

Tetrachlorethylene is the drug of choice when ascariasis is not also present. The aim in treatment is simply to reduce the worm burden, and this can be accomplished by one or two courses of tetrachlorethylene. Complete eradication of the infection is unnecessary and in *A. duodenale* infection, moreover, may be extremely difficult. Established procedures in the use of tetrachloroethylene and related drugs (e.g., elimination of fat and alcohol from the diet, purging, etc.) must be followed to avoid toxicity and obtain maximum effect. The usual dose for an adult is 3 ml., for children, 3 minims for each year of age.

When ascariasis coexists, hexylresorcinol should be used first. If large numbers of hookworm eggs persist, tetrachloroethylene may be given after an interval of one week.

Prognosis. Generally, the immediate prognosis is good. When opportunity for reinfection persists and nutrition cannot be maintained, a state of chronic debility develops. In children development is impaired, and in adults intercurrent disease proves serious.

Prevention. Many of the measures required are obvious, but difficult to apply on a large scale. Even if facilities for proper disposal of feces are provided, it is no simple matter to educate the population in their use. Soil pollution must be eliminated and, until this is accomplished, avoidance of direct skin contact with the soil (as by wearing of shoes) should be encouraged. Periodic mass treatment of the population has been used in some hookworm control programs. Not all programs have been so successful as those conducted in the southern United States, where, in one study covering eight states, the incidence was reduced from 36.6 to 11.2 per cent.

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Creeping Eruption

Gustave J. Dammin

Definition
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Definition. Creeping eruption is an infection of the skin in man caused by the larvae of the dog and cat hookworm, *Ancylostoma braziliense*. The

term "larva migrans" is also applied to this infection. *Uncinaria stenocephala*, the European dog hookworm, and *Gasterophilus*, the horse bot-fly, in their larval stage may produce a similar cutaneous infection.

Etiology. The adult stage of *Ancylostoma braziliense* occurs regularly only in the dog and cat. The larvae emerging from eggs discharged in the feces develop to the filariform stage and then

are capable of penetrating the skin. In man, the larvae usually remain in the skin and migrate, producing an irregular erythematous tunnel visible on the skin surface (fig. 163). Should the larvae penetrate the skin of the appropriate



FIG. 163. Creeping eruption in a middle-aged woman, showing multiple uninfected rapidly developing lesions of approximately two weeks' duration. Both limbs were involved. (After Kirby-Smith, Dove and White. Courtesy, Stitt-Strong: "Diagnosis, Prevention and Treatment of Tropical Diseases," Philadelphia, The Blakiston Company.)

animal host, the dog or cat, further development resembles that of *Necator americanus* and *Ancylostoma duodenale* in man. The adults are smaller than those of the other hookworms of man, but the eggs are similar. Another dog hookworm, *Ancylostoma caninum*, is not known to produce this clinical picture in man.

Epidemiology and Distribution. Dogs and cats constitute the reservoir of infection for man. Transmission among animals and to man requires environmental temperature and humidity appropriate for development of the egg to the in-

fective filariform larva stage. Such conditions are found in the southeastern United States, coastal areas of Central America, northern South America, northern and southern Africa, and some areas of the Far East. Beaches and other moist, sandy areas are hazardous, because animals choose such areas for defecation and the *Ancylostoma braziliense* eggs develop well in such soil.

Pathogenesis and Clinical Manifestations. The site of penetration of the skin by the larva becomes apparent in a few hours. The hands and legs are most frequently involved. The migration of the larva in the skin is accompanied by severe itching. Scratching may lead to bacterial infection. In the course of one week the initial red papule develops into an irregular, erythematous, linear lesion which may attain a length of 15 to 20 cm. The older portions of the lesion become dry and crusted.

Wright and Gold have observed Loeffler's syndrome in 26 of 52 cases of creeping eruption. Transient, migratory pulmonary infiltrations were associated with an increase in eosinophils in the blood and sputum. The lesions have been interpreted as an allergic reaction to the helminthic infection.

Laboratory Findings. Eosinophils occur in the lesion, but eosinophilic leukocytosis is slight, except when Loeffler's syndrome appears. The percentage of eosinophils in the blood may then rise to 51 per cent, and in the sputum to 90 per cent.

Treatment. Carbon dioxide snow or ethyl chloride spray may be applied locally to destroy the larva. If ineffective, local treatment with chenopodium oil can be added. Superficial bacterial infections are improved by wet dressings and elevation of the extremity.

Prognosis. Untreated infections may last several months. Treatment is usually sought because of severe pruritus and moderate incapacitation. The above treatment is usually successful.

Prevention. Dogs and cats should be prevented from contaminating recreation areas. Contact of the skin with the soil should be avoided in areas suspected of being contaminated.

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Strongyloidiasis

Gustave J. Dammin

Definition
Etiology
Epidemiology and Distribution
Pathogenesis and Clinical Manifestations
Laboratory Findings
Treatment
Prognosis
Prevention

Definition. Strongyloidiasis is an intestinal infection of man and other higher mammals, caused by *Strongyloides stercoralis*.

Etiology. The adult female measures 2.5 mm. in length and 40 to 50 microns in width, and resides in the mucosa of the upper small intestine. The embryonated eggs (55 microns by 30 microns) liberated into or near the lumen soon develop into the rhabditiform larvae (250 by 13 microns), in which form they are observed in the feces (fig. 168, p. 1136). The rhabditiform larva resembles that of the hookworm, except that its buccal cavity is shallower and the genital organ larger. Further larval development may take one of several courses: (1) In a suitable external environment, the indirect or sexual cycle occurs. Free-living males and females develop, ova are produced following copulation, and these mature to the rhabditiform, then infective filariform stage. (2) Under less suitable external circumstances, the rhabditiform larvae develop into the infective filariform stage (direct or asexual cycle). (3) Development to the infective stage is presumed to occur as well in the lower intestine, the filariform larvae then entering the body through the skin of the perineum, or through the intestinal wall. Mechanisms such as those mentioned in (3), above, must be operative to explain the long periods of infection observed (20 to 30 years) in those who have left endemic areas.

The adult males do not penetrate the intestinal mucosa and are eliminated soon after mating.

The course of the filariform larvae of *S. stercoralis* after entering the skin, the oral mucosa, or the intestinal mucosa resembles that of the hookworm larvae. The larvae enter vessels which ultimately carry them to the lungs. They leave the alveolar capillaries, enter the alveoli,

pass successively to the bronchi, trachea, and pharynx, are swallowed, and reach the intestine. Development to maturity and insemination are believed by some to occur in the lungs as well as in the intestine. Rarely, adult females may remain in the bronchi, larvae then being present in the sputum. In the intestine the females burrow into the mucosa, from which site embryonated eggs are discharged. It appears that insemination is part of the initial process of reproduction, but recent study of animal infection supports the view that the female Strongyloididae are parthenogenetic.

Epidemiology and Distribution. The usual mode of infection is the penetration of the skin by larvae present in contaminated soil. Some infections may result from ingestion of contaminated food and drink, and some are believed to be transmitted by contact. As mentioned, in hyperinfection the infective larvae developing within the intestinal lumen penetrate the intestinal wall or the perianal skin, and begin another cycle of development to the adult stage. *S. stercoralis* infections potentially have the longest duration of any of the helminthic infections.

Infections can be produced in dogs and monkeys, and natural infection in dogs has been reported.

It is accepted that the sexual cycle occurs under optimal external conditions, and the direct cycle under suboptimal conditions; also that the free-living adults cannot withstand desiccation, nor can they survive in water. Much remains to be learned about the life cycle of this unique helminth.

Endemic areas are found primarily in the tropics, although sporadic cases have appeared in temperate regions. Strongyloidiasis is prevalent in the moist tropical areas of the Far East, Africa, and Central and South America, but is less common in the southern United States and the Mediterranean countries.

Pathogenesis and Clinical Manifestations. Erythema with petechiae and pruritus charac-

terizes the site of cutaneous penetration by the larvae. Cough, occasionally with dyspnea and hemoptysis, accompanies the stage of migration through the lungs. X-rays may exhibit pulmonary infiltration at this stage.

Abdominal pain and tenderness and diarrhea alternating with constipation are observed during the intestinal phase of development. Intestinal ulceration and sloughing are noted in severe cases. As with hookworm infection, many asymptomatic infections occur, and most symptomatic infections occasion only vague complaints.

In massive infection, and particularly hyperinfection, there may be serious complications. The extensive involvement possible is illustrated by the fatal case described by Kyle *et al.*, in which extensive pulmonary hemorrhage and edema were observed. Larvae were found in the myocardium, lungs, trachea, liver, and gallbladder, in addition to the intestine. In other fatal cases, intestinal perforation and peritonitis have been encountered.

Laboratory Findings. Although the nature of the clinical findings may be suggestive, the definitive diagnosis must be made in the laboratory. The number of larvae present in the feces, even in severe infections, may be relatively small. Stool concentration methods are occasionally required, and repeated examination necessary. Fresh fecal specimens should be examined to avoid confusion with hookworm infection; generally, fresh specimens contain larvae in strongyloidiasis infections, while in hookworm infection they contain eggs. When pulmonary involvement is present, the sputum should be examined for larvae. They may also be found in pleural exudate and in duodenal and stomach washings. Microscopic examination of the duodenal washings

may readily establish the diagnosis. It should be performed when other studies are negative, and in determining the efficacy of treatment.

Eosinophilic leukocytosis is common, except in very severe cases in which eosinophilic leukocytes may be entirely absent.

Blood loss as a result of infection is slight, and anemia is much less common than in hookworm disease.

Treatment. Gentian violet administered orally continues to be the most satisfactory treatment, although it is only moderately effective. It is given in enteric-coated capsules, 0.06 Gm. three times daily for 7 to 14 days. Some advocate administration by duodenal tube when the oral drug is ineffective. For severe hyperinfective cases, gentian violet has been given intravenously (25 ml. of a 0.5 per cent solution). Careful and prolonged post-treatment laboratory study is necessary to determine effectiveness of the drug in each case.

Prognosis. In the usual case, the prognosis is good. Since the occurrence of hyperinfection is unpredictable, every effort should be made to eradicate the infection in each case. In severe cases with hyperinfection, the prognosis is poor.

Prevention. In general, the measures are those for the control of hookworm infection. In addition, it is well to remember that infection may be contracted by ingestion of contaminated food (especially uncooked vegetables) or of contaminated drinking water, and by contact.

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Trichostrongyliasis

Gustave J. Dammin

Definition
Etiology
Pathogenesis
Manifestations
Laboratory Diagnosis
Treatment
Prevention

Definition. Trichostrongyliasis is an infection caused by members of the genus *Trichostrongylus*.

Etiology. Almost a dozen species of *Trichostrongylus* are known to have infected man. The Trichostrongylidae are commonly parasites of sheep and goats. Human infections have been observed with highest frequency in the Middle and Far East, and in Africa. Few human infections have been reported in the United States. In view of the high frequency of animal infections here, the low incidence of human infections is difficult to understand. The possibility exists that some may be diagnosed as hookworm infection.

The life cycle of the Trichostrongylidae resembles that of the hookworms of man except that there is no pulmonary phase. The adults are small (0.08 mm. by 5 to 6 mm.) and have an unarmed mouth. The ova resemble those of the hookworm but are larger (40 microns by 90 microns), and, when observed in a fresh fecal specimen, show a more advanced stage of segmentation (16- to 32-celled stage). (See fig. 168, p. 1136.)

Pathogenesis. Infection is probably acquired by ingestion of the filariform larvae, rather than by their penetration of the skin. The adults inhabit the small intestine. The unarmed mouth and small size of the adult may account in part for the relatively asymptomatic nature of the infection in man. The adult maintains residence in the intestine for long periods. Sandground,

who infected himself, observed infection to last more than eight years.

Manifestations. Diarrhea is observed occasionally when infection is massive, but most infections are asymptomatic. The parasite owes its importance primarily to the resemblance of its ova to those of the hookworms. Unless the ova are identified, an incorrect diagnosis of hookworm infection may be made. Moreover, because the Trichostrongylidae do not respond to anthelmintics effective in hookworm infection, it may be assumed incorrectly that one is dealing with refractory hookworm infection.

In animals, the Trichostrongylidae produce anemia and emaciation. Heavy infections are often fatal for young animals.

Laboratory Diagnosis. The diagnosis depends upon the finding of the ova in the feces. Since they are few in number, they are usually found only when a concentration method is used. The adults occur in small numbers in infections of man, and are rarely found in the feces.

Treatment. Tetrachloroethylene, carbon tetrachloride, thymol, chenopodium oil, gentian violet, carbarsone, and emetine have been found ineffective. Phenothiazine is reported to be effective in the treatment of animal infections, but is still to be evaluated in human infections.

Prevention. Contamination of the hands and food by soil is to be avoided.

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Ascariasis

Gustave J. Dammin

Definition
Etiology
Epidemiology and Distribution
Pathogenesis and Clinical Manifestations
Laboratory Findings
Treatment
Prognosis
Prevention

Definition. Ascariasis is an infection caused by *Ascaris lumbricoides*.

Etiology. The adult ascarids are large (20 to 40 cm. in length) and cylindric in shape, with each extremity tapering to a blunt point. Their usual habitat is the small intestine, but they are prone to migration. The female discharges enormous numbers of eggs daily (about 200,000). The eggs are elliptic (30 to 40 microns by 50 to 60 microns) and have an irregular, dense outer shell and a regular, translucent inner shell. (See figure 168, p. 1136.) They are not infective upon discharge from the body. Under proper conditions of warmth and moisture the ovum develops to the infective larval stage in about four to five weeks. Upon ingestion of the egg at this stage, the larva is liberated in the small intestine. It migrates through the wall and, by way of venous channels, ultimately reaches the inferior vena cava, and the lungs. It may reach the same destination by way of the intestinal lymphatics and the thoracic duct. After about 10 days in the pulmonary capillaries and alveoli, the larvae pass in turn to the bronchioles, bronchi, trachea, and epiglottis, are swallowed, and develop into male and female adults in the small intestine.

Epidemiology and Distribution. Infection follows the ingestion of the embryonated egg contained in contaminated food, or, more commonly, the introduction of the eggs into the mouth by the hands after contact with contaminated soil. Since the eggs are resistant to desiccation and wide variations in temperature, the disease has a world-wide distribution.

Pathogenesis and Clinical Manifestations. Because of the extensive migration of which both the larvae and adults are capable, clinical manifestations may be unusually diverse. In heavy

infections, severe bronchopneumonia, occasionally fatal in children, can occur during the migration of the larvae through the lungs. Those larvae, which do not leave the pulmonary capillaries during this phase, may be transported by the systemic circulation to the kidneys, brain, and other viscera, where focal hemorrhagic lesions may result. Infection characterized by few adult ascarids is usually asymptomatic. When present in large number, they may produce intestinal obstruction. Light infections assume importance when single or several adult ascarids obstruct the appendix, the bile, the pancreatic ducts, or other hollow structures of the upper intestinal or respiratory tracts.

Laboratory Findings. The diagnosis is usually made by finding the ova in the feces. The intact ova are characteristic, and not easily confused with other ova. Unfertilized or decorticated ova may be difficult to identify as *Ascaris* ova.

X-ray study with barium may reveal adult worms in the intestine (fig. 164) at times when the stool examination is negative. This applies especially to the early stage of infection and to infections in which only male adults are present.

Symptomatic infection, especially during the phase of larval migration through the lung, is usually accompanied by fever and eosinophilic leukocytosis. Asymptomatic infections may show slight eosinophilia.

Treatment. Hexylresorcinol in the form of crystals contained in hard gelatin capsules is recommended as being as efficient as, and much safer than, santonin or chenopodium oil. For children aged 10 or older, and adults, the dose is 1 Gm. For younger children, 0.1 Gm. is given for each year of age. Such treatment may be repeated several times, if necessary, at three-day intervals, and patients may remain ambulatory. "Hetrazan" (1-diethylcarbamyl-4-methyl-piperazine hydrochloride), which has been introduced primarily as a filaricide, is of low toxicity, and in initial studies has been found effective in human and canine ascariasis.



FIG. 164. Radiograph two hours after ingestion of barium, showing two groups of roundworms. (Courtesy, Strang and Warrick: *Brit. J. Radiol.*, **21**:575, 1948.)

Prognosis. The prognosis in intestinal infection is generally good. When acute or chronic obstruction of ducts or hollow viscera has occurred, the immediate prognosis is determined by the promptness in diagnosis and treatment. The prognosis as to complete recovery is determined by the nature and extent of the inflammatory reaction in the organ affected.

Prevention. Ascariasis is primarily a household infection of rural areas. All infections should be treated, personal hygiene stressed, and adequate toilet facilities provided.

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Trichuriasis (Whipworm Infection; Trichocephaliasis)

Gustave J. Dammin

Definition
Etiology
Epidemiology and Distribution
Pathogenesis and Clinical Manifestations

Laboratory Findings
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Prevention

Definition. Trichuriasis is an intestinal infection of man caused by *Trichuris trichiura*.

Etiology. The adult whipworms, usually 30 to

50 mm. in length, possess a threadlike anterior two thirds and a stouter posterior third, giving them a whiplike structure. The males and females

together inhabit the cecum and colon with their anterior extremities buried in the mucosa. The eggs measure about 50 microns by 20 microns and are characteristic, being barrel-shaped, brown, and translucent and having knoblike extremities (see figure 168, p. 1136). They are noninfective when discharged. Moisture is necessary for embryonal development, which requires several weeks to months. Following ingestion, the larva emerges in the duodenum and develops to maturity in about three months.

Epidemiology and Distribution. The mode of spread resembles that of ascariasis, the eggs generally being introduced into the mouth by contaminated fingers. Because of their playing habits, children represent an important factor in maintaining *Trichuris* and *Ascaris* infections in a community. These infections generally coexist, trichuriasis being somewhat more prevalent in areas of higher rainfall, ascariasis in areas of lower rainfall. They are among the commonest helminthic infections of man.

Pathogenesis and Clinical Manifestations. Symptomatic infection generally requires the presence of large numbers of adult whipworms and may be correlated in part with the degree of mucosal involvement. Heavy infections usually occur only in children and may be accompanied by nausea, abdominal pain, and diarrhea. Four instances of massive infection terminating fatally are described by Getz. Asymptomatic infection is the rule in adults.

Laboratory Findings. In symptomatic infection, large numbers of eggs are present in the feces. Eosinophilic leukocytosis and anemia may accompany such infections. Light infections may be detected only by use of concentration technics.

Treatment. The most readily available, least toxic, though not the most efficient, drug is hexylresorcinol. It is administered as prescribed for ascariasis (Chapter 191). Tetrachloroethylene and chenopodium oil given simultaneously may be used. When available, leche de higueron should be used. The efficacy of these drugs appears to be increased by preliminary purging and enemas. Emetine hydrochloride, given orally, has been found active against *Trichuris*, but further study of its toxicity for man is required before it can be recommended for routine therapy.

Prognosis. In uncomplicated *Trichuris* infection the prognosis is good. Symptomatic infection can be controlled with the drugs mentioned, although eradication of the infection is difficult.

Prevention. Measures recommended for ascariasis apply also to trichuriasis.

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Enterobiasis (Pinworm, Seatworm, or Threadworm Infection; Oxyuriasis)

Gustave J. Dammin

Definition
 Etiology
 Epidemiology and Distribution
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Definition. Enterobiasis is an intestinal infection of man caused by *Enterobius vermicularis*.

Etiology. The adults are small fusiform worms

usually inhabiting the cecum and colon, attached to the mucosa. The female averages 10 mm. in length, the male 3 mm. The eggs (fig. 168, p. 1136)

are deposited by the female on the perineal skin, the migration generally occurring at night. Each egg contains an embryo which, a few hours after being deposited, develops into the infective larva. After ingestion of the egg, the larva is released in the small intestine. The adult stage is

under the nails may reveal ova. The diagnosis can be made by examining the feces for adult worms following a laxative or an enema. Eosinophilic leukocytosis is inconstant.

Treatment. Many methods of treatment have been used, none uniformly successful. Anthel-

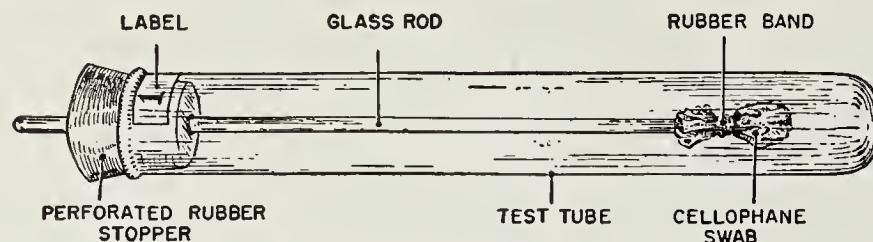


FIG. 165. National Institutes of Health (NIH) anal swab for pinworm.
(Courtesy, Stitt, Clough, and Branham: "Practical Bacteriology, Hematology, and Parasitology," Philadelphia, The Blakiston Company.)

soon reached and, in less than one month from the time of ingestion, newly developed gravid females are again discharging eggs. They are planoconvex and measure approximately 20 microns by 50 microns. The shell is clear and doubly contoured.

Epidemiology and Distribution. The eggs usually reach the mouth of the human host by way of contaminated hands, food, or drink, although airborne transmission may also occur. They are relatively resistant to desiccation and, because they are infective soon after discharge from the body, transmission within family and children's groups occurs readily. Enterobiasis is found in all climates and is probably the commonest helminthic infection of man. Its low incidence in some tropical areas, however, defies explanation.

Pathogenesis and Clinical Manifestations. The presence of large numbers of adult worms attached to the intestinal mucosa in the vicinity of the cecum produces an inflammatory reaction which may manifest itself as appendicitis. There is, however, no constant direct relationship between enterobiasis and appendicitis. The adult worms are known to migrate from the perineum into the vagina and ultimately to the Fallopian tubes and peritoneal cavity. The commonest symptom is pruritus ani, which is most troublesome at night, being related to the migration of the gravid female worms. Scratching may lead to perineal eczema or pyogenic infection.

Laboratory Findings. Examination of material obtained from the perineal skin for ova by means of a "Cellophane" or "Scotch Tape" swab (fig. 165) is essential for the detection of enterobiasis. Less than 5 per cent of infections are diagnosed by searching for ova in the feces. Scrapings from

mintics are administered for their possible toxic effect on the maturing adults, and enemas usually to remove the adults from the colon mechanically. Gentian violet medicinal contained in enteric-coated tablets is the drug of choice. Hexylresorcinol is worthy of trial when the therapeutic response to gentian violet medicinal is inadequate. Phenothiazine seldom need be resorted to, particularly because it causes occasional toxicity in children. "Acranil," an acridine derivative, which has been found effective against most tape-worms, has given encouraging results in enterobiasis. A single dose of 10 mg. per kg. is given in the morning, the patient not having eaten since noon of the preceding day. Three hours after administration of the "Acranil" a saline purge is given.

Prognosis. When reinfection can be prevented, both treated and untreated cases have a good prognosis.

Prevention. Methods of preventing autoinfection and dissemination within a group involving children are difficult to apply. Personal and environmental hygiene should be stressed, and anthelmintic and symptomatic treatment of pruritus ani instituted. To control infection within a group, simultaneous treatment of all cases must be carried out.

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Trichinosis

Gustave J. Dammin

Definition

Etiology

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Pathogenesis and Clinical Manifestations

Laboratory Findings

Differential Diagnosis

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Prognosis

Prevention

Definition. Trichinosis is an infection caused by *Trichinella spiralis*, and characterized by an initial intestinal phase related to the presence of the adult worms, and later by systemic manifestations related to the invasion of skeletal muscle by the larvae.

Etiology. The adult males and females inhabit the small intestine early in the course of the infection. The adult male measures about 1.5 mm. in length and 50 microns in diameter, the female 3 to 4 mm. in length and 70 microns in diameter. After copulation, the females penetrate the mucosa and discharge larvae (100 microns by 6 microns), which enter veins and lymphatics and are distributed throughout the body. Larvae are produced and liberated for about four to six weeks. The adult males survive for a variable length of time, and ultimately are discharged with the feces. The larvae enter skeletal muscle and encyst (fig. 166). The muscles of the diaphragm, tongue, and eye, the deltoid, pectoral, and intercostal muscles are most often affected. Larvae carried to sites other than skeletal muscles do not encyst, but disintegrate. In skeletal muscle, a cyst capsule is produced around the larva, which ultimately reaches 1 mm. in length. The larva is coiled up in the cyst and may remain viable for as long as 10 years. Some encysted larvae die and may calcify as soon as six months after encystation. The life cycle can be carried further only if a new host ingests the encysted larvae. After ingestion, the larvae are liberated in the intestine and develop there to maturity in a few days.

Epidemiology and Distribution. Infection in man follows the ingestion of inadequately cooked meat, usually pork. The *T. spiralis* exhibits little

host specificity, infection having been produced or observed in the bear, wild boar, horse, cow, dog, cat, rabbit, guinea pig, mouse, and other animals, including some fowl. The important animal hosts bearing on transmission to man are

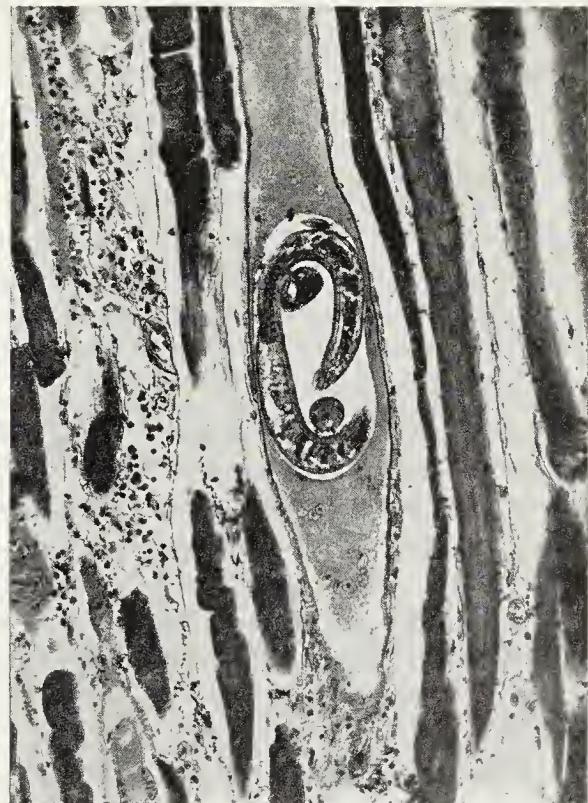


FIG. 166. *Trichinella spiralis*. Larva encysting within a skeletal muscle fiber. At this stage, myositis and edema have partially subsided. ($\times 135$.)

the pig and the rat. Among pigs, infection is maintained by feeding on uncooked pork scraps, less often by eating infected rats. Rats also feed on uncooked pork scraps and, in addition, maintain a high incidence of infection by their cannibalism.

The life cycle of *T. spiralis* is unique in human helminthology, because both the adult and larval forms develop in the same individual host. Moreover, since there is no stage of development outside the host, climatic factors have little bearing on the geographic distribution of trichinosis. It is common in Europe and North America and un-

common in other parts of the world. In the United States, where the incidence is between 15 and 20 per cent, there is "more than three times as much trichinosis as is known in all of the rest of the world put together." The ratio of asymptomatic to symptomatic infection is high.

Pathogenesis and Clinical Manifestations. The course and symptomatology vary remarkably. The clinical diagnosis in the sporadic case may be difficult. Diarrhea is an early manifestation related to the development of the adults in the intestinal mucosa, and is observed in about half of the cases. The next stage, that of muscular invasion, begins about the end of the first week and may last for as long as six weeks. The larvae migrate into the intestinal vessels and are carried ultimately to the left side of the heart and distributed by the circulation to all parts of the body. Most of the clinical manifestations are related to the invasion and encystment of the larvae in skeletal muscles. A myositis is produced, with basophilic granular degeneration of the invaded muscle fiber. Adjacent fibers exhibit hyaline or hydropic degeneration, and the focus becomes infiltrated with neutrophilic and eosinophilic leukocytes, some lymphocytes, and mononuclear macrophages. Hyperemia, edema, and hemorrhages are constant features. The inflammatory reaction subsides after several weeks, or during completion of the encapsulation. The clinical myositis appears to be related more to the intensity of the inflammatory reaction than to the size of the infecting dose.

Larvae do not encyst in cardiac muscle, nor can they be found readily there. Despite this, an intense myocarditis has been observed, and may be of significance in fatal cases.

Larvae have been observed in association with less severe focal lesions in the lungs and brain, and in other viscera, with no associated inflammatory reaction.

The significant clinical manifestations are noted during the period of migration and muscle invasion. Fever is probably the commonest manifestation. It is probably related both to the disintegration of the larvae and the degeneration of skeletal muscle. Ocular manifestations may be among the most striking. Edema of the eyelids, usually accompanied by conjunctivitis and chemosis, is caused by larval invasion of the eye muscles. Also a constant manifestation is the muscular pain and tenderness. Symptoms related

to the respiratory tract are linked to larval migration through the lungs and in the muscles of respiration. Headache is moderately common and, when severe, central nervous system involvements should be suspected. Manifestations in the skin and appendages include (1) a maculopapular rash which usually lasts for several days, and (2) subungual "splinter hemorrhages."

The convalescence in severe cases may be protracted.

The nature of the transmission of trichinosis accounts for its occurrence as a group (e.g., family) infection. Epidemiologic data are often helpful in arriving at a clinical diagnosis.

Laboratory Findings. The most constant finding, and one of significance early in the course of the disease, is the eosinophilic leukocytosis (over 500 eosinophilic leukocytes per cubic millimeter). It appears generally before the end of the second week, and rises. In cases of moderate severity the percentage of eosinophilic leukocytes ranges between 15 and 50 per cent. In severe cases, particularly terminally, the eosinophilic leukocytes may disappear entirely.

The skin test becomes positive early in the third week of infection. The antigen is prepared from larvae and used in a dilution of about 1:10,000. One one hundredth of a millimeter is injected intradermally and immediate and delayed reactions looked for. The usual positive response is immediate, with a wheal 5 mm. or more appearing within 30 minutes. Nonspecific reactions may be related to the ingestion of meat containing nonviable trichinae.

The precipitin reaction becomes positive after the third week. Its value in diagnosis is increased if the reaction is initially negative and becomes positive, or if the titer rises during the patient's course. It remains positive for about a year. A modification of the precipitin test in the form of a slide flocculation method has been introduced. The complement-fixation test is too complex for general use.

In attempting to arrive at a definitive diagnosis, examination of the feces for the adult worms is of little help. Examination of the blood, cerebrospinal fluid, or muscle biopsy is more rewarding. Microscopic study of laked venous, capillary, or arterial blood is the simplest test which may make a definitive diagnosis possible. Larvae may be present in the cerebrospinal fluid in the absence of clinical central nervous system involve-

ment. Biopsied muscle is best studied by use of a compressor which permits examination of the entire specimen. Maceration and digestion methods are used in survey studies of diaphragms obtained at autopsy, and for biopsy specimens as well.

Differential Diagnosis. Trichinosis must be distinguished from acute glomerulonephritis, typhoid fever, meningitis, rheumatic fever, rheumatoid arthritis, eosinophilic leukemia, dermatomyositis, and periarteritis nodosa.

Treatment. There is, as yet, no specific treatment for trichinosis. Symptomatic treatment is directed toward the relief of pain, maintenance of an adequate caloric and fluid intake, and assuring the patient of adequate sleep by use of sedatives. The use of convalescent serum probably deserves further study. "Hetrazan" (Lederle) has been found effective against the adult worms in experimental infections, but has not been evaluated in man.

Prognosis. The prognosis in children is usually better than in adults. If there is no serious involvement of the myocardium or respiratory muscles, the prognosis is generally good. The

longer the appearance of symptoms is delayed, the better the prognosis. Diarrhea early in the course is a favorable sign. Analysis of larger series of sporadic and epidemic cases shows the mortality rate to be about 5 per cent.

Prevention. The responsibility for control rests with the consumer. Adequate cooking of pork involves heating all portions of the meat to 55° C. Freezing procedures to kill the larvae require a temperature of -15° C. for 20 days, or -18° C. for 24 hours. Proper smoking and pickling will also destroy the larvae. Important in control is the cooking of garbage fed to hogs. There is at present no practical method of inspection which will detect trichinous pork.

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Filariasis

L. T. Coggeshall

Definition
Filariasis (*W. bancrofti*)
Etiology
Pathogenesis

DEFINITION

Filariasis is a general term for a group of diseases of man and animals caused by pathogenic nematodes as they permeate various tissues, particularly subcutaneous tissues and those of the lymphatic system, where local reactions are incited. The most important to man are *Wuchereria bancrofti*, *Wuchereria malayi*, *Loa loa*, and *Onchocerca volvulus*. Since the separate organisms

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are attended by different behaviors in the human host, they will be presented separately.

FILARIASIS (*W. bancrofti*)

One type of filariasis is caused by the nematode (roundworm) *Wuchereria bancrofti*. It produces lymphedema, lymphadenopathy, and lymphangitis in the acute stages and, in the chronic stages, is frequently associated with elephantia-

sis. It is the type that occurred in approximately 15,000 servicemen in World War II. The reader is referred to an excellent article by Wartman on this phase of the subject.

Historically, this type of filariasis has been recognized for centuries primarily because of the distinctive elephantiasis seen in some long-standing cases. A stage in the development of the organism, the microfilaria, was first observed in 1863 by Demarquay in the hydrocele fluid of a patient in Paris. Wucherer also observed these embryonic forms in the chylous urine of a patient in 1866, and in 1872 Lewis found them in the blood of an infected patient. In 1878 Manson made the classic studies on the transmission of the disease by the *Culex* mosquitoes. Subsequent studies have more clearly defined the life cycle, established its geographic location, and extended the number of known vectors.

Etiology. The adult translucent worms possess a tough cuticle and live coiled together in dilated lymphatics. The males are about 35 mm. and the females 50 to 100 mm. in length. After the females become gravid, embryos are expressed at periodic intervals and migrate to the blood stream. Here they develop into microfilariae, and the maximum numbers are usually encountered between 9:00 p.m. and 2:00 a.m., although in Fiji, Samoa, and certain other Western Pacific islands no periodic behavior is noted. The microfilariae are not infectious to man unless they pass through an appropriate mosquito host, and blood from infected hosts may be used for transfusion without harm, although this is not recommended. These microfilariae are ingested by the female mosquito with the blood meal. They undergo further development in the body cavity of the mosquito over a 12-day period when the infected forms first appear in the proboscis of the mosquito. They enter the human host through the puncture wound when the mosquito bites, or they can penetrate unbroken skin.

The larvae migrate to the larger lymphatics and, as they become sexually mature, they mate. There is little or no immunity to this infection in any race and the disease itself apparently confers no specific immunity upon the host.

Pathogenesis. The entrance of the larvae into the skin produces only a mild redness and itching. However, there exists in the lake regions of the northern United States a species of filaria non-pathogenic for man, whose normal hosts are the

aquatic birds and snails. The free-swimming larvac will penetrate the human skin rather than perish as the water on the bather evaporates. An intense reaction, known as "swimmer's itch," attended by urticaria and uncontrollable itching, results for a few hours as the larvae die in an unnatural host.

The larvae of *W. bancrofti* produce both local and general reactions, presumably as the result of secretions or actual destruction of some larvae by the body, as they migrate to the large lymphatics. The lymph channels become irritated and areas of localized edema occasionally occur. When the immature worm reaches the lymph node, there is invasion to the inner structure where the male and female complete their development. This process is attended by a considerable reaction, particularly in the previously uninfected individual. The node undergoes hypertrophy, chiefly consisting of granulomatous tissue, and frequently enlarges to the point where lymphatic obstruction occurs. This can be associated with a retrograde lymphangitis that may extend the length of an extremity. If this process is repeated over a number of years, the resulting fibrotic tissue leads to an extensive permanent blockage, and elephantiasis occurs. Fortunately, every larva that penetrates the human host does not reach maturity; likewise, the defensive mechanism of the host gradually eliminates the adult forms. Thus, in the absence of repeated re-infections, filariasis is a self-limited disease.

Manifestations. All manifestations of the disease are attributable to the migration of the larvae and their development into adult forms. In the event of heavy infections, there is a relatively acute systemic reaction, principally noted as a low-grade fever and malaise with a tendency to recur at brief intervals. The outstanding objective manifestations of early filariasis are lymphedema, lymphadenopathy, and lymphangitis, principally encountered in the areas of the greater lymphatic channels and nodes of the spermatic cords, groins, and axillas. Subjectively, one notes severe drawing pains and cramps.

In the early stages of infection, moderate to severe exertion is frequently followed by an exacerbation of symptoms, particularly lymphangitis and cramplike or drawing pains of the spermatic cords. Following rest these manifestations disappear rapidly, usually within 24 to 48 hours, without permanent damage. Chronic infections

may be accompanied by complications, although some may be asymptomatic indefinitely. The most noticeable and frequent complication is elephantiasis involving the scrotum and lower extremities. Hydroceles resulting from inflammation or obstruction are frequently encountered. The obstruction of the thoracic duct often produces a chyluria.

Laboratory Findings. Microfilariae, when present, can be seen either in thin blood smears stained by the Giemsa or Wright method, or in wet, fresh smears, since they are motile. Thick smears are recommended when the numbers are few. The adult filariae, either alive or dead, may be observed in biopsied enlarged lymph nodes, although this procedure is not recommended for diagnosis. There are complement-fixation and cutaneous tests, but neither is completely reliable for the individual case. The blood picture is not diagnostic; eosinophilia may or may not be present.

Treatment. No drugs have been shown to be specific for filariasis, although several compounds have been shown to reduce the microfilarial count, particularly certain antimony compounds. In recent studies a piperazine compound, 1-diethylcarbamyl-4-methylpiperazine hydrochloride ("Hetrazan"), has been discovered that seems to

offer considerable promise, as it will destroy the adult worms of experimental animals. Also, its use in human infections results in the disappearance of microfilariae for many months. Otherwise, treatment is symptomatic. Vaccines and serums have not been of value. For elephantiasis much can be done by bed rest, massage, bandaging early cases, and surgery for advanced cases.

The prognosis is good, apart from the disability produced in those cases with elephantiasis. This is especially true if infected individuals remove themselves from endemic areas or protect themselves from reinfection.

FILARIASIS (*W. malayi*)

Filariasis caused by *W. malayi* is not essentially different from that caused by *W. bancrofti* except in its distribution.

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Onchocerciasis

L. T. Coggeshall

Onchocerciasis is a nematode infection produced by *Onchocerca volvulus*, characterized by subcutaneous swellings or nodules, and is transmitted by several different species of *Simulium* flies. This condition occurs in the Western Hemisphere, particularly in the highlands of Guatemala and southern Mexico. There is widespread distribution in Central Africa. Both the adult worms and microfilariae may be found in the nodules, which vary in size from 2 to 3 mm. and 5 to 6 cm. in diameter. In Central America there

is a tendency for the nodules to occur in the region of the head, while in Africa they are usually found in the trunk and pelvis.

Diagnosis is made by examining the aspirated contents of the nodules, and their surgical removal constitutes the treatment. As in filariasis produced by *W. bancrofti*, "Hetrazan" has been shown to be exceedingly promising in preliminary studies. Unless the infection invades the eye or unless there is an excessive number of nodules (more than 50), the prognosis is not unfavorable.

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Loiasis

L. T. Coggleshall

Loiasis, a form of filariasis produced by *Loa loa*, is prevalent in West and Central Africa. Frequently the patient is asymptomatic, although there may be a localized allergic reaction in the subcutaneous tissue (Calabar swellings). *Loa loa* is also known as the "eye worm," as it is frequently noted beneath the conjunctiva of the

eye. Certain *Chrysops* flies transmit the infection. Diagnosis is made by finding the adult worm in subcutaneous tissues, particularly in the eye, or by detection of the microfilariae in the aspirated contents of the Calabar swellings or in stained blood smears. There is no specific treatment. Prognosis is good.

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Dracunculiasis (Dracontiasis, Guinea Worm Infection)

Gustave J. Dammin

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Definition. Dracunculiasis is an infection of the cutaneous, subcutaneous, and connective tissues of man and other higher mammals, caused by *Dracunculus medinensis*.

Etiology. Among those helminths in which the sexes are separate, the adult female *Dracunculus* is the largest, usually measuring about 1 m. in length. The major portion of the body is occupied by the uterus, which contains many embryos. The anterior extremity of the female penetrates the host's skin, from its subcutaneous lair, to

effect release of the embryos to the outside world. Parturition usually occurs only when the anterior extremity of the worm has contact with water. The larvae may survive in water for several weeks. A small crustacean, *Cyclops*, is the intermediate host. The *Cyclops* is probably infected by the oral route, the larvae completing metamorphosis in the course of several weeks. Man acquires the infection by ingesting the larva-containing *Cyclops*. The larvae are liberated from the *Cyclops* by action of the gastric juice. They penetrate the intestinal wall and migrate to the subcutaneous tissues, usually of the extremities. The mature male is small, measuring 2 to 3 mm. in length. The male probably fertilizes the female early during their subcutaneous existence and then disintegrates. The female matures in ap-

proximately one year, and is then prepared to discharge larvae. This she does after penetrating the skin and gaining access to the skin surface.

Epidemiology and Distribution. Probably a dozen species of *Cyclops* are satisfactory hosts for the larval stage of *Dracunculus medinensis*. The appropriate species thrive in quiet waters such as step-wells and cisterns. Since such water supplies are used for bathing and drinking purposes in poorly sanitized tropical areas, dissemination of the infection occurs readily. Areas of the highest endemicity are found in Africa and Asia. Current estimates place the number of infections at about 48 million, about one third in Africa and two thirds in Asia, primarily in western India.

Many of the higher wild and domesticated mammals are known to be susceptible, but their role in transmission of the disease to man is not exactly known.

Pathogenesis and Clinical Manifestations. Symptoms which are often anaphylactoid in nature are related to the presence of the adult female worm in the subcutaneous tissues, especially during the period of cutaneous penetration by the cephalic extremity. The legs are the site of penetration in over 90 per cent of the cases. Burning and itching sensations precede the appearance of the local lesion. This begins as a vesicle, but often becomes secondarily infected and ulcerates. The application of water or wet dressings appears to stimulate the worm to discharge larvae. Secondary bacterial infection in the proximity of joints occasionally leads to permanent disability. Calcified female worms can be detected by x-ray, and localization of viable worms determined by injection with radiopaque materials (fig. 167). Although many patients harbor only a single worm, the presence of two or more worms is not uncommon.

Laboratory Findings. Examination of washings from the skin lesion, or of the milky fluid which appears periodically in the site, will reveal variable numbers of *Dracunculus* larvae.

Eosinophilia is moderate when it occurs, but it does not appear regularly.

Skin-testing antigens are not specific enough to aid in diagnosis.

Treatment. The anaphylactoid symptoms may be relieved by epinephrine. The newer anti-histaminic drugs are worthy of trial in this stage of the disease.

The patient should be placed at rest and gen-

eral measures applied for treatment of the skin lesion. Antibiotics may be required for ulcerative lesions and cellulitis.

Removal of the worm may be attempted by the customary method of slow extraction by



FIG. 167. *Dracunculus* radiograph. (After Boutreau-Roussell. Courtesy, Stitt-Strong: "Diagnosis, Prevention and Treatment of Tropical Diseases," Philadelphia, The Blakiston Company.)

winding on a stick. Although this may require as long as two weeks, it is probably safer than surgical extraction. Injections of phenothiazine and other drugs to destroy the worm have not proved to be safer or more practical than the customary method.

Prognosis. The prognosis is good, particularly because of more successful methods of treating secondary bacterial infections. The incidence of disability due to pyogenic arthritis should be lowered by the same token.

Prevention. Since the infection is acquired by ingestion of the *Cyclops* containing the *Dracunculus* larvae, (1) contamination of wells by human and animal hosts of *Dracunculus medinensis* should be guarded against; (2) chemical (lime) and biologic (fish feeding on *Cyclops*) control should be instituted in addition; or (3) where feasible, a supply of filtered water for drinking purposes should be provided.

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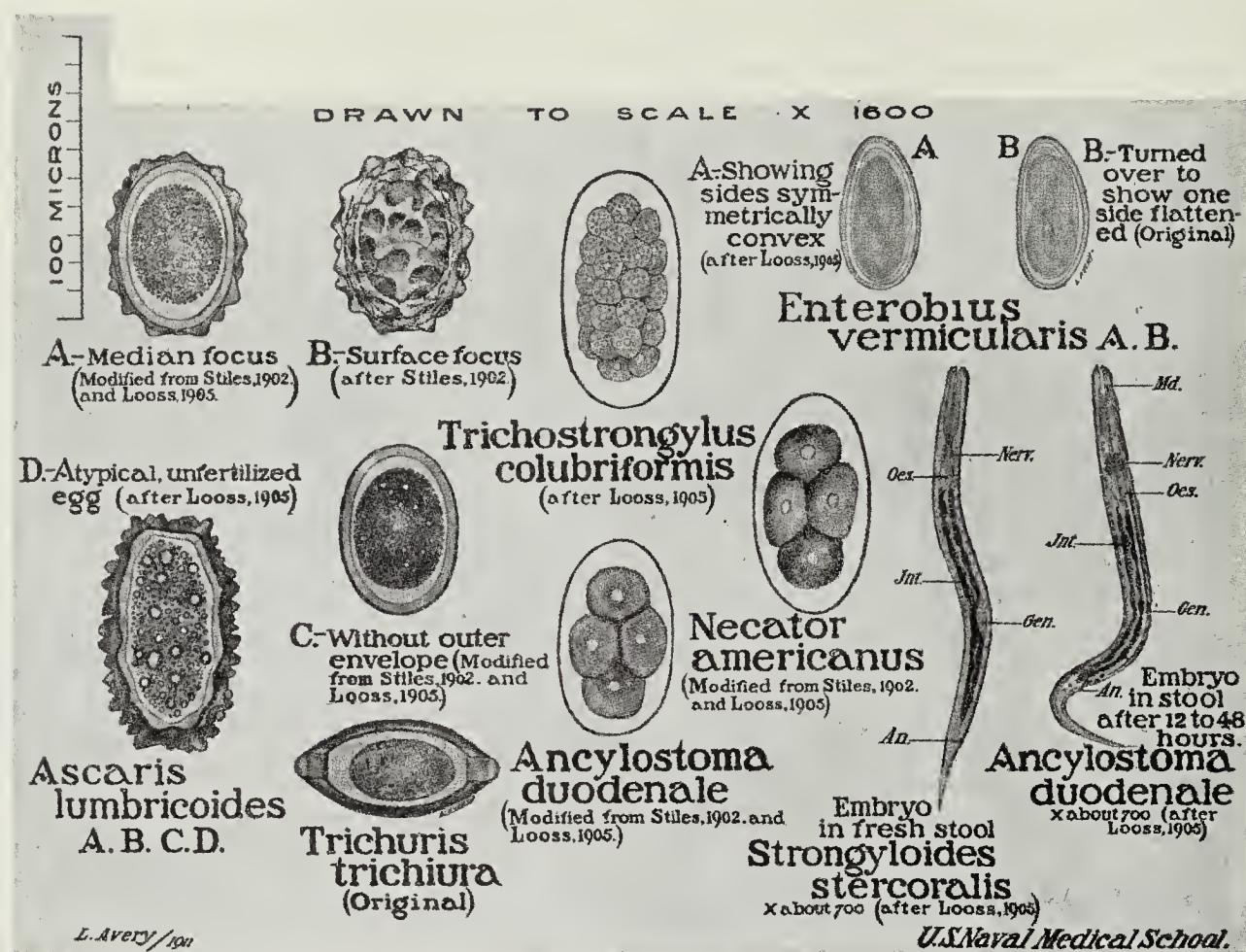


FIG. 168. Ova of the parasitic worms of man: Nematodes. (Courtesy, Stitt-Strong: "Diagnosis, Prevention and Treatment of Tropical Diseases," Philadelphia, The Blakiston Company.)

Schistosomiasis Mansoni

Gustave J. Dammin

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Definition. Schistosomiasis mansoni is an infection caused by *Schistosoma mansoni*, involving primarily the colon and liver.

Etiology. The male and female adult worms inhabit the mesenteric veins. The male measures about 8 mm. in length and the female about 12 mm. The female worms migrate to the smaller mesenteric veins in the wall of the colon and discharge their eggs there. Under the influence of (1) increased pressure in the involved vein caused by the presence of the female worm and the deposited eggs, (2) intestinal movements, and possibly other factors, the eggs are extruded into the intestinal lumen and ultimately leave the body with the feces. The eggs (120 microns by 60 microns) have a long oval shape and possess a lateral spine (see fig. 173, p. 1149). In water, the miracidium is released from the egg. The free-swimming miracidium enters the intermediate host, a snail of the genus *Australorbis* or *Planorbis*. Within the snail, the infective stage or cercaria develops. The cercaria measures about 0.5 mm., and possesses a forked tail. Upon contact with the skin or mucous membrane of man or other appropriate definitive host, the cercaria enters with the aid of lytic enzymes. Cercariae have been shown to contain hyaluronidase. In the process of penetration, the forked tail is lost. Ultimately, vessels are entered which carry the metacercariae to the heart, then to various parts of the body. Maturation to the adult stage occurs in the larger branches of the portal vein. The adults migrate against the venous flow to the smaller mesenteric veins, where copulation occurs. The females then wander to the still smaller

mesenteric veins and there they deposit their eggs.

Epidemiology and Distribution. Infection generally occurs during contact of the skin with water containing the cercariae. Waterways are polluted either directly or by flow of sewage. Still waters and slowly flowing streams containing the appropriate species of *Planorbis* or *Australorbis* are more hazardous than rapidly flowing streams. Because of the conditions required for transmission, the highest infection rates occur along waterways in any region. Infection is acquired by use of polluted water for domestic and industrial purposes.

Schistosomiasis has been observed or produced in a wide variety of animal species. Infection is produced readily in the monkey, rabbit, hamster, and other laboratory animals. Animals probably play an insignificant role in maintaining foci as endemic, man being the important factor in the pollution of waterways.

Schistosomiasis mansoni has the widest distribution of the three types of schistosomiasis. It is endemic in many parts of Africa, in one region of Arabia, in Brazil, Venezuela, Dutch Guiana, and many of the Caribbean islands. No cases have originated in the United States, but a native snail, *Tropicorbis havanensis*, has been shown to be an appropriate intermediate host.

Pathogenesis and Clinical Manifestations. Penetration of the skin is accompanied by erythema and intense pruritus. During the migration of the metacercariae, transient fever, leukocytosis with an increase in eosinophilic leukocytes, nausea, anorexia, cough, and vague intestinal symptoms occur. After maturation, six or seven weeks from the time of exposure, fever is a more prominent manifestation. Eggs are produced and those which disintegrate in the tissues, particularly in the intestinal wall, the liver, and the lung, excite an inflammatory response which

results in the formation of pseudotubercles. Dysentery, enlargement of the liver, and bronchopneumonia are observed. Eosinophilic leukocytosis is constant in this stage. As this stage subsides, usually only the manifestations of chronic colitis persist. There is superficial mucosal ulceration and polyp formation. If the initial infection is massive, or if repeated infection occurs—as it usually does in endemic areas—then manifestations related to cirrhosis of the liver become prominent. Splenomegaly, esophageal varices, ascites, anemia, and hemorrhagic tendencies develop. Hematemesis occurs, and not uncommonly is the immediate cause of death. The liver is usually finely nodular and firm. The fibrosis involves the portal areas, and pseudotubercles, containing eggs in various stages of degeneration, may be concentrated in these areas. The colon, especially in its distal portion, is thickened, and degenerate eggs are seen in the fibrotic areas. Polypoid growths occasionally protrude externally from the rectum (fig. 169).



FIG. 169. *Schistosoma mansoni*. Anal polyp with adult male and female in a dilated vein and eggs in the adjacent submucosa. ($\times 28$.)

Loeffler's syndrome occurs, as it does in other helminthic infections. Pulmonary fibrosis may be observed in the late stage of the infection, occasionally with cor pulmonale.

In rare instances, eggs have been observed in

the brain, both in the presence and in the absence of cerebral symptoms. Such ectopic lesions are commoner in schistosomiasis japonica. Their development has been reviewed by Faust.

Laboratory Findings. The diagnosis is usually based upon the finding of the eggs in the feces. The large, lateral-spined eggs are detected readily under low power of the microscope. In the usual case seen in an endemic area, a stool concentration method is not required. If the direct examination is negative, then, for study of the individual case, a sedimentation method involving concentration of a relatively large portion of stool is recommended. For routine diagnostic and survey purposes, the acid-ether method incorporating a detergent or xylol (AEX method) is useful. A hatching technic which involves incubation of the fecal specimen in water and examination of the supernate for miracidia is preferred by some. In the individual case, proctoscopy combined with removal of suspected material with an applicator, or combined with biopsy, may be helpful in establishing the diagnosis or observing the effects of therapy. Precipitin, complement-fixation, and skin tests are aids in diagnosis, but their usefulness and limitations are still to be determined. An antibody which produces a precipitate around the cercariae, and therefore resembling that observed in *Nippostrongylus muris*, *Ancylostoma caninum*, and *Trichinella spiralis* infections, has been demonstrated in *S. mansoni* infection. Needle biopsy of the liver has proved helpful in some instances.

Leukocytosis, with increase of the eosinophilic leukocytes, occurs regularly, early in the disease. Late in the disease, anemia is present and the liver function tests give evidence of parenchymatous damage and reduction of functioning parenchyma.

Treatment. Tartar emetic (sodium or potassium antimony tartrate), a trivalent antimonial, has been used widely and is generally considered to be the most effective drug. It is given intravenously as a 1 per cent solution, in doses of 5 ml. on alternate days until about 120 ml. have been given. There is a cumulative effect but, by careful observation, toxic effects on the myocardium can be avoided. Good results have also been reported with "Fuadin" and "Anthiomaline," which are also antimony salts.

"Miracil D," a thioxanthone derivative recently introduced, has been evaluated in experi-

mental infection and subjected to brief clinical trial. If given in adequate doses, the drug has a specific lethal action on the adults of *S. mansoni* and *S. haematobium* in infected mice, jebils, and monkeys. In clinical trials, the drug has been given orally in a dosage of 1 Gm. distributed over a period of about one week. Clinical improvement has been observed with greater regularity in adults than in children. Better results have been obtained in mansoni than in haematobia infections.

Prognosis. The clinical course is milder and more chronic than that of japonica and haematobia infections. The prognosis is relatively good with reference to recovery from the active stages of the disease. Late in the course, when cirrhosis, anemia, splenomegaly, and emaciation have developed, the prognosis is poor.

Prevention. Measures may be taken (1) to prevent fecal contamination of waterways inhabited by snail hosts, (2) to control snail hosts, (3) to destroy cercariae, (4) to prevent infection by use of cercarial repellents, (5) to educate the population in ways to prevent dissemination and acquisition of the disease, and (6) to provide means of producing safe water supplies for domestic and industrial purposes, whichever measures are most appropriate. Successful, permanent control can follow only on prevention of

fecal contamination of waterways, since control of snail hosts, as by use of ammonium sulfate, copper sulfate, copper carbonate, live steam, and the drying of canals and clearing them of vegetation, is difficult, usually temporary, and ultimately more costly. The destruction of cercariae may be effected by chlorination. This procedure, boiling, or filtration may be used to provide safe water for domestic purposes. Preparations containing benzyl benzoate, dibutyl phthalate, dimethyl phthalate, and other chemicals in various combinations have been found effective in preventing infection in the experimental animal when applied directly to the skin or tested as cloth impregnants.

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Schistosomiasis Japonica

Gustave J. Dammin

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Definition. Schistosomiasis japonica is an infection of man and domestic and wild animals, caused by *Schistosoma japonicum* and characterized in man by a clinical course more acute and

severe than that observed in schistosomiasis mansoni and schistosomiasis haematobia.

Etiology. The male and female adults possess a spinous rather than a tuberculated integument such as is possessed by *Schistosoma mansoni* and *Schistosoma haematobium*. The male measures about 16 mm. in length and the female about 26 mm. The adults live in the mesenteric and portal veins, the female depositing eggs, 70 microns by 90 microns (see figure 173, p. 1149), in the smaller

mesenteric venules. Those eggs which reach the intestinal lumen and are discharged with the feces hatch in water, liberating the miracidium. The miracidium enters the intermediate snail host (genus *Oncomelania*, *Katayama*, and *Schistosomophora*). After development, the cercariae are released from the snail and seek a definitive host. After penetration of the skin or mucous membranes of a new host, the larvae, as metacercariae, reach small veins and lymphatics, are carried to the heart, then distributed throughout the body. Generally, development to maturity occurs only in the portal and mesenteric veins (fig. 170).

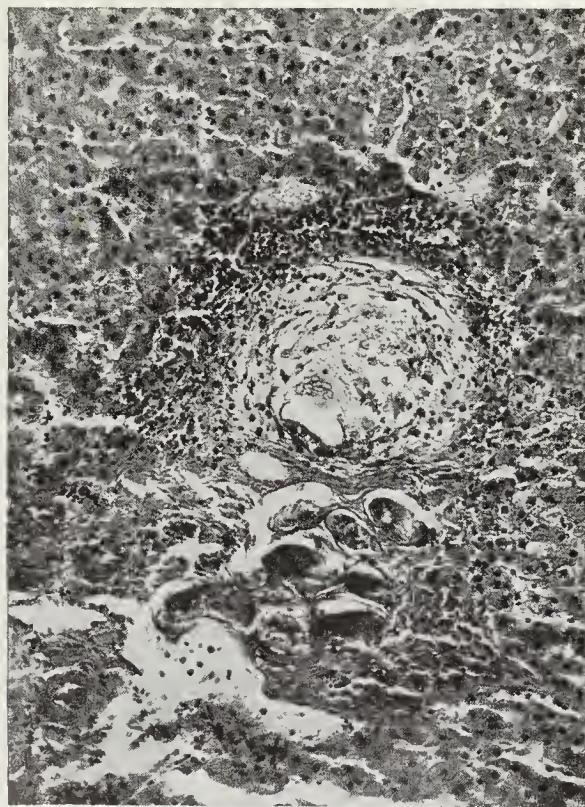


FIG. 170. A cluster of intact eggs of *Schistosoma japonicum* in a portal area with a pseudotubercle developing around disintegrating egg. ($\times 125$.)

Epidemiology and Distribution. Infection follows exposure in waters containing an appropriate snail host and polluted with feces from infected human beings or animals. In endemic areas, initial infections occur early in life through various contacts with polluted fresh waters, and in later life through contact with water used for industrial (e.g., rice cultivation) and domestic purposes. Deposition of sewage and night soil and defecation directly into the snail-containing waterways account for the pollution. Infection in

many domestic and wild animals adds to the pollution of waterways.

Schistosomiasis japonica is endemic in Japan, China, the Philippines, Formosa, and Celebes. Most of the infections among American servicemen were contracted in the Philippines, notably Leyte.

Extensive studies in native North American snails have shown none to be complete hosts, but partial development was observed in *Pomatiopsis lapidaria*.

As in bacterial, viral, and other helminthic infections which occur in epidemic form, asymptomatic infections have been observed in epidemic schistosomiasis japonica and their importance emphasized.

Pathogenesis and Clinical Manifestations. The penetration of the skin is accompanied by pruritus and cutaneous eruption less often than in mansoni and haematobia infections. During the month or so between the time of penetration and that of maturation, fever, pulmonary symptoms, urticaria, weakness, and diarrhea are observed. After maturation and the beginning of deposition of eggs, for a period of several months, dysentery becomes a prominent manifestation, the fever is more pronounced, and there are epigastric pain and tenderness, enlargement of the liver and spleen, abdominal cramping pain, anorexia, and loss of weight. The early tissue reaction around the eggs consists of eosinophilic and neutrophilic leukocytes with foci of necrosis varying in size. This is followed by the appearance of epithelioid and giant cells. Lymphocytes and plasma cells appear later, and finally there is fibroblastic proliferation and ultimately fibrosis. There is endothelial swelling in the smaller vessels of the affected areas. The principal involvement is in the large and small intestines, the liver, and the lungs. The finding of intestinal nodules by sigmoidoscopy has been helpful in establishing the diagnosis when stool examination is negative. In some acute as well as chronic cases, eggs may also be found in the brain, meninges, adrenal medulla, skin, and mesenteric lymph nodes. Cerebral symptoms in acute cases consist of drowsiness, coma, incontinence, and signs of pyramidal tract involvement; in chronic cases, of Jacksonian convulsions and hemiplegias.

In the later stages of the disease, cirrhosis of the liver, splenomegaly, ascites, peripheral edema, anemia, and chronic dysentery are com-

mon. As the fibrosis and papillomatosis of the intestine progresses, more eggs pass with the venous flow to the liver, thus increasing the tissue reaction there.

Laboratory Findings. The laboratory diagnosis generally is based on the demonstration of the characteristic eggs in the feces. In the acute stage the eggs are usually present in large numbers and may be found in direct fecal smears. When concentration of the specimen is necessary, one of the sedimentation methods using a detergent is recommended. Such methods usually are required for diagnosis in the chronic stage. As in mansoni infection (Chapter 199), scraping or aspirating material from the rectal and sigmoidal mucosa may be helpful. Skin tests, complement-fixation tests, and liver biopsy are also useful.

In the acute stage, leukocytosis and eosinophilia are common. Later, anemia and leukopenia appear, but the percentage of eosinophilic leukocytes usually remains elevated. Depressed liver function usually can be demonstrated in this stage.

Treatment. Various trivalent antimonials have been used. Tarter emetic is probably the most efficacious. Dosages are higher than those used for mansoni infections. Most recommends a total dose of 2.2 Gm. or 440 ml. of a $\frac{1}{2}$ per cent solution. With the use of "Fuadin," a 42 per cent relapse rate has been reported. Because of the gravity of the cerebral lesions, every effort should

be made to diagnose and treat japonica infections. Cerebral manifestations accompanying the acute stage have responded satisfactorily to chemotherapy. Neurosurgery may be required for chronic lesions. "Miracil D" has not been evaluated in japonica infections.

Prognosis. Japonica infections are the most severe of the schistosome infections. Treated early and adequately, a moderate to high degree of symptomatic improvement can be expected in acute stage infections. The prognosis in late stages of the disease is poor.

Prevention. Factors in prevention and methods of control are similar to those described for schistosomiasis mansoni. The effective role which sewage treatment processes can play in control is considered in detail by Jones *et al.*

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Schistosomiasis Haematobia

Gustave J. Dammin

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Definition. Schistosomiasis haematobia is an infection, principally in man, caused by *Schisto-*

soma haematobium and characterized by hematuria and cystitis.

Etiology. The adult male (12 mm.) and female (20 mm.) inhabit the pelvic venous plexuses, the female depositing eggs in the smaller veins of the urinary bladder (fig. 171) and occasionally the rectum. Superficial mucosal ulceration results in entrance of the eggs into the lumen of the urinary

bladder. Many eggs, however, are retained in the tissues. When deposited in water, those eggs in the urine release the miracidium which searches for an appropriate snail host (genus *Bulinus*, *Planorbis*, or *Physopsis*). After entry and further

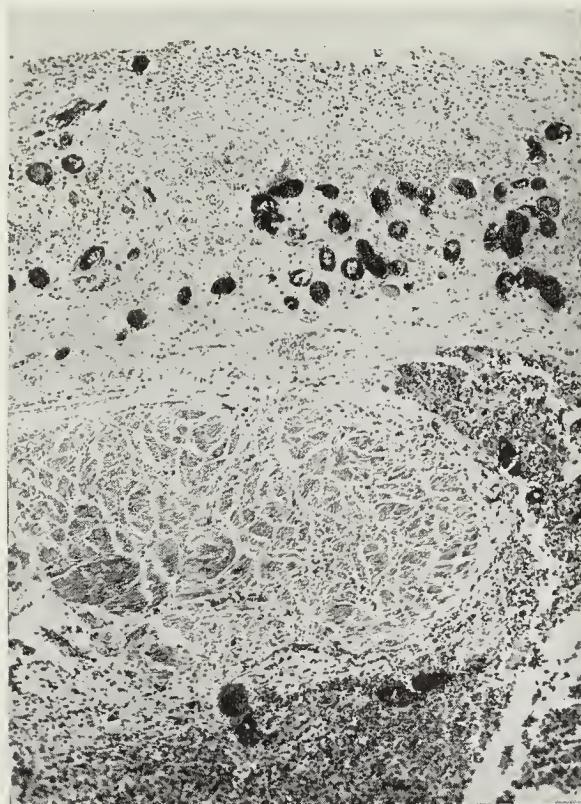


FIG. 171. Calcified eggs of *Schistosoma haematobium* in thickened mucosa of the urinary bladder. Portions of a carcinoma of the bladder are present in the muscularis. ($\times 50$.)

development, cercariae leave the snail in search of man, the principal definitive host. The skin is penetrated and the metacercariae are distributed in the body as in other schistosome infections. Development to the adult stage, however, usually occurs only in the pelvic venous plexuses and their branches.

The eggs measure about 140 microns by 60 microns and possess a prominent terminal spine. (See fig. 173, p. 1149.)

Epidemiology and Distribution. Infection is acquired by exposure in cercaria-infested waters. The infection cycle is essentially that of man—snail—man. As with the other types of schistosomiasis, water used for domestic and industrial purposes brings the infection to man. Certain religious customs involving ablution represent another type of exposure. Snails of the genus *Bulinus* are common in North Africa and thrive in sewage-polluted waters. Irrigation canals and

ditches constitute an important hazard, and much infection is contracted in such water. Use of the canals for sewage and irrigation facilitates transmission.

The disease is endemic in many parts of Africa, in the Middle East, in some parts of Europe bordering on the Mediterranean, and in the islands east of Africa.

Pathogenesis and Clinical Manifestations. As in mansoni infection, the cutaneous penetration by the cercariae is accompanied by the appearance of itching papules and edema, followed by an urticarial rash, fever, headache, and generalized aching sensations. Such symptoms subside and then after a period of variable duration, hematuria, particularly in the terminal portion of the urine, appears. The initial symptoms mentioned above may be mild or even absent. Signs of involvement of the urinary bladder may follow many years after the presumed exposure. Frequency of micturition, nocturia, dysuria, and perineal pain often appear when the hematuria becomes manifest. The eggs of *S. haematobium* are usually demonstrated most readily in the terminal blood-tinged portion of urine. Many of the eggs retained in the bladder mucosa calcify, and calculi form as well in the lumen of the urinary bladder. Cystoscopically one observes relatively early a granulation tissue with focal epithelial proliferation in the form of papillomas. Eggs are numerous at this stage. In the latter stages, there is mucosal atrophy as well, but eggs can still be found in the urine and bladder biopsy. The incidence of carcinoma of the bladder is high in hematobia infection and appears as early as the second decade of life in endemic areas. The infection may extend to involve the prostate and seminal vesicles, or the ureters with development of hydronephrosis and pyelonephritis, or the urethra with fistula formation. Involvement of the vagina and cervix can also result in serious complications. Eggs have been found in the skin of the scrotum and groin, and adults have been recovered from the subcutaneous tissue of the groin.

Eggs are carried to the lungs in a high percentage of cases, and rarely, because of diffuse arterial involvement, a syndrome similar to Ayerza's disease is produced. A small number may reach the liver and produce focal fibrosis. Central nervous system involvement also occurs, though less commonly than in japonica infections.

The development of the individual lesions is similar to that observed in mansoni and japonica infections.

Laboratory Findings. The diagnosis is usually made by finding the eggs in the urine, particularly the terminal portion. Cystoscopy with biopsy is helpful in late cases. With rectal involvement present, the diagnosis may be made by examination of the feces or rectal scrapings, or by proctoscopy.

Leukocytosis with eosinophilia may be prominent early in most symptomatic cases. Later examination of the blood provides little supportive evidence of infection. Complement-fixation and skin tests are useful in indicating past infection.

Treatment. Intravenously administered tartar emetic in dosages as for the other schistosome infections is the preferred drug. It probably acts on both adults and eggs. Rapid symptomatic improvement is the rule, although complete cures are not obtained in a high percentage of cases. Treatment early in the course of the disease is highly desirable because it may avert the serious complications mentioned above. Equally good results have been reported with "Fuadin" and "Anthiomaline." However, in a carefully observed instance of voluntary infection, treatment with potassium antimony tartrate was successful after "Fuadin" had failed. Further clinical trials with "Miracil D," which is given orally, are awaited, although up to the present better results have been obtained in mansoni than haematobia infections.

Prognosis. The prognosis is good when treatment is instituted early. In late cases when there is chronic urinary tract infection with irreversible tissue alteration, treatment accomplishes little, the patient is subject to serious complications, and the prognosis is poor.

Prevention. The problems in control are essentially as described for schistosomiasis mansoni. In regard to molluscicides, although copper sulfate is still most widely used, Halawani in Egypt has reported the delta isomer of hexachlorocyclohexane to be effective against *Bulinus truncatus* and *Planorbis boissyi*. Field control must be adjusted to the economy of a region, and irrigation projects and snail control closely integrated. Although the ultimate aim in control is the prevention of pollution of waterways, it is currently considered most practical to stress snail control.

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Schistosome Dermatitis

Gustave J. Dammin

Definition
Distribution
Pathogenesis and Clinical Manifestations
Treatment
Prevention

Definition. The cercariae of schistosomes having definitive hosts other than man may invade

the skin of man and produce a dermatitis referred to commonly as "swimmer's itch," or "water itch." The definitive hosts of some of the schistosomes concerned are known to be the muskrat in some instances, and migratory birds in others, but not all definitive hosts have yet been recog-

nized. The intermediate hosts are snails of the genus *Stagnicola*, *Lymnaea*, or *Physa*.

Distribution. In North America, schistosome dermatitis is common in Oregon, the lake region of the north central United States, and the neighboring portion of Canada. It has also been reported from parts of Central America, western Europe, and the Far East.

Pathogenesis and Clinical Manifestations. It is now clear from the work of Macfarlane and Olivier that the principal cutaneous manifestations are related to a re-exposure to cercariae of schistosomes having definitive hosts other than man, and, therefore, represent an allergic phenomenon. Studies in volunteers showed that initial exposure to *Cercaria longicauda* or *Trichobilharzia stagnicolae* produced inconspicuous cutaneous involvement, often mild enough to go unnoticed. This primary lesion began as a macule and proceeded to the formation of a nonpruritic, pale papule in the course of one week. The secondary lesion which occurred on subsequent exposure was a pruritic red papule, vesicle, or wheal. In the primary lesion there was slow dissolution of the cercariae in the epidermis, whereas in the secondary lesion there was a rapid removal. The efficacy of local antihistaminic therapy in relieving the pruritus was accepted as further evidence for the allergic nature of the secondary lesion.

Treatment. Local application of antipruritic lotions such as calamine with menthol or phenol

is used to allay itching and thereby to reduce the likelihood of secondary infection. Local treatment with the antihistaminic drugs should be recommended with caution because of the possibility of inducing local sensitization.

Prevention. Immediate drying of the skin has been recommended as a prophylactic measure. It is of doubtful value since Olivier has shown that cercariae will penetrate while fully submerged. In some areas, control has been effected by destruction of the snail hosts. Copper sulfate and copper carbonate have been used for this purpose. It is most effective in small bodies of water. Treatment of shallow near-shore waters where snail breeding is abundant has been moderately effective. Cercarial repellents such as those mentioned in the chapter on "Schistosomiasis Mansonii" (Chapter 199), and copper soaps are still to be evaluated.

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Clonorchiasis

Gustave J. Dammin

Definition
Etiology
Epidemiology and Distribution
Clinical Manifestations
Laboratory Diagnosis
Treatment
Prevention

Definition. Clonorchiasis is an infection caused by *Clonorchis sinensis*, and is characterized by

hepatic lesions produced by the adult worms in the biliary passages.

Etiology. *Clonorchis sinensis*, the most important liver fluke in man, is a hermaphroditic worm measuring about 15 mm. by 5 mm., and possessing a pointed anterior and a rounded posterior extremity. Its usual site in the definitive host

is the biliary tract, and occasionally the pancreatic ducts. The small operculate eggs, 30 microns by 15 microns (see figure 173, p. 1149), discharged by the mature adult appear in the feces. If these are deposited in water containing the appropriate snail host (subfamily Bithyniinae) and ingested by the snail, then the miracidium emerges. In the snail, the first intermediate host, there is development to the cercarial stage. After liberation from the snail, the cercariae seek fish, which they penetrate, and then undergo encystation in the musculature. Most fresh-water fish in the Far East can serve as this second intermediate host. Infection of the definitive host follows on ingestion of raw fish containing the larval *Clonorchis*. Many fish-eating mammals can serve as definitive hosts (dog, cat, pig, badger, guinea pig, and others). The encysted larva is released and migrates from the duodenum into the biliary tract, where it develops into the adult form. Judging from studies on individuals who have left endemic areas, the adult *Clonorchis* is capable of living as long as 25 years.

Epidemiology and Distribution. Infection is contracted only by the ingestion of raw fish harboring encysted larvae. Deposition of animal and human feces into waterways accounts for the high incidence of infection in fresh-water fish; and the habit of eating raw or partially cooked fish, for the high incidence of infection in man in endemic areas. Clonorchiasis occurs throughout the Far East. At one time, infected individuals were not admitted into the United States, but, when it was apparent that infection could not be propagated here, this restriction was lifted. A recent unusual epidemic occurring in Shanghai has been described by Koenigstein.

Clinical Manifestations. The percentage of asymptomatic infections is probably high. The bile ducts become thickened and dilated, and there is chronic pericholangitis and atrophy of parenchyma, but cirrhosis with the usual clinical manifestations is uncommon. Cirrhosis can be expected only in endemic areas in which opportunity for frequent reinfection exists. Adult worms are found in the pancreatic ducts in about 10 per cent of cases, but symptoms rarely are related to such involvement. In heavy infections of long standing, anemia and weight loss occur. The high incidence of primary carcinoma of the liver is related by some to *Clonorchis* infection, despite the uncommon occurrence of portal cirrhosis.

Laboratory Diagnosis. The diagnosis usually depends on the demonstration of the eggs in the feces or the duodenal contents. An eosinophilic leukocytosis is found regularly in the early stages only.

Treatment. No method of treatment has been consistently successful, but some success has been noted with tartar emetic and gentian violet.

Prevention. Adequate cooking of fresh-water fish will prevent infection. The emphasis in control should be on making the population aware of the dangers of consuming raw or partially cooked fresh-water fish, rather than on control of the larval stages and snail hosts.

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Opisthorchiasis

Gustave J. Dammin

Opisthorchiasis is caused by *Opisthorchis felineus*, and is characterized by hepatic lesions occasioned by the presence of the adult worms in the larger bile ducts. The adults, which are hermaphroditic, are elongate and flat with a slightly pointed anterior extremity, and measure about 1.0 cm. by 0.3 cm. The life cycle resembles that of *Clonorchis sinensis*. The adult fluke is found as a natural parasite of the dog, hog, cat, and fox. The operculated eggs, 30 microns by 12 microns (see figure 173, p. 1149), when discharged with the feces into water, are ingested by the snail, the first intermediate host (genus *Bulinus*). The miracidium contained in the egg develops to the cercaria stage in the snail. The free-swimming cercaria penetrates fresh-water fish and en-

cysts in the muscles as a metacercaria. In the upper intestine of the definitive host, after the ingestion of raw fish containing the metacercaria, excystment occurs, followed by migration to, and development in, the bile ducts to the adult stage. The lesions and clinical manifestations resemble those produced by *C. sinensis*. The geographic distribution differs in that it is endemic in eastern and central Europe and in Siberia, and occurs in some parts of Asia. The diagnosis usually is based on the finding of the eggs in the feces or duodenal contents. Treatment as recommended for clonorchiasis may be used. Infection can be prevented by eating only well-cooked fish.

Fascioliasis

Gustave J. Dammin

Fascioliasis is caused by the hermaphroditic leaf-shaped fluke, *Fasciola hepatica*, which inhabits the bile ducts of the definitive host. When fully matured, the adult measures about 3 cm. by 1 cm., and discharges large operculate eggs, 140 mm. by 70 mm. (see figure 173, p. 1149). When eggs are deposited in a moist environment, the miracidium emerges and enters the snail host (e.g., genus *Lymnaea*). The cercariae which develop in the snail host encyst on aquatic plants after liberation. When the cyst form is ingested by an appropriate definitive host, it excysts in the upper intestine, penetrates the intestinal wall,

passes to the liver, and develops to maturity (fig. 172) in the larger bile ducts.

Fascioliasis produces so-called "liver rot" in the sheep, the principal definitive host. The disease is most common in sheep- and cattle-raising countries, but has been reported from many parts of the world. On the North American continent it occurs in the southern and western United States, Central America, and in the Caribbean islands. As definitive hosts, the horse, dog, rabbit, goat, squirrel, and monkey, among others, have been reported in addition to sheep, cattle, and man.

Infection is contracted by ingestion of the encysted form attached to edible aquatic plants such as water cress. Ponds and slowly flowing waterways are most likely to be hazardous. Pollution of waterways is constant because the feces

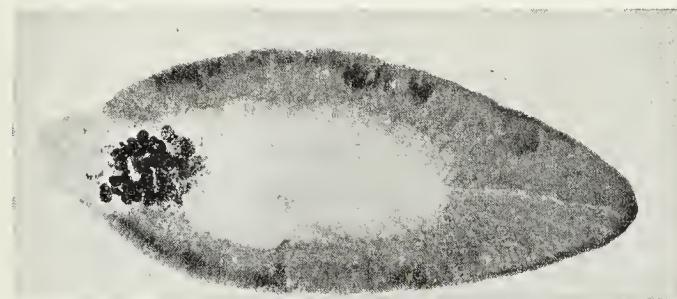


FIG. 172. Mature *Fasciola hepatica*. ($\times 2.5$.)

of infected animals are often deposited directly into the waterways.

Early clinical manifestations are related to the migration of the larval form to and within the liver. Epigastric pain, fever, diarrhea, jaundice, urticaria, pruritus, arthralgia, and eosinophilia may be observed during this stage (Arenas *et al.*, Kourí). Cirrhosis of the liver of the variety found in clonorchiasis may be a late manifestation appearing only after prolonged residence of many adult worms in the bile ducts. Light infections are usually asymptomatic. A pharyngeal

form of the disease may follow on the ingestion of infected raw liver, the adults attaching themselves to the pharyngeal mucosa, occasionally interfering with respiration.

The diagnosis usually is based on the finding of the eggs in the feces or in the duodenal contents. It is difficult to distinguish the eggs from those of *Fasciolopsis buski*.

Emetine and aspidium oleoresin have been used in treatment, emetine being the drug of choice.

To prevent infection in man, aquatic plants such as water cress should not be eaten, vegetables grown in fields irrigated with polluted water should be boiled, and safe drinking water should be provided. In the field, control is directed toward destruction of snails and encysted cercariae.

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Fasciolopsiasis

Gustave J. Dammin

Fasciolopsiasis is caused by the large intestinal fluke, *Fasciolopsis buski*, which inhabits the upper intestine of its definitive host. The principal definitive host is the pig. In parts of China, India, and other parts of the Far East, infection of man is common. The adults (4.5 cm. by 1.5 cm.) are hermaphroditic, and discharge large (120 microns by 90 microns), oval, operculated eggs (see figure 173, p. 1149) into the intestinal contents. The miracidium emerges from the egg when deposited in water, and a snail host is sought. After development in the snail host, the

cercariae are liberated and encyst on aquatic plants. Infection is contracted following ingestion, or peeling with the teeth, of water chestnuts and other edible aquatic plants. The large adults attach themselves to the intestinal mucosa, and these sites may later ulcerate. Diarrhea and abdominal pain appear early. Later, if heavy infection continues, asthenia with ascites and anasarca occurs. Diagnosis is based upon the history and the finding of eggs in the feces. The eggs closely resemble those of *Fasciola hepatica*. The prognosis in untreated heavy infections, espe-

cially in children, is poor. Treatment with hexylresorcinol, in the form of crystoids, is effective, and is indicated for all symptomatic infections (McCoy and Chu). The most practicable control measure is the brief immersion of all edible aquatic plants in boiling water. Where feasible,

snail control with copper sulfate, and treatment of cases should be carried out.

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Paragonimiasis

Gustave J. Dammin

Paragonimiasis, also known as endemic hemoptysis, is an infection, primarily of the lung, caused by *Paragonimus westermanii*. In addition to man, also the dog, cat, pig, rat, and some wild carnivores serve as definitive hosts. The adult lung flukes are hermaphroditic, and measure about 15 mm. by 8 mm. The operculate eggs are relatively large, measuring 85 microns by 50 microns in size. They are deposited into cystlike pulmonary lesions produced by the adult flukes, ultimately being discharged with the sputum or, if swallowed, with the feces. The miracidium is released from the egg after maturation in water, and seeks a suitable snail host. After the cercariae develop in the snail, they are released and enter the second intermediate host, a crustacean (crab, crayfish, or mollusk), where development of the encysted form occurs. After ingestion of the crustacean containing the encysted metacercaria, excystment takes place in the upper intestine of the definitive host. The excysted metacercaria penetrates the intestinal wall and enters the peritoneal cavity. Most of the metacercariae burrow through the diaphragm into the pleural cavity and into the lungs, where, in cyst-like lesions adjacent to bronchi and bronchioles, development into the adult stage occurs. These lesions measure up to about 1 cm. in diameter and, when of long standing, have a stout wall composed of fibrous connective tissue. Other smaller lesions may be in the form of nodules representing reaction around deposited eggs. Such lesions may progress to abscess formation.

Those metacercariae which do not penetrate the diaphragm may invade the intestine, and develop into adults in the intestinal wall. Ulceration of the intestinal mucosa permits release of eggs into the feces. Eggs also appear in the feces when sputum from pulmonary lesions is swallowed. In heavy infections, lesions may also be found in the liver, mesentery, skeletal muscle, and brain. According to the sites of predominant involvement, cases may be classified as pulmonary, abdominal, or cerebral. In the pulmonary type, abundant brownish sputum is produced, and bouts of hemoptysis occur. Abdominal pain and dysentery characterize the abdominal type. Various types of paralysis and epilepsy are observed with cerebral involvement. Eosinophilia is rather constant in all varieties of paragonimiasis. Eggs (see figure 173) should be searched for in the sputum and feces, in attempting to establish the diagnosis. Using an antigen prepared from the adult trematodes, complement-fixing antibodies can be demonstrated. This may be helpful in identifying occult abdominal and cerebral infections.

Treatment with emetine or tartar emetic has been found to produce temporary improvement. Prevention of superimposed infections is important, since the infection is, in a sense, self-limiting.

Paragonimiasis has probably the widest geographic distribution of any of the diseases produced by the hermaphroditic trematodes. It is endemic in many parts of the Far East, and has

been reported from parts of Africa and northern South America.

Field control directed against reservoir and intermediate hosts is not practicable. The most practicable measure is the adequate cooking of all shellfish to be used as food. Infection may be contracted by drinking water into which disintegrating shellfish have discharged encysted larvae.

Sources of drinking water suspected of being contaminated in this manner should be boiled or filtered before use.

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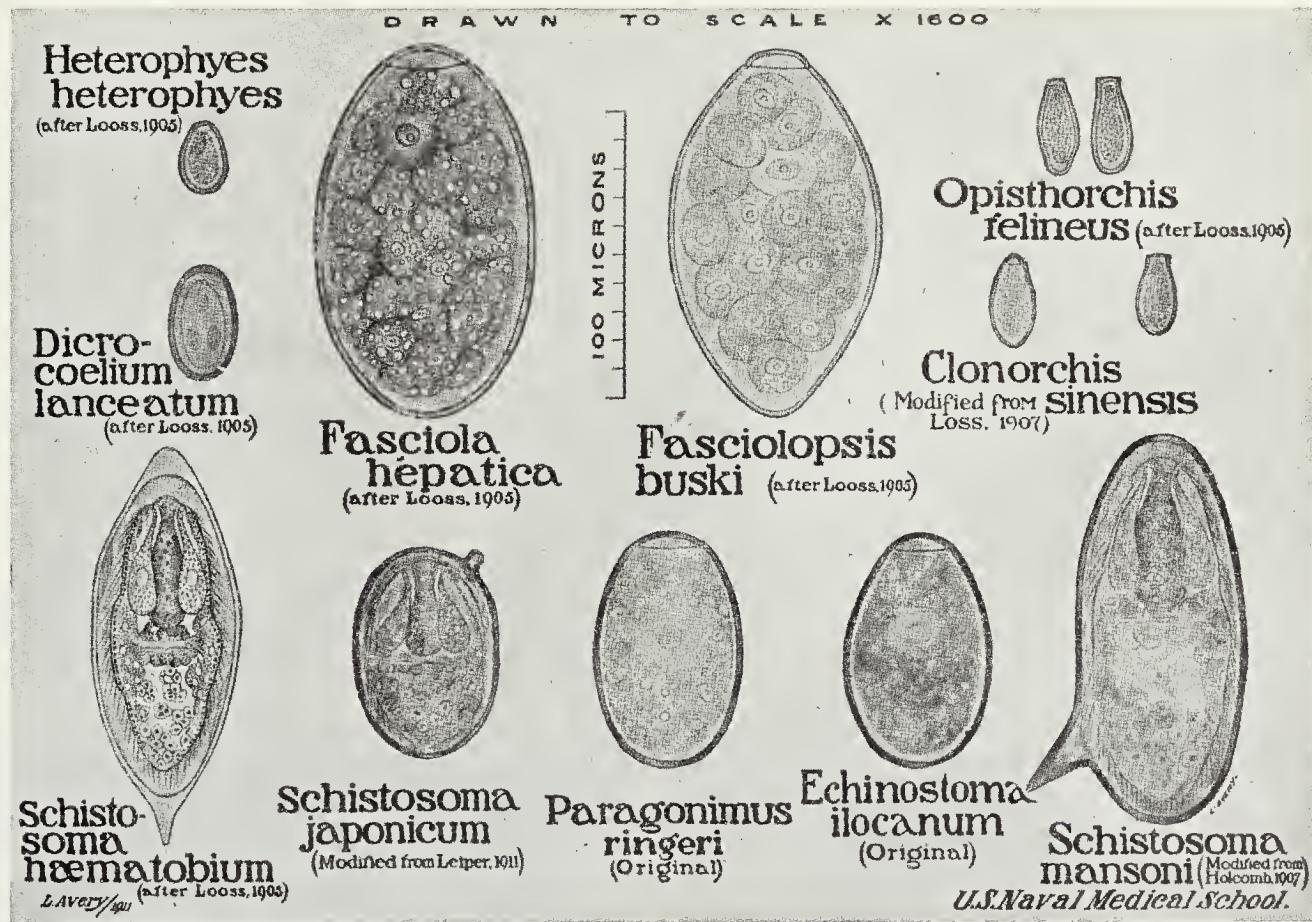


FIG. 173. Ova of the parasitic worms of man: Trematodes. (Courtesy, Stitt-Strong: "Diagnosis, Prevention and Treatment of Tropical Diseases," Philadelphia, The Blakiston Company.)

Diphyllobothriasis Latum and Sparganosis

Gustave J. Dammin

Diphyllobothriasis Latum

Definition

Etiology

Pathogenesis

Distribution

Clinical Manifestations

Treatment

Prevention

Sparganosis

DIPHYLLOBOTHRIASIS LATUM

Definition. *Diphyllobothrium latum*, the fish tapeworm or broad tapeworm, produces in man and its other definitive hosts infection characterized by the presence of the hermaphroditic adult worm in the intestinal lumen.

Etiology. The adult worm may measure from 5 to 10 meters and possess between 3000 and 4000 proglottids (fig. 174). The mature proglot-

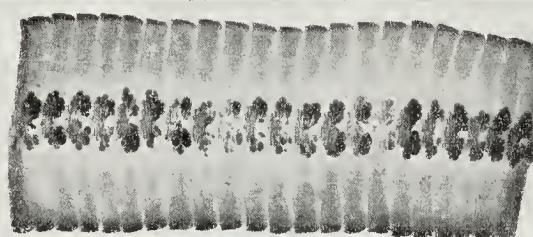


FIG. 174. Gravid proglottids of *Diphyllobothrium latum*. ($\times 2$.)

tids measure about 3 to 5 mm. in length, and 10 to 15 mm. in width. Proglottids and/or the operculate eggs, 45 microns by 65 microns (see figure 178, p. 1158), are discharged in the feces of the definitive host. A ciliated embryo leaves the egg after development in fresh water, and is ingested by a copepod of the genus *Cyclops* or *Diaptomus*. The larva encysts (procercoid stage) in the copepod, which in turn is ingested by the second intermediate host, a fresh-water fish (e.g., salmon, pike, perch, etc.). The stage in this host is known as the plerocercoid larva or sparganum. It is found in large numbers in the muscles and other tissues of the fish.

Pathogenesis. Ingestion of infected fish in the uncooked or undercooked state by man, the dog, the cat, or the bear results in infection. The plerocercoid larva develops into the adult form in the intestine in about three weeks, and is then capable of discharging eggs. The adults of *D. latum* have been known to survive for periods of 5 to 10 years.

Distribution. Fish tapeworm infection is common in the Baltic and Scandinavian countries, Switzerland, Italy, Russia, Japan, Siberia, and Central Africa. It has also been established in the north central United States and in south central Canada.

Clinical Manifestations. Most infections either are asymptomatic or produce slight transient abdominal discomfort. Infrequently, severe abdominal pain, weakness, and loss of weight are noted.

The relationship of the infection to an anemia which closely resembles pernicious anemia has not yet been defined adequately. The tapeworm anemia occurs infrequently, usually in 0.1 to 0.5 per cent of infections. It has been found almost exclusively in Finland. Apparently, therefore, a hereditary or racial predisposition is required. It has been thought that those affected have such a predisposition, since some later develop pernicious anemia. It has been observed that the anemia will improve following removal of the worm, but also following administration of liver, stomach extract, or folic acid, before removal of the worm. It has been suggested that, since there is no deficiency of either extrinsic or intrinsic factor, the worm interferes with the interaction of these factors.

Treatment. In the presence of anemia, liver extract or folic acid should be given and an adequate response obtained before treatment with an anthelmintic is considered. Both the anthelmintics known to be effective—aspidium oleo-

resin and carbon tetrachloride—must be used cautiously because of their toxicity. The various anthelmintics used in tapeworm infections have usually been found to be about equally effective in *D. latum*, *Taenia saginata*, *Taenia solium*, and *Hymenolepis nana* infections. Recently, quinacline and the related acridine derivative, "Acranil," have been used with success in the treatment of *T. saginata* and *H. nana* infections. *H. nana* infections have also responded well to chloroquine. Encouraging preliminary results have been obtained with these acridine derivatives in *D. latum* and *T. solium* infections. Even if further studies show these drugs to be no more effective than aspidium oleoresin and carbon tetrachloride, their use as anthelmintics represents a distinct advance, because in the doses required their toxicity is low. Present indications are that these acridine derivatives may eventually constitute the treatment of choice. "Acranil" may be given in a single dose or in two divided doses equivalent to 10 mg. per kilogram of body weight. The drug is given orally in the morning, the patient not having eaten since the previous noon. It is considered advisable to administer a saline purge three hours after the "Acranil."

Prevention. The most practical control measure is the thorough cooking of all fresh-water fish. Children should not be permitted access to fish markets or to kitchens when fresh-water fish is being prepared, because of the possibility that they may consume some uncooked. To reduce contamination of waterways, dogs and cats should not be fed raw fresh-water fish.

SPARGANOSIS

The sparganum or plerocercoid larva of *Diphyllobothrium mansoni* will develop in man following ingestion, usually in drinking water, of a *Cyclops* bearing the procercoid larva. Sparganosis also follows application of infected fresh frog flesh used as a poultice. The frog tissues contain the sparganum, which is capable of invading human tissues. The dog and cat are definitive hosts for *D. mansoni*. The location of the larvae determines the prognosis of the infection in man. Surgery and local alcohol injection are the only methods of treatment.

Sparganum proliferum, the adult stage of which is unknown, produces a more severe infection because of its unusual multiplication in the human host. Nodules containing the larvae form in the skin, lungs, intestine, brain, and other sites. The prognosis is poor in severe infections.

Sparganum mansonioides probably accounts for most of the cases of sparganosis observed in the United States.

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Taeniasis Saginata

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Definition
 Etiology and Pathogenesis
 Distribution
 Clinical Manifestations
 Laboratory Findings
 Treatment
 Prevention

Definition. *Taenia saginata*, the beef tapeworm, is a hermaphroditic cestode which inhabits the intestinal tract of man, its only definitive host.

Etiology and Pathogenesis. In its adult stage, the *T. saginata* measures from 5 to 10 meters in length and possesses about a thousand proglottids. The gravid proglottid (fig. 175) measures

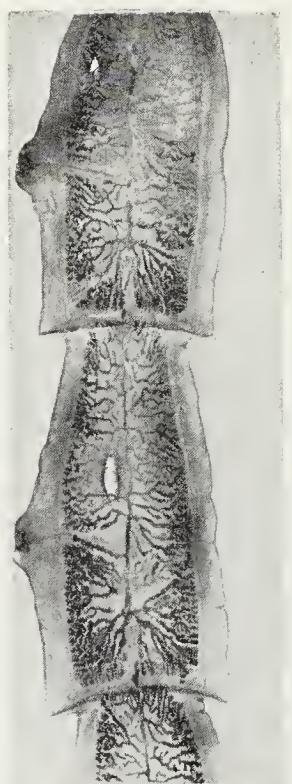


FIG. 175. Gravid proglottids of *Taenia saginata*. ($\times 2$.)

about 5 mm. in width and 20 mm. in length. It possesses 15 to 30 lateral uterine branches, thus distinguishing it from *Taenia solium*, which has 8 to 12. The proglottids may show independent motion for long periods after discharge with the feces. The head or scolex measures 1 to 2 mm. in diameter, possesses prominent suckers,

but no hooks. The eggs are ovoid, 30 microns by 40 microns (see figure 178, p. 1158), consist of a radially striated shell enclosing a hexacanth embryo, and are indistinguishable from those of *T. solium*. When the eggs are ingested by cattle, the embryo is released in the intestine, invades the intestinal wall, and is carried by vascular channels to striated muscle in the hindlimbs, diaphragm, and tongue, the common sites for formation of the cysticercus stage (*Cysticercus bovis*). *C. bovis* measures about 5 mm. by 10 mm., and consists of a scolex held in a cystlike structure. When *C. bovis* is ingested in raw or undercooked beef by man, the adult tapeworm develops in the intestine in about two months.

Distribution. *Taeniasis saginata* occurs in countries in which it is the custom to eat raw or undercooked beef. It has been estimated that in the USSR alone there are about 18 million infections, and in the world's population almost 40 million. It is not common in the United States.

Clinical Manifestations. Symptoms in man, when present, consist of mild epigastric pain, diarrhea, hunger sensations, weight loss, and occasionally an increase in appetite. Movements of the worm may be apparent to the host. Rarely, segments may become impacted in the vermiform appendix with almost simultaneous development of appendicitis. Many infections are asymptomatic.

Laboratory Findings. Gravid proglottids as well as eggs may be observed in the feces. Branchings of the uterus must be counted to differentiate between the proglottids of *T. saginata* and *T. solium*. When the scolex is obtained, it may be examined for suckers and the absence of rostellum and hooks, to identify it as *T. saginata*. The above study is necessary since the ova observed in the feces cannot be distinguished from those of *T. solium*. A slight eosinophilia may accompany this infection.

Treatment. Carbon tetrachloride and aspidium oleoresin have long been accepted as efficacious, but their occasional toxicity has stimulated

search for other agents. The administration of a hexylresorcinol emulsion by duodenal tube has been attended by good results. The response to quinacrine and "Acranil" has been encouraging. Treatment can be considered successful only if the scolex has been removed. If it remains in the intestine, regeneration will occur.

Prevention. The only practical means of preventing infection is the thorough cooking of beef. Temperatures as low as 71° C. for as little as five minutes will destroy *C. bovis*. Refrigeration and salting for prolonged periods also destroy the

cysticercus. Adequate meat inspection and disposal of human excreta will also aid in control, but are costly and seldom practical.

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Taeniasis Solium

Gustave J. Dammin

Definition
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Definition. *Taenia solium*, the pork tapeworm, usually manifests itself as a parasite of man by inhabiting the intestinal lumen. Man is the only definitive host, but under some circumstances may act also as the intermediate host harboring the larval stage, *Cysticercus cellulosae*. The usual intermediate host is the hog.

Distribution. *Taeniasis solium* has a worldwide distribution, but is commonest in the USSR, Asia, and Africa.

Etiology and Pathogenesis. The hermaphroditic adult tapeworm measures about 3 meters in length, and possesses a globular scolex containing a rostellum with about two dozen hooklets. There are seldom more than a thousand proglottids. The gravid proglottid measures about 6 mm. in width and 12 mm. in length, and contains a uterus with 8 to 12 lateral branchings. The eggs resemble those of *Taenia saginata* (see figure 178, p. 1158). When ingested by the hog, the embryo is released from the egg, penetrates the intestinal wall, and is carried by vascular channels to all parts of the body. Localization

with development to the encysted larval stage, *Cysticercus cellulosae* ("bladder worm") occurs predominantly in striated muscle, particularly that of the tongue, neck, and girdle muscles. The cysticerci are ovoid, gray-white, opalescent structures measuring about 1 cm. in diameter. An opaque white spot denotes the site of the scolex. "Measly pork" is the term applied to muscle containing cysticerci. Man becomes infected following ingestion of undercooked pork containing cysticerci. The scolex is freed and attaches itself to the intestinal mucosa, and development to the adult stage begins.

Clinical Manifestations. Clinical manifestations related to the presence of the adult tape-worm resemble those associated with *T. saginata*. The manifestations differ when man serves as the intermediate host. This may occur following ingestion of the eggs or the return of gravid segments to the stomach by reverse peristalsis. The released embryo bores into the intestinal wall and is distributed by vascular channels to various parts of the body. Cysticerci develop in the subcutaneous tissues, in muscles, in viscera, and—of most significance—in the eye and brain. Only moderate tissue reaction occurs while the scolex is viable. The dead larva, however, behaves like a foreign body and provokes a marked tissue re-

sponse. Symptoms are related to active larval encystment only in heavy infections. Muscular pains, weakness, and slight fever may be observed. The involvement in the brain may be in the form of a meningoencephalitis when the cysticerci are widely distributed. However, epilepsy, brain tumor, encephalitis, and other types of neurologic disorder may be simulated. Eosinophilic leukocytosis of the blood and spinal fluid accompanying such clinical manifestations suggests cerebral cysticercosis. Degenerate cysticerci ultimately calcify.

As in other tapeworm infections, a slight to moderate eosinophilia is a fairly constant finding. The finding of eggs in the feces will identify the infection as taeniasis but, for the specific diagnosis, proglottids or the scolex must be obtained.

Roentgenographic demonstration of calcified foci may aid in diagnosis of cysticercosis. The prognosis is in large part determined by the stage and location of the parasite. Surgery may be indicated in cerebral and ocular cysticercosis.

Treatment. For removal of the adult stage worm, see Chapter 209.

Prevention. The simplest and most effective preventive measure is the thorough cooking of pork. Treatment of recognized cases will reduce the hazard of larval stage development as well as the spread of the infection.

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Echinococcosis

Gustave J. Dammin

Definition
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Definition. Echinococcosis, or hydatid disease, is caused by the larval stage of *Echinococcus granulosus* (*Taenia echinococcus*) and is manifested in man and other intermediate hosts by the development of cystic structures in the viscera, particularly the liver and lungs.

Etiology. Infection in man, cattle, sheep, horses, and hogs, the principal intermediate hosts, is contracted by ingestion of the eggs present in the feces of the dog, the principal definitive host. Following ingestion, the embryos escape from the eggs, penetrate the intestinal mucosa, and enter venous and lymphatic channels. Some soon arrive in the liver and may form hydatid cysts there, and those entering the lymphatics are carried ultimately to the lungs. Transmission to the definitive host occurs following ingestion of the hydatid cysts which contain scolices. An adult

worm may develop from each scolex in the intestine of the dog, wolf, coyote, and other Canidae. The adult is small, measuring about 5 mm. in length, and consists of no more than five or six segments.

Distribution. Echinococcosis has its highest incidence in sheep- and cattle-raising countries, particularly in North and South Africa, Australasia, Central Europe, and South America. In Iceland, a high incidence of infection in man and the dog has been markedly reduced by control measures.

Pathogenesis and Clinical Manifestations. Two principal types of hydatid cyst develop in the intermediate host, the unilocular type and the alveolar type. The former is more common, grows slowly, and consists of an external laminated cuticula and an inner germinal layer. Fluid fills and distends the cyst. Daughter cysts (fig. 176) and brood capsules (fig. 177) develop from the germinal layer, representing endogenous development. "Hydatid sand" found in the cyst consists of scolices liberated from ruptured brood cap-



FIG. 176. Daughter cysts occur frequently in large old unilocular hydatid cysts. They are thin-walled balloons formed by herniations of the wall of the mother cyst and lie free in the cyst fluid. Free hooklets are also found floating in this fluid. (Courtesy, Ash and Spitz: "Pathology of Tropical Diseases," Philadelphia, W. B. Saunders Co.)

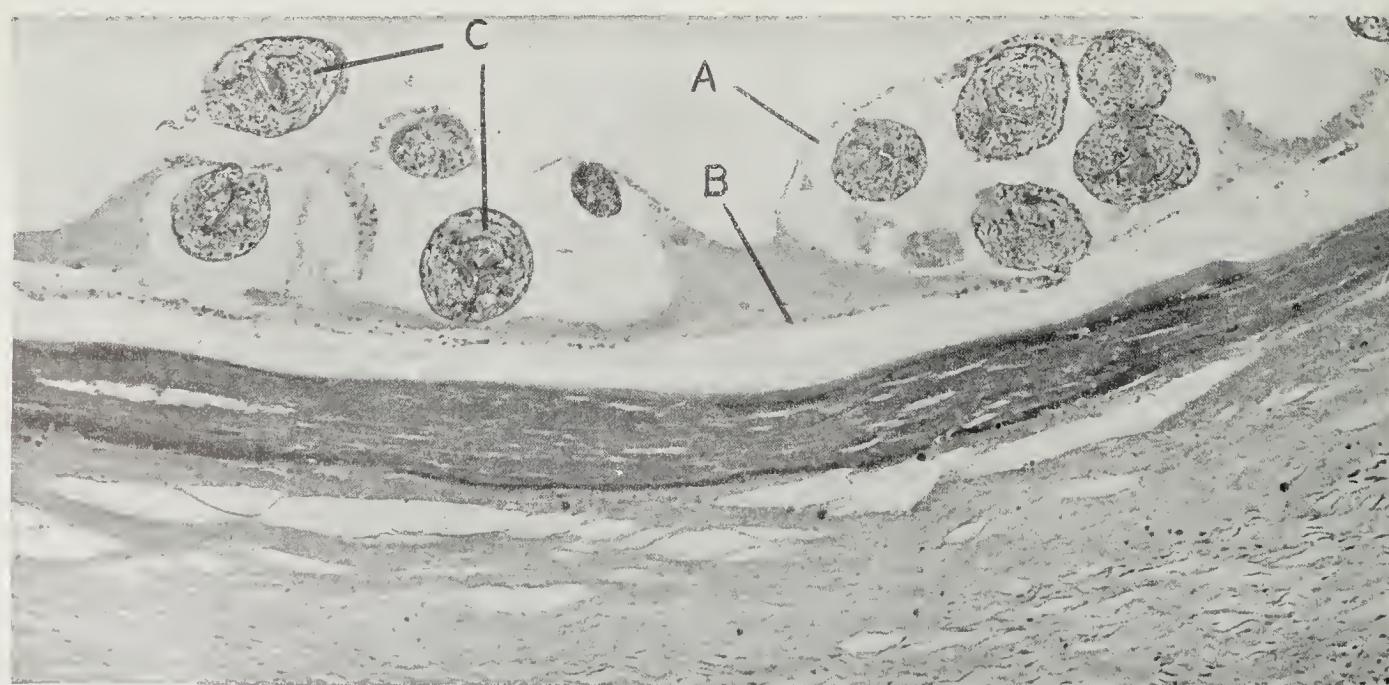


FIG. 177. Brood capsules are vesicles of single-cell layer (A) which arise from the germinal membrane (B). Invaginated scoleces (C) arise as buds from the inner surface of the brood capsule. (Courtesy, Ash and Spitz: "Pathology of Tropical Diseases," Philadelphia, W. B. Saunders Co.)

sules. Exogenous development results from evagination of the cyst wall, and ultimately produces the multilocular or alveolar type of lesion. Metastatic lesions occur when growth extends into vessels. The alveolar type of lesion has been observed most frequently in Central Europe.

Symptoms produced depend upon the size attained by the cystic lesion and the amount of tissue destroyed. Unilocular lesions may become barren following resolution of secondary bacterial infection. Rupture into the peritoneal or pleural cavities may produce an anaphylactoid reaction, which occasionally is fatal. The unilocular type of hepatic lesion progresses slowly, and is most amenable to surgical treatment. The alveolar type progresses more rapidly, with metastatic lesions developing in the bones, brain, and other sites. Pathologic fractures occur and cerebral involvement may be manifested by epilepsy.

Diagnosis and Treatment. Clinical manifestations seldom are characteristic enough to suggest the diagnosis, but roentgenographic appearance of the lesion, especially when calcification is present, is often helpful (Schlanger and Schlanger). Eosinophilia is suggestive, although seldom present. Inquiry should be made concerning residence in an endemic area, and skin (Casoni or substitute antigen) and/or serologic tests performed,

before exploration is considered. Exploration may be required as both a diagnostic and a therapeutic measure. Because of serious reactions to the leakage of cyst fluid into the tissues and body cavities, aspiration should be attempted only during exploration. Aspirated cyst fluid should be examined carefully for scolices, hooklets, and laminated cyst wall. The size of the lesion will determine whether excision or marsupialization is the procedure of choice. Only surgical treatment offers hope of cure.

Prevention. In prevention, (1) contact with infected dogs should be avoided, particularly fecal contamination of the hands and food; (2) infected carcasses and offal should be burned or buried in order to prevent access of dogs to material containing scolices; and (3) dogs should be treated if found to be infected. The reduction of the incidence of echinococcosis in Iceland is an example of the efficacy of control measures.

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Hymenolepiasis Nana

Gustave J. Dammin

Definition
 Etiology
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Definition. Hymenolepiasis nana is an intestinal infection of man caused by *Hymenolepis nana*, the dwarf tapeworm.

Etiology. The life cycle is unique in that both the larval and adult phases of development occur in the same host. Man, mice, and rats readily contract infection upon ingestion of the eggs. In

the small intestine the oncosphere is liberated from the egg, enters a villus, and develops into the larval cercocyst. This larval form breaks into the intestinal lumen, and in the course of about two weeks develops into the adult tapeworm stage. The adult measures about 2 cm. in length and may possess over a hundred proglottids. The gravid proglottids measure about 0.2 mm. in length by 0.9 mm. in width, and liberate eggs which are immediately infective. The eggs measure about 35 microns by 50 microns and have distinctive filaments arising from an inner shell

which surrounds a hexacanth embryo (see figure 178).

Distribution. The presence of dwarf tapeworm infection has been reported in temperate and tropical regions around the globe. It is the commonest tapeworm found in the United States, most of the infections occurring in the southern states. The highest incidence occurs in children. The chief source is probably man, although rats and mice readily acquire the infection.

Clinical Manifestations and Laboratory Findings. This tapeworm infection is characterized by the presence of many adult worms in the host's intestine. When infection is massive, diarrhea and abdominal pain occur. Most infections are asymptomatic. A slight eosinophilia is common. The diagnosis is made by finding the eggs in the feces.

Treatment. Hexylresorcinol, in the form of "Crystoids Anthelmintic," and aspidium oleoresin are moderately efficacious. Recently, quinacrine, "Acranil," and chloroquine have given encouraging results. These drugs have been

found to be effective in other tapeworm infections as well.

Prevention. This is difficult, since the problem is similar to that encountered in enterobiasis. Only a single host is involved, and the eggs are immediately infective. Personal hygiene should be stressed. The contamination of food by rats and mice should be prevented. Hyperinfection within the intestinal tract of man has not been demonstrated, but the possibility exists that eggs discharged in the intestine may liberate the oncospheres and a new cycle may be initiated. Both therapeutic and prophylactic measures are required in the control of group infections.

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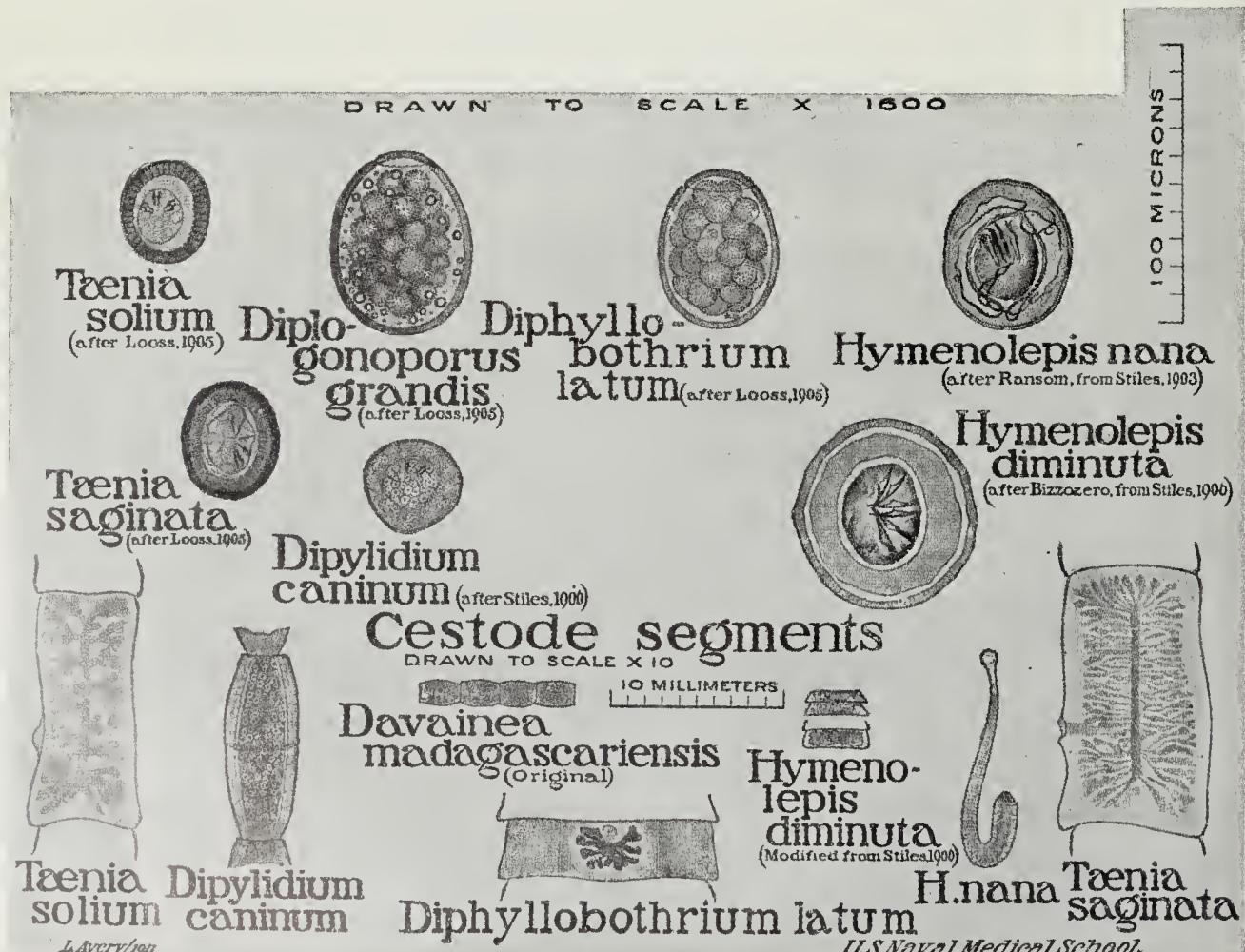


FIG. 178. Ova of the parasitic worms of man: Cestodes. (Courtesy, Stitt-Strong: "Diagnosis, Prevention and Treatment of Tropical Diseases," Philadelphia, The Blakiston Company.)

Section 25—Disorders Due to Venoms

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Snake Bite

J. C. Ransmeier

Pit Vipers (Family Crotalidae)
Coral Snakes (Family Elapidae)
Factors Affecting Danger of Snake Bite
Actions of Snake Venom
Symptoms of Snake Bite
Treatment
Prognosis

There are about 2400 species of snakes, of which some 200 are poisonous to man. These consist of five families known as the Elapidae, including the cobras and coral snakes; the Viperidae or true vipers; the Crotalidae or pit vipers; the Hydrophidae or sea snakes; and the Colubridae, which include many harmless species. In the United States poisonous members of only two families occur. The Crotalidae are represented by the rattlesnakes, copperhead, and water moccasin, and the Elapidae by the coral snakes. It has been estimated that approximately 1000 persons are bitten by snakes annually in the United States, with perhaps 100 to 150 deaths. The Crotalidae are responsible for almost all these accidents.

PIT VIPERS (FAMILY CROTALIDAE)

The pit vipers are distinguished by a small pit located between the eye and the nostril. The head is triangular, being wider posteriorly because of the presence of large venom glands in the temporal regions. The glands are connected by ducts to two anteriorly located hollow fangs which are attached to the upper jaw with a hingelike apparatus. When the mouth is closed the fangs fold posteriorly and are covered by a fleshy sheath.

Pit vipers strike from a partly coiled or S-shaped position. The head is propelled forward to a distance of one-half to two-thirds the snake's length as the body straightens. The mouth opens widely; the fangs spring erect and are sunk into the victim's flesh to a depth of 5 to 15 mm. A squeeze of the jaw muscles expels the venom. These snakes have upper and lower teeth for

holding the prey, but when biting large animals they strike and withdraw in a fraction of a second.

The many varieties of rattlesnakes are easily recognized by the horny rattle on the end of the tail which emits a buzzing sound when the snake is angered or alarmed. The diamondbacks (*Crotalus adamanteus* in the Southeast and *C. atrox* in the Southwest) are the largest and the most dangerous snakes of the United States, often attaining a length of 2 m. and a weight of 7 kg. The fangs may be as much as 2 cm. long. The prairie rattlesnake (*C. confluentus*) grows almost as large. The timber rattlesnake (*C. horridus*), found in the South and in the northeastern states, is usually slightly smaller. Pygmy rattlers of the genus *Sistrurus* do not exceed 1 m. in length and their bites are practically never fatal for man.

The water moccasin (*Agkistrodon piscivorus*), also called the cottonmouth, is abundant in the Southeast and Gulf states, and in the Mississippi Valley. It frequents the borders of streams and swampy places. Its back is dull olive or brownish with dark bands indistinctly marking its paler lateral surfaces. It may approach 2 m. in length and, next to the rattler, is the most dangerous of North American snakes.

The copperhead (*Agkistrodon mokasen*) is characterized by reddish brown, transverse, hour-glass-shaped markings on the back, contrasting with a basic light tan coloration. It grows to 1.25 m. in length and secretes a smaller amount of venom than the large rattlers and the moccasin. In the North it is found in woods, sometimes in rocky or swampy areas. In the South it prefers higher ground and is sometimes called the "highland moccasin."

CORAL SNAKES (FAMILY ELAPIDAE)

The coral snakes (genera *Micrurus* and *Micruroides*) occur in the southern United States from

Florida to Arizona. They are nocturnal, are seldom seen, and rarely bite man. The adult is less than 1 m. in length, usually much smaller. Broad black bands bordered by narrow yellow ones encircle the body, alternating with wide bands of crimson. The head is long and slender without the posterior bulge characteristic of the pit vipers. It is black and ringed with a yellow stripe in the temporal region. The fangs, permanently erect, are short and penetrate clothing poorly. Like the cobra, the snake holds on for several seconds when biting, advancing the fangs with chewing movements and making multiple punctures. The venom is highly toxic and may be fatal, especially to children.

FACTORS AFFECTING DANGER OF SNAKE BITE

The danger of a snake bite depends upon many factors. Nonpoisonous snakes cause minor lacerations which are important only if they become secondarily infected. The venoms of poisonous species differ in toxicity. Although the young are poisonous from birth, the larger the snake the greater is the amount of venom secreted. The quantity injected is variable. Sometimes "blind strikes" are made with the mouth closed, or the blow may be glancing and the fangs fail to penetrate. Fur or clothing may interfere with the insertion of the fangs. With one or both fangs broken, a reduced amount of venom is introduced. During hibernation, sometimes in captivity, and especially when the snake has fed recently, the venom is diminished. If the venom happens to enter a vein, quick death may result. In general, small animals succumb more rapidly than larger ones. The snake's mouth and the victim's skin may harbor microorganisms which can be introduced into the tissues. Most dangerous of these are *Clostridium tetani* and *Cl. welchii*. Infection with either may be fatal in the presence of tissue necrotized by venom, even after the bite of a small snake from which the victim would otherwise have recovered. These and other variables make it difficult to evaluate the results of treatment in snake bite.

ACTIONS OF SNAKE VENOM

Snake venoms are complex mixtures and vary in their toxic constituents. All exert several actions, among which the most readily distinguished are the neurotoxic and local necrotizing

effects. Associated phenomena are hemolytic activity and disturbances in blood coagulation. These actions are attributed to proteolytic enzymes, phosphatases, and neurotoxins. The venom of the Elapidae is primarily neurotoxic and causes death by respiratory paralysis; intravascular coagulation may be produced. In contrast, the venom of the Crotalidae causes massive edema and local necrosis associated with hemolysis and hemorrhage; death occurs in a shocklike state. Blood coagulation may be inhibited. Some venoms, especially those of the Crotalidae, contain a spreading factor which speeds diffusion and increases capillary permeability.

Some of the constituents of snake venom are antigenic. When dried venom is injected in increasing doses into a horse, the animal's serum slowly develops neutralizing power for the venom used and for that of related species. Such a serum is called an antivenin. There is little or no cross neutralization for the venoms of snakes of other families. Thus cobra antivenin is active against venoms of various elapine snakes but not against those of the Viperidae or Crotalidae. In the United States a polyvalent antivenin ("Antivenin, Nearctic Crotalidae") is prepared by injecting into horses a mixture of 80 percent rattlesnake and 20 percent moeasian venom. This serum contains antibodies against the venoms of all North American pit vipers but is of no value against the bite of the coral snake, for which no antivenin is commercially available in the United States.

The minimum lethal dose of dried rattlesnake venom for man has been postulated to be 1 mg. per 6 lb. of body weight. The average diamondback rattlesnake yields 220 mg. of venom, the moeasian 150 mg., and the copperhead 45 mg. Since these venoms are qualitatively similar, the larger quantity injected appears to account for the greater deadliness of the diamondback.

When a lethal dose of rattlesnake venom is introduced subcutaneously, it immediately begins to diffuse through the tissues, damaging the small vessels and capillaries and producing intravascular thrombi and necrosis. Massive edema develops. By diapedesis or rupture of the vessel walls, erythrocytes escape into the tissue spaces where many of them undergo hemolysis. Local swelling and ecchymosis spread as the venom diffuses. At the advancing margin of the

lesion the venom-containing edema fluid is absorbed into the lymphatics, producing inflammatory changes in the lymph nodes and entering the blood stream. Severe intravascular hemolysis follows. The erythrocyte count and hemoglobin may fall to less than half their original values. Casts of blood pigment and desquamated cells may appear in the renal tubules. Petechial hemorrhages occur in all tissues. Shock develops with falling blood pressure, increase in volume of the extremities, and initial contraction of the abdominal viscera. In the terminal stages the abdominal organs become swollen and congested, showing capillary dilatation, focal hemorrhages, and fatty or granular degeneration. The blood in the heart and large vessels remains fluid for several hours post mortem.

With smaller doses of venom death does not occur, but the tissues where the venom was introduced become gangrenous and slough. Secondary infection is common.

SYMPTOMS OF SNAKE BITE

Within three to five minutes after the bite of a viper or pit viper there is intense burning pain. Swelling appears in about 10 minutes and increases rapidly, with extensive ecchymosis. Pinkish edema fluid containing hemolyzed blood oozes from the fang punctures. The limb may increase to three or four times its normal size, and the swelling spreads upward onto the body. Bullae form over the most involved areas. Shock develops with prostration, clammy skin, thirst, rapid pulse, and falling blood pressure. Mild jaundice, vomiting, proteinuria, hematuria, hematemesis, bloody diarrhea, and hemorrhages into the skin and mucous membranes may be noted. Terminal convulsions often occur. Sometimes death supervenes within an hour or two after the bite; it is thought that in such cases the venom was injected intravenously. More commonly the patient lives 6 to 48 hours. If he survives, gangrene and secondary infection develop in the tissues around the bite.

The bites of elapine snakes cause little pain. The fang marks are small and exude no fluid. Slight edema develops. There is local numbness and paresis. The gait becomes ataxic and the limbs weak but not completely paralyzed. Bilateral ptosis of the lids is noted. The pupils become dilated and do not react to light or on accommodation. Paralysis of the tongue and

palate render the speech slurred and indistinct, and swallowing is difficult. Salivation, nausea, and vomiting may occur. Coma develops. The respirations become slow and shallow, and finally cease within a few hours to two or three days after the bite. Death is sometimes preceded by convulsions.

TREATMENT

One should first determine whether the patient has been bitten by a poisonous snake—i.e., a pit viper or a coral snake. All other snakes of the United States are nonpoisonous; their bites are treated as simple lacerations. (Nonpoisonous snakes have no rattle, lack the posteriorly bulging head, the large anteriorly placed fangs, and the pit between eye and nostril which are characteristic of pit vipers. Harmless snakes resembling the coral snake have broad yellow encircling bands with narrow black borders instead of the reverse, as detailed in the preceding description of the coral snake.) If no fang punctures are visible and no pain, edema, ecchymosis, or other local reaction has occurred within 15 minutes, it is almost certain that the snake was nonpoisonous or that the fangs did not penetrate.

After the bite of a poisonous snake the patient should not walk or exercise. If the wound is on a limb, the extremity should be kept in a dependent position and a tourniquet should be applied *at once* above the knee or elbow, tightly enough to increase venous congestion and impede lymphatic drainage but not so tightly as to cut off arterial blood supply. It should be loosened for a minute or two every half hour. Cruciate incisions 10 mm. long and 5 mm. deep should be made *immediately* through the fang marks, with one limb of each incision perpendicular to a line joining the two punctures. Suction should be applied over the incisions for at least 30 minutes. (This can be done with the mouth, with a rubber bulb, or with a breast pump, an ear speculum, a small glass funnel, or the inverted barrel of a syringe attached to a vacuum line.) If this treatment is applied within an hour after the bite, no other mechanical measures may be needed. Moist compresses should be applied over the incisions, and the tourniquet may be released in a few hours when serosanguineous drainage ceases.

For all bites caused by pit vipers, antivenin should be given. Sensitivity tests for horse serum are first performed. If these are negative, anti-

venin is administered, infiltrating the tissues around the bite with half the dose and giving the remainder intramuscularly in several places high up on the bitten extremity. Fifteen milliliters of reconstituted lyophilized serum are said to suffice for an adult bitten by the copperhead, pygmy rattler, and average moccasin. For the bites of larger moccasins or rattlesnakes, and for bites of any pit vipers in children, 45 to 75 ml. are recommended. If systemic symptoms have developed, large doses should be given intravenously. Antivenin is most effective when given promptly, but may be useful up to 24 hours after the bite.

When the patient is seen after some delay, or if the above treatment is not entirely effective, a considerable swelling may be present. The tourniquet should be continued or applied proximally. In addition to incisions over the fang marks, it has been advocated that a series of small cruciate incisions, each about 3 mm. long and 3 mm. deep, be made proximal to the swelling encircling the entire limb, at intervals of 2 to 3 cm. Similar incisions may be made over the area of maximum swelling. Using multiple rubber bulbs or other devices, suction can be applied over each incision for 15 minutes out of every hour, the limb being wrapped meanwhile in hot wet compresses. If the incisions close, new ones can be made, more proximally if the swelling is progressing. The bloody fluid draining from such punctures contains venom for several hours after the bite, and it is claimed that several lethal doses can be removed in this manner. When the swelling ceases to progress and serosanguineous drainage is negligible, the tourniquet may be removed.

Codeine and barbiturates may be used, but seldom completely relieve the severe pain. Caffeine may be given if a stimulant is needed. Alcohol should be avoided because it increases peripheral vasodilatation. Morphine is dangerous because of its depressant effect upon the respiration. Treatment is indicated for dehydration, shock, hemolytic anemia, and respiratory depression. Intravenous fluids, plasma products, transfusions, and oxygen may be required. Tetanus antitoxin, or a booster dose of toxoid, should be administered. Parenteral injections of penicillin are indicated to combat secondary infection.

For the bite of the coral snake no antivenin is available. Treatment is otherwise similar. If the

patient is choking because of inability to swallow, frequent aspiration of the pharynx should be performed. Oxygen should be given if there is respiratory involvement. A respirator may be used if breathing becomes inadequate.

In snake-infested regions high shoes, leggings, and gloves afford considerable protection from snake bite. As provision for emergency treatment it is well to carry a rubber tourniquet, a sharp knife or razor blade, antiseptic, and a suction bulb. Expeditions and installations in inaccessible areas should include appropriate antivenin in their equipment.

PROGNOSIS

The larger the snake, the more dangerous is its bite. Big rattlesnakes are most deadly, with the moccasin next in line. Copperhead bites are common but seldom fatal. All these bites are more serious in children than in adults, and the mortality is higher when the bite is on the head, trunk, or upper extremity. If the patient recovers, some local necrosis occurs, occasionally necessitating amputation of the limb.

In two series of rattlesnake bites recorded before popularization of antivenin and multiple incisions, the mortality was 8 per cent and 11.7 per cent. It has been claimed that in the Southwest, where diamondback bites are more frequent, the mortality may approach 35 per cent. In a series of 482 miscellaneous snake bites collected in 1929, 137 were caused by the copperhead, 94 by the western diamondback, 39 by the moccasin, 31 by the timber rattler, 14 by the eastern diamondback, and the remainder by unidentified or less formidable species. Antivenin was used in 399 cases with a mortality of 3.75 per cent, while in 83 cases which did not receive antivenin the mortality was 15.66 per cent. It is difficult to interpret such figures, since circumstances and additional treatment doubtless varied widely. None of the copperhead bites proved fatal. Although there seems no doubt that treatment is effective, carefully controlled modern statistics on snake bite in the United States are not available.

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Spider Bite

J. C. Ransmeier

Etiology
Pathogenesis
Manifestations
Differential Diagnosis
Treatment

Etiology. The bites of various spiders cause local irritation, but those of the genus *Latrodectus* are notorious in many parts of the world for the alarming systemic illness which they produce. *Latrodectus mactans*, the black widow or shoe-button spider, is widely distributed in the United States and Canada, where it is the only spider whose bite is of clinical importance. The adult female is responsible for bites in man. She is glossy black with a globular abdomen 1 cm. in diameter, on the under surface of which there is a red hourglass-shaped marking (fig. 179). Occasionally one or two additional spots are present distally. The venom glands are located in the small cephalothorax and communicate with hollow fangs attached to a pair of modified mouth-parts. The eight legs have a span of 5 cm. The web is coarse and irregular without geometric pattern, usually containing a central nest to which the spider retreats when frightened. Such webs are found under loose rocks, in holes made by animals, in trash piles, sheds, garages, basements, and outdoor toilets. The spider is especially aggressive when guarding her egg sac. She bites man when accidentally touched or compressed, and possibly when in darkness the web is agitated and she cannot determine the nature of the disturbance.

Pathogenesis. The venom glands from one spider, extracted in saline, yield an average of 0.126 mg. of solids having a high toxicity. A dose of 0.096 mg., injected intraperitoneally, is lethal

for young rats. It is said that this venom is 15 times as potent per unit of dry weight as that obtained from the rattlesnake. The toxic principle



FIG. 179. *Latrodectus mactans*, female (black widow). Ventral surface showing the orange-red hourglass spot. (Approximately actual size.) (Courtesy, Stitt-Strong: "Diagnosis, Prevention and Treatment of Tropical Diseases," Philadelphia, The Blakiston Company.)

is thought to be a protein, probably an albumin. It is antigenic; repeated injection of venom into rats, sheep, or horses yields antiserum which will neutralize the toxic action of venom *in vivo*.

Experimental studies in the cat show that the venom contains a neurotoxic substance which diffusely excites nervous tissue as evidenced by increased electric activity in cortex, spinal cord, and motor nerves with resulting spasm of the voluntary muscles. There is also stimulation of the autonomic nervous system with a rise in arterial blood pressure resulting from generalized vasoconstriction.

Manifestations. In the United States, spider bites occur chiefly between April and October. Most of the patients are males who are bitten on the buttocks or genitalia while using a privy. Occasional bites occur on the hands, legs, and other parts of the body. There is a momentary burning sensation like the prick of a hot needle. Early, there is slight redness at the site of the bite, but in three or four hours nothing is visible locally.

If the bite is on the genitalia, after 15 to 45 minutes a cramping, aching pain begins in the hips. It increases rapidly in severity and spreads down the thighs and legs to the feet, and upward into the abdomen. The cramplike pain is excruciating. The restless, suffering patient may refuse to stay in bed, or he may turn incessantly from side to side, lying with thighs drawn up on the abdomen, knees flexed, and arms hugging the chest. There is boardlike rigidity of the abdomen.

After a bite on the hand the pain begins in the arm and spreads to the shoulders. There may be spasm of the abductors of the thumbs and flexor muscles of the forearms, followed by spasm of the thoracic muscles with splinting of the chest, difficult respiration, and expiratory grunting. The agonizing pain spreads downward into the lumbar regions and abdomen, sometimes even into the legs and feet. Rigidity of the abdomen often develops.

Regardless of the site of the bite, malaise, nausea, vomiting, headache, sweating, salivation, and lacrimation usually occur. Some patients complain of paresthesia in hands and feet. The tendon reflexes are hyperactive, and muscular twitching and tremor may be noted. Priapism and urinary retention have been recorded. The temperature is frequently normal but there may be a degree or so of fever. The systolic blood pressure is often elevated 20 to 40 mm. above the patient's usual level with little change in the diastolic reading. A moderate leukocytosis is common.

As a rule the pain begins to lessen after several hours, although it may recur in milder form for two or three days. Occasionally there is some muscular aching for a week after the bite. Recovery is usually complete. Very few fatalities have been reported.

Differential Diagnosis. Differentiation from surgical emergencies such as perforated peptic ulcer is important. In spider poisoning, history of a bite may be elicited and slight redness may be seen at the site. The pain begins near the bitten area and spreads to the abdomen. There are also cramps in the extremities. Although rigid, the abdomen moves with respiration and is not acutely tender. There is little or no evidence of shock. The patient is restless and can sit up or move about. No air is seen beneath the diaphragm on x-ray examination. Other diagnoses which are usually easy to rule out include appendicitis, pancreatitis, volvulus, renal and biliary colic, gastroenteritis, coronary occlusion, lobar pneumonia, tetanus, and strychnine poisoning.

Treatment. Hot baths or packs temporarily lessen spasm and ease the pain. Morphine should be administered in full doses but is only partially effective. Intravenous injections of magnesium sulfate (20 ml. of 10 per cent solution) or of calcium gluconate (10 ml. of 10 per cent solution) sometimes afford considerable relief. Barbiturates may be given to combat restlessness, with care that in synergism with morphine they do not unduly depress the respirations.

A specific antiserum ("Antivenin Latrodectus Mactans") is available. Intramuscular injection of a dose of 2.5 ml. is recommended. Prompt relief of pain has been reported following such injections, but cannot always be expected. Furthermore, serum sickness may occur later. In general, except possibly for infants, old people, or complicated and extraordinarily severe cases, the use of antivenin seems unnecessary since the symptoms subside spontaneously in two or three days and the danger of death is slight.

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Bee Sting

J. C. Ransmeier

Etiology**Pathogenesis****Manifestations in Normal Individuals****Manifestations in Hypersensitive Individuals****Treatment**

Etiology. The sting of the worker honeybee (*Apis mellifera*) is used in defense of the hive. It is a hollow barbed apparatus located in the posterior extremity of the abdomen, connecting with a poison sac in which venom produced by specialized glands is stored. When the sting is driven into the skin of a victim the barbs anchor it firmly. As the bee hurries to escape, the entire poison equipment is torn free and continues pumping venom into the wound. The bee dies later from the injury. Queen bees have a large sting without barbs; the drones (males) are stingless.

Pathogenesis. Bee venom resembles snake venom, having hemolytic and neurotoxic properties. In addition it has a strong histamine-like action upon living tissue. There is some evidence that it contains an antigenic substance present also in the body of the bee. It is said that one to five stings may kill a mouse, while 20 stings are fatal to guinea pigs weighing 250 to 300 Gm. Multiple stings cause much local discomfort in man but are usually not dangerous unless received in enormous numbers. An onslaught of 500 to 1000 stings may cause death. Bee keepers become immune to the venom and can withstand many stings without ill effect.

Manifestations in Normal Individuals. Most people react to a single bee or wasp sting with pain followed by a wheal and erythema. There is annoying pruritus. If the sting is on loose tissues like that of the eyelid or genitalia, considerable local edema may develop. This edema is dangerous only in exceptional cases when a bee is swallowed or inhaled so that the sting occurs in the hypopharynx or glottis, causing respiratory obstruction. Ordinarily the reaction subsides spontaneously in a few hours, or at most in a day or two, and requires only palliative treatment. The

sting itself is usually brushed away by the patient on rubbing the pruritic area.

Manifestations in Hypersensitive Individuals.

Rare instances of allergic reactions to bees and bee venom have been reported. Apiarists may gradually develop hypersensitivity, manifested first by allergic rhinitis and later by asthma when near bees or objects with which bees have been in contact. Such individuals may react to a single sting with alarming anaphylactic manifestations. Similar reactions have occurred in others who have received previous stings, as well as in persons with no known bee contact. Evidence of hypersensitivity to other allergens may or may not be obtainable.

In hypersensitive patients a bee sting causes no more than the usual local reaction. Within a few minutes, however, there is tingling of the skin, and generalized urticaria with extreme pruritus develops. Nausea, vomiting, and abdominal cramps may occur; uterine cramping and bleeding have also been recorded. Sometimes there is cough and asthmatic breathing. Angioneurotic edema follows quickly, involving the face, especially the lips and eyelids, sometimes the hands and genitalia, and the glottis. Dyspnea and cyanosis appear; respiratory obstruction increases rapidly. Shock supervenes with cold, clammy extremities, unconsciousness, rapid or imperceptible pulse, and precipitously falling blood pressure. Death may occur.

Treatment. Epinephrine may be life-saving in the anaphylactic type of reaction. In mild cases subcutaneous administration of 0.3 to 0.5 ml. of a 1:1000 solution may suffice, the dose being repeated at intervals of 20 minutes to an hour or more as symptoms recur. In severe cases the initial dose should be 0.5 ml. injected intramuscularly or 0.3 ml. given intravenously. Oxygen is indicated until the respiration is normal. When the acute symptoms have subsided, ephedrine should be given orally in doses of 25 mg. three times daily for two or three days, or antihis-

taminic drugs might be used to prevent recurrence of symptoms. Recovery is usually complete in 48 hours. Desensitization has been accomplished by repeated injection of extracts of whole bee body followed by bee stings. If desensitization is not practical, contact with bees should be avoided.

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Scorpion Sting

J. C. Ransmeier

Etiology
 Pathogenesis and Mortality
 Manifestations
 Treatment

Etiology. Scorpions are small, eight-legged arthropods belonging to the Arachnida. They have powerful claws for seizing spiders and insects upon which they prey. A gland in the terminal segment produces venom which is injected into the victim by a stinger located on the tip of the tail. In tropical countries scorpions are numerous and often enter dwellings, where they get into shoes and clothing which are not being worn, and even into bedding. They do not attack man, but accidental contact results in a sting.

Pathogenesis and Mortality. The venom is neurotoxic; it acts locally upon sensory nerves and centrally upon the medulla and involuntary nervous system, causing circulatory, respiratory, and widespread autonomic disturbances. A hemolytic effect has been demonstrated in vitro. The amount of venom produced varies with the size of the scorpion. The smallest are practically harmless, causing only a local reaction similar to a bee sting. The largest ones, which sometimes attain a length of 18 cm., may be more dangerous, but the potency of the venom varies in different species. Several small and medium-sized species are found in the Gulf and southwestern portions of the United States, the most important being those of the genus *Centruroides*. The sting

of *C. sculpturatus* may be fatal to old people or to young children, but seldom to a healthy adult. In countries where more formidable varieties are encountered, the mortality of scorpion sting is exceedingly high in infants and is impressive in children less than 10 years of age. The following age specific mortality rates were recorded in 698 cases in Trinidad: 1 to 5 years, 25 per cent; 6 to 10 years, 5.2 per cent; 11 to 20 years, 2.6 per cent; over 21 years, 0.25 per cent. The over-all case fatality rate was 4.7 per cent. A mortality of 13 per cent was reported in 985 patients of various ages observed in Brazil.

Manifestations. The sting causes an immediate burning sensation with minimal erythema and edema which rapidly subside. Local pain develops, often followed by formication, hyperesthesia, or numbness. In severe cases the pain spreads to involve the whole extremity, and general manifestations appear within an hour or two, including headache, malaise, giddiness, restlessness, lacrimation, rhinorrhea, salivation, nausea, and vomiting. The emeses frequently contain blood. Transient hypertension and glycosuria have been recorded. There is profuse perspiration, the extremities become cold and clammy, and the body temperature is lowered. In fatal cases dyspnea occurs without cyanosis, and there is tachycardia with muffled heart sounds, feeble pulse, and premature contractions. Later there may be bradycardia and respiratory depression, sometimes with irregular or Cheyne-Stokes

breathing, and pulmonary edema develops terminally. The patient passes from an agitated state into coma, sometimes with convulsions; death may result at any time from a few hours to two days after the sting.

Treatment. Supportive treatment is directed at combating shock and dehydration. In countries where scorpion sting is frequent, antivenins have been prepared and are said to be highly effective. No antivenin is produced in the United States. Barbiturates are useful in reducing rest-

lessness, but morphine is contraindicated because of its depressant effect upon the respiration.

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Tick Paralysis

J. C. Ransmeier

Distribution, Etiology, and Pathogenesis

Clinical Picture

Differential Diagnosis

Treatment

Prognosis

Distribution, Etiology, and Pathogenesis. Tick paralysis is a reversible disorder of the nervous system which sometimes develops in the host while a tick is engorging. It may occur in man or animals, especially affecting the young. Sheep, cows, horses, rabbits, guinea pigs, dogs, cats, and other animals are susceptible. The disease has been reported from Australia, South Africa, Canada, the United States, Crete, and Yugoslavia. It has long been recognized in the northwestern United States and western Canada, where the wood tick *Dermacentor andersoni* Stiles is responsible. More recently the dog tick *Dermacentor variabilis* Say has been identified in a number of cases occurring in the eastern states.

While engorging, the tick apparently injects a neurotoxin which acts upon the spinal cord and bulbar nuclei, causing incoordination, weakness, and paralysis. The toxin is rapidly destroyed or excreted, for when the tick is removed the nerve cells soon regain normal function.

Tick paralysis has been produced in experimental animals only with gravid female ticks, suggesting that the toxin might be elaborated by

the ova. However, injection of extracts prepared from tick eggs has failed to reproduce the clinical picture in convincing fashion.

The tick must feed for several days before symptoms develop. Female ticks commonly remain attached for seven to nine days or longer. Paralysis is seen in experimental animals after five to seven days of engorgement. Male ticks feed for a shorter period, a fact which may explain why they are less likely to cause paralysis.

Experimental confirmation of the theory that the toxin is produced in tick salivary glands is also lacking. It has been found that not all gravid female ticks of incriminated species cause paralysis. The nature, site of production, and mode of action of the toxin have not been established.

Clinical Picture. Most human cases occur in children, generally in young girls. The tick is usually attached to the scalp and hidden by the hair, but may be found on any part of the body, especially the ear, axilla, groin, vulva, or popliteal region. Both white and Negro races are susceptible.

The patient may be irritable for 24 hours before motor involvement appears. Mild diarrhea may occur. Frequently the first striking symptoms are noted in the morning, when there is weakness and poor control of the legs. The pa-

tient walks "as though drunk," staggering and falling. The tendon reflexes in the legs are diminished or absent and the Romberg sign is positive. Temporary improvement may occur, and if the tick is removed at this stage true paralysis may never develop. Otherwise the symptoms recur within 24 hours, often with flaccid paralysis which extends in one or more days to involve the trunk, arms, neck, tongue, and pharynx. Tendon reflexes in the arms disappear and the abdominal reflexes are unobtainable. Sensory changes are usually absent, but there may be paresthesia and hyperesthesia in the affected extremities. Muscle spasm and stiffness of the back and neck are lacking. With involvement of the bulbar nuclei the voice becomes thick and nasal; the patient is unable to swallow and chokes on pharyngeal secretions. Nystagmus, strabismus, and facial paralysis are sometimes noted, and in infants terminal convulsions may occur. The respirations become shallow, rapid, and finally irregular. The restless patient sinks into stupor, cyanosis appears, and death results from respiratory paralysis or from obstruction of the airway by aspirated material.

There is little or no fever unless a secondary infection is present. The leukocyte count is usually not elevated, but moderate leukocytosis may occur. The spinal fluid is almost always normal.

Differential Diagnosis. Tick paralysis is apt to be confused with poliomyelitis, the more so because ticks are active in warm weather when poliomyelitis is most prevalent. In tick paralysis, however, there is little or no fever and the spinal fluid is normal. Muscle spasm and stiffness of the neck and back are minimal or absent. Ataxia, sometimes with paresthesia, often precedes paralysis by hours or days, first in the legs, then in the arms. Ascending involvement is characteristic, while progression of paralysis without fever is exceptional in poliomyelitis. The muscular weakness is usually diffuse, bilateral, and symmetric, in contrast to the spotty involvement in poliomyelitis. Local paralysis does occur rarely, however, as exemplified by cases in which there is weakness of one arm with a tick attached in the axilla, or facial nerve paralysis with a tick attached in the external auditory meatus.

Among other diseases which might be considered in differential diagnosis are polyneuritis,

transverse myelitis, infectious neuronitis (Guillain-Barré syndrome), syringomyelia, and spinal cord tumor. These show characteristic sensory involvement. In tick paralysis, hyperesthesia and paresthesia may be seen but cutaneous anesthesia seldom if ever occurs.

Treatment. The tick should be removed immediately, with care to avoid breaking off the mouth parts. Mouth parts retained in the skin should be promptly excised. The patient's body should be searched for other ticks.

In bulbar cases with accumulation of pharyngeal secretions, the foot of the bed should be drastically elevated and the head turned to the side to promote postural drainage. The pharynx should be aspirated frequently. Nothing should be given by mouth until swallowing is normal. Parenteral fluids are indicated. Oxygen should be given, preferably by nasal catheter because a tent or mask interferes with aspiration of the pharynx. Intramuscular injections of penicillin and streptomycin aid in combating aspiration pneumonia. Sedatives and narcotics should be avoided because of the danger of respiratory depression. When there is paralysis of the diaphragm and intercostal muscles, artificial respiration by a respirator or other method may be life-saving. If avoidable, however, the respirator should not be used on patients with puddling of pharyngeal secretions, as serious aspiration into the lungs is likely to result. In tick paralysis this critical period is of relatively short duration. There may be striking improvement in the respiration within a few hours after removal of the tick.

Prognosis. If the tick is removed before bulbar involvement develops, the paralysis subsides and recovery is complete in a few days, sometimes within 24 hours. The patient should be observed until the recovery trend is established, because if other ticks or retained mouth parts have been overlooked, the paralysis may progress. When bulbar or respiratory paralysis is present, death may occur if the tick is not removed in time.

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Infectious Mononucleosis

M. M. Wintrobe

Definition
History
Etiology and Pathogenesis
Clinical Picture
Blood Picture
Diagnosis
Treatment

Definition. This is a disorder of unknown etiology, usually benign and probably of infectious origin, which is characterized by irregular fever, sore throat, lymphadenopathy, and enlargement of the spleen, as well as by an absolute lymphocytosis made up of cells of a peculiar type. High concentrations of antibodies against sheep erythrocytes are usually demonstrable in the blood serum.

History. Since the designation "infectious mononucleosis" was first proposed by Sprunt and Evans in 1920, an ever increasing number of cases has been observed and reported, especially since 1935. This is due, at least in part, to better recognition of the disease. Prior to 1920 a few sporadic cases had been observed and a number of epidemics in children had been described under the title of "glandular fever."

Etiology and Pathogenesis. This is a disease of young people, including children, which has now been observed practically throughout the world. In America, infectious mononucleosis has been somewhat less frequent in Negroes than in white persons. It is a relatively common condition in interns, medical students, and nurses but many cases among other persons undoubtedly pass unnoticed. This may be partly due to the mild or nonspecific character of many of the symptoms, but is often attributable to the fact that appropriate blood examinations have not been made. With increasing frequency, sporadic cases and even epidemics have been observed wherever young people live together, as in boarding schools, colleges, and military groups.

The etiology is unknown although it is generally believed that the disease is infectious in

nature. It is likely that individual susceptibility is low and that the causative agent is extremely labile. A few instances of possible successful experimental transmission to human subjects have been reported but, in the main, experiments both in man and in animals have yielded little knowledge as to the nature of the causative agent.

Clinical Picture. The clinical picture differs to some extent in accordance with the stage of the disease. In the *prodromal period*, which may be three to six days in duration, the symptoms may be vague and nonspecific, such as chilly sensations and slight fever, malaise, sore throat, swollen cervical glands, stiff neck, and, occasionally, cough. The temperature curve is irregular, rising each evening to a higher level. In the *midstage* the clinical picture is more characteristic, although the manifestations of this disorder are protean. In this second week of the illness, *cervical glandular enlargement* is a very common sign (77 per cent of cases) and often the adenopathy is generalized. The glands are single or in clumps but they are usually discrete and only slightly tender except where they drain a secondarily infected area. The *throat* is often sore and in more than half the cases a brilliant red color can be observed in the pharynx, over the arches, soft palate, and uvula. At the same time there may be a *translucent edema* involving the soft palate and the uvula. Such edema may be present even when there is no pain in the throat. In other cases the throat presents the typical picture of follicular tonsillitis or that of Vincent's angina or of diphtheria. Stomatitis may be present.

A diffuse or patchy, often *"morbilliform"* rash, usually limited to the trunk, eye signs (conjunctivitis, *pain in or back of the eyes*, photophobia), and *jaundice* may be encountered in various cases. The liver may be found enlarged even in the absence of jaundice, and liver func-

Table 93

SYMPTOMS AND SIGNS OF INFECTIOUS MONONUCLEOSIS, EXCLUDING FEVER AND HEADACHE*

<i>Prodromata or Early Symptoms</i>	<i>1st and 2d Week Symptoms (Excluding Malaise)</i>	<i>Late and/or Convalescent Signs and Symptoms</i>		
Malaise	51 %	Swollen cervical glands	77 %	Glands may remain enlarged for weeks—a small percentage
Sore throat	49 %	General glandular enlargement	70 %	Severe cases may leave the patients feeling below par for months
Swollen cervical glands	21 %	Throat		
Chills	20 %	Red	57 %	
Cough	12 %	Sore	50 %	
Eyes "sore," or pain back of eyes	10 %	Spleen enlarged	43 %	
Neck sore and stiff	9 %	Stomatitis and/or Vineent's angina	36 %	
Abdominal pain	7 %	Rash	15 %	
Pain in shoulder	4 %	Eye signs†	15 %	
		Liver enlarged	13 %	
		Jaundice	5 %	
		Cough	3 %	

* From Gardner and Paul: *Yale J. Biol. & Med.*, 19:846, 1947.

† These include: swollen eyelids, 5%; conjunctivitis, 5%; pain in or back of eye, 9%; photophobia, 4%.

tion tests indicate that hepatic involvement without symptoms is common. The spleen is palpable in more than half the cases.

X This midstage lasts from 4 to 20 days and is followed by a *period of convalescence* which sometimes is slow and may be associated with marked prostration. Recrudescences are very common. Relapse has occurred in about 6 per cent of cases. Recovery is the rule, but death has been observed in a few instances from such complications as rupture of the spleen, respiratory paralysis in association with nervous system involvement, pneumonia, edema of the glottis, and hemorrhage from a deep tonsillar ulceration.

Classification of infectious mononucleosis under the headings (1) glandular form, (2) anginose type, and (3) febrile type, emphasizes the three most common forms of the disease but fails to make clear that this is a disorder of very diverse manifestations ranging from cases with no fever or constitutional symptoms to those with severe, prostrating complaints of great variety. Headache may be so severe as to suggest meningitis. Epistaxis, purpura, hematuria, rectal bleeding, marked tachycardia with cyanosis, electrocardiographic evidence of cardiac involvement, convulsions, stupor, coma, stiff neck, and various pareses and paralyses involving cranial nerves or lower motor neurons, are among other symptoms and signs which may develop. Involvement of mesenteric nodes may be associated with signs which mimic acute appendicitis.

Blood Picture. The leukocyte count is usually increased but, in the first week especially, there may be leukopenia due to granulocytopenia. The leukocytosis is usually moderate (10,000 to 15,000 per cu. mm.), but it may sometimes be very marked. It is due to an increase in lymphocytes, and these in the main are of a peculiar type: their nucleus may be oval, kidney-shaped, or slightly lobulated, and the cytoplasm is often somewhat basophilic and may be vacuolated or foamy in appearance. The nuclear chromatin is usually coarse and irregular and nucleoli are rarely seen. These cells make up 60 per cent or more of all the leukocytes.

Anemia does not occur and thrombocytopenia is rare. The bone marrow reveals a slight myeloid hyperplasia and immaturity; there may be an increase in lymphocytes.

The serum characteristically contains agglutinins against sheep red cells in high titer (heterophil antibodies, Paul-Bunnell test). This has been observed, in different series, in 60 to 92 per cent of cases. "Significant" titers differ according to the technic used, but would be greater than 1:64 in the most popular one. The agglutinin titer tends to rise to its highest level during the second to the fourth week of the disease, and then falls. It is not correlated with the severity of the disease or the degree of lymphocytosis. The serologic test for syphilis may become transiently positive.

Renal function is rarely impaired, but albumin

and red cells may be found in the urine. The cerebrospinal fluid pressure may be moderately elevated and pleocytosis due to lymphocytes may be found.

Diagnosis. While glandular enlargement, sore throat, fever, the characteristic cells in the blood and an increased titer of heterophil antibodies are a combination of findings which makes recognition of this disease easy in many instances, the protean manifestations of infectious mononucleosis may produce a clinical picture which taxes the acumen of the physician. Acute appendicitis, German measles, follicular tonsillitis, infectious hepatitis, and influenza are a few of the diseases which may be simulated. Acute leukemia is another, but anemia, the presence of very immature leukocytes and of nucleated red cells in the blood, and thrombocytopenia, as well as the characteristic bone marrow picture, should make differentiation not difficult.

As already indicated, the clinical picture and the blood findings may be so characteristic that a diagnosis of infectious mononucleosis can be made at times with reasonable assurance in the absence of a positive heterophil antibody reaction. A rising titer as the disease progresses is of significance even if the increase is only within the "normal" range. In the absence of the characteristic blood picture, the diagnosis of infectious mononucleosis is unjustified unless well-defined changes in heterophil antibodies are observed.

The clinical picture may be like that of serum sickness, a condition in which lymphocytes quite similar to those seen in infectious mononucleosis may be found and a positive heterophil antibody test may be obtained. Appropriate methods are available which distinguish between the antibody reactions in infectious mononucleosis and

the rise in titer produced by horse serum. Lymphocytosis, relative or absolute, may be encountered regularly or occasionally in a number of the diseases with which infectious mononucleosis may be confused on clinical grounds. Marked leukocytosis (40,000 or even higher), due chiefly to the presence of small lymphocytes of normal appearance, characterizes a benign disorder, acute infectious lymphocytosis, which has been observed chiefly in children and is accompanied by only mild constitutional manifestations and no lymphadenopathy, splenomegaly, or positive heterophil agglutination reactions.

Treatment is purely symptomatic. Relapses are not uncommon and may be late, but recurrences are very rare. A positive heterophil antibody reaction may persist for as long as five or six months, rarely longer. Anamnestic reactions of heterophil antibodies in significant titers have not been described.

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Epidemic Pleurodynia

Paul B. Beeson

Definition
Epidemiology and Etiology
Manifestations
Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. This is an acute illness of unknown etiology, characterized by abrupt onset of fever and severe muscle pain, often localized in the upper abdominal or lower thoracic regions. Other names which have been applied to this disease are epidemic myalgia, Bornholm disease, and "Devil's grip."

Epidemiology and Etiology. The disease has been observed in many parts of Europe and in the United States. It occurs in epidemics, usually in the late summer months, attacking principally children and young adults. The mode of contagion is unknown. Because of the short duration of symptoms, most of the affected persons do not enter hospitals and much of our knowledge of it has come from observations of patients seen in their homes. The etiologic agent has not yet been identified.

Manifestations. The incubation period is probably two to five days. The onset of symptoms is usually very sudden. An apparently well child may be seized with severe muscular pain while playing. The pain is located most frequently in the muscles of the abdominal wall or the intercostal spaces. Less commonly, muscles of the back, gluteal regions, neck, and shoulders are involved. The pain is often extremely severe. When located in the chest or upper abdomen, breathing becomes difficult and painful. The affected areas are tender to pressure.

Fever is nearly always present, usually 101° to 102° F., but occasionally as high as 104° or even 105° F. There may be some injection of the conjunctivas or the pharynx. In some epidemics coryza has been frequent, while in others it has not been observed. In rare instances pleural or pericardial friction rub has been noted. An even rarer complication is meningoencephalitis, characterized by severe headache, photophobia, and some stiffness of the neck.

Laboratory Findings. There is no diagnostic test for the disease. The white blood cell count is variable. In some epidemics leukocytosis up to 20,000 per cu. mm. has been observed, while in others the leukocyte count has usually been within the normal range. A few counts have shown an increase in the number of eosinophils. In cases with meningoencephalitis there may be an increase in the number of lymphocytes in the spinal fluid.

The *course* is somewhat variable but the duration of symptoms is usually short, pain and fever lasting only one or two days. One or more relapses may occur.

Differential Diagnosis. In the absence of a specific laboratory test for the disease, a diagnosis of epidemic pleurodynia is usually possible only during an epidemic. The diseases with which it is most often confused are the pneumonias. These can be differentiated by careful physical and roentgenologic examination of the chest. Patients with epidemic pleurodynia have been subjected to surgery because of erroneous diagnosis of acute appendicitis, perforated peptic ulcer, or gallbladder disease.

Treatment. Measures to relieve the pain are all that can be offered. Salicylates, codeine, and occasionally morphine may be used. Local application of heat or cold may be helpful. It might be expected that measures which alleviate pleuritic pain would be effective in this disease. These include intravenous injection of 5 to 20 ml. of 10 per cent calcium gluconate, spraying the skin over the painful area with ethyl chloride, or intercostal nerve block with 1 per cent procaine.

Prognosis. The disease is never fatal and recovery is complete.

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Weber-Christian Disease

Paul B. Beeson

This disease, also known as relapsing febrile nodular nonsuppurative panniculitis, is a comparatively rare disorder which affects females more frequently than males. It occurs in all age groups, but most commonly in those between 20 and 40 years of age. The course is variable, usually consisting of symptomatic episodes lasting from a few days to a few weeks, separated by free intervals of similar duration. Cases have been observed to continue for as long as 15 years. The characteristic clinical feature is the appearance of painful, tender subcutaneous nodules, usually on the extremities, occasionally on the trunk, neck, and head. These are elevated and the overlying skin usually is reddened. They range in size from less than 1 cm. to 12 or 15 cm. in diameter, and vary in number from 1 or 2 to as many as 50. When the inflammation subsides, atrophy of the subcutaneous tissue occurs, leaving depressed areas in the skin. Fever usually accompanies the evolution of nodules, and the temperature may

reach 104° F. There is often a leukopenia in the early stages of the disease; later the leukocyte count is normal or elevated. Biopsy of a nodule during the acute stage is the only method by which the diagnosis can be made. Histologic examination reveals inflammation of subcutaneous fat with infiltration by polymorphonuclear leukocytes, lymphocytes, and macrophages. A few patients with this disease have died, and at autopsy inflammatory changes have been found in adipose tissue throughout the body.

The etiology is unknown. No relationship with any microorganism has been demonstrated. Some cases have appeared to be related to ingestion of iodides. The suggestion has been made that Weber-Christian disease is related to dermatomyositis, or to other collagen or arteritic diseases. There is no specific treatment.

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Erythema Multiforme

Paul B. Beeson

Definition
Etiology
Pathology
Manifestations
Course

Laboratory Findings
Differential Diagnosis
Treatment
Prognosis

Definition. Erythema multiforme is a self-limited disease of uncertain etiology, characterized by lesions of the skin and mucous membranes. It has many different names, including erythema exudativum multiforme of Hebra, ectodermosis erosiva pluriorificialis, and Stevens-Johnson syndrome.

Etiology. The disease affects both children and adults, but is most common between the ages of 20 and 40, and the sexes are affected about equally. In some instances erythema multiforme appears to be a manifestation of drug sensitivity, a syndrome indistinguishable from it having been observed following the use of sulfonamides

and phenolphthalein. In most cases, however, no history of drug ingestion can be obtained, and allergy to external agents cannot be demonstrated. No infectious agent has been proved to be associated etiologically, although the onset is often characterized by symptoms of respiratory infection. Pneumonia occurs occasionally, and in a few instances serologic evidence of concomitant psittacosis or ornithosis infection has been obtained.

Pathology. Histologic examination of the skin lesions reveals an acute inflammation in the epidermis, with vascular dilatation and lymphocyte infiltration. Exudation of fluid into the affected area may cause the formation of vesicles or bullae.

Manifestations. There may be prodromal symptoms of malaise, feverishness, coryza, or cough, lasting one to four days. The skin lesions are widely distributed, usually being most numerous on the extensor surfaces of the hands and feet; they also appear on the palms, soles, forearms, legs, and occasionally on thighs, arms, trunk, and face. Mucosal lesions, present in about one third of all cases, are found in the mouth, conjunctivas, urethral meatus, and glans penis or vulva. The term Stevens-Johnson syndrome is applied to cases in which mucosal lesions are present. The skin lesions may be macular or papular, vesicular or bullous, and, as the name implies, great variation may be observed between the individual lesions. Lesions on the extremities often show an "iris" pattern—i.e., two or three concentric rings of varying coloration. Vesicles or bullae are likely to be secondarily infected. Lesions in the mouth rapidly undergo superficial necrosis, leaving shallow erosions which bleed easily. The erosions in the mouth and on the lips are often painful, so that eating and drinking cause great discomfort. When conjunctival involvement is present there may be a copious purulent discharge. Fever is nearly always present, varying from 99° to 102° F., occasionally reaching 104° F.

Course. The total duration of symptoms is usually two or three weeks. New lesions continue to appear during the first week, after which the process generally begins to subside. Occasionally, the course is more indolent and of several weeks' duration. Recovery is the rule and there is little or no residual scarring. A rare but serious complication is panophthalmitis associated with se-

vere conjunctivitis. Recurrence is observed in about 20 per cent of cases.

Laboratory Findings. The white blood cell count is usually within normal limits. There may be eosinophilia. Roentgenogram of the chest occasionally reveals a pneumonic process resembling that seen in atypical pneumonia. Biopsy of skin lesions shows the histologic changes mentioned previously, but the picture is not diagnostic.

Differential Diagnosis. The skin lesions may resemble those in *toxic erythemas* produced by a variety of drugs—e.g., barbiturates, sulfonamides, bromides, etc. These usually clear rapidly on discontinuance of the drug. Bullous forms of erythema multiforme may resemble pemphigus; helpful differential points are the variability in the type of lesion in erythema multiforme and the prolonged chronic course of pemphigus. *Reiter's syndrome* (arthritis, conjunctivitis, and urethritis) may cause confusion, but in Reiter's syndrome cutaneous lesions are uncommon and the arthritis is a prominent manifestation. In young children various *exanthematous diseases* may have to be differentiated.

Treatment. There is no specific therapy. The patient should be protected from further contact with a drug or other agent which might possibly have played a part in the etiology. Care of the lesions in the mouth and eyes is of special importance. Cleansing mouth washes of normal saline or sodium perborate are helpful. Boric acid irrigations of the conjunctiva at frequent intervals are indicated to remove collections of purulent exudate. The cutaneous lesions rarely require any local therapy. In view of the frequency of secondary infections in cutaneous and conjunctival lesions, it is probably advisable to administer penicillin.

Prognosis. Recovery is the rule. A few deaths have occurred in patients with pneumonia.

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Erythema Nodosum

Paul B. Beeson

Definition
 Etiology and Pathogenesis
 Manifestations
 Laboratory Findings
 Differential Diagnosis
 Treatment
 Prognosis

Definition. Erythema nodosum is an acute illness, usually of several weeks' duration, characterized by the development of painful erythematous plaques in the skin, often accompanied by fever and arthralgia.

Etiology and Pathogenesis. The disease is three to five times more common in females than in males. It may occur at any age, but the highest incidence is during the third decade of life. There is a seasonal variation, the disease occurring most frequently during the winter and spring, perhaps because of the increased incidence of respiratory infections at that time.

Erythema nodosum has been regarded by some as a manifestation of either tuberculosis or rheumatic fever. The view that it is a form of tuberculosis has been advanced particularly in Scandinavia, studies there having indicated that 95 per cent of cases in children appear at about the time of development of tuberculin sensitivity. In adults, however, no such close relationship to tuberculosis can be demonstrated. There is little to support the view that erythema nodosum is a manifestation of rheumatic fever. In America the syndrome is observed as a sequel to or associated with a variety of specific infections, the most common of these being hemolytic streptococcal infections of the upper respiratory tract. In areas where coccidioidomycosis is endemic, erythema nodosum is observed in about 5 per cent of cases of that disease. A syndrome indistinguishable from erythema nodosum may also result from ingestion of such drugs as potassium iodide and sulfathiazole. To summarize, the available evidence favors the view that erythema nodosum is a nonspecific syndrome which may develop in association with different kinds of infection or intoxication, possibly due to some form of allergic reaction.

In persons with erythema nodosum, new skin lesions can be produced artificially by making sustained pressure on the skin and subcutaneous tissue. This suggests the possibility that trauma may be partly responsible for the natural predilection of the skin lesions for the anterior surfaces of the legs. Histologically, the fully developed lesions are characterized by vascular dilatation, edema of collagen, and lymphocyte infiltration, most marked in the deeper layers of the corium.

Manifestations. The *skin lesion* develops first as a subcutaneous nodule. Within a few hours the overlying skin becomes thickened, raised, warm, and exquisitely tender. The involved area is usually 1 to 6 cm. in diameter, roughly circular in configuration, and sharply demarcated from the normal surrounding skin. The lesion persists for several days, after which the tenderness, redness, and induration begin to subside, leaving a purplish red area which later becomes bronzed, then gradually fades. New lesions may continue to appear for several weeks. They usually number 8 to 10 at a time, and are most common over the shins, where they are symmetrically distributed. Less commonly, they develop over the ulna, on the thighs, arms, buttocks, or even on the face and scalp. *Fever* is nearly always present, usually 99° to 101° F., but occasionally reaching 104° F. *Arthralgia* occurs in 60 to 80 per cent of cases, being felt in the fingers, ankles, knees, wrists, elbows, and shoulders. Occasionally, there is evidence of some effusion into a joint, but redness of the overlying skin is rare. Enlargement of superficial lymph nodes and spleen is not characteristic of erythema nodosum.

The course of the disease is variable. Sometimes the total duration is only a week, and in the majority of cases symptoms subside within six weeks, but occasionally the manifestations become more or less chronic, persisting for many months.

Recurrences are not unusual. In about 10 per cent of cases a history of a previous episode can be obtained.

Laboratory Findings. The leukocyte count is usually in the normal range, but leukocytosis up to 25,000 per cu. mm. can occur. Culture of the throat yields beta-hemolytic streptococcus in about half of all cases. Roentgenogram of the chest shows enlargement of the hilar lymph nodes in about 25 per cent of all cases. This may persist as long as six months. It is not a sign of tuberculosis.

Differential Diagnosis. *Chronic meningococcemia* may simulate erythema nodosum in the character of the skin lesions, the fever, and arthralgia. It can be distinguished by demonstration of meningococcemia and by prompt subsidence following sulfonamide therapy. Similar skin lesions may be observed in *erythema multiforme*, but they are more widely distributed, more variable, and less tender. The skin lesions of *sarcoidosis* may appear similar, but they are more indolent and less tender, and evidences of sar-

coidosis in other parts of the body can be found. Biopsy will differentiate them.

Treatment. There is no specific treatment for erythema nodosum. The patient should be confined to bed while fever and arthralgia are present. A cradle over the legs may prevent discomfort from pressure of bedclothes. Salicylates are helpful for their analgesic effect.

Prognosis. This depends on the nature of the initiating process. Erythema nodosum is in itself a benign manifestation.

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Part VII
DISEASES OF ORGAN SYSTEMS

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Introduction

M. M. Wintrobe

The hemopoietic system includes the circulating blood, the bone marrow, the spleen, and the lymph nodes, supplemented by the reticuloendothelial cells scattered about the body. The liver, through the presence there of reticuloendothelial cells, as well as by reason of other functions, is also intimately concerned in blood formation and destruction. Since the function of the red corpuscles is to hold in nondiffusible form the pigment, hemoglobin, essential for the transport of oxygen, any alteration in the quantity of red corpuscles or in their hemoglobin content affects the function of all the organs of the body. An important function of the leukocytes is to take part in the reaction to injury, particularly in the defense against infection. The blood platelets are concerned in maintaining the integrity of the vascular endothelium and in the clotting of blood. The blood plasma, which carries these three types of corpuscles, is also the medium for the transport of many substances intimately concerned in the metabolism of the organism.

Since the blood and its constituents are so intimately related to the body as a whole, much will be found concerning the blood in various chapters in this book and particularly in those in Part I. In regard to the red blood corpuscles, attention should be called especially to Chapter 12 (Anoxemia, Cyanosis, and Polycythemia) and to Chapter 22 (Pallor and Anemia). In the latter, the classification and management of anemia are considered, as well as the pathogenesis, symptomatology, and methods of study of a patient with anemia. Certain aspects of red corpuscle destruction are discussed in Chapter 18 (Jaundice and Disorders of Liver Function). The section on the Leukocytes (p. 407) in Chapter 33 (Reactions to Injury) describes in a general way the various types of changes in these cells which

may be encountered in health and disease. Finally the platelets, the phenomenon of coagulation, and the various ways in which bleeding is produced receive attention in Chapter 23 (Bleeding).

In the present section, disorders of the hemopoietic system will be considered. It is evident that such disorders make themselves known in a variety of ways. These may be such that discovering their cause may tax the acumen of even the most discerning physician. In the main, however, they are characterized in part or whole by symptoms and signs such as pallor, cyanosis, jaundice, bleeding, or enlargement of the lymph nodes or spleen. A thorough understanding of these manifestations of disease is a prerequisite to the correct differentiation as well as the effective treatment of the disorders of the hemopoietic system.

The *approach* to the patient suspected of having a hemopoietic disorder is discussed, therefore, in Part I under headings such as Bleeding, Enlargement of Lymph Nodes and Spleen, Jaundice and Disorders of Liver Function, etc. Although, in the subsequent pages, descriptions of the various recognized disorders of the hemopoietic system will be found and their treatment discussed, it is urged that the reader confronted with a problem, for example, of anemia, first study the chapter on Pallor and Anemia, because he will find there a discussion of anemias in general and he will thereby find his way more readily through the pages that follow or, for that matter, through other sections in this textbook. The same is true, in principle, if the problem is one of bleeding or cyanosis or splenomegaly.

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The Anemias

M. M. Wintrobe

Posthemorrhagic Anemia
Acute Posthemorrhagic Anemia
Chronic Posthemorrhagic Anemia
Iron Deficiency Anemia
Macrocytic Anemias
Pernicious Anemia
Megaloblastic Macrocytic Anemias Other than Pernicious Anemia
Hemolytic Anemias
Manifestations
Classification
Mechanisms of Hemolysis
Study of a Patient with a Hemolytic Disorder
Prognosis and Treatment
Congenital Hemolytic Jaundice
Sickle-Cell Anemia
Paroxysmal (Cold) Hemoglobinuria
Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria
Anemias Associated with Infections and Various Other Disorders, Chiefly Chronic
Mediterranean Anemia

POSTHEMORRHAGIC ANEMIA

Anemia resulting from blood loss may have developed suddenly due to the rapid loss of a large quantity of blood, or it may have come about very gradually over a period of many months or even years. Obviously there are also many possible variations between these two extremes. The causes of posthemorrhagic anemia are numerous and the manifestations differ widely, the latter depending in part on the nature of the underlying disorder and in part on the quantity and speed of blood loss. It is convenient to consider acute and chronic posthemorrhagic anemias separately because their manifestations and, in certain respects, their treatment differ so greatly. It should be realized, however, that these two syndromes represent two extremes depending, in the main, on the same underlying defect, and that in practice variations will be encountered which represent all stages between these ends.

ACUTE POSTHEMORRHAGIC ANEMIA

Etiology. Trauma, the rupture of a peptic ulcer or of an ectopic pregnancy, and bleeding in connection with hemophilia or purpura hemorrhagica are examples of the widely varied possible causes of acute blood loss. They indicate that the

blood loss may be external and recognizable at once, or internal and, consequently, sometimes not readily discovered.

Symptomatology. The rapid loss of blood leads to reduction in blood volume and the clinical manifestations are mainly circulatory. If the blood loss is great, "acute posthemorrhagic shock" develops (see Chapter 14). If the hemorrhage is visible to the subject, whether the amount of blood lost is great or small, symptoms may arise from the psychic effect of such bleeding. Generally speaking, symptoms are likely to appear sooner and are more pronounced in relation to the amount of blood lost when the bleeding is external than when it is not recognizable by the subject. The manifestations of anemia in general have been discussed already (p. 251). In addition, the symptoms of the underlying disorder may be present as well.

Blood Picture. Polymorphonuclear leukocytosis with the appearance of immature forms ("shift to the left") is the first discernible change. An increase in platelets often takes place as well. The anemia may not be apparent at once since, at first, plasma is lost as well as red corpuscles, so that the ratio of cells to plasma remains the same. As fluid is drawn from the tissues to restore the blood volume, anemia becomes apparent. This is normocytic at first. Blood loss in an otherwise healthy organism, however, profoundly stimulates the bone marrow. This becomes hyperplastic and immature corpuscles are liberated in larger numbers than usual. Reticulocytosis ensues, polychromatophilia is found, and even nucleated red corpuscles find their way into the blood. At this stage the anemia may be macrocytic since the immature cells are larger than the older forms. Reticulocytes begin to appear within 48 hours following a brisk hemorrhage and may continue to increase for several more days. A persistent reticulocytosis, forming a plateau-like curve, suggests that bleeding is continuing, for cessation of hemorrhage is marked by quick restoration of physiologic balance with rapid regres-

sion of the signs of stimulated hemopoiesis. If the iron stores of the body are good and the blood loss has not been extreme, iron deficiency does not occur and hypochromia is slight or absent. When the drain on iron is greater than can be readily replenished, iron deficiency begins.

When the acute hemorrhage is internal, destruction of the blood and absorption of the products may lead to an increased excretion of urobilinogen in the urine and stools, and even slight bilirubinemia may be found. Bowel hemorrhage is often associated with an increase in the blood urea nitrogen level.

Diagnosis. When acute hemorrhage is not evident, such signs as pallor, faintness, restlessness, sweating, and palpitation should lead to a search for hemorrhage. If the subject is recumbent, much blood may be lost before these signs appear. They can be brought out by tilting the patient to the erect position. Late signs of acute blood loss are air hunger, thirst, and a falling blood pressure.

Prognosis. The amount and rapidity of the blood loss, the acuteness of the physician in discovering it, the availability of blood for transfusion, and the accessibility of the site of bleeding are the important considerations.

Treatment. Stopping of the hemorrhage and restoration of the blood volume to normal, preferably by transfusions of whole blood, otherwise by administration of plasma or other fluids, are the essentials. Speed in restoration of blood volume is more important than whether plasma or whole blood is used. If the blood loss has been great and the blood volume is profoundly reduced, multiple portals should be used for administration of blood, and even intraarterial administration may be advisable. Fluids by mouth (unless the bleeding is from the upper portion of the alimentary tract) and by hypodermoclysis, are valuable adjuncts, as are rest and quiet, induced by morphine if necessary. Following the acute phase, a good diet containing meat, fruit, and vegetables affords the proteins and vitamins needed for erythropoiesis. Iron can be given in the form of ferrous sulfate (0.2 to 0.4 Gm. t.i.d.), but is not needed in previously normal individuals unless blood loss has been extreme.

CHRONIC POSTHEMORRHAGIC ANEMIA

This refers to that state in which blood loss has produced a chronic anemia, and a deficiency of

substances necessary for blood formation has developed. Although the factors essential for erythropoiesis are many, the chief deficiency resulting from chronic blood loss is that of iron. The manifestations of chronic posthemorrhagic anemia can therefore be discussed in the section which follows.

IRON DEFICIENCY ANEMIA

(Hypochromic Microcytic Anemia; Idiopathic, Chronic, or Nutritional Hypochromic Anemia; Chlorosis, Chlorotic Anemia, Chloranemia)

Etiology. Iron is normally obtained by digestion of food and is absorbed chiefly in the upper portion of the gastrointestinal tract. This is aided by the acid secretion of the stomach. The absorbed iron is utilized for hemoglobin formation, as well as for the production of myoglobin and other enzymes. Normally a large reserve is stored in the liver, spleen, and other tissues. Once absorbed, extremely little iron is lost, except through hemorrhage, for there is practically no normal excretion of iron.

Any circumstance which leads to a greater demand on the iron stores of the body than can be supplied results in iron deficiency. In logical order, the possible factors leading to iron deficiency are: (1) insufficient iron in the diet, (2) impaired absorption, (3) increased requirements, and (4) loss of blood. Of these, the *chronic loss of blood* by hemorrhage is by far the most common factor in the development of iron deficiency. Excessive menstruation and occult bleeding from the gastrointestinal tract (peptic ulcer, esophageal varices, hookworm infection, etc.) are the most common types of bleeding which may result in iron deficiency, since the former is but an exaggeration of a physiologic process and may thus receive little attention, while the latter may pass unnoticed for a long time.

Impaired absorption of iron is rarely an important factor. Although the gastric hydrochloric acid favors ionization and thus absorption, many persons are encountered in whom achlorhydria has existed for years without iron deficiency developing. Chronic diarrhea, however, may be of more importance. Certainly iron deficiency may be encountered in sprue.

Deficiency of iron in the diet alone is rarely a cause of iron deficiency except in infants receiv-

ing a milk diet exclusively, and occasionally in elderly people who have had no blood loss for many years but have followed a diet very low in iron.

In children and adolescents the iron needs for growth are very important, and it is largely because of the demands made by the ever expanding blood volume that infants receiving an unplemented diet of milk develop iron deficiency. In older children and adolescents, poverty or faulty habits may lead to a diet too low in iron to supply the needs. In girls, the menstrual loss of blood accentuates this deficiency. *Chlorosis*, the "green sickness" of the last century and before, was probably no more than iron deficiency in adolescent girls in whom low dietary iron was insufficient to meet the needs. In adult women the iron requirement during *pregnancy* and *lactation* are factors which may lead to the development of iron deficiency anemia. Often these circumstances are superimposed on a state of gradually increasing iron depletion which may have had its beginning in adolescence. The ultimate combined effect of chronic loss of blood, increased demands, and faulty diet may not become clearly manifest until 30 to 45 years of age, the period in which the *chronic hypochromic anemia* of women is most often seen. It is of interest that in such individuals certain *constitutional features* similar to those encountered in pernicious anemia may be observed, such as early graying of the hair and achlorhydria.

Since practically no iron is excreted normally, iron deficiency can develop in the adult male only from loss of blood or from deficient diet or impaired absorption which has existed over a period of many years. In the male, ulcerative lesions in the gastrointestinal tract are by far the most likely causes of long-continued, undetected loss of blood.

Symptomatology. The symptoms are those common to all chronic anemias and may include a variety of vague gastrointestinal complaints such as anorexia, capricious appetite, or "heart burn," as well as sore tongue, sore mouth, and dysphagia ("Plummer-Vinson syndrome"); or palpitation, dyspnea, and edema about the ankles; or neuralgic pains, vasomotor disturbances, or numbness and tingling. Menstrual disturbances are common—menorrhagia, irregularity of flow, or even phases of amenorrhea.

A tired, lifeless appearance; pallor; inelastic

and often dry and wrinkled skin, sometimes with a brownish hue; dry and often scanty hair; and blue scleras are found in cases of long standing. In many, some degree of papillary atrophy of the tongue, slight cardiac enlargement, functional systolic murmurs, and a palpable spleen are discernible. The nails may be flattened, longitudinally ridged, or even concave (*koilonychia*), and may break easily. The sore tongue, dysphagia, and changes in hair, nails, and skin may occur in iron deficiency prior to the development of anemia.

Blood Picture. A good blood smear will reveal thin, pale red corpuscles poorly filled with hemoglobin (fig. 180). In some cases these may be mere rings. Tiny microcytes, "target"-like cells, elliptic cells, and bizarre poikilocytes are also found, as well as a certain proportion of normally filled corpuscles. The anemia is hypochromic and microcytic. Only in this type of anemia is substantially reduced mean corpuscular hemoglobin concentration (MCHC) encountered (less than 30 per cent). This hypochromia is more significant than the microcytosis, although the latter may be extreme (mean corpuscular volume 55 to 75 cubic microns). The red corpuscle count may be normal or nearly so, or even greater than normal, while the hemoglobin and volume of packed red corpuscles are greatly reduced. The leukocyte count is normal or slightly reduced, and a slight thrombocytopenia may exist.

The bone marrow is hyperplastic, and contains an excessive number of normoblasts.

Diagnosis. Although the symptoms are varied and may arouse suspicion of a great variety of conditions, adequate blood examination should make it clear that hypochromic microcytic anemia exists. This type of anemia, with the exception of the rare Mediterranean anemia (p. 1199), signifies iron deficiency. The cause of the deficiency should be sought out and sources of blood loss, in particular, must be looked for.

Prognosis. This is excellent in so far as the possibility of relieving the anemia is concerned. The prognosis otherwise depends on the character of the contributory causes.

Treatment. Only in iron deficiency anemia is iron therapy of value. Here the administration of ferrous sulfate or ferrous gluconate is followed by a reticulocyte response, and subsequently rapid red corpuscle regeneration occurs. Gastric irritation is less likely to occur if tablets of 0.2 to 0.3

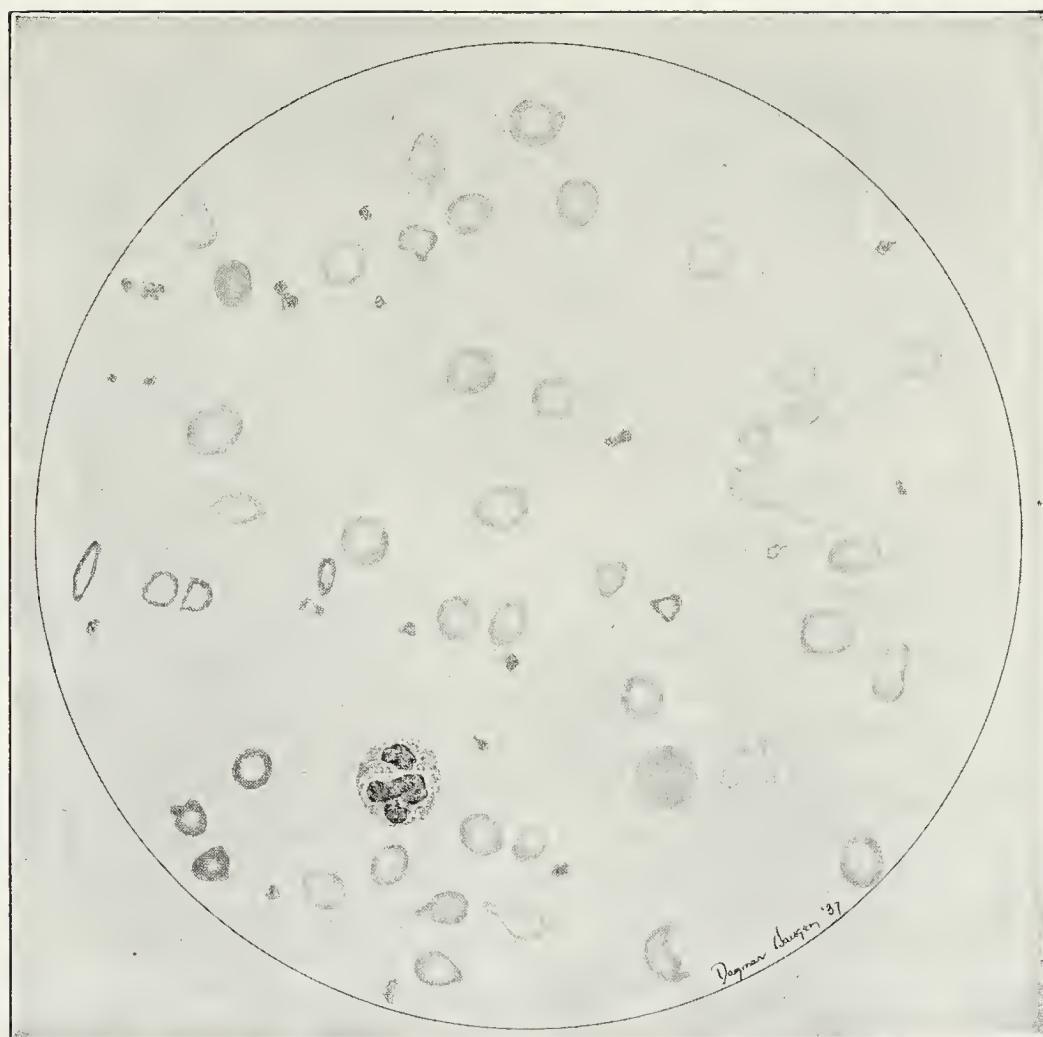


FIG. 180. Blood smear from a case of chronic hypochromic anemia. (Courtesy, Wintrobe: "Clinical Hematology," Philadelphia, Lea & Febiger.)

Gm. size are taken on a full stomach. To allow the patient to become accustomed to it, at first a total of 0.4 to 0.6 Gm. is given per day, but this may be increased to 1 or 1.2 Gm. In addition to iron therapy, a good diet containing meat, fruit, and vegetables is to be recommended, and any underlying or associated disorder should be corrected. Transfusion of blood is rarely if ever needed, even in the most anemic, and free hydrochloric acid is not required even if achlorhydria is present.

MACROCYTIC ANEMIAS

Elucidation of the pathogenesis of pernicious anemia, even though still incomplete, has made clear the fact that there are a number of closely related disorders which have in common a characteristic type of anemia, megaloblastic hyperplasia of the bone marrow, and the capacity to respond to liver therapy, yeast, pteroylglutamic acid, vitamin B₁₂, or related substances. These conditions, the *megaloblastic macrocytic anemias*,

must be differentiated from those instances of macrocytosis which represent increases in mean corpuscular volume from other causes, usually from the presence in the circulation of a relatively large number of immature red corpuscles appearing in response to such hemopoietic stimulants as severe hemorrhage or acute blood destruction (table 94). In this second type of macrocytic anemia the bone marrow is not megaloblastic and liver therapy has no value. The clinical differentiation is usually easy.

PERNICIOUS ANEMIA

(Addisonian Pernicious Anemia, Addison's or Biermer's Anemia, Primary Anemia)

Definition. Pernicious anemia is a chronic disorder characterized by macrocytic anemia, megaloblastic hyperplasia of the bone marrow, gastric achlorhydria, and often glossitis and changes in the nervous system. These conditions appear to be the consequence of a gastric secretory defect

Table 94
CLASSIFICATION OF MACROCYTIC ANEMIAS

I. MEALOBLASTIC MACROCYTIC ANEMIAS:

A. Conditions responding to administration of purified liver extract or pteroylglutamic acid:

<i>Disorder</i>	<i>Probable Pathogenesis</i>
1. Pernicious anemia*	Lack of gastric ("intrinsic") factor
2. Sprue, idiopathic steatorrhea	Impaired absorption
3. Resection of small intestine	Impaired absorption
4. Nontropical nutritional macrocytic anemia	Dietary deficiency
5. Tropical macrocytic anemia	Dietary deficiency
6. Macrocytic anemia with <i>Diphyllobothrium</i> infestation	Inhibition of interaction between extrinsic and intrinsic factors (when worm is sufficiently high in intestine)
7. Megaloblastic anemia of infancy	Dietary deficiency
B. Conditions apparently responding only to administration of crude liver extracts or pteroylglutamic acid:	
8. Megaloblastic anemia of pregnancy	Dietary deficiency? Impaired absorption? Increased requirements for fetus?
9. "Refractory megaloblastic" anemia	Impaired utilization of liver extract?
10. "Achrestic" anemia	Impaired utilization of liver extract?

II. NONMEALOBLASTIC MACROCYTIC ANEMIAS:

Some instances of

1. Acute posthemorrhagic anemia	Presence in blood of many immature erythrocytes
2. Hemolytic anemia	Presence in blood of many immature erythrocytes
3. Aplastic anemia	Unknown
4. Hypothyroidism	Unknown
5. Liver disease	Unknown

* Pernicious anemia is distinguished from the other conditions listed in that achlorhydria is always present and neurologic changes may occur.

N.B. In practice, the most common cause of "macrocytic anemia" is *laboratory error*, and this is most often due to errors in red corpuscle counting.

which results in a deficiency in the body of a substance derived from food. The deficiency can be corrected by supplying a substance present in certain liver extracts.

History. Although the disorder was described at least as early as 1823 by Combe, it was the picture given by Thomas Addison in 1855 and the comprehensive description by Biermer in 1872 which drew attention to this ultimately fatal (therefore "pernicious") anemia. The discovery of the value of liver therapy by Minot and Murphy in 1926 and the elucidation of the role of the stomach in the pathogenesis of the disorder by Castle in 1929 completely changed the prognosis of the condition and profoundly stimulated hematologic research in general.

Etiology. This disorder is very rare in persons under the age of 30 and is encountered much more frequently in light-haired, blue-eyed individuals than in the darker races or in Orientals. It is seen especially in natives of the British Isles, the Scandinavian countries, and other more northern regions, as well as in their offspring in

other parts of the world. Nevertheless, although less common, pernicious anemia is seen in Negroes.

A familial incidence is not unusual. Those affected often have turned gray prematurely, and they may have broad faces and large, bony frames. Males and females are affected about equally.

That a gastric secretory defect is a fundamental factor in the pathogenesis of pernicious anemia was suspected almost as early as the disease was recognized. It was shown later that absence of hydrochloric acid in the gastric secretion and a greatly reduced total gastric secretion (achylia) precede the development of the anemia by many years. It has also been shown that such achylia is a defect which persists in spite of successful antianemic therapy. Castle demonstrated that the significant abnormality in gastric secretion is not lack of hydrochloric acid but absence of an "intrinsic factor" which normally acts upon an "extrinsic factor" derived from food. The material so produced has been regarded as

leading to the formation of an unidentified substance stored in the liver without which normal hemopoiesis cannot take place. The gastric factor is thermolabile and may be an enzyme. The thermostable food factor is present in meat, eggs, cereals, and other natural sources of the vitamin-B complex and is also present in liver. The liver factor likewise is thermostable and is soluble in 70 per cent alcohol. The incubation of liver with gastric juice enhances its potency 10 to 20 times. Desiccated hog's stomach given orally has the same hemopoietic effect in pernicious anemia as liver and its effectiveness has been assumed to be due to the interaction of the intrinsic and extrinsic factors in gastric tissue. However, that there is a qualitative difference between the extrinsic factor and the liver factor has become a debatable point since the discovery of a cobalt complex, vitamin B_{12} , which is therapeutically effective when given parenterally in amounts as small as 1 to 5 micrograms, but which is also active orally after small amounts have been incubated in normal gastric juice.

The vitamin pteroylglutamic acid ("folic acid") has been shown to produce a hemopoietic response in pernicious anemia when given orally or parenterally. Its relationship to liver extract is not clear; it is neither Castle's intrinsic factor nor the extrinsic factor. In nature it is found in conjugated form, as the heptaglutamate (yeast) or as triglutamate. Whereas the administration of liver or liver extract prevents the development or advancement of the neural manifestations of pernicious anemia, these may appear in spite of folic acid therapy. The distinction between a hemopoietic factor and a neural factor, suspected before on clinical grounds, is thus further supported.

The red corpuscles of patients with untreated pernicious anemia appear to have a shortened survival time. Thus the bilirubinemia and urobilinogenuria so characteristic of pernicious anemia can be regarded as manifestations of a more rapid blood destruction which may be the consequence of imperfect construction of the red corpuscles resulting from a deficiency of building materials.

Pathology. The significant findings are in the alimentary tract, the bone marrow, and the nervous system. The tongue usually appears smooth and the papillae may be absent. Atrophy of the mucous membrane may be striking in the

tongue and in the stomach. The changes in the stomach have been observed particularly in the fundic zone, where the parietal and chief cells are usually absent.

Appropriate staining reveals the liver as well as the spleen and kidneys to be abnormally laden with iron. In the liver this is found in the periphery of the lobules and in the Kupffer cells. There may also be fatty degeneration in the central cells of the lobules of the liver. The heavy deposit of iron is the consequence of the fault in red corpuscle formation which leads to the development of anemia; when active blood regeneration follows liver therapy, the iron is used in blood formation.

The *bone marrow* is red and is found to be crowded with cells. Cells of the red series make up 30 to 50 per cent, rather than about 20 per cent of the cells of the marrow. The degree of hyperplasia and the degree of immaturity of the cells are roughly proportional to the severity of the anemia. The nucleated red corpuscles ("megaloblasts") differ from those found in other types of anemia in several respects. They are exceptionally large and, what is more significant, the nuclear chromatin is fine and sievelike, unlike the relatively coarse and "lumpy" material seen in normoblasts. The cytoplasm of these cells may be polychromatophilic or orthochromatic, and, in a few, is basophilic. Many abnormal mitotic figures may be present. At the same time, extraordinarily large leukocytes may be found in the marrow; in particular, large metamyelocytes can be seen with bizarre-shaped nuclei and peculiarly staining or vacuolated cytoplasm. Megakaryocytes may be reduced in number and may be morphologically abnormal. In spite of the evidence of cellular activity, hemopoiesis is inefficient and anemia develops.

In the nervous system, degenerative changes may be found in the dorsal and lateral tracts of the cord, in the dorsal root ganglia, and in the peripheral nerves. Myelin degeneration and loss of nerve fibers occur. More rarely, changes are encountered in the brain.

Symptomatology. The onset of the disease is generally insidious. In many instances at least two of the diagnostic triad of symptoms are encountered; namely, weakness, sore tongue, and numbness and tingling in the extremities. However, there may be other complaints which overshadow these, and the presenting clinical picture

may suggest some disorder of the digestive tract because of anorexia, diarrhea, and various other gastrointestinal symptoms; it may simulate cardiac dysfunction of the anginal or the congestive failure type; or one may be led to search for some malignant neoplasm or an obscure infection. In some instances the neural involvement is so pronounced that a primary neurologic disease is considered. Even renal or genitourinary disease or a mental disorder may be simulated.

The degree of soreness of the tongue varies greatly and the involvement may be complete or patchy. The color may be "beefy" red when the symptoms are pronounced and is less red and smooth when they subside. The gastrointestinal symptoms are very variable. However, one which is consistently found in relapse is anorexia. Symptoms referable to the circulatory system include dyspnea, palpitation, sensations of extra beats, weakness, vertigo, tinnitus, and precordial pain. Since pernicious anemia often appears for the first time in the older age groups, it may be difficult to determine to what extent anemia or the degenerative changes of old age have contributed to the development of heart failure.

Pallor, a flabby rather than wasted appearance; a slight or pronounced yellowish color of the skin together with faint icterus of the scleras; a tongue which is often glazed in appearance and sometimes is red and sore; a rapid pulse with slight cardiac enlargement and often precordial hemic murmurs; in many a spleen which is just palpable; and often a slightly enlarged liver are the chief findings outside the nervous system. In the nervous system, loss of vibratory sense in the lower extremities (not necessarily symmetric), incoordination of the lower extremities, loss of finer coordination of the fingers, signs suggestive of lateral as well as posterior spinal cord involvement, and evidence of peripheral nerve degeneration are the most common findings, and may be present in all degrees from slight or none to extensive involvement. Positive Babinski response, positive Romberg's sign, disturbed position sense, spasticity, increased or diminished reflexes, and sphincter disturbances may be encountered. Minor mental disturbances (irritability, memory disturbances, mild depression) or more serious mental symptoms may develop.

Laboratory Findings: BLOOD. The anemia is usually more severe than the complaints and physical examination would lead one to suspect.

In the blood smear, macrocytes, often oval in shape, are characteristically seen (fig. 181), but there is actually a great range in the size of the cells and, in addition, many bizarre-shaped corpuscles are found (poikilocytosis). Since the ab-

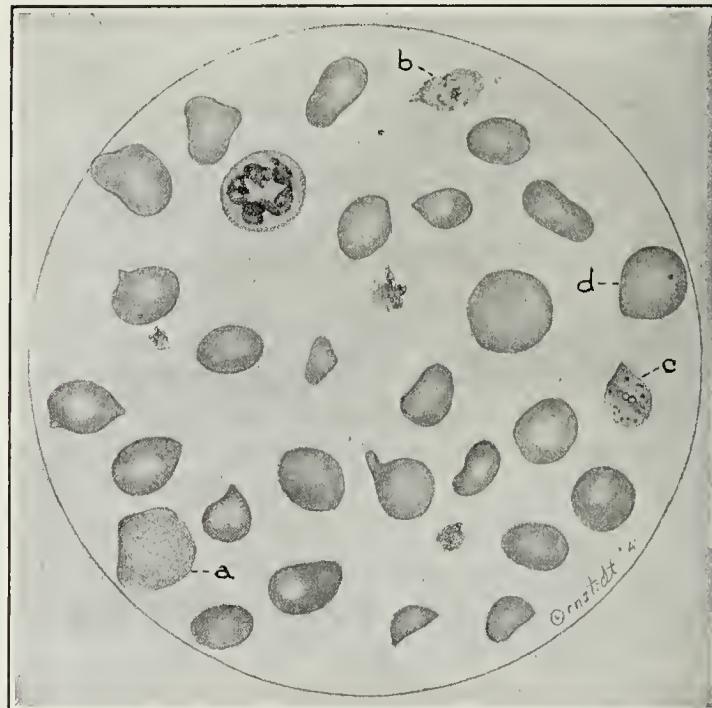


FIG. 181. Drawing of a blood smear from a case of pernicious anemia in relapse. From a preparation stained with Wright's and magnified $\times 960$. Note the extreme variation in the size and shape of the red corpuscles, the large polychromatophilic red corpuscle (a), the cells containing nuclear remnants and Howell-Jolly bodies (b, c) and a Cabot "ring" (c), the "granule red corpuscle" (d), and the multisegmented polymorphonuclear leukocyte. (Courtesy, Wintrobe: "Clinical Hematology," Philadelphia, Lea & Febiger.)

normally large cells predominate, the mean corpuscular volume is found to be greater than normal and ranges between 100 and 160 microns (fig. 182). There is a corresponding increase in the hemoglobin content of the red corpuscles (mean corpuscular hemoglobin), so that the concentration of hemoglobin in the corpuscles (mean corpuscular hemoglobin concentration) is normal. The red corpuscles in pernicious anemia and in other macrocytic anemias are not "hyperchromic," but, being thicker as well as larger in diameter than normal corpuscles, they appear to be supersaturated with hemoglobin as one looks at them through a microscope. Some degree of diffuse polychromatophilia as well as basophilic stippling is found, and occasional nucleated red corpuscles may be encountered. The most striking changes, described in classic cases, are only observed when the anemia is very severe. Since

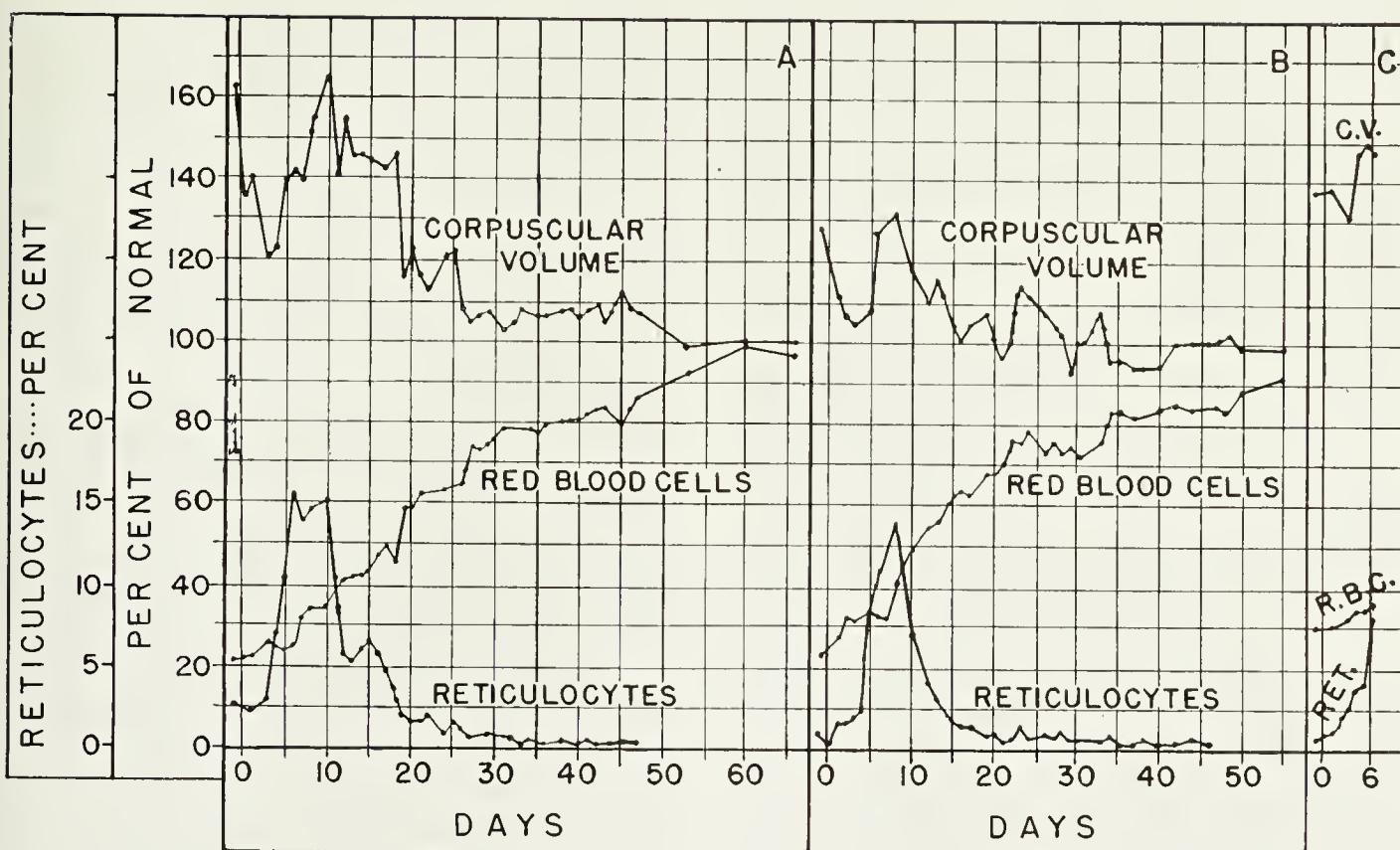


FIG. 182. Variations in mean volume of red corpuscles compared with reticulocyte count in three cases of pernicious anemia. The mean corpuscular volume (C.V.) and the red cell count (R.B.C.) are represented as percentages of their respective average normal values. By this method the red cell count and mean corpuscular volume of a hypothetical normal individual would fall on the line at 100 per cent. Reticulocytes are recorded directly. The abscissa records days following the commencement of liver therapy. (Courtesy, Wintrobe: Relation of variations in mean corpuscular volume to number of reticulocytes in pernicious anemia, *J. Clin. Investigation*, 13:669, 1934.)

the anemia is macrocytic, the red corpuscle count is reduced more than proportionately as compared with the hemoglobin or the volume of packed red corpuscles. Reticulocytes are usually within normal limits in untreated patients or, at most, do not run higher than 3 or 4 per cent.

The leukocyte count is usually lower than normal, due chiefly to a granulocytopenia. Thus, there is relative lymphocytosis. The polymorphonuclear neutrophilic leukocytes often show an unusual number of segments and may be exceptionally large. An occasional myelocyte is present in many cases. Sometimes some degree of eosinophilia is encountered. The platelets are generally reduced in number, sometimes to levels below 100,000 per cu. mm., and bizarre forms, including giant platelets, may be found. When there is thrombocytopenia, the bleeding time may be prolonged, the blood clot retracts poorly, and purpura may develop.

The resistance of the red corpuscles to hypotonic saline solutions is not significantly altered. The icterus index usually ranges between 10 and

15; sometimes it is as high as 20 or 25. The average plasma bilirubin content is 1 mg. per 100 ml. and the van den Bergh reaction is "indirect."

OTHER LABORATORY FINDINGS. With extremely rare exceptions, there is, in cases of pernicious anemia, persistent failure to secrete hydrochloric acid in the stomach even following the injection of histamine. Furthermore, in the great majority of cases, the enzymes are deficient as well, and only a small amount of mucus rewards the gastric extraction.

In addition to the bilirubinemia, already mentioned, the urobilinogen content of the urine and stools is increased. Detailed examinations reveal many other evidences of metabolic disturbance involving especially protein and uric acid as well as fat metabolism.

Diagnosis. When the combination of the classic symptoms, weakness, sore tongue, and numbness and tingling, together with macrocytic anemia and achlorhydria, is found, there need be no difficulty in diagnosis. Confusion may arise if the symptoms have attracted attention to some other

condition and the blood examination has not been appropriate to demonstrate the existence of a macrocytic anemia. Confusion may also arise when symptoms referable to the nervous system are prominent and anemia is only moderate or slight in degree. For all practical purposes, since achlorhydria is so characteristic a feature of pernicious anemia, a diagnosis of pernicious anemia should never be made without demonstrating a failure to secrete hydrochloric acid following the injection of histamine. The existence of a macrocytic anemia, as indicated by calculation of red corpuscle size, should, furthermore, be confirmed by examination of the blood smear. In practically all cases such anemia is found to be associated with evidences of altered pigment metabolism such as some increase in plasma bilirubin and an increased output of urobilinogen in the urine and stools. Where anemia is slight in degree, the combination of achlorhydria, slight macrocytosis as indicated by calculation of mean corpuscular volume and by the presence of macrocytes in the blood smear, together with a slight degree of bilirubinemia, makes the case a highly likely one.

It must be kept in mind that the demonstration of macrocytic anemia is not in itself diagnostic of pernicious anemia, for, as already indicated, macrocytic anemia may appear under a variety of circumstances. When the macrocytic anemia is part of another disorder such as "aplastic" anemia, aleukemic leukemia, or some type of hemolytic anemia, differentiation is important, for liver therapy is valueless. In aplastic anemia, achlorhydria is only sometimes present, glossitis is rare, and signs of involvement of the nervous system, such as loss of vibratory sense, are unusual. In "aleukemic" leukemia sternal marrow examination should reveal a characteristic picture quite different from that of pernicious anemia, and in hemolytic anemia the marrow is normoblastic, not megaloblastic. Even when the macrocytic anemia is due to a deficiency of the anti-pernicious anemia principle, differentiation is important since some forms, unlike pernicious anemia, are not permanent in character and do not require treatment for the remainder of the patient's life. Certain rare megaloblastic macrocytic anemias, furthermore, do not respond to the administration of refined liver extract. Some of these conditions will be described briefly below.

It is important that diagnosis be established

accurately before treatment is initiated since, as already indicated, a diagnosis of pernicious anemia implies the need for therapy for the rest of the patient's life. In doubtful cases, a therapeutic test, if properly performed, can be very helpful. It is important that the test be made with liver extract alone and not with some agent containing iron or other substances in addition to liver extract, and that the reticulocyte response be observed daily.

Prognosis. With appropriate therapy it is now possible to restore the blood to normal and to promote a return of the general nutrition to normal. If changes are present in the nervous system, their advance can at least be halted, and in some cases improvement may take place. The danger in pernicious anemia arises from failure to continue therapy and from complications and intercurrent conditions. In a chronic ailment like pernicious anemia, other diseases develop in the course of time. Among these, carcinoma of the stomach is particularly noteworthy since the incidence of this disease in patients with pernicious anemia is more than three times as great as in other individuals. When changes in the nervous system exist, particularly if they involve the urinary sphincter, infection may occur. The existence of infection at the time of relapse may seriously interfere with the response to therapy.

Treatment. Treatment, in so far as the blood changes are concerned, is extremely simple. The administration of an adequate amount of liver extract is followed by a reticulocyte response which reaches its maximum five to seven or eight days following initiation of therapy. This is succeeded, as the reticulocyte count falls to normal, by a rapid disappearance of anemia and the production of cells of normal size and shape. The leukocyte and the platelet counts likewise return to normal, bilirubinemia disappears, and the increased quantities of urobilinogen in the urine and stools are reduced to the normal range. The gastric achlorhydria persists.

Effective treatment may produce subjective improvement within 48 hours, and evidence of a change is often noted by the patient before the reticulocytes increase. There is a gain in appetite and a sense of well-being. Tongue symptoms, if present, disappear promptly. On the other hand, neural symptoms do not change quickly. Although in the course of two months from the beginning of treatment the patient usually at-

tains a normal blood, the neurologic symptoms may still be present, although those of milder intensity may have decreased or disappeared.

The most efficient means of treatment is by the intramuscular injection of liver extract. This is available in highly concentrated form, the most useful of which is that which contains 15 U.S.P. units per milliliter. A U.S.P. unit is that amount which, when given daily to an average case in relapse, will produce a "satisfactory" or average reticulocyte response and good blood regeneration. Although a single injection of, say, 3 ml. (45 units) should suffice to produce a return to normal, it is somewhat better to give this amount daily until a satisfactory response is assured. If the reticulocytes are measured daily, there will be evidence of response after five to seven days, and the injections may be reduced to 1 or 2 ml. per week, this being continued until the blood has returned to normal. It is best to give more liver extract than is actually needed because liver extract is, at least in large measure, stored, and a reserve is thus built up. The only objection to the administration of an initial large dose is that an occasional patient who has received liver extract previously may be found to be sensitive to it and a severe allergic reaction may thus be produced.

Maintenance therapy with liver extract can be calculated on the basis of 1 unit per day, but need be given only at two- to eight- or even twelve-week intervals, depending on convenience to the patient, 15, 60, or even 90 units being injected at one time.

Intravenous therapy is unnecessary. Oral therapy is inconvenient since comparatively large amounts have to be taken and thus daily intake is necessary. Only where some idiosyncrasy on the part of the patient exists or where sensitivity to the parenteral administration of liver extract cannot be overcome otherwise, is oral therapy justified. The substances available are liver extract, liver solution, or liver with stomach (U.S.P. XIII). These should be given in doses of 1 unit per day. Pteroylglutamic acid (folic acid), 5 to 20 mg. daily, has also been used in such cases, but since it may fail to protect the patient against the development of changes in the nervous system, this procedure is not recommended.

Evidence is accumulating that ~~X~~ vitamin B₁₂ is a useful agent in liver-sensitive cases and is, in fact, satisfactory for use in any case of per-

nicious anemia since it appears to be the anti-anemic factor of liver extract which is effective in pernicious anemia. One microgram of B₁₂ is roughly equivalent to one U.S.P. unit of liver extract.

The diet should be such as to restore the patient to a state of normal nutrition and to maintain him so, but need not contain any unusual foods except perhaps where neurologic changes are present. In such cases, it seems wise to recommend the consumption of, say, a half pound or more of cooked liver per week. This recommendation is made since information is still lacking as to the nature of the deficiency which leads to the development of changes in the nervous system. By the consumption of whole liver the patient possibly obtains substances of value in addition to the antianemic factor.

Transfusion is rarely, if ever, required in pernicious anemia, since a physiologic response can be achieved in 48 to 72 hours if liver extract is given parenterally. Since the patient's anemia has developed gradually, he has become adjusted to the existent anemia. Where the cardiovascular system seems imperfect, transfusion, by producing a sudden increase in blood volume, may sometimes be harmful and may precipitate acute cardiac failure with pulmonary edema. Iron is not needed as an adjunct except where iron deficiency exists as well. Supplementary therapy with various vitamins is likewise unnecessary. These can be and should be furnished in the diet in the form of food. The administration of diluted hydrochloric acid (U.S.P.), in amounts of 4 to 8 ml. three times daily with meals, is of value when gastrointestinal complaints persist, particularly eructations or frequent bowel movements. In the absence of such complaints hydrochloric acid is unnecessary.

Particularly where changes in the nervous system exist, confinement to bed should be as brief as possible, and the patient should be encouraged to use the limbs even when lying in bed. In addition, passive movement, massage, and dry heat are valuable for improving the tone of the muscles. Physiotherapy may permit adjustment to permanent damage resulting from the disease.

The development of an intercurrent disease, particularly infection, calls for an increase in the amount of liver therapy, since requirements for liver extract under such conditions seem to be increased.

To do

Sensitivity to liver extract may develop, as indicated by the occurrence of severe flushing, dizziness, a sense of oppression, or urticaria. Sometimes peripheral vascular collapse may occur. Often relief cannot be obtained by changing to another source of liver extract. Antihistamine drugs may be helpful. If reactions persist, desensitization may be accomplished by giving 0.1 ml. of a 1:10 dilution of the liver extract and progressively doubling the dose every 15 minutes until the desired amount has been given. A total of 90 or more units may be given in this way to serve the patient for 90 or more days, the procedure being repeated at these intervals. Alternatively in such cases, liver extract may subsequently be given at intervals of two weeks or less. If this is done, no further allergic reactions appear since this does not allow time for immune bodies to be built up in sufficient quantity to cause a reaction. As already mentioned, patients sensitive to liver extract have responded without trouble to vitamin B₁₂, and consequently it appears that this substance may be substituted for liver extract.

MEGALOBLASTIC MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA

Nutritional Macrocytic Anemia. This term refers to macrocytic anemia arising from dietary deficiency, as distinguished from deficiency resulting from lack of "intrinsic factor" or from faulty absorption. Since such anemia has been seen in the tropics, *tropical macrocytic anemia* is another synonym. The condition is particularly common in pregnant women. Weakness, shortness of breath, sore mouth, sore tongue, diarrhea, and edema are common complaints. In contrast to pernicious anemia, in nutritional macrocytic anemia achlorhydria is no more common than in the population in general, and degenerative changes in the nervous system are practically never found. The blood picture and bone marrow are indistinguishable from those of pernicious anemia. Dietary deficiency appears to be the cause of the anemia, which can be corrected by giving yeast, "Marmite" (autolyzed yeast), or liver. Highly refined liver extracts have not been effective in a number of cases; consequently the need for a factor (Wills's factor) other than that deficient in pernicious anemia has been postulated. In a few cases, however, a good hemopoietic

response to vitamin B₁₂ has been reported. In any event, whatever the pathogenesis of this disorder may be, it seems clear that, after successful treatment, the disease does not recur if the diet is satisfactory.

Much less often, such cases are encountered in *temperate zones*. Some of the instances of macrocytic anemia seen in *pellagra* can be accounted for by a lack of "extrinsic factor" in the diet. In other cases faulty absorption is important, and in many both mechanisms play a role. In *sprue* and in *idiopathic steatorrhea*, as described elsewhere (p. 539), inadequate absorption is the main cause for the development of macrocytic anemia. Macrocytic anemia occurring following *total gastrectomy* may be the consequence of lack of intrinsic factor. The pathogenesis of the macrocytic anemia seen in association with *intestinal strictures* and *anastomoses* has been attributed to impaired absorption or to the possible absorption of products which interfere with the utilization of liver extract.

The particular roles which anti-pernicious anemia liver extract and pteroylglutamic acid play in hemopoiesis are not clear. The various types of macrocytic anemia which may be classified as "megaloblastic" are listed in table 94 according to their response to these two therapeutic agents. Further study will be required to reveal why certain conditions are relieved by the administration of pteroylglutamic acid and crude liver but are not influenced by highly concentrated liver extract. The effects of vitamin B₁₂ appear to be similar to those of refined liver extract.

Although macrocytic anemia is seen in some cases of hypothyroidism, it is noteworthy that the bone marrow is hypoplastic and normoblastic, and desiccated thyroid, not liver extract, is effective in relieving the anemia. Likewise, the macrocytic anemia encountered in association with some cases of severe, chronic liver disease should not be classed with the "megaloblastic" macrocytic anemias, since the bone marrow is normoblastic and a response to liver extract therapy has been seen only in rare cases.

HEMOLYTIC ANEMIAS

MANIFESTATIONS

Under the heading of hemolytic anemias a number of conditions can be included which differ widely in etiology, symptomatology, severity,

and course. The symptoms depend upon the rapidity and extent of hemolysis, its duration, and whether or not hemolysis is taking place in the blood stream or in the reticuloendothelial system. Jaundice is a sign common to all, but its degree may be such as to be barely perceptible (when it is often overlooked) or so great as to be very striking. Other symptoms may be entirely absent. Thus patients with congenital hemolytic jaundice are "more yellow than sick" except when a hemolytic crisis occurs. There may be slowly progressive anemia and gradually increasing jaundice. The anemia may become profound and yet there may be few manifestations, since in such cases there is time for cardiovascular adjustments (p. 251) to be made. Splenomegaly is common and enlargement of the liver may be present. Complications such as gallbladder disease or chronic leg ulcers may develop.

On the other hand, the onset of hemolytic anemia may be heralded by a severe, shaking chill followed by high fever, malaise, headache, and pain in the back, abdomen, or limbs. The abdominal pain may be so severe and may be accompanied by such marked muscular rigidity and spasm as to simulate an acute surgical condition. If the hemolysis is rapid and severe enough, profound prostration and shock, accompanied by anuria and oliguria, may ensue. When urine is passed, it is found to be very dark. Jaundice develops rapidly. As anemia ensues, weakness, palpitation, dyspnea, tachycardia, cyanosis, cardiac enlargement, hemic murmurs, vertigo, faintness, and the other manifestations of rapidly developing anemia (Chapter 22) make their appearance. In certain types of acute hemolytic reactions, urticaria, vascular disturbances suggesting Raynaud's phenomena, and thrombosis and gangrene may develop.

All grades between such acute fulminating disorders of several days' duration and extremely benign conditions of many years' standing may be encountered. A chronic, congenital process may be interrupted by acute exacerbations.

Hematologic Manifestations. The hematologic manifestations which accompany acute blood destruction consist of an initial phase of rapid destruction of red corpuscles and a second phase of rapid blood regeneration. These two phases usually overlap, especially when the hemolytic agent acts over a prolonged period of time.

The anemia may be mild or severe, depending

upon the intensity and duration of the hemolytic process. It is usually normocytic but may be macrocytic, especially during the stage of rapid regeneration when many relatively immature and reticulated cells are present. It is not uncommon to find 10 to 25 per cent reticulocytes in chronic cases, and as many as 60 per cent or even more in acute cases. Polychromatophilia, nucleated red blood corpuscles, and Howell-Jolly bodies are usually present. There generally is marked variation in the size of the cells (anisocytosis) and usually little variation in their shape (poikilocytosis), except in patients with sickle-cell anemia.

Marked stimulation of the leukopoietic tissues, manifested by leukocytosis and a "shift to the left," with myelocytes and even rare myeloblasts, accompanies the red corpuscle regeneration. Platelets may increase in number, and large, bizarre forms may make their appearance. In certain cases, however, and especially in paroxysmal nocturnal hemoglobinuria, leukopenia and thrombocytopenia may be present.

The bone marrow is hyperplastic. There is a great increase in normoblasts and a consequent reduction in the leukocyte/erythrocyte ratio from the normal of 4 or 5:1 to about 1:1 or even less. The normoblasts are chiefly polychromatophilic and orthochromatic forms; as a rule there are not many pronormoblasts or basophilic normoblasts. Megaloblasts, so characteristic of pernicious anemia and related macrocytic anemias, are not present.

Pigment Metabolism. When the degree and rate of blood destruction are very great, hemoglobin is liberated into the plasma and, if the renal threshold is exceeded, hemoglobinuria occurs. Under certain circumstances hematin may be released. This compound unites with the plasma albumin to form methemalbumin. Because of rapid conversion of these two compounds into bilirubin, hemoglobinemia and methemalbuminemia are always associated with bilirubinemia. The finding of red urine must not be assumed to be necessarily indicative of hemoglobinuria. The color may also be produced by intact red corpuscles, porphyrin, or myoglobin. Microscopic and spectroscopic examination of the urine will reveal the cause of the abnormal color.

More often, blood destruction is less rapid. In such cases hemoglobinemia and hemoglobinuria

are not found and there is only an increase in the icterus index, serum bilirubin, and urobilinogen excretion in the urine and feces. The stools assume a dark color and from 300 to 4000 mg. of urobilinogen may be found in a 24-hour stool, as compared with the normal of 40 to 280 mg. The 24-hour urine may contain 5 to 200 mg. of urobilinogen (normal, 0 to 3.5 mg.). The fecal urobilinogen may be increased when the urine urobilinogen and the bilirubin in the blood are not significantly greater than normal.

The quantity of bilirubin in the plasma may rise as high as 10 mg. per cent. The reaction is indirect (T-1") but some increase in "one-minute" bilirubin may also occur. The intensity of the bilirubinemia depends not only on the extent of the blood destruction but also on the capacity of the liver to remove the pigment from the blood stream and excrete it in the bile. A normally functioning liver is capable of excreting large quantities of bilirubin, but, as anemia and consequent anoxemia develop, its functional capacity becomes impaired and bilirubin accumulates in the blood stream.

CLASSIFICATION

The hemolytic disorders may be classified in various ways, none of which is entirely satisfactory. A clinical classification based on the severity of the manifestations may be confusing since a chronic process may come to notice only during an acute exacerbation. Differentiation of congenital and acquired forms is useful. Better still, however, is classification on the basis of pathogenesis, even though understanding of the pathogenesis of the hemolytic anemias is still incomplete.

By transfusing corpuscles which differ from those of the recipient with respect to their MN or Rh type or by giving group O corpuscles to recipients belonging to one of the other three major blood groups, it has been shown that when normal corpuscles are transfused to patients in whom there is an extracorporeal cause for hemolysis, the donated corpuscles are destroyed as rapidly as the patient's own corpuscles. If, on the other hand, the patient's corpuscles are removed from their abnormal environment and transfused to a normal recipient, their survival time is normal. Hemolytic anemias which have been shown to be or are thought to be of this type are listed in group I of table 95. Group II includes disorders in which hemolysis is the result of a defect in the

subject's own red corpuscles. The patient's corpuscles, when given to a normal recipient, can be shown to be disposed of more rapidly than those of the recipient, while the latter's corpuscles, if transfused into the patient, maintain a normal "life span." It may be noted that, in the main, hemolytic anemias due to intracorporeal defects are familial and hereditary, while those produced by extracorporeal factors are "acquired."

Acute Hemolytic Anemias Due to Immune Body Reactions. The naturally occurring agglutinins α and β cause hemolysis when incompatible blood is given by transfusion. When hemolytic transfusion reactions take place in spite of A, B, and O blood group compatibility, they are attributable in most instances to the development of anti-Rh agglutinins. Such agglutinins are also responsible for the development of hemolytic disease of the newborn (*erythroblastosis foetalis*), a condition in which the red corpuscles of an Rh-positive fetus are destroyed as the result of the action of antibodies produced in the Rh-negative woman carrying the fetus.

Cold agglutinins have been observed in some cases of hemolytic anemia, both congenital and acquired. They are found most frequently, however, in atypical pneumonia, usually in the absence of hemolytic anemia. It is supposed that cold agglutinins may cause hemolysis *in vivo* when blood is cooled in the extremities of the body. In vitro, the mechanical fragility of agglutinated red corpuscles is increased. Cold hemolysins have been shown to be responsible for the hemolysis observed in paroxysmal cold hemoglobinuria, a disorder which will be discussed separately below. That warm hemolysins and that "univalent" or "blocking" antibodies may be responsible for excessive blood destruction in other cases is a reasonably good possibility.

Other Hemolytic Anemias, Presumably Due to Extracorporeal Causes. Not all instances of "acquired" hemolytic jaundice or of "atypical" hemolytic anemia have been demonstrated as being due to immune body reactions. Some ("symptomatic hemolytic anemias") are associated with other diseases, a few of which are listed in table 95. Others are obscure as to etiology. Such cases may be acute or chronic, are non-familial, and are often more severe than congenital hemolytic jaundice.

In addition to these, there are hemolytic anemias which can be attributed to well-recognized

Table 95
CLASSIFICATION OF HEMOLYTIC DISORDERS

I. EXTRACORPUSCULAR CAUSES:

- A. Acute hemolytic anemias due to immune body reaction:
 - 1. Isoagglutinins anti-A, anti-B (transfusion reactions)
 - 2. Isoagglutinins anti-Rh, anti-Hr (hemolytic disease of the newborn, "intragroup" transfusion reactions)
 - 3. Cold agglutinins
- B. Idiopathic hemolytic anemia without demonstrable hemolysins or agglutinins
- C. Secondary or symptomatic hemolytic anemias:
 - 1. Hodgkin's disease
 - 2. Leukemia
 - 3. Lymphosarcoma
- D. Infectious agents:
 - 1. Malaria
 - 2. *Bartonella* (Oroya fever)
 - 3. Septicemia: *Clostridium welchii*, *Streptococcus pyogenes*, *S. mitis*, *Escherichia coli*, pneumocoeci, staphylococci
- E. Chemical agents:

1. Phenylhydrazine	7. Toluene	13. Aniline
2. Allyl-propyl-disulfide	8. Lead	14. Phenol compounds
3. Saponin	9. Colloidal silver	15. Acetanilid
4. Lysolecithin	10. Arseniuretted hydrogen	16. Sulfonamides
5. Methyl chloride	11. Trinitrotoluene	17. Quinine
6. Benzene	12. Dinitrobenzene	
- F. Physical agents (heat—severe thermal burns)
- G. Vegetable and animal poisons:
 - 1. Vegetable poisons:
 - a. Fava bean (*Vicia faba*)
 - b. Castor bean (ricin)
 - 2. Animal poisons
 - a. Snake venoms

II. INTRACORPUSCULAR DEFECTS:

- A. Familial or congenital hemolytic jaundice
- B. Sickle-cell anemia
- C. Paroxysmal nocturnal hemoglobinuria
- D. "Mediterranean" anemia
- E. Atypical hemolytic anemias

infectious, chemical, or physical agents or to poisons of vegetable or animal origin, as shown in table 95. Certain agents, such as saponin, act directly on the red corpuscles. Others, of which phenylhydrazine is an example, have an indirect effect. Still others, such as sulfanilamide, depend for their action on an abnormality of the host ("sensitivity").

Intracorpuscular Defects. A number of the disorders coming under this head will be described separately below. "Mediterranean" anemia will be discussed later (p. 1199). While evidence of increased blood destruction is found in this disorder, this does not appear to be the primary or most important defect. The same is true of pernicious anemia, which was once grouped among the hemolytic anemias.

MECHANISMS OF HEMOLYSIS

Various processes condition or cause the destruction of red corpuscles in the body: phago-

cytosis, hemolysins, osmotic lysis, mechanical factors, and "erythrostasis." The importance of phagocytosis is not clear. Some regard this as a primary and important factor, while others relate it to an accessory role dependent on other mechanisms of red corpuscle destruction. Various types of hemolysins have been described, as already mentioned. Immune hemolysins are not found free in the serum except in disorders which require special conditions for their maximum operation. Thus in paroxysmal cold hemoglobinuria a fall in temperature is required for maximum activity of the hemolytic system, while in paroxysmal nocturnal hemoglobinuria a fall in the pH of the blood is necessary. In most instances immune hemolysins remain attached to the red corpuscle. The Coombs or "developing" test serves to demonstrate such factors.

The role of mechanical factors is indicated by the fact that the osmotic and mechanical fragilities of the red corpuscles increase when the cor-

puscles are placed in natural or artificial immune serums in which hemolysins and agglutinins are present. Similar changes in fragility have been observed in association with the action of hemolytic agents such as saponin or physical factors such as heat. Osmotic lysis, usually determined by the familiar hypotonic saline fragility test, probably does not operate *in vivo* except perhaps in the spleen under certain conditions. It is a plausible hypothesis that mechanical trauma is the ultimate mechanism whereby cell destruction occurs under normal circumstances and in many varieties of hemolytic anemia. It has been shown that nearly spherical cells, strongly agglutinated cells, and those with weakened cell membranes are abnormally susceptible to mechanical destruction. In certain cases of acquired hemolytic jaundice, increased mechanical fragility has been observed when osmotic fragility was normal. It was found that such cells did not survive normally in the circulation of normal individuals. The increased mechanical fragility of sickled masses of erythrocytes may explain the increased red corpuscle destruction in sickle-cell anemia.

The term *erythrostasis* has been applied to the processes to which red corpuscles are subjected when denied free access to fresh plasma. The spleen appears to have the property of selectively removing and concentrating spheroidal cells. Erythrostasis may lead to increased osmotic and mechanical fragility of the red corpuscles and thereby favor their destruction. It has been suggested that the spleen is of importance in congenital hemolytic jaundice because of the inherently abnormal susceptibility of the red corpuscles to the effects of erythrostasis. It has been demonstrated in a patient with congenital hemolytic jaundice who had received transfusions of identifiable normal corpuscles, that the spleen, removed at operation, had selectively retained the patient's own corpuscles. Perfusion experiments have shown that even the spleen from a case of purpura hemorrhagica, where no hemolytic process existed, likewise selectively removed transfused red corpuscles from cases of congenital hemolytic jaundice but did not retain normal corpuscles.

STUDY OF A PATIENT WITH A HEMOLYTIC DISORDER

Hemolytic anemia can be recognized by the development of certain symptoms and signs, cer-

tain changes in the blood and bone marrow, and characteristic alterations in pigment metabolism, as outlined already. The differentiation of the various hemolytic disorders is important since treatment depends on their nature. The history alone may suffice to reveal an etiologic agent or may indicate that one is dealing with one of the familial or hereditary disorders. Physical examination may reveal one of the conditions of which hemolytic anemia can be symptomatic. In addition, certain simple tests have been devised which give some clue to the nature of the disorder.

1. Osmotic Fragility Test. In certain cases of hemolytic anemia one demonstrates by this test the susceptibility of red corpuscles to hemolysis in concentrations of salt which fail to cause rupture of normal corpuscles. Such osmotic fragility is characteristic of corpuscles which are more nearly spherical than normal corpuscles. The test is generally positive in congenital hemolytic jaundice and negative in acquired forms. Unfortunately, however, there are exceptions to this statement. Spherocytosis and increased osmotic fragility are encountered in certain acquired cases. The sensitivity of the test can be increased by first incubating the corpuscles to be tested *in vitro* at body temperature for 24 hours. Under such conditions the fragility of normal corpuscles is increased slightly; that of corpuscles from cases of congenital hemolytic jaundice is increased markedly.

2. Mechanical Fragility Test. A small amount of oxalated or defibrinated blood is placed in an Erlenmeyer flask containing glass beads, and rotated, following which the hemoglobin liberated from the cells is measured and compared with controls. Increased mechanical fragility has been observed in congenital hemolytic jaundice, in sickle-cell anemia, and in the presence of cold agglutinins and isoagglutinins after agglutination of the cells in the cold, as well as in a few cases of atypical hemolytic anemia in which osmotic fragility was normal or decreased.

3. Serologic Tests. A simple presumptive test is performed by placing washed red corpuscles from fresh defibrinated blood in each of three test tubes. The first is incubated for one to two hours at body temperature and then centrifuged. If hemoglobin is present in the supernatant serum, the presence of a *warm hemolysin* is suggested. The second tube is chilled for 20 minutes in cracked ice, then incubated for one hour and

centrifuged. If results are positive, the presence of a *cold hemolysin* is indicated. The test tube should be examined before it has been warmed. If only *cold agglutinins* are present and no hemolysins, it will be seen that the red corpuscles agglutinate in the cold but fail to hemolyze when the tube is warmed, the clumps disappearing instead. When *cold agglutinins* are present, one must be careful not to shake the cells too much while they are agglutinated in the cold, since they may hemolyze and give a false *cold hemolysin* test. The blood placed in the third tube is acidified with carbon dioxide. If hemolysis is apparent after incubation for one hour and subsequent centrifugation, *increased acid hemolysis* is suggested. This test is positive in paroxysmal nocturnal hemoglobinuria.

When positive results are obtained in any one of these tubes, the test should be repeated with adequate controls and by the more complete procedures which have been described. Thus, if a *cold hemolysin* appears to be present, the Donath-Landsteiner test should be carried out.

A test for "incomplete" ("blocking") or "univalent" antibodies may also be desirable. "Incomplete" antibodies are so called because they alone are incapable of causing visible clumping of red corpuscles. When a serum containing this type of antibody is mixed with corpuscles with which the antibodies react, agglutination will not occur if the diluent is saline, but if the diluent is plasma, serum, or concentrated albumin solution, clumping of the corpuscles may occur. If this method fails, the "developing" or *Coombs test* is useful. This test employs serum from rabbits immunized to human gamma-globulin or whole serum. The sensitized red corpuscles of patients with certain types of acquired hemolytic anemia will be agglutinated by this antiserum even after thorough washing. This occurs, presumably, because the antibody globulin is adsorbed to their surfaces. It has been shown that the spleen is a source of this substance. The Coombs test is important because serum from certain cases may contain no demonstrable agglutinins or hemolysins. Various modifications of this test are being developed.

PROGNOSIS AND TREATMENT

Prognosis and treatment depend on the nature and cause of the hemolytic disorder. The causative agent, such as a parasite or chemical, if dis-

covered, must be removed. An acute attack of hemolysis requires rest, maintenance of fluid balance, and relief of pain. Blood transfusion may be dangerous if the cause of the hemolysis is extracorporeal and still operating, for then the introduced blood may also be destroyed. Yet the possibility of death from circulatory collapse is so great when blood destruction is so acute that hemoglobinemia and hemoglobinuria are present, that frequent and sometimes massive blood transfusions must be given. However, the greatest care must be used in matching the bloods, and only entirely compatible bloods should be employed. Examples of the value of transfusion are seen in severe burns and in hemolytic disease of the newborn. Splenectomy carries a mortality of as much as 40 per cent in such cases and therefore should be considered only if blood transfusions fail. The desperate state of these patients makes it most difficult to evaluate therapeutic procedures.

Splenectomy is almost invariably beneficial in congenital hemolytic jaundice, and may produce dramatic results in certain "acquired" and "atypical" cases, especially in the more chronic forms. Splenectomy is of no value, however, in sickle-cell anemia, "Mediterranean" anemia, or paroxysmal nocturnal hemoglobinuria.

CONGENITAL HEMOLYTIC JAUNDICE

(Chronic Acholuric Jaundice, Spherocytic Anemia, Chronic Familial Icterus)

Definition. This is a familial and hereditary disorder characterized by spherocytosis, increased osmotic fragility of the red corpuscles, splenomegaly, and a variable degree of hemolytic anemia.

History. Chiefly as the result of the observations of the French school, during the early part of the present century the familial disorder was clearly defined, becoming known as the type of Chauffard and Minkowski, and was distinguished from the acquired form of hemolytic anemia of Hayem and Widal.

Etiology. Transmitted as a Mendelian dominant by either parent, this disorder is due to an inherited defect of the red corpuscles, which tend to be more spheroid than normal and thus are more subject to destruction. The significance of spheroidicity of the red corpuscles and of increased osmotic fragility and the role of the spleen have been discussed already (p. 1194).

Morbid Anatomy. The spleen is greatly enlarged, often weighing 1000 to 1500 Gm. The pulp and, to a lesser extent, the sinuses are greatly congested. Depending on the degree of anemia and the extent of blood destruction, hyperplasia and even metaplasia of the bone marrow occur, and deposits of iron pigment are found in the liver, kidneys, and even lymph nodes.

Symptoms. Jaundice and splenomegaly are the most common manifestations and may pass unnoticed for many years. A persistent sallow appearance rather than obvious jaundice may be present. Symptoms of anemia are usually absent or mild. At any time from birth to late adult life, attention may be drawn to the disorder by the "*crise de déglobulisation*" which is characterized by fever, lassitude, palpitation and shortness of breath or even violent abdominal pain, vomiting, and anorexia. Rather than being episodes of increased blood destruction, as has always been assumed, these crises have been observed by several investigators to be associated with sudden temporary cessation of blood formation. Since the "life span" of the red corpuscles of congenital hemolytic icterus is very brief, anemia develops rapidly under these circumstances. It remains to be shown how often such a mechanism, rather than hemolysis, is the cause of the crises which occur in this disease. It has been suggested that both mechanisms play a role and that both are manifestations of "hypersplenism."

The liver may or may not be enlarged. Developmental anomalies are often present. A chronic leg ulcer may be found. Cholelithiasis is a frequent complication, and symptoms due to this cause may first bring the patient to the physician.

The anemia is usually moderate in degree, but may be very mild or severe. It is normocytic or simple microcytic in type but, when severe and associated with marked reticulocytosis, it can be macrocytic. There is little poikilocytosis, but small, bright, deeply staining red corpuscles (spherocytes) are often seen scattered among the cells of normal size. Reticulocytes are characteristically increased in number, most often numbering 5 to 20 per cent. Polychromatophilia and normoblasts may be seen in the blood smear. The leukocytes are usually normal in number or slightly increased. The platelet count is generally normal.

Increased osmotic fragility of the red corpuscles is characteristic. Hemolysis beginning at

0.64 per cent saline solution is not unusual and may be complete at the point where hemolysis normally begins.

Bilirubinemia of the "indirect" type and increased quantities of urobilinogen in the urine and stools, without bile in the urine ("acholuric"), are the characteristic changes in pigment metabolism.

Diagnosis. Splenomegaly, icterus of the hemolytic type, reticulocytosis, increased osmotic fragility, and a positive family history form a characteristic picture. When the picture is not entirely typical, a careful study to rule out other types of hemolytic anemia must be made, as outlined previously.

Treatment. This is the one disorder in which splenectomy is associated with consistently satisfactory results. The operation is indicated in every patient in whom clinical manifestations are present. Although remissions develop and latent periods of many years' duration may occur, spontaneous recovery does not take place. At operation, a careful search should be made for accessory spleens, and these should be removed if found. Following operation, anemia, jaundice, and reticulocytosis disappear. The osmotic fragility of the red corpuscles, however, as well as the spherocytosis, may persist.

During a crisis, repeated blood transfusions must be given.

SICKLE-CELL ANEMIA

Definition. This is a hereditary and familial hemolytic anemia, essentially peculiar to Negroes and characterized by the presence of red corpuscles which, under appropriate conditions, assume sickle-shaped or oat-shaped forms.

Etiology and Pathogenesis. Just as congenital hemolytic jaundice is rare in the Negro, sickle-cell anemia is extremely rare except in Negroes or when mixture with Negro blood has occurred. The anomaly appears to be inherited as a Mendelian dominant. Two forms, which appear to be distinct from one another, have been observed: the sickle-cell trait, which is not accompanied by symptoms or by anemia; and sickle-cell anemia, which possesses all the characteristics of a chronic hemolytic anemia.

The fundamental defect is in the red corpuscle. The sickled shape is assumed in an atmosphere deprived of oxygen and is favored by lowering of pH. The cause of the hemolysis is obscure. It

seems likely that conditions producing anoxemia and stasis favor sickling and increase the mechanical fragility of the red corpuscles, but this remains to be proved.

Pathology. In addition to the signs of a chronic hemolytic anemia (normoblastic hyperplasia of the bone marrow, hemosiderosis), evidence of thromboses, infarction, necrosis, or hemorrhage may be present, especially in the lungs, spleen, and nervous system. The spleen may be shrunken to a tiny, wrinkled mass.

Symptoms. Jaundice and a chronic anemia with few or no complaints are interrupted by periods of increased weakness, episodes of aching pain in the joints or elsewhere in the extremities, or sudden attacks of severe abdominal pain which have often been mistaken for ruptured peptic ulcer, intestinal obstruction, or some other abdominal emergency.

The victims of sickle-cell anemia are often poorly developed, and bony deformities of various types may be discovered. The scleras are icteric and there may be slight general glandular enlargement, but splenomegaly is encountered in only about 15 to 20 per cent of cases. The heart may be enlarged and the physical signs may closely simulate those of mitral stenosis due to rheumatic fever. In many instances chronic leg ulcers are found over the internal or external malleoli. Roentgenograms may reveal radial striation in the skull, osteoporosis in the vertebral bodies, or other changes in the long bones.

The anemia is usually surprisingly severe, erythrocyte counts below 2.5 million being common. The anemia may be normocytic or macrocytic. Oval, cigar-shaped, or other bizarre forms of red corpuscles may be seen in the stained blood smear. The sickling is brought out clearly in wet films of blood which have been fixed under a cover glass and sealed with paraffin. In cases with sickle-cell anemia the typical sickled and oat-shaped forms with elongated, pointed filaments appear within a few hours. When only the sickle-cell trait exists, 24 hours is often required to produce this change and only a proportion rather than practically all of the cells are affected. By the use of reducing agents such as sodium bisulfite, sickling can be hastened and the characteristic forms appear promptly.

In sickle-cell anemia, reticulocytosis, polychromatophilia, normoblasts, leukocytosis with "shift to the left" in the myeloid series, and an

increase in platelets are found as well as hyperbilirubinemia and increased urobilinogen in the urine and stools. Osmotic fragility is decreased, not increased. The bone marrow shows striking normoblastic hyperplasia.

Diagnosis. Sickle-cell anemia is often mistaken for some other disease. Rheumatic fever, peptic ulcer, renal or biliary calculus, osteomyelitis, and various neurologic disorders may be simulated. Recognition depends on the demonstration of sickling and the finding of anemia of the hemolytic type.

In distinguishing persons with the sickle-cell trait who may have some disorder accompanied by anemia from those who have sickle-cell anemia, it must be kept in mind that the former may develop any type of anemia while in the latter the anemia is always hemolytic in type.

Treatment. There is no satisfactory treatment. Splenectomy is of no value. Blood transfusion may be helpful in the abdominal crisis if shock is present. The disease is ultimately fatal, often before the age of 30.

PAROXYSMAL (COLD) HEMOGLOBINURIA

This is an uncommon disorder characterized by the sudden passage of hemoglobin in the urine following local or general exposure to cold. Aching and pain in the back, legs, or abdomen, and other symptoms of acute hemolysis such as a chill, fever, and malaise, are associated with the passage of dark, brownish urine. Other findings are those characteristic of acute hemolytic anemia. Symptoms may appear at any time from a few minutes to seven or eight hours following exposure.

Donath and Landsteiner showed that the hemoglobinuria is due to the sudden intravascular hemolysis of blood as the result of the action of an autohemolysin contained in the patient's blood. The hemolysin unites with the red corpuscles only at a low temperature, but destruction of the corpuscles occurs only after the temperature of the blood has returned to body temperature. Appropriate tests have been devised to demonstrate such a cold hemolysin. With few exceptions, paroxysmal hemoglobinuria is a manifestation of syphilis, especially the congenital form. In such cases thorough antisyphilitic therapy ends the clinical manifestations.

CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

(Marchiafava-Micheli Syndrome)

This is a rare disorder of insidious onset which is characterized by signs of hemolytic anemia and is marked by attacks of hemoglobinuria which occur chiefly at night. The symptoms are those of long-standing anemia, but there may be abdominal, lumbar, or substernal pain, which often ushers in an attack of hemoglobinuria. The findings are similar to those in other hemolytic anemias and include splenomegaly and well-marked anemia. The osmotic fragility of the red corpuscles is normal. There may be hemoglobinemias even when there is no hemoglobinuria. Leukopenia is usual and may be marked, and there may be thrombocytopenia. The urine contains increased amounts of urobilinogen as well as hemoglobin. Hemosiderin can often be demonstrated in the leukocytes or epithelial cells of the urine.

The fault appears to reside in the red corpuscles, which are unusually susceptible to acid hemolysis. A simple test for this has been described already (p. 1194). It has been suggested that the destruction of the cells is promoted by the accumulation of carbon dioxide during sleep. The cause of the disorder is unknown and its treatment is purely symptomatic. Splenectomy is of no value. The transfusion of saline-washed cells in these patients does not appear to precipitate hemolytic reactions. The transfusion of plasma may do so. A fatal termination ensues in three to six years as a rule, but sometimes the disorder is compatible with life for many years.

ANEMIAS ASSOCIATED WITH INFECTIONS AND VARIOUS OTHER DISORDERS, CHIEFLY CHRONIC

In the preceding sections, anemia resulting from blood loss, as well as anemias due to excessive blood destruction and those associated with deficiency of certain factors concerned in erythropoiesis, were discussed. The characteristics of these anemias are, in the main, well defined, and much has been learned in recent years about their pathogenesis. The hemolytic anemias and the specific nutritional deficiency anemias are, however, relatively uncommon. Far more frequent in occurrence and yet much less well understood are

the anemias associated with various chronic disorders and with infection. Such anemia is usually only moderate in degree: hemoglobin values of 13 to 10 Gm. per 100 ml. of blood are seen more frequently than lower values. The anemia is usually normocytic, and in the smear the red corpuscles generally show little abnormality in size or shape, a monotonous picture unaccompanied by polychromatophilia, basophilic stippling, or nucleated red corpuscles. Exceptions are found in *lead poisoning*, where basophilic stippling is characteristically seen; in the so-called *myelophthisic anemias*, such as those associated with metastases to the bone marrow, leukemia, multiple myeloma, or myelosclerosis; and in severe *renal disease*. There, often corresponding rather closely to the gravity of the renal disorder, hemoglobin values down even to 5 Gm. per 100 ml. are found, and the blood smear may reveal normoblasts, stippling, and moderate anisocytosis and poikilocytosis. The anemia may be somewhat microcytic or hypochromic, and occasionally is macrocytic. If the renal disease has been insidious in onset and is chronic in type, the clinical manifestations and the anemia may be quite confusing unless one is aware of the fact that striking degrees of anemia may be encountered in the absence of impressive signs of renal disorder.

The *bone marrow* in these conditions shows nothing characteristic. The nucleated red corpuscles are of the normoblastic type. The marrow may appear hyperplastic, normal, or hypoplastic. Hyperplasia of the leukopoietic tissue is found if the disorder is one which calls forth a leukocytic response.

The *pathogenesis* of the anemia in these conditions is not clear. Perhaps a variety of mechanisms can and do lead to the same morphologic consequences. On the other hand, it is plausible to think of the anemia in these disorders as being the result of some fault in the construction of red corpuscles, as distinguished from anemia due to a lack of building substances or to excessive destruction. In association with *infection*, it has been observed, as already indicated elsewhere (p. 250), that there is a partial failure in the synthesis of hemoglobin which is accompanied by a disturbance in the metabolism of iron. The impact of infection on erythropoiesis is such that no form of antianemic therapy, such as the administration of liver extract or of iron, has any influence. The anemia disappears spontaneously, how-

ever, if the infection is successfully treated or subsides as the result of the defense reactions of the host. Speaking broadly, the anemia of infection appears to be part of a reaction to injury and is only one manifestation of a widespread systemic disturbance (see Chapter 33).

The anemia of *renal disease* differs in some respects from that associated with infection. Thus, for example, hypoferremia is not a constant feature. Again, the anemia may be much more severe than that seen in infection, and is correlated to some degree with the retention of nitrogenous and other waste products. Like that of infection, however, the anemia of renal insufficiency is closely tied with the underlying disorder and is uninfluenced by measures other than those which affect renal function.

Malignant disease is not necessarily accompanied by anemia. Whether certain types of malignant disease impair erythropoiesis by a means comparable with the effects of infection or chronic renal disease is not clear. Anemia accompanies malignancy in the alimentary tract more often than elsewhere. In such cases nutritional deficiency may play an important role in the pathogenesis of the anemia, and in many cases blood loss is also a contributory factor. Malignant disease of the kidneys, breast, prostate, thyroid, and lungs, in particular, may metastasize to bones, and in such an event "*myelophthisic*" anemia may develop. The picture then may be that of a pancytopenia (see p. 1212), or a leukemoid picture may result. The latter is marked by leukocytosis together with a moderate "shift to the left" in the leukocytic formula, and normocytic anemia. When a number of nucleated red corpuscles also appear in the peripheral blood, as they sometimes do, the term "*leukoerythroblastic*" anemia appropriately describes what is found.

Endocrine insufficiency may be associated with anemia. Hypothyroidism is often accompanied by anemia of moderate degree. This is usually normocytic, but can be macrocytic (p. 1190). Slight or moderate anemia, usually normocytic, is found in Addison's disease and in pituitary insufficiency (Simmonds' disease).

As already described, the anemia of *iron deficiency* is hypochromic microcytic in type, and that due to lack of anti-pernicious anemia principle and related substances is macrocytic. *Protein deficiency* is characterized by the presence of

normocytic anemia. Deficiencies of the various B vitamins are rarely encountered in man in pure form. Multiple nutritional deficiencies are associated, as a rule, with only moderate anemia, usually normocytic in type.

MEDITERRANEAN ANEMIA

(Cooley's Anemia, Erythroblastic Anemia, Thalassemia, Target-Cell Anemia, Familial Microcytic Anemia)

Definition. An inherited disorder seen particularly in individuals residing in countries bordering the Mediterranean or in their offspring elsewhere, which is characterized by the presence of unusually thin red corpuscles, microcytosis, various degrees of anemia, and, when the anemia is severe, numerous nucleated red corpuscles.

History. Cooley and Lee (1925) described a chronic progressive anemia commencing early in life, which was associated with a characteristic facies, splenomegaly, and a familial and racial incidence. Later it became clear that this was the severe and fatal form of a disorder which in milder form is seen in adolescence and in adults.

Etiology. Those affected have been chiefly of Italian, Greek, Syrian, or Armenian parentage. In certain communities of Italians, the anomaly has been observed in as many as 4 per cent of those examined. In other groups few or no cases have been found. The disorder is probably due to the inheritance of a factor which leads to an anomaly of red corpuscle production. When this is heterozygous, the effect is slight and often overlooked (thalassemia minor). When it is homozygous—that is, when inherited from both parents—the result is a severe and usually fatal anemia (thalassemia major).

Symptomatology. The full-blown disorder (*Thalassemia major*, *Cooley's anemia*) develops insidiously within the first year or two of life, perhaps at birth, and is marked by pallor and great enlargement of the spleen and often of the liver. The appearance of the child is often "Mongoloid." Roentgenograms reveal great thickening of the diploë of the skull with perpendicular striation, increase in the medullary portion of the long bones with thinning of the cortex, and other changes attributable to the extreme hyperplasia of the bone marrow. Anemia is severe, hypochromic and microcytic in type, and the red corpuscles contain so little pigment and are so thin

that their "buckling" produces forms which have the appearance of targets. Fragility tests in hypotonic saline solutions reveal that the corpuscles are unusually resistant to hemolysis by this means. Normoblasts and microblasts, as well as polychromatophilia, basophilic stippling, Howell-Jolly bodies, and moderate reticulocytosis, in addition to leukocytosis (19,000 to 25,000 per cu. mm.) with "shift to the left," reflect the myeloid hyperactivity. There is usually slight or moderate bilirubinemia, with a corresponding increase in the urobilinogen content of the urine and stools.

Thalassemia minor, on the other hand, may pass entirely unnoticed, since painstaking examination may be necessary to reveal any abnormality. Slight anemia, splenic enlargement, microcytosis and hypochromia, "target" cells, poikilocytosis out of proportion to the existent anemia, decreased hypotonic saline fragility, basophilic stippling of the red corpuscles, and bilirubinemia are some of the signs which, singly or in various combinations, mark this disorder. Roentgenographic changes in the bones, similar though less pronounced than those found in the severe form, may be observed.

Diagnosis. Plumbism, congenital hemolytic jaundice, and sickle-cell anemia are among the disorders which must be distinguished on the basis of the characteristics already described.

Prognosis. The severe form is fatal and seems to be more grave the earlier it becomes manifest. Less severe forms are compatible with life, and the mildest forms may even have no influence whatever on life span.

Treatment. This is the only form of hypochromic microcytic anemia in man which does not respond to iron therapy. Splenectomy is of no value, nor are any other measures now known.

Pathology. Evidences of pronounced myeloid hyperplasia, both medullary and extramedullary, the effects of such changes on the bones, and deposits of iron-containing pigment in the liver, pancreas, and other tissues are the most significant findings.

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Erythremia (Polycythemia Rubra Vera, Splenomegalic Polycythemia, Vaquez' Disease, Osler's Disease)

M. M. Wintrobe

Definition
History
Etiology and Pathogenesis
Pathology
Symptomatology

Blood
Other Laboratory Findings
Diagnosis
Course and Complications
Treatment

Definition. Erythremia is a disease of unknown etiology and of insidious onset and slow, chronic course, which is characterized by a striking ab-

solute increase in the quantity of circulating red corpuscles and, often, by evidence of increased production of myeloid leukocytes and even of

platelets. Splenomegaly and a red "cyanosis" of the skin, as well as increase in the viscosity of the blood and in the total volume of the blood, are additional features of this disorder.

History. Vaquez in 1892 described a case of polycythemia which he had originally attributed to congenital heart disease. Osler gave a more complete description in 1903.

Etiology and Pathogenesis. None of the recognized causes of erythrocytosis, already discussed in Chapter 12 (p. 140), appears to play a role in this disorder. It appears usually in middle or late life and has been seen more often in Jews than in other racial groups. Familial cases have been described.

Since oxygen want is known to produce polycytemia, anoxemia of the bone marrow has been proposed as the fault underlying the development of erythremia. This hypothesis ignores the fact that the increase in red corpuscles is but a part of a generalized myeloid hyperplasia which may be manifested in leukocyte counts as high as 60,000 per cu. mm. and an increase in platelets. A close relationship to chronic myelocytic leukemia is suggested by such cases. A failure of hemopoietic balance can also be postulated but, unfortunately, the factors which regulate and maintain the blood at "normal" are unknown.

Pathology. The striking changes are those related to the increase in total blood volume. All the organs are engorged with blood, the veins stand out like "bunches of thick worms," and there may be thromboses or anemic infarcts. The bone marrow is dark red in color and very cellular. Microscopically, this is found in most instances to be due to hyperplasia of all the marrow elements. In some cases the percentage of normoblasts is increased, in others the proportions of myelocytes and myeloblasts or of basophilic and eosinophilic cells may be greater than normal.

The spleen is enlarged, chiefly from hyperplasia of the pulp and distention with blood. Infarcts are common. There may be foci of extra-medullary blood formation in the spleen, the liver, and occasionally elsewhere as well. Cirrhosis of the liver has been observed in a number of instances.

Symptomatology. The onset is insidious and the progress gradual. Headache, dizziness, ringing in the ears, or visual disturbances; dyspnea, lassitude, or weakness; skin or mucous membrane hemorrhages; a sense of weight in the

abdomen due to the enlargement of the spleen; or irritability, depression, forgetfulness, or vague symptoms suggesting neurasthenia, are complaints which are encountered in many cases. Various gastrointestinal symptoms such as fullness, belching, or constipation may be present, or symptoms of peptic ulcer may be found. Sometimes the symptoms are those attributable to increased metabolism: lassitude, increased sweating, and loss of weight. Swelling and pain in the extremities may be very troublesome.

The color of the face is a deep red rather than truly cyanotic, and the color is most noticeable in the lips, cheeks, tip of the nose, ears, and neck. The distal portions of the extremities may be more truly cyanotic since the highly viscous blood circulates more sluggishly there than is normal. Ecchymoses are common, and epistaxis and bleeding of the gums are frequently encountered. Cardiac abnormality is unusual, but vascular disturbances are common. These include venous thromboses, coronary thrombosis, and cerebrovascular accidents. The blood pressure is more often normal than elevated. Enlargement of the liver is frequent and splenomegaly is found in at least 75 per cent of cases. The spleen may be just palpable but it may even extend to the pelvic brim.

Blood. Erythrocyte counts of 7 to 10 million cells per cu. mm. are common. Unless hemorrhage has occurred or venesections have been performed, there is a corresponding increase in hemoglobin and in volume of packed red corpuscles. The individual red corpuscles appear normal, although occasional polychromatophilia or basophilic stippling may be noted. The finding of nucleated red corpuscles and the appearance of small numbers of myelocytes and even earlier forms in the blood give a clue to the hyperplastic state of the bone marrow; leukocytosis, sometimes to marked degree (60,000 per cu. mm.), due to an increase of the myeloid cells, and high platelet counts, when present, give further evidence of overactivity. The percentage of reticulocytes is not increased unless there has been recent bleeding. The osmotic fragility of the red corpuscles is not significantly altered. There may be some evidence of increased blood destruction, in the form of slight bilirubinemia and increased excretion of urobilinogen. The viscosity of the blood is greatly increased, even five- to tenfold. The thick, sticky blood may be slow to coagulate

and the clot may not retract. Bleeding and clotting times are usually normal, however.

The total blood volume is substantially increased (150 to 300 per cent of normal), due entirely to an increase in red corpuscle mass.

Other Laboratory Findings. These include increased basal metabolic rate in many cases; normal, increased, or reduced gastric secretion, even achlorhydria; and normal urine or slight proteinuria.

Diagnosis. The symptoms of erythremia alone may suggest a variety of disorders but, once the blood has been examined, the problem is to differentiate secondary forms of polycythemia (erythrocytosis) from the "primary" disorder. Failure to discover a cause for the polycythemia, and the presence of a reddish rather than bluish cyanosis favor the diagnosis of erythremia. Splenomegaly is very unusual in erythrocytosis, even when the erythrocyte count is very much increased. What is more, in the latter condition, leukocytosis, immature leukocytes, and an increase in the platelet count are hardly ever found and normoblasts are much more uncommon in the blood than in erythremia. The measurement of total blood volume is rarely necessary for diagnosis, since relative polycythemia is usually recognized readily if the patient is examined thoroughly and is observed for a short time, the factors leading to a reduction in plasma volume being usually quite obvious as well as temporary in character; erythrocytosis, like erythremia, is associated with an absolute increase in red corpuscle mass.

Course and Complications. Barring the development of serious complications, the course of erythremia is chronic and the disorder is often compatible with many years of life. The most dangerous complications are vascular: thrombosis or hemorrhage. Therapy, by keeping the red corpuscle mass at a nearly normal level, can effectively reduce blood viscosity, and thus serves to reduce the likelihood of such vascular accidents. Intercurrent infections, especially of the respiratory tract, may be troublesome, and bronchitis and emphysema may develop. Duodenal ulcer, cirrhosis of the liver, or hypertension may occur. Gout is a rare complication. The appearance of typical chronic myelocytic leukemia in occasional cases of erythremia has given support to the view that there may be a close relationship between these two disorders.

Treatment. Treatment is symptomatic, since the cause of erythremia is unknown. Symptomatic relief is best achieved by reducing the red corpuscle mass to something approaching normal. This is most quickly achieved by *venesection*. Approximately a pint of blood is removed twice a week or even more often, until the volume of packed red corpuscles approaches normal. Then the procedure may need to be repeated only once a month or less often. *Phenylhydrazine hydrochloride* may be used to destroy the red corpuscles, but it is best first to use venesection to lower the blood level to normal, subsequently giving only enough of the hemolytic agent to maintain the blood at normal. For this purpose 0.1 Gm., in capsules, once a day, every other day, or every third day should be adequate. The use of such small doses will avoid complications of phenylhydrazine therapy such as thrombosis and acute hemolytic anemia. This drug should not be used in bedridden patients or in those who have thrombosis already.

Instead of removing or destroying the excessive red corpuscles, hemopoiesis may be inhibited by irradiation or by nitrogen mustard therapy. The effects of *irradiation* are slow to appear, however, and consequently venesection must be used at the same time initially. The intravenous injection of radioactive phosphorus (P^{32}) is more satisfactory than roentgen therapy. The procedure depends on the fact that the radioactive phosphorus passes to tissues which have a high phosphorus content. The concentration of P^{32} in the bones places this agent in a strategic position. An effect may not be observed for 30 to 60 days but, once the correct amount has been determined, the management of erythremia by this means becomes very simple. *Nitrogen mustard* is likewise given intravenously, a dose of 0.1 mg. per kg. of body weight, repeated two or three times, being the usual amount. This or smaller quantities are repeated at intervals, as necessary. With both irradiated phosphorus and nitrogen mustard, the possibility of producing leukopenia and thrombocytopenia must be kept in mind and the blood should be examined at intervals of one or two weeks or longer. Nitrogen mustard therapy may be accompanied by temporary nausea and vomiting. Following external irradiation, a similar effect may be produced, whereas, after the administration of P^{32} , irradiation sickness does not occur.

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The Purpuras

M. M. Wintrobe

Definition
Thrombocytopenic Purpura
Definition
History
Etiology and Pathogenesis
Symptomatology
Blood and Bone Marrow Findings
Diagnosis
Treatment and Prognosis
Nonthrombocytopenic Purpuras
Allergic Purpura
Hereditary Hemorrhagic Diathesis

Definition. The term *purpura* refers to extravasations into the skin or mucous membranes. These may vary from the size of a pin point or slightly bigger (petechiae) to much larger areas (ecchymoses). Purpura is but one manifestation of abnormal bleeding, a subject which has been discussed already (p. 260).

THROMBOCYTOPENIC PURPURA

Definition. This term refers to purpura which is accompanied by a significant reduction in the platelet count. There is at the same time prolongation of bleeding time, a positive tourniquet test, and poor clot retraction, but the coagulation time and prothrombin time are normal. The purpura may be *essential* or *primary*, this also being known as *purpura hemorrhagica* or *Werlhof's disease*; or it may be symptomatic: the effect of various chemical, vegetable, animal, or physical agents, the accompaniment of certain infections, or a part of the picture of various blood disorders.

History. Werlhof, in 1735, distinguished purpura hemorrhagia as an entity distinct from the purpura manifestations of various pestilential fevers and differing from other hemorrhagic disorders. Denys noted the thrombocytopenia in

1887, while Kaznelson proposed treatment by splenectomy in 1916.

Etiology and Pathogenesis. Purpura hemorrhagia occurs most frequently in children and in young adults, and is somewhat more common in the female than in males. No more than 10 per cent of cases begin after the age of 40. Not infrequently there is a family history of excessive bleeding. The condition is rare in Negroes.

The cause is obscure. Although there is thrombocytopenia, the number of megakaryocytes in the bone marrow is normal or may even be increased. Morphologic abnormalities may be seen in these cells, however, and, in contrast to the normal picture, few or no platelets are seen about their margins. Such findings suggest that there is a primary qualitative fault in the production of platelets by the megakaryocytes (Plate II). That the spleen may liberate a substance which has this inhibitory effect is suggested by the improvement following splenectomy in many cases. The influence of splenectomy has also led to the hypothesis that the disease is caused by excessive destruction of platelets by the spleen.

That there is, in addition to thrombocytopenia, a defect in the capillary endothelium is suggested by the fact that hemorrhage in this disease is not always closely correlated to the degree of platelet reduction. It has been proposed that the capillaries are unusually permeable or that they are incapable of adequate contraction. For the latter hypothesis, evidence has been presented which is based on direct observation.

The *prolonged bleeding time* is explained by a failure of the capillaries to retract as well as by

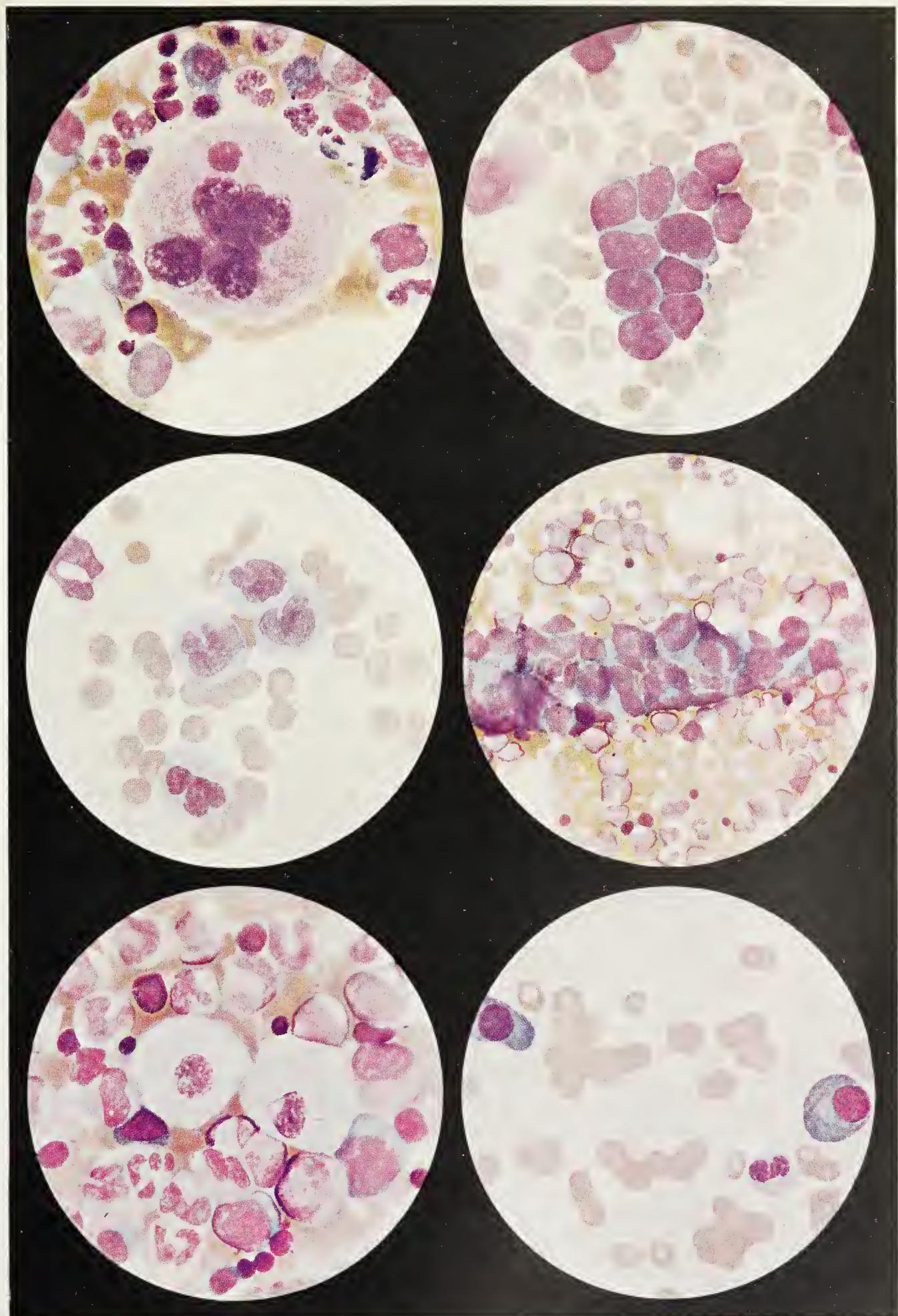


PLATE II

(A) Bone marrow from case of thrombocytopenic purpura showing megakaryocyte without platelets about it ($\times 665$).
 (B) Bone marrow from case of acute myeloblastic leukemia ($\times 665$). (C) Blood from a case of acute monocytic leukemia ($\times 665$). (D) Bone marrow from a case of carcinoma with metastases showing a syncytium of metastatic cells ($\times 340$). (E) Bone marrow from a case of Gaucher's disease showing the typical cells ($\times 665$). (F) Blood smear from a case of multiple myeloma showing the typical "myeloma" or "plasma" cells as well as pronounced agglutination of the red cells ($\times 665$). (Courtesy, Dr. Nathan Rosenthal and Clay-Adams Company, Inc.)

the lack of sufficient platelets to plug the opening of a bleeding vessel. The intracutaneous oozing of blood when capillary pressure is increased (tourniquet test) is explained in the same way. Coagulation time is normal because few platelets are needed to initiate clotting. The clot, however, is loose and retracts poorly because a large number of platelets are needed for syneresis.

Symptomatology. Purpura hemorrhagica may begin abruptly and disappear spontaneously just as suddenly; or its manifestations may seem to have always been characteristic of the individual concerned. The bleeding may be mild with perhaps only inconspicuous purpuric spots in the skin; or it may be severe and not only may lead to serious loss of blood but also may occur into vital areas such as the cranium or the diaphragm. All variations between these extremes may be encountered and the disorder may wax and wane in intensity. Acute and chronic forms of the disorder have been described, and by some are regarded as different entities. It is not unusual for symptoms first to become apparent following an acute infection.

The lesions in the skin usually consist of minute, red hemorrhages which differ from telangiectases in that they do not blanch on pressure. Often ecchymoses are found as well. Mucous membrane hemorrhages are common, bleeding from the nose, mouth, or uterus being particularly frequent and sometimes severe. Not rare are instances in which menorrhagia is the chief complaint, and this often is the only prominent clinical sign other than the abnormalities in the blood. Bleeding, however, may occur into any tissue and from any orifice. Frequently, also, excessive bleeding may be noted following tooth extraction, tonsillectomy, operations, or injuries.

Fever of mild degree may be present in acute cases. The spleen may extend a finger breadth below the costal margin. There is no general glandular enlargement, sternal tenderness, or other physical sign other than those attributable to hemorrhage or anemia.

Blood and Bone Marrow Findings. These have, in the main, been mentioned already. What platelets may be seen in the blood smear are often unusual in appearance: giant or minute forms, or deeply stained ones. The bleeding time may be slightly, moderately, or greatly prolonged (8 to 60 minutes or more). Anemia, if present, is proportional to the amount of blood lost. If there has

been much bleeding, signs of stimulated erythropoiesis will be found: reticulocytosis, polychromatophilia, even occasional normoblasts. The leukocyte count may be normal, but if acute blood loss has taken place there may be a moderate leukocytosis with slight "shift to the left." In some chronic cases lymphocytosis has been observed.

Diagnosis. Hemorrhage not due to obvious cause, if associated with thrombocytopenia, prolonged bleeding time, poor clot retraction, and positive tourniquet test, can be attributed to thrombocytopenic purpura. Prolonged bleeding time is characteristic of the hereditary hemorrhagic diathesis (p. 1207) and may be found, though rarely, in a number of conditions in which coagulation time is prolonged, provided the blood and tissues are severely impoverished in coagulation factor (see table 25, Chapter 23, p. 268). These include hemophilia and hypoprothrombinemia. A positive tourniquet test is found in senile purpuras, scurvy, Weil's disease, and other infections, as well as in hypertension and in some normal individuals. Poor retraction of the clot is found, with rare exceptions, only when the platelets are reduced in number. The combination of these abnormalities, however, is characteristic of thrombocytopenic purpura.

Before a diagnosis of purpura hemorrhagica can be made, however, the recognized causes of thrombocytopenic purpura must be excluded. These are listed in table 96. The history and physical examination will serve to rule out many of these conditions. Adenopathy and sternal tenderness, as well as anemia out of proportion to the blood loss, even in the absence of striking changes in the leukocytes, should suggest leukemia. Persistent leukopenia suggests leukemia, aplastic anemia, or one of the splenic disorders.

Treatment and Prognosis. The first principles in the therapy of thrombocytopenic purpura are expectant management and a search for possible etiologic factors. If one is found or suspected, further exposure should be stopped. Expectant therapy includes rest in bed if bleeding is moderate or severe, good nursing, appropriate diet, and, if anemia is present as the result of blood loss, iron. If bleeding is moderately severe, blood transfusion may be required; if it is severe, transfusion is necessary.

These measures are recommended because spontaneous remissions are common in purpura

Table 96

CLASSIFICATION OF THROMBOCYTOPENIC PURPURAS*

- I. "Essential" or "Primary" Purpura Hemorrhagica
- II. Symptomatic Purpuras:
 - A. Chemical, vegetable, animal, and physical agents:
 - 1. *Chemical:* Organic arsenicals, "Sedormid," gold salts, benzene; possibly phenobarbital, dinitrophenol, quinine, quinidine, ergot, bismuth, iodine, organic hair dyes, sulfonamides
 - 2. *Vegetable:* Foods, orris root
 - 3. *Animal:* Snake venoms, pertussis vaccine, insect bite, extensive burns
 - 4. *Physical:* X-rays, radium, heat stroke
 - B. Blood disorders:
 - 1. *Leukemias:* Acute, or late stages of chronic
 - 2. *Anemias:* (a) Aplastic—idiopathic or due to physical or chemical agents
(b) Myelophthisic (tumors in bone marrow, osteosclerosis, etc.)
(c) Pernicious anemia
(d) Chronic hypochromic anemia
 - 3. *Splenic disorders:* Banti's syndrome, Gaucher's disease, Felty's syndrome, hemolytic icterus, rarely Hodgkin's disease
 - 4. *Miscellaneous:* Acute purpura with platelet thrombi in capillaries ("thrombotic thrombocytopenic purpura"), purpura hemorrhagica with lymphocytosis
 - C. Infections and other conditions:
 - Septicemia, subacute bacterial endocarditis, typhus, etc.; lupus erythematosus

* Adapted from M. M. Wintrobe: "Clinical Hematology," 2d ed., Philadelphia, Lea & Febiger, 1946.

hemorrhagica, especially in children. If they do not suffice, splenectomy must be considered. Until the pathogenesis of this disorder becomes more clear, the rationale of splenectomy will be debatable, but the fact that improvement follows this operation in the majority of cases cannot be denied. Benefit is less likely to follow splenectomy in acute phases of bleeding than in the more chronic phases, and the operative mortality is higher; consequently hasty resort to operation should be avoided. Recovery following splenectomy may not be complete, or a relapse may occur, but this is less likely to happen than in patients treated "medically."

Following splenectomy the platelet count may increase rapidly and to abnormally high levels, an effect which carries the danger of postoperative thrombosis; or it may rise gradually. Bleeding often ceases even though the platelet count may not have increased greatly, an effect which suggests an influence of the spleen on capillary function. In the bone marrow the previously abnormal megakaryocytes in most instances soon appear to be quite normal again and are seen to be surrounded by platelets.

Other measures appear to have much less value. Irradiation of the spleen has been observed to be associated with improvement. Because of the tendency for spontaneous improvement, it is difficult to evaluate the many therapeutic procedures which have been proposed from time to time.

Spontaneous recovery is not rare in acute cases, but is less common in the more chronic forms. Recurrences are seen twice as often in females as in males. With appropriate treatment the prognosis in general is good, even in acute cases, barring such accidents as hemorrhage into a vital tissue or failure to recover from splenectomy. The presence of accessory spleens may be the cause of postoperative recurrences.

NONTROMBOCYTOPENIC PURPURAS

There are a number of types of purpura which are not accompanied by thrombocytopenia. In none of these disorders has an abnormality of the blood been recognized. In all but one of these, a very rare syndrome known as hereditary hemorrhagic diathesis, bleeding time is also normal. These purpuras have been discussed already (p. 263), but allergic purpura and the hereditary hemorrhagic diathesis deserve more complete consideration.

ALLERGIC PURPURA

In this form of purpura there is found one or more of the common symptoms of allergy such as erythema, urticaria, or effusions of serum into subcutaneous or submucous tissues or viscera. There may be concomitant articular symptoms (*Schönlein's purpura*, *peliosis rheumatica*), crises of abdominal pain (*Henoch's purpura*) or no localized signs (*purpura simplex*). Constitutional

symptoms such as fever and malaise may be present. The manifestations may wax and wane in intensity, extent, and nature. In various combinations, erythema (multiforme, bullous, vesiculosum, nodosum), urticaria, and edema may be encountered. Necrotic areas may develop, to be followed by the formation of bullae or ulcers. The skin lesions may appear in crops and may be accompanied by itching or paresthesias. There may be hemorrhage from the visible mucous membranes. Kidney lesions similar in nature to those found in the skin may develop and cause hematuria, proteinuria, and profound though temporary disturbance of renal function.

Etiology and Pathogenesis. These purpuras are more common in children and young adults than in older age groups. Many cases of purpura simplex are familial. The true nature of these purpuras is unknown. The resemblance to serum sickness suggests an allergic basis, but only in a minority has an allergic cause been demonstrated. In some cases the exciting agent appears to have been bacterial (streptococcus, antityphoid vaccine) or an article of food (milk, eggs, pork, strawberries, etc.). In others, hypersensitivity to cold has appeared to be the factor.

It is likely that an antigen-antibody reaction occurs which takes place especially in the endothelium of certain blood vessels. As a result, there is an alteration in the permeability of the small blood vessels. Perivascular inflammation has been observed about the small vessels of the corium of the skin. The various manifestations arise from extravasations of varying proportions of plasma and formed elements of the blood. Mechanical factors may possibly influence the localization of the lesions in addition to the local vascular changes. In Henoch's purpura, an urticarial, sero-hemorrhagic effusion into the intestinal wall is the cause of the colicky pain and sometimes even leads to intussusception.

Diagnosis. Diagnosis is most difficult when purpura is not present or not obvious. In Henoch's purpura, crises of pain may develop which, in the absence of purpura and accompanied as they may be by leukocytosis, cannot be clearly distinguished from acute abdominal conditions which call for operative intervention. Eosinophilia may be present, and then an allergic rather than an inflammatory reaction may be suspected. Acute nephritis may be simulated when the kidney is involved. Hematuria may be a prominent

symptom in such cases, just as melena may occur in Henoch's purpura. The Schönlein type may be mistaken for rheumatic fever.

When purpura is discovered and there are exudative skin lesions at the same time, diagnosis is much easier, since these lesions are not encountered in other forms of purpura as a rule. Various chemical agents may also produce non-thrombocytopenic purpura. Furthermore, this may be a symptom of a variety of diseases. These have all been discussed already (p. 263).

Treatment and Prognosis. Treatment is purely symptomatic. Naturally, if an etiologic agent is discovered or suspected, further exposure should be eliminated. Desensitization may be attempted if the exciting agent is protein in nature. Allergic purpura is rarely fatal. Individual attacks last from one to six weeks. Recurrences at intervals of months or years are not unusual, however.

HEREDITARY HEMORRHAGIC DIATHESIS

This is a rare type of hemorrhagic disorder which may be regarded as a form of nonthrombocytopenic purpura. It is usually familial and affects the sexes about equally. The cases described by Glanzmann as *hereditary hemorrhagic thrombasthenia* were characterized by normal bleeding time, but no similar cases have since been reported. Other cases have been described under such titles as *constitutional thrombopathy*, *thrombasthenic purpura*, and *pseudohemophilia*. In these cases the bleeding time was prolonged and the clot retraction was usually normal. The tourniquet test has been positive in many cases, but the platelets were normal, as was the coagulation time. The manifestations may include multiple ecchymoses, recurrent epistaxes, mucous membrane hemorrhages, and post-traumatic and postoperative bleeding. Petechiae are rare. These symptoms may recur for many years, beginning often in childhood. The prognosis for life is usually excellent. The disorder has been attributed to a qualitative defect in the platelets but it appears more likely that the defect is vascular. Treatment includes pressure over bleeding sites, the application of thrombin-fibrin foam, and blood transfusion if necessary. Surgical procedures should be avoided.

The term *pseudohemophilia*, which has been applied to this condition, is more appropriately applied to cases of abnormal bleeding associated

with prolonged coagulation time in which the clotting defect is similar to that in true hemophilia but which cannot be so regarded for genetic reasons. Such cases have been described in women.

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Hemophilia

M. M. Wintrobe

Hemophilia
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HEMOPHILIA

Definition. Hemophilia is a constitutional anomaly of blood coagulation which depends on the inheritance of a sex-linked, recessive Mendelian trait which is transmitted by the female and affects only males. It is characterized by a life-long tendency to excessive bleeding. The coagulation time is prolonged.

History. Although a clear description of this disorder was not published until 1803 by Otto of Philadelphia, it is apparent from passages in the

Talmud that the condition was known to the ancient Jews, who even proscribed circumcision in those whose family history suggested this disorder.

Etiology and Pathogenesis. The factor or gene responsible for the development of hemophilia appears to be carried in the X chromosome of the reproductive cells. The disease is limited to the male and is transmitted from the male through an unaffected daughter to a grandson. The daughters of an affected male transmit the trait as an evident defect to half of their sons and as a hidden (recessive) characteristic to half of their daughters. Although reports of hemophilia in the female appear from time to time, no authentic case has yet been described. Sporadic cases of hemophilia have also been described in which the family history has been negative. These can sometimes be explained by long inheritance through females with the males being, by chance, unaffected. Illegitimacy may be responsible for

other instances, while still others may represent the disease arising *de novo*.

The exact nature of the inherited defect is not clear. The fault is manifest in the greatly prolonged coagulation time. It has been demonstrated quite clearly that the addition of normal plasma to hemophilic blood, or of a substance derived from normal plasma ("coagulation globulin," "fraction I") reduces the coagulation time. It is not known whether by so doing one is supplying (1) a substance related to plasma thromboplastin ("thromboplastinogen") which is deficient in hemophilic blood (Quick); (2) a "thrombocytolysin" which normally disrupts platelets to furnish thromboplastin (Brinkhous); or (3) a substance which counteracts the effect of an anticoagulant (anticephalin) which appears to be present in hemophilia in excess (Tocantins).

Symptomatology. Hemorrhage, usually following trauma but sometimes spontaneous, is the essential symptom. The bleeding is in the nature of a persistent, slow oozing which is out of all proportion to the extent of the injury. This tendency to prolonged bleeding usually appears in early childhood, even in infancy. The bleeding may last not only hours but days and even weeks, and may lead to profound anemia. Subcutaneous and intramuscular hemorrhages are common. Petechiae are very rare. Hematomas may be large. There may be severe bleeding from the mouth, gums, lips, tongue, or gastrointestinal tract. Epistaxis is a common symptom. The eruption and loss of teeth may be accompanied by severe bleeding. Hematuria is relatively common and hemorrhage into joints is characteristic. Recurrences are the rule, and ultimately a permanently swollen joint with local deformity, contractures, and muscular atrophy is produced.

The *blood* is normal except for the prolonged coagulation time and the manifestations which hemorrhage produces (see p. 266). Curiously, the degree of prolongation of coagulation time, like the symptoms of this disorder, varies from time to time. Platelets are normal in number. Only rarely is bleeding time prolonged. In contrast to normal blood, the clotting time of recalcified hemophilic plasma, centrifuged rapidly to make it free of platelets, is much longer than that of such plasma centrifuged more slowly.

The *bone marrow* is normal except for normoblastic hyperplasia when hemorrhage has been severe.

Diagnosis. It is more often the case that local injury or disease is the cause of unusually prolonged bleeding than that the patient is a true "bleeder," a designation which is made much too freely. The diagnosis of hemophilia depends on a history of repeated, protracted hemorrhage, often from more than one source; prolonged coagulation time; and a characteristic family history. Occasionally one may encounter instances otherwise resembling hemophilia in which the family history is negative; sometimes coagulation time is prolonged for some reason other than hemophilia. These rare conditions were discussed in Chapter 23 (p. 264). It should be remembered that only when prothrombin time is less than 10 per cent of normal is coagulation time prolonged because of prothrombin deficiency.

Although hemophilia and purpura hemorrhagica are often confused with one another, differentiation is easy, for in the latter condition there are thrombocytopenia, prolonged bleeding time, poor clot retraction, and a positive tourniquet test. In hemophilia the patient is normal in these respects, and coagulation time is prolonged. Of the various bleeding disorders in which a family history may be obtained, hemophilia is the only one in which a sex-linked trait has been described.

Occasionally difficulty in diagnosis may arise if attention is attracted only to the joint manifestations or to a swelling which is not recognized to be a hematoma. In a similar manner, the bleeding may suggest kidney disease, pulmonary disease, or peptic ulcer.

Course and Prognosis. The tendency to bleed varies from time to time and differs in degree from one case to another. It is rare, however, for a true hemophiliac to survive to adulthood without suffering some disabling deformity of the joints. Death may occur from exsanguination following surgical procedures or accidental cuts. Less often it is due to internal hemorrhage.

Treatment. The prevention of hemophilia depends on appropriate restriction of marriage or at least of propagation. Only unaffected males can marry with any assurance that the hemorrhagic tendency will not be transmitted.

Affected individuals and male children of tainted stock must be guarded against trauma, and surgical measures should be avoided whenever possible. If some procedure which may entail bleeding is absolutely necessary, this should

be done only when blood is available for transfusion which has been found to shorten the clotting time. It is desirable to reduce the clotting time to normal by transfusion of plasma or whole blood or by injecting "coagulation globulin" ("fraction I") before the procedure is started. Teeth should be removed by the application of orthodontia bands when feasible. If local bleeding occurs in the mouth or elsewhere, thrombin ("hemostatic globulin") should be applied in dry form and kept in place by a firm dressing or pack. In an emergency, a sponge soaked in normal plasma or whole blood can be applied to the bleeding site.

When hemorrhage is actually in progress, rest and quiet, local measures, and blood transfusion in such quantities as are necessary to replace the blood lost and to reduce the coagulation time, are the essential steps. If whole blood is not necessary, plasma may be given in 100 to 250 ml. quantities for its antihemophilic properties. Such injections may need to be repeated every 6 to 48 hours. The antihemophilic activity of whole blood or plasma gradually disappears when preserved even at refrigerator temperatures, and consequently such blood and plasma should not be over 24 hours old. Plasma separated soon after phlebotomy and preserved in the frozen state maintains its activity well.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Definition. This is a vascular anomaly characterized by multiple dilatations of capillaries and venules which are found in the skin and mucous

membranes. The anomaly is transmitted as a simple dominant by both sexes.

Etiology. The telangiectases may be found in childhood, but they increase in number as age advances. Bleeding may not commence until adult life has been reached.

Symptomatology. Epistaxis is especially common, but bleeding may come from telangiectases wherever they be: the face, tongue, lips, or gastrointestinal, respiratory, or genitourinary tracts. Those on the skin are less likely to bleed than are telangiectases on mucous membranes. The telangiectases range from pin point to about 3 mm. in diameter, are bright red or violaceous in color, and characteristically blanch on pressure. The blood is normal except for the effects hemorrhage may have produced. The tourniquet test is negative.

Diagnosis. This depends on recognition of the vascular anomalies. Purpuric spots do not fade on pressure.

Treatment. Electrocoagulation has been effective in destroying the lesions, but the hemorrhage itself must be treated by pressure, thermocautery or escharotics.

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Agranulocytosis and the Pancytopenias

M. M. Wintrobe

Agranulocytosis
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 Etiology and Pathogenesis
 Symptomatology
 Diagnosis
 Treatment and Prognosis
 The Pancytopenias
 Aplastic Anemia
 Myelophthisic Anemia
 Diagnosis and Treatment

AGRANULOCYTOSIS

(Agranulocytic Angina)

Definition. This term refers to a disorder which is characterized by severe sore throat, marked prostration, and extreme reduction or even complete disappearance of the granulocytes from the blood. This clinical picture, first recognized by Schultz in 1922, was observed most frequently in women of middle age and often ended in sepsis and death. An etiologic relationship to the taking of certain drugs has been demonstrated.

Etiology and Pathogenesis. In 1931 Kracke pointed out that the sudden appearance of this syndrome corresponded with the introduction of certain coal-tar derivatives as therapeutic agents. This was borne out by considerable circumstantial evidence which incriminated, in particular, the antipyretic, aminopyrine ("Pyramidon"). The mode of action of the drug is not clear. A peculiar sensitivity or idiosyncrasy on the part of the patient must be postulated. It has been shown that, in patients who have recovered from the disorder, the administration of small amounts (0.2 Gm.) of the drug may be followed within 6 to 10 hours by disappearance of all the neutrophils from the blood. The course of events in affected individuals would seem to be (1) granulocytopenia as the result of some effect induced by the drug; (2) loss of resistance to infection, development of sore throat; (3) overwhelming sepsis and death. That some form of tissue injury, in addition to leukopenia, may be a factor in the pathogenesis of this syndrome is suggested by the frequency with which one may encounter leukopenia, even of severe degree, following nitrogen mustard therapy without sepsis developing.

The reasons for such drug sensitivity are obscure. Other manifestations of idiosyncrasy such as rash, urticaria, edema, and asthma may be associated in some individuals with the taking of many of the drugs which have produced agranulocytosis. The most striking change observed in the bone marrow is a lack of juvenile and segmented neutrophilic leukocytes, less mature forms being plentiful. This picture has been referred to as "maturation arrest," but it could as readily result from abnormal peripheral destruction of the leukocytes or their segregation somewhere.

Drugs producing leukopenia may be divided into two groups—namely, those which produce this effect in all individuals if given in sufficient amounts, and those which cause leukopenia only in certain "sensitive" persons. Of the first group, many will produce thrombocytopenia and anemia as well, the whole bone marrow being injured. Benzene, organic arsenicals, nitrogen mustard, and gold salts are of this type. This division, however, is not absolute. The effects on the blood of gold salts and of the arsenicals vary greatly in different patients receiving treatment with these agents, so that a constitutional factor must be considered. Drugs which produce leukopenia in only a small proportion of persons receiving them include the sulfonamides, thiouracil, dinitrophenol, and possibly, on rare occasions, barbiturates, bismuth, quinine, pamaquine naphthoate, salol, and antimony.

A certain number of cases have been encountered in which it was not possible to incriminate any drug. In addition, recurrent, cyclic, and chronic forms of granulocytopenia have been described. These are very rare.

Symptomatology. When the prodromal period is marked only by malaise or moderate fever, it often is overlooked. Then the onset appears to be sudden and is marked by a chill, high fever, and often sore throat. Prostration is extreme. Gangrenous ulceration may be found on the gums, tonsils, soft palate, lips, pharynx, or buccal mu-

cous membranes. Regional adenopathy may be present, but generalized adenopathy and sternal tenderness are not found, and splenomegaly, when present, is minimal. Brawny edema of the neck can become extreme. Necrosis of the gastrointestinal tract may occur. Jaundice has been described in some cases. In fatal cases the duration of the illness is three to nine days.

In the *blood*, granulocytopenia is the outstanding finding. Since the leukocyte count is usually under 3000 per cu. mm. and often is as low as 500, a reduction in the absolute number of all cells actually takes place. Of the leukocytes which remain, 95 to 100 per cent may be lymphocytes. Anemia and thrombocytopenia are not found. If present, another cause should be suspected.

The *bone marrow* is normal except for the "maturation arrest" described already.

Diagnosis. The clinical picture may suggest a variety of buccal and pharyngeal infections. The great majority of these, however, are accompanied by leukocytosis. Infections characteristically accompanied by leukopenia, such as measles, undulant fever, and typhoid, should rarely give difficulty, although influenza may. "Aleukemic" leukemia may present a similar clinical picture, but the presence of sternal tenderness, general glandular enlargement, and splenomegaly, as well as anemia, thrombocytopenia, and, usually, very immature leukocytes in the blood, makes differentiation no serious problem. Aplastic anemia is recognized by evidence of involvement of red corpuscles and platelets as well as leukocytes.

Primary splenic neutropenia is a name applied to a clinical picture characterized by fever, pain over the splenic region and splenic enlargement, granulocytopenia, and essentially normal or somewhat hyperplastic bone marrow. The manifestations may be acute, subacute, or chronic, and have been attributed to excessive lysis of neutrophils by the spleen. Splenectomy is reported as bringing complete relief, and excessive phagocytosis of leukocytes can then be demonstrated in that organ. The disorder is very rare.

Treatment and Prognosis. The offending drug must be uncovered and its further use prohibited. Of equal importance is the administration of chemotherapeutic agents, such as penicillin, which will hold the infection in abeyance until leukocyte formation becomes normal and is able to cope with the offending organisms. There is

no conclusive evidence that various agents which have been proposed as stimulants of leukocyte recovery, including even the most popular, "Pentnucleotide," are of any value. Before the sulfonamides and penicillin were available, the prognosis was very poor. Mortality was as high as 70 to 90 per cent. With modern chemotherapy, only a small proportion of patients fail to recover. During recovery, with the reappearance of leukocytes, abscesses may develop which will require appropriate therapy.

THE PANCYTOPENIAS

Definition. The term *pancytopenia* refers to a reduction in the number of all three formed elements of the blood: the red corpuscles, the leukocytes, and the platelets. This is not a disease entity but a triad which is encountered under a widely differing group of circumstances.

Classification. This triad may be encountered in "aplastic" or "hypoplastic" anemia, in "aleukemic" or subleukemic leukemia, in myelosclerosis and other myelophthisic anemias, in pernicious anemia, and in association with a number of disorders of the spleen. Under this heading "agnogenic myeloid metaplasia" and "primary splenic panhematopenia" must also be considered.

APLASTIC ANEMIA

This term, in its strict sense, refers to a condition in which signs of hemopoiesis are lacking in the bone marrow, fat having replaced the blood-forming tissue. At the same time, there is anemia, granulocytopenia, and thrombocytopenia. There are no signs of blood regeneration. The reticulocyte count is very low or zero, there is no polychromatophilia or basophilic stippling, and nucleated red corpuscles and immature leukocytes of all types are absent. The anemia is usually normocytic, sometimes macrocytic; the red corpuscles vary little in size and not at all in shape. Bleeding time is usually moderately prolonged, the clot retracts poorly, and the tourniquet test is positive. Coagulation time is normal.

The onset of the disorder is insidious. The symptoms may be those attributable to anemia, or the effects of thrombocytopenia or of granulocytopenia may dominate the clinical picture. There is striking, often "waxy" pallor, but weight loss is unusual. There may be bleeding from the nose, mouth, vagina, or elsewhere.

Hemorrhages may be found in the eyegrounds or skin. Ulceration in the mouth and pharynx or other evidence of infection may be encountered. There is no sternal tenderness, splenomegaly, or hepatomegaly; and lymph node enlargement, if present, is found only in relation to local infection.

This picture may follow exposure to a variety of *chemical and physical agents*. These include *benzene*, a coal-tar derivative which is used in many industries (leather, enamel, rubber, lacquer, electroplating, airplane, linoleum, celluloid, etc.); *organic arsenicals* such as sulfarsphenamine and neoarsphenamine; *gold compounds*; *nitrogen mustards*; and various hair dyes and volatile insecticides. Excessive exposure to radioactive substances, including roentgen rays and irradiated phosphorus, produces a similar effect.

“*Idiopathic*” cases have also been described in which exposure to an offending agent could not be discovered. Such cases have been observed most frequently in young adults or adolescents. In a few cases a familial incidence, as well as hypoplasia of the gonads and pigmentation of the skin, have been reported.

In addition to such cases of “pure” aplastic anemia, a very similar clinical and hematologic picture can be observed in the face of a bone marrow picture which is cellular or even hyperplastic. In still other cases little or no reduction was present in the leukocyte or platelet count. Occasional nucleated red corpuscles, polychromatophilia, stippling, and immature white cells have been found in the blood, and splenic and hepatic enlargement and even general lymphadenopathy have been described. Whether all these cases should be classed with the true aplastic anemias under one category of “refractory anemias” is a question which cannot be settled until their pathogenesis is clear. That these various pictures may be but variants of the same fundamental process is suggested by the observation that benzene poisoning not only may produce aplastic anemia but also can be associated with a regenerative blood picture, including even a leukemic reaction, and the bone marrow may be hyperplastic rather than acellular. Again, *internal irradiation* produced by the ingestion of radium by watch dial workers was found to be characterized by macrocytic anemia with nucleated red corpuscles in the blood, and bone marrow with primitive red corpuscle and leukocyte hyperplasia.

MYELOPHTHISIC ANEMIA

This term is applied to the type of anemia associated with space-occupying disorders of the bone marrow. Metastatic carcinoma (for example, that arising from malignancy of the breast, prostate, lungs, adrenals, or thyroid), leukemia, multiple myeloma, and a rare disorder known as myelosclerosis, are conditions which produce myelophthisic anemia. In *myelosclerosis* there is an irregular increase of fibrous or bony tissue in the bone marrow which is often associated with progressive anemia. The outstanding symptom is splenomegaly. The course is very slow. Bone marrow involvement may also occur in Hodgkin’s disease and in the primary xanthomatoses (Gaucher’s disease, Niemann-Pick disease, Schüller-Christian disease).

While the *blood picture* in these conditions may be that of a pancytopenia, it is necessary to stress that this is not always the case. Anemia is variable in degree. It may be normocytic or macrocytic, and nucleated red corpuscles may be seen in the blood even when there is little anemia. Reticulocytes may be increased and polychromatophilia and stippling may be present. The leukocyte count may be normal, reduced, or increased. If there is leukopenia there may be a uniform reduction in all the cells. The blood may contain myelocytes and myeloblasts. The platelet count may be normal or moderately reduced.

“*Agnogenic myeloid metaplasia*” is a term which has been applied to cases in which the spleen showed marked myeloid metaplasia, apparently as the result of a compensatory reaction. This does not seem to be a disease entity. The bone marrow has been variously fibrotic, hyperplastic, aplastic, or normal. The blood picture has varied, like that described under myelophthisic anemia above. In some cases jaundice was present. In a number of instances a history of exposure to certain industrial solvents, including benzene and carbon tetrachloride, was obtained.

“*Primary splenic panhematopenia*” is the term which has been applied to cases associated with splenomegaly in which all three formed elements of the blood have been reduced in number, and where excessive phagocytosis of these elements by the splenic macrophages has been conceived as being the fundamental disorder. Splenectomy

is described as producing dramatic improvement. In these cases little or no evidence of increased blood destruction has been observed, the reticulocyte percentage has been slightly or greatly increased, polychromatophilia has been noted, and the bone marrow picture has been one of hyperplasia. As will be pointed out in the next section, many splenic disorders are accompanied by pancytopenia.

DIAGNOSIS AND TREATMENT

It is evident from this outline that pancytopenia may be due to a number of causes of greatly varying nature. The recognition of the underlying disorder will depend on thorough study, which includes a painstaking history with careful inquiry about possible etiologic agents, thorough physical examination and bone marrow examination, in addition to a complete survey of the blood. Marrow punctures in various sites (sternum, pelvic crest, spinous processes) may be required before tumor cells are discovered. Roentgenograms, especially of the bones, may be helpful, and trephine biopsy of the marrow may be necessary. If an enlarged lymph node is accessible, it may be advisable to examine this microscopically, and other procedures may need to be carried out in the search for malignancy. A diagnosis of "idiopathic" aplastic anemia or of "primary splenic panhematopenia" should be one of exclusion.

Treatment will depend on the nature of the underlying disorder. Blood transfusions are of temporary value in all the conditions which may produce this picture. Ultimately, if many transfusions are given, hemochromatosis is produced, since the iron from the transfused cells cannot be excreted. Liver extract and iron are of no value. The temptation to remove an enlarged spleen must be tempered with good judgment. This is especially important in those cases in which the spleen has assumed the function of the bone marrow, for in such cases splenectomy is harmful.

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Leukemia

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General Considerations
Definition
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Varieties of Leukemia and Incidence of Various Types
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Chronic Myelocytic Leukemia

GENERAL CONSIDERATIONS

Definition. Leukemia is a disease, probably of neoplastic nature, which is characterized by wide-

Chronic Lymphocytic Leukemia
Acute Leukemia
Less Common Types of Leukemia
Diagnosis
Course and Prognosis
Treatment
Irradiation
Chemotherapy

spread and abnormal proliferation of the leukocytes and their precursors throughout the body, and particularly in the bone marrow, spleen, and

lymph nodes. There are different types of leukemia, differentiated mainly according to the predominant abnormal cell forms. The morbidity of the process ranges from a very acute disorder of but a few weeks' duration to a very chronic one compatible with life even for many years. The termination, however, is always fatal.

History. Knowledge of leukemia can be traced back to the period from 1839 to 1845 when Donné made the first microscopic observations and Craigie, Bennett, and Virchow distinguished the clinical entity. Virchow recognized the cells as being leukocytes, not pus cells, and distinguished a lymphatic and a splenic type of leukemia. With the development of Ehrlich's blood-staining methods in 1891, Neumann's myelogenous form was recognized as being the same as Virchow's splenomegalic type. Acute leukemia was recognized by von Friedreich in 1857 and by Ebstein in 1889, and the myeloblastic form was separated from the lymphoblastic type when Naegeli described the myeloblast in 1900. Reischad and Schilling-Torgau described monocytic leukemia in 1913. Since then variations from the classic pictures have been recognized and methods for palliative management have been developed, but little advance has been made in gaining an understanding of the actual cause of this invariably fatal process, or in its prevention or specific treatment.

Varieties of Leukemia and Incidence of Various Types. Acute and chronic forms of leukemia can be distinguished on clinical grounds as well as on the basis of the predominant abnormal cell types. Acute leukemia usually terminates fatally within six months; the duration of life in chronic leukemia may be several, usually three to five, sometimes one or two and in other cases ten or more, years. "Subacute" leukemia is not truly intermediate between acute and chronic leukemia. The course and the clinical and the hematologic pictures resemble those of the acute form, but death usually is delayed until 6 to 12 months from the onset of the disease. Since myeloblasts, lymphoblasts, myelocytes, lymphocytes, or monocytes are the predominant cells in the great majority of cases of leukemia, the terms "acute" or "chronic" (and, if one wishes, "subacute"), qualified by the name of the predominant cell type, appear to be the most satisfactory designations for the different varieties of leukemia.

Leukocytosis is found in the majority of cases

of leukemia. "Aleukemic" or, more correctly, subleukemic leukemia refers to cases in which leukocytosis is absent.

Leukemia is as common a cause of death as diphtheria or measles. Deaths from leukemia represent about 3.6 per cent of those due to cancer. Chronic myelocytic leukemia is the most common of all the types of leukemia, with chronic lymphocytic leukemia taking second place. Chronic leukemia is perhaps twice as common as the acute variety. The incidence of the various type of acute leukemia, including monocytic leukemia, is difficult to determine because conclusions must be based on differences in interpretation. In various series, 11 to 33 per cent of the cases were subleukemic.

Etiology and Pathogenesis. While any variety of leukemia may occur at any age, it is nevertheless true that acute leukemia is much more common before the age of 25 than later, and is especially frequent under 5 years of age; chronic myelocytic leukemia has its highest incidence between the ages of 25 and 45, and chronic lymphocytic leukemia is seen especially after the age of 45 or 50. A difference in the sex incidence of leukemia becomes perceptible as age advances, there being essentially no difference in the occurrence of acute leukemia in male and female children and young adults, a slight preponderance of chronic myelocytic leukemia in males and a distinct preponderance of chronic lymphocytic leukemia in males (3:1).

On the basis of past experience it can be stated that the probability that leukemia will occur more than once in a family is very small. This seems strange when one considers the fact that susceptibility to experimental leukemia and the transmission of the spontaneous disease in experimental animals follow definite genetic laws. The explanation probably lies in the fact that, although hereditary factors do exert an influence on the etiology of human leukemia, as exemplified by familial cases of chronic lymphocytic leukemia especially, their effect is modified by external influences and by other genes. External factors include the effects of irradiation and perhaps also of trauma. Leukemia has been described so much more often in persons exposed to radiation than in those not so exposed that this agent cannot be overlooked in a consideration of etiologic factors. Less convincing, but nevertheless deserving serious consideration, are the cases of leukemia which

have developed following trauma, especially to bones.

The cause of leukemia is unknown. The febrile character of acute leukemia and the evidences of infection, about the mouth especially, which can be seen in many cases have led some to hold the opinion that the disease is caused by an infectious agent. Such a concept is difficult to accept in view of the fact that none of the other customary evidences of infection have been observed, such as transmission from man to man or from mother to fetus. Experimental fowl leukemia, it is true, is carried by a filtrable agent, but this is the case also with certain other types of neoplasms. Newer knowledge is developing concerning the existence of transmissible cytoplasmic agents which determine the character of cells. It is the more general view, therefore, that leukemia is neoplastic in character. The transmission of experimental mammalian leukemia depends upon the transfer of viable cells. In many cases of leukemia, furthermore, peculiarities can be observed in the leukemic cells which are like those of neoplastic cells, including abnormal size and number of nucleoli and atypical as well as abnormal mitoses.

Pathology. The fundamental change in leukemia is widespread proliferation in the tissues, and usually also in the blood stream, of cells of a particular type. In chronic myelocytic leukemia the bone marrow and spleen are chiefly involved, but the lymph nodes, liver, kidneys, lungs, skin, and other organs are also infiltrated. The splenic pulp is full of myeloid cells, and infarcts are commonly present. In the chronic lymphocytic variety the lymphoid organs in particular show striking hyperplasia with disturbance of architecture, and the liver, bone marrow, and other tissues are affected as well. In acute leukemia the changes are similar and are accompanied by evidences of hemorrhage, the result of the accompanying thrombocytopenia.

CLINICAL MANIFESTATIONS

The clinical manifestations of the chronic and the acute leukemias differ from one another a great deal, but there is comparatively little difference in the symptomatology of the various types of chronic leukemia, and essentially no difference in the clinical pictures of the different forms of acute leukemia.

Chronic Myelocytic Leukemia. The onset is insidious and complaints may not develop until

the disease has been in progress for a long time, perhaps a year or two. The most common symptoms are those of anemia (weakness, pallor, palpitation, or dyspnea); or a dragging sensation or a swelling in the left side of the abdomen, due to the splenic enlargement; or complaints attributable to the increased metabolic rate which develops as the disease progresses (loss of weight, weakness, nervousness, cachexia, etc.). There may be slight fever, rising as high as 101° F., rarely higher. As the disease advances, the clinical picture may become more "acute" in that chills and fever may develop, weight loss may become excessive, and an abnormal tendency to bleed may become manifest.

The appearance of the patient ranges from that of seeming perfect health to one of extreme cachexia with marked pallor. Splenomegaly is often the first physical sign of the disease. The spleen may be just palpable or it may be huge, the abdomen, protuberant from this cause, standing out in striking contrast to the general emaciation. Lymph node enlargement is rarely significant, but tenderness, elicited on pressure over the lower portion of the sternum, is a moderately early sign.

Other symptoms and signs are less common, but any system of the body can be affected. The liver is often enlarged, sometimes greatly, and, like the spleen, is firm and not tender. The skin may show small, bluish gray, elevated nodules, due to specific infiltration. The retinas may show hemorrhages and leukemic infiltrations. There may be subperiosteal infiltration and even destructive lesions of bone leading to pathologic fractures. Deafness, from infiltration in the middle or inner ears, or from hemorrhage; evidences of nervous system involvement due to the same causes; hematuria in association with infiltration of the kidney; or other still less common manifestations may be observed. Pain may develop from perisplenitis, or in some cases pleural effusion may occur.

The blood picture depends on the stage of the disease. The earliest manifestation is leukocytosis, due to an increase in the myeloid series of cells. Early in the disease the "shift to the left" is usually orderly with fewer metamyelocytes than segmented neutrophils, fewer myelocytes than older forms, and often few or no myeloblasts. Later the myelocytes tend to dominate the picture, especially in the most advanced and

more "acute" stages. Eosinophils and basophilic leukocytes are likely to be found, sometimes in substantial numbers. If they are very numerous, the terms *eosinophilic leukemia* and *basophilic leukemia* are appropriate. The leukocyte count most often ranges between 100,000 and 500,000 cells per cu. mm. when the disease is first discovered, but values as great as 1,000,000 are sometimes seen. Monocytes are present in normal or slightly increased numbers, whereas lymphocytes, though reduced in percentage, maintain about a normal absolute value.

The degree of anemia is a good index of the extent of the leukemic process. In the earliest stages there is no anemia; in far advanced cases it is profound. The manner in which anemia is relieved when therapy reduces the extent of myeloid infiltration or becomes more severe as the disease advances gives support to the view that its cause is encroachment on the erythrocyte-forming elements by the leukemic cells. The anemia is usually normocytic in type. A few normoblasts are likely to be seen in the blood smear, as well as slight polychromatophilia and occasional stippling.

The platelets are normal in number or increased, except in the terminal stages of the disease when infiltration is very extensive. Then hemorrhagic manifestations, prolonged bleeding time, and other signs of secondary thrombocytopenic purpura are found. In rare cases the platelet count may be extremely high, and even megakaryocytes or fragments thereof may be found in the circulating blood.

Chronic Lymphocytic Leukemia. The onset is insidious, as in the myelocytic form, but the first symptom is likely to be painless enlargement of lymph nodes in the neck, axilla, or groin. In other instances manifestations of anemia may dominate the picture, and less commonly splenic enlargement or hemorrhagic manifestations may be the presenting complaints. The skin is more often involved in the lymphocytic form than in the myelocytic, as are also the gastrointestinal tract and the mediastinum. There may be itching and burning, with yellowish brown, red, bluish red, or purple, nodular skin lesions. Bone tenderness is less frequent than in myelocytic leukemia. The lymph nodes vary in size from that of a pea to that of a hen's egg and, though they are discrete, several lying together may produce a huge mass. They are moderately firm and smooth. Other

manifestations are similar to those encountered in chronic myelocytic leukemia.

~~X~~ The *blood picture* is that of a monotonous collection of small lymphocytes each looking just like its fellow, contrasting strikingly with the colorful picture of myelocytic leukemia. The leukocyte count more often ranges between 50,000 and 250,000 per cu. mm. than at higher levels, and 90 per cent or more of these cells are lymphocytes. They often possess only a narrow rim of cytoplasm and may even appear to have none. Larger lymphocytes may be seen, but true "blast" forms with clearly defined nucleoli are unusual.

As in myelocytic leukemia, the presence or absence of anemia and its degree are good indexes of the extent of infiltration. The anemia is normocytic and there may be occasional immature red cell forms in the blood smear. Early, the platelet count is normal; as the disease advances, it becomes greatly reduced and hemorrhagic manifestations may develop.

Acute Leukemia. The onset of acute leukemia is frequently rather abrupt and, depending on the location and nature of the initial disturbance, a great variety of clinical pictures may be encountered. The initial symptoms may arise from leukemic infiltrations and glandular enlargement, from hemorrhages, or as the result of the systemic effects of the disease, including those associated with anemia. Sore throat, abnormal bleeding from the mucous membranes or petechiae or ecchymoses in the skin, cough or dyspnea resulting from enlargement of the thymus or mediastinal lymph nodes, rheumatoid pains, and a variety of neurologic complaints are among the manifestations which may be encountered. Excessive bleeding following the extracting of a tooth or from minor injuries may be the first evidence of the disease. Fever, headache, and general malaise may be soon followed by marked prostration, and the onset of some severe, malignantly virulent form of sepsis may be suspected.

Lymph node enlargement is usually less conspicuous than in chronic leukemia, but a systematic search will frequently reveal more or less generalized involvement of the lymph nodes. The spleen is usually palpable but is rarely very large. The liver is often enlarged. The gums may be swollen and purplish in color and there may be ulceration in the mouth. Sternal tenderness is present in the great majority of cases.

The various types of acute leukemia cannot be differentiated on clinical grounds, and this is often difficult even from the *blood examination*. Anemia is practically always present when the disease is first discovered; often it is severe. The anemia is usually normocytic, sometimes macrocytic. Polychromatophilia as well as normoblasts is often found. The platelet count is usually decreased, at least to some degree, even when the disease is first discovered. The bleeding time then is prolonged, the clot retracts poorly, and the tourniquet test is positive.

The leukocyte count rarely attains levels higher than 100,000 per cu. mm.; not infrequently it is below normal, even 10,000. At first glance the predominant cells are likely to be mistaken for lymphocytes. Well-stained, thin smears are needed to demonstrate that the cells are abnormal and contain nucleoli. Differences in nuclear characteristics are difficult to recognize even by those with considerable experience. Furthermore, both myeloblasts and lymphoblasts possess little cytoplasm, and this contains no granules. In *acute myeloblastic leukemia* a small proportion of cells of slightly later development will often be found which contain peroxidase positive granules (Plates II, III). Since such cells are lacking in *acute lymphoblastic leukemia*, differentiation can sometimes be made on this basis. *Acute monocytic leukemia* is distinguished more easily (Plates II, III). The "pure" and rarer form, the "*Schilling type*," is characterized by the presence of large cells with lacy chromatin, irregular nuclei, inconspicuous nucleoli, and irregular cell borders. The cytoplasm contains innumerable very fine, dustlike granules. At the same time a few nongranular, "blastlike" cells with nucleoli are found, probably "monoblasts." In the "*Naegeli type*" of monocytic leukemia, myelocytes are found in relatively large numbers, in addition to cells resembling monocytes.

Less Common Types of Leukemia: SUBLEUKEMIC (ALEUKEMIC) LEUKEMIA. This term refers to those cases of leukemia of any type in which the leukocyte count is only slightly elevated, normal, or less than normal. In such cases the abnormal cells may not predominate in the blood smear; in fact, they may be scarce and not be readily discovered. In most instances in which leukemic cells are stated to be absent, however, a good smear and stain and careful scrutiny by a person with some experience will usually reveal

at least a few. In any event, the bone marrow contains a large number of the abnormal cells, although sometimes these may be held together so firmly that they are not readily aspirated.

A normal or subnormal leukocyte count may be encountered at some stage of chronic or acute (and subacute) leukemia, especially the latter. This may be followed by a prolonged phase of leukocytosis or, more often, leukocytosis may be only a terminal event. Sometimes leukocytosis never develops. Sternal marrow examination, however, will usually reveal a preponderance of the abnormal cell type no matter what the leukocyte count may be.

CHLOROMA. This term refers to a variant of acute leukemia which is characterized by the presence of greenish localized tumors, connected particularly with the periosteum and ligamentous structures of the skull, paranasal sinuses, orbits, spine, ribs, and sacrum. Protrusion of an eyeball, with diplopia and loss of vision, pain, deafness, and signs of various cranial nerve palsies, or other effects of pressure or infiltrative growth, should lead to suspicion of chloroma in a case otherwise consistent with a diagnosis of acute myeloblastic leukemia.

CHRONIC MONOCYTIC LEUKEMIA. The great majority of cases of monocytic leukemia are acute or subacute, as already described. A small number are slower in their course. Relatively low or subnormal leukocyte counts, bone pain, and cutaneous manifestations have characterized these cases.

LYMPHOSARCOMA-CELL LEUKEMIA. The "lymphosarcoma cell" is about 9 to 14 microns in diameter, has a sparse but deeply basophilic cytoplasm, an oval, oblong, or kidney-shaped nucleus with coarsely reticular, spongy chromatin, and a single, prominent nucleolus. Such cells are seen in cases fitting the category of "leukosarcoma," proposed by Sternberg. Enlargement of lymph nodes in any one of many sites, but especially in the anterior mediastinum, or symptoms referable to anemia, may for months or even years precede the appearance of these cells in the blood. The leukocyte count may remain normal or low for a long time or even throughout the illness, even though 30 to 98 per cent of the cells may ultimately be of the lymphosarcoma cell type.

PLASMA-CELL LEUKEMIA is the term applied to rare cases in which plasma cells have been

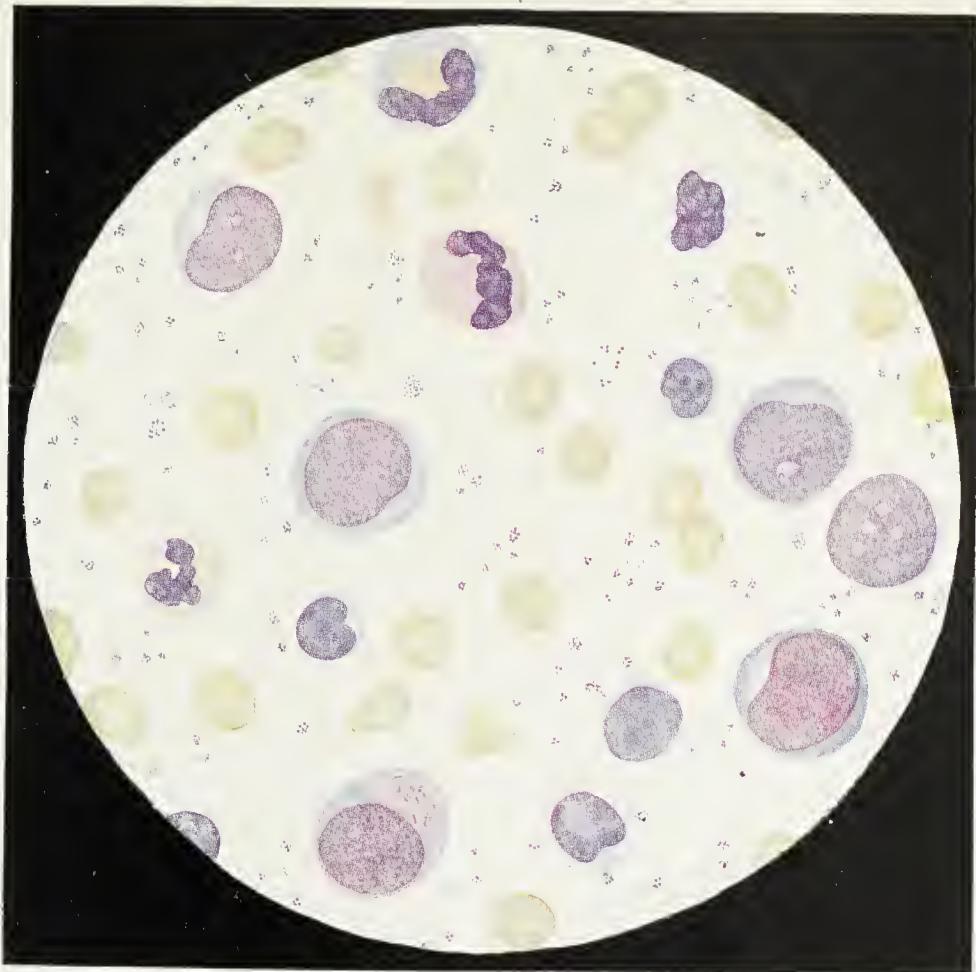


PLATE III

(Top) Acute leukopenic myelogenous leukemia. (W.B.C. 3000.) Film from buffy coat. Actual field. Five myeloblasts, several showing nucleoli. (Lower left) Promyelocyte. Three nonsegmented neutrophils, practically destitute of granules (toxic-degenerative changes). (Lower right) Two megakaryocyte nuclei with shreds of platelet material attached.

(Bottom) Cells from case of acute monocytic leukemia. (1 to 14) Monocytes. (1 and 3) Monoblasts.

(Courtesy, Stitt, Clough, and Branham, "Practical Bacteriology, Hematology, and Parasitology," 10th ed., Philadelphia, The Blakiston Company.)

found in the blood but which in other respects resemble leukemia—i.e., with leukocytosis, anemia, and splenic and frequently lymph node and hepatic enlargement. This disorder is perhaps but a variant of *plasmacytoma*, a disorder in which tumors consisting of plasma cells are found in the bone, the upper respiratory passages, the cornea, the pleura, and elsewhere.

A number of other, still more rare forms of leukemia have been described which cannot be discussed here. Such cases, and lymphosarcoma-cell leukemia, plasma-cell leukemia, and cases of lymphocytic leukemia with only minor changes in the blood, give support to the view, now widely held, that these conditions and those chiefly affecting lymph nodes, such as lymphosarcoma, as well as multiple myeloma, are very closely related disorders or simply variations of a single abnormal process.

DIAGNOSIS

The diagnosis of leukemia is not difficult in most cases. Confusion may arise when the blood has not been examined thoroughly, when the question of a leukemoid reaction arises, or when the blood is subleukemic.

Instances of chronic leukemia because of lymph node or splenic enlargement may suggest one of the various disorders affecting lymph nodes or the spleen (p. 1225) or, if the chief symptoms draw attention to other systems of the body, a very great variety of conditions may be simulated. Acute leukemia, as already mentioned, may suggest acute inflammatory conditions of various kinds, purpura hemorrhagica, or other disorders.

Hemopoietic responses which suggest leukemia ("leukemoid pictures") may be observed under a variety of circumstances:

1. In association with *infections*. A picture resembling myelogenous leukemia is sometimes associated with pneumococcal and meningococcal infections and rarely is seen in diphtheria and tuberculosis. Lymphocytic leukemia may be suggested by the leukocytic reaction in whooping cough, infectious mononucleosis, and infectious lymphocytosis, in particular, and sometimes in chickenpox.

2. *Intoxications*. In rare instances of eclampsia, severe burns, diabetic acidosis, and mercury poisoning, leukemoid pictures have been observed.

3. *Malignancy*, especially with bone metastases,

as well as in multiple myeloma, myelosclerosis, and Hodgkin's disease.

4. Following *severe hemorrhage or the rapid destruction of blood*, when the profound stimulus to the bone marrow may bring forth a marked leukocytosis as well as immature forms of the nucleated red corpuscle series.

The essential findings in the blood which favor leukemia rather than a leukemoid reaction are (1) pronounced immaturity of the leukocytes, which is more significant than their number; and (2) evidence of other hemopoietic disturbances. This includes (a) anemia; (b) the presence of immature red corpuscle forms in the blood, such as nucleated red corpuscles and polychromatophilia; and (c) platelet abnormalities, especially thrombocytopenia. Only in the early stages of chronic leukemia are anemia and other signs of disturbed hemopoiesis lacking. In leukemia the immaturity of the leukocytes often is not orderly as in the case of a physiologic response, where there are successively fewer numbers of the various immature forms, with at most but a small number of myelocytes and but 1 or 2 per cent of myeloblasts.

These criteria usually suffice to distinguish leukemia from a leukemoid reaction. In addition, the clinical findings, such as splenomegaly, lymphadenopathy, and sternal tenderness, make it apparent that one is dealing with leukemia. On rare occasions, however, differentiation is quite difficult, for the disease simulating leukemia may be accompanied by some of these physical signs, and even immature forms of the red corpuscle series may find their way into the blood.

In subleukemic leukemia especially, and in the less clear instances where leukocytosis is present, the *bone marrow* examination is very helpful, for there abnormalities will usually be found which are well beyond the normal variations. Only in the early stages of chronic lymphocytic leukemia or in the rare cases in which the marrow involvement is not diffuse is the sternal puncture likely to be disappointing. In chronic myelocytic leukemia the cells in the bone marrow may be at a slightly less mature level than in the blood. In acute myeloblastic leukemia, even when there are few immature forms in the blood, the marrow is crowded with myeloblasts. In other types of acute leukemia the corresponding cells or their precursors will be found in large numbers in the marrow (see p. 255).

Other examinations which may be helpful in

reaching a diagnosis include *roentgenography* of the bones, which may reveal subperiosteal infiltration, osteolytic or tumor-like changes; measurement of the *basal metabolic rate*, which is increased in many cases of leukemia; and sometimes lymph node biopsy.

COURSE AND PROGNOSIS

With the possible exception of four instances, there are no authentic reports of cure of leukemia. In chronic leukemia the course is rarely if ever interrupted by spontaneous remissions. In acute leukemia such remissions are observed occasionally and may last for several weeks. The duration of life in cases of chronic leukemia varies greatly. In some, death ensues in a year or two after symptoms first appear; in others, the course may be extremely protracted, extending over 10 or 15 years and, very rarely, even longer. In certain cases such apparent long or short duration depends respectively upon early diagnosis or late discovery of the disease. In most instances the essential factor probably consists in different intensities of the pathologic process. The average duration of life in chronic leukemia of all varieties is three and a quarter years. Perhaps 10 per cent of cases survive more than five years. In acute leukemia, survival for but eight weeks, at the most, is encountered in about three quarters of the cases, the remainder living as long as three to six months, rarely longer.

In chronic leukemia, treatment, even though it may not increase survival time by more than six months or a year, can for much of the time make the difference between a state of chronic invalidism and a condition of well-being which may approach normality. In acute leukemia such benefit from treatment is rare, but newer methods are beginning to offer more promise.

Prognosis in chronic leukemia can be judged more from the degree of anemia and the extent of weight loss than from the magnitude of the leukocyte count, especially if these fail to respond following therapy. Thrombocytopenia is also an unfavorable sign, for, except in occasional cases of chronic myelocytic leukemia, this indicates extensive infiltration of a degree not likely to be greatly influenced by treatment.

TREATMENT

There is no specific therapy for leukemia but, in chronic leukemia, irradiation or chemotherapy

may bring about considerable improvement and produce a state of relatively good health for a significant length of time. Blood transfusion is of temporary value in both chronic and acute leukemia. Certain chemotherapeutic agents may offer a measure of relief in acute leukemia. In addition to these procedures, general measures and rest in bed when there is fever, a well-balanced and nourishing diet, and, especially in acute leukemia, good oral hygiene should be provided. Antibiotics such as penicillin are helpful if infection develops or when severe leukopenia is present.

Irradiation. This is of value in chronic leukemia and may be given by means of roentgen rays, radioactive phosphorus (P^{32}), radium, thorium X, or mesothorium. Only the first two are now used. Increasing anemia, loss of weight, pressure symptoms, invasion of tissues with production of pain, or disfiguring or uncomfortable glandular enlargement are indications for treatment. These are of more importance than a high or rising leukocyte count. While hemorrhagic manifestations and thrombocytopenia, like anemia, may be due to marrow infiltration by leukemic cells and thus may be alleviated by treatment, more often they are part of the terminal picture of chronic leukemia and indicate that treatment is likely to be ineffective. Acute leukemia is another contraindication to irradiation. Such treatment is not only of little or no value but may be harmful.

Although roentgen therapy has been the generally accepted form of radiation therapy, the choice between this and treatment with P^{32} may be mainly a matter of availability and convenience. The details of dosage are matters for the specialist. Serial daily doses of 100 to 200 r or as little as 25 to 50 r, appropriately filtered and over specified areas, are used by various workers.

Treatment is stopped when the leukocyte count has fallen to approximately 25,000 per cu. mm., but this is not an absolute criterion since irradiation, given cautiously, may prove effective even in cases with leukopenia.

Treatment with phosphorus made radioactive (P^{32}) offers the advantage that the radioactive material is concentrated in the position where it is especially required—that is, in those tissues which have a high phosphorus content and metabolize phosphorus rapidly: the liver, spleen, kidneys, and bone marrow. The material can be given orally or intravenously and, unlike roent-

gen irradiation, it does not result in radiation sickness.

Chemotherapy. Benzene, solution of potassium arsenite (Fowler's solution), nitrogen mustard (HN₂ or methyl-bis [β-chloroethyl]amine hydrochloride), urethane (ethyl carbamate), and folic acid antagonists such as aminopterin, are the agents which have been used. Benzene is no longer employed, partly because of the danger of serious toxic effects. ~~If Fowler's solution is a useful substance since it is readily available and is administered easily. A simple procedure consists in the administration of 0.3 ml. (5 minims) three times daily for two days, preferably in orange juice, immediately after or with meals. The quantity is successively stepped up in the course of 10 days until 0.6 ml. are being taken three times daily. The dose can then be increased more slowly until nausea, anorexia, vomiting, diarrhea, or other toxic manifestations develop or a therapeutic effect has been achieved. If toxic symptoms appear or the leukocyte count is falling, medication can be omitted for two to five days, and then is decreased from the maximum in a stepwise fashion until a maintenance dose of 0.3 to 0.6 ml. three times daily is reached. A disadvantage of this form of therapy is that administration of Fowler's solution cannot be interrupted if the disease is to be controlled at all.~~

~~X Nitrogen mustard is given intravenously in doses ranging from 0.1 to 1 mg. per kg. of body weight. In the average case of chronic myelocytic leukemia, 0.6 to 1 mg., given in divided doses, is necessary to bring the leukocyte count to normal and to produce significant improvement. Cases of chronic lymphocytic leukemia are sometimes very sensitive to this drug and as little as 0.2 mg. may produce a marked fall in the leukocyte count. The drug is available in vials containing 10 mg. In order to prevent thrombosis, a solution of normal saline is first introduced intravenously, and when this is flowing freely, 10 ml. of saline is added to the vial, where the drug dissolves readily. The appropriate dose is withdrawn and injected through the rubber tubing of the saline infusion. Nausea and even vomiting may follow several hours after injection of the drug, but this is usually of shorter duration, even though sometimes more intense, than that seen in irradiation sickness. Once the patient has attained a remission with nitrogen mustard therapy, a state of good health may be maintained by injections of~~

0.1 to 0.3 mg. per kg. of body weight at intervals of two to four or more weeks.

~~Urethane~~, given in doses of 1 to 6 Gm. daily by mouth, has proved of value in many cases of chronic myelocytic leukemia, less often in the lymphocytic form. Nausea and anorexia may be produced by the drug, but if such symptoms are lacking or not troublesome, the drug is continued until there has been a reduction in the leukocyte count and in anemia, as well as clinical improvement. The amount required to achieve this goal may total 150 Gm. Smaller amounts (0.5 to 2 Gm. daily) will serve for maintenance therapy, or the drug may be given intermittently.

These agents, as already indicated, will bring symptomatic relief in many cases of chronic leukemia: lymph nodes will decrease in size, the spleen will become smaller, anemia will decrease or disappear, weight will be gained, and a sense of well-being will return, to remain for variable lengths of time. The various agents described are more likely to be beneficial in cases of chronic myelocytic leukemia than in the lymphocytic form, except in the early stages of the latter, but considerable individual variation is encountered. Of great importance is the fact that where one therapeutic agent is failing another may be helpful for a time. Furthermore, convenience and availability of the various therapeutic agents sometimes are considerations of importance.

Although these agents are of little value in acute leukemia, it is worth keeping in mind that nitrogen mustard may give at least temporary relief when bone pain exists. ~~The folic acid antagonists~~, such as aminopterin (4-amino, pteroyl-glutamic acid), appear to offer more temporary benefit in acute leukemia than any agents used heretofore. Remissions have been observed in as many as 30 per cent or more of cases, especially in children. Exchange transfusions have also been described as producing striking though temporary benefit in acute leukemia. The effects of the administration of adrenocorticotropic hormone (ACTH) and of the adrenal cortex hormone, cortisone, are being studied.

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Diseases of the Spleen and Reticuloendothelial System

M. M. Wintrobe

Chronic Congestive Splenomegaly

- Definition
- History
- Etiology
- Pathology
- Symptoms
- Diagnosis
- Prognosis and Treatment
- Gaucher's Disease
- Definition
- Etiology, Morbid Anatomy, and Pathogenesis
- Symptoms
- Diagnosis
- Treatment and Prognosis
- Niemann-Pick Disease
- Hand-Schüller-Christian Disease

The functions of the spleen were outlined in an earlier chapter (p. 271). Disorders of the spleen most frequently produce enlargement of this organ. The significance of splenic enlargement has been considered already, and the differential diagnosis of splenomegaly was discussed there (p. 272). Here several of the disorders which involve the spleen, in particular, will be described.

Disorders of the spleen not hitherto considered include congenital anomalies, rupture, and infarction. *Congenital anomalies* may take various forms. Instead of being a single organ, the spleen may be subdivided into numerous small spleens, or a spleen of normal size and shape may be accompanied by one or more accessory spleens. Rarely, the spleen assumes a retroperitoneal position and may force the left kidney downward. A *movable* spleen may be found in any part of the abdomen. If its pedicle becomes twisted, there may be sudden pain, enlargement, and signs of shock, as well as fever and vomiting if the torsion has developed acutely. Less severe symptoms occur if the process is more gradual.

Rupture of the spleen may occur following trauma, particularly if the spleen is diseased.

Malaria, typhoid fever, and infectious mononucleosis are among the diseases in which this has been observed. Agonizing abdominal pain or pain in the left scapular region, together with signs of internal hemorrhage, characterize this catastrophe. Anemia develops rapidly and leukocytosis occurs. Prompt surgical treatment is imperative.

Infarction of the spleen may be sterile, in which event it is followed eventually by fibrosis and shrinkage. This has been observed as a complication of leukemia. A septic infarct may terminate with the formation of an abscess. The most common symptom of infarction is pain. Careful examination will reveal a friction rub. Unless an abscess forms, necessitating surgical intervention, sedation and abdominal support to impair movement of the spleen suffice.

CHRONIC CONGESTIVE SPLENOMEGLY

(Banti's Syndrome, Splenic Anemia)

Definition. These terms refer to a syndrome characterized by splenic enlargement, leukopenia, anemia and often thrombocytopenia, a tendency to gastric hemorrhage, and, in many cases, cirrhotic changes in the liver.

History. The term *splenic anemia* was originally used (1866) to refer to cases of anemia with splenomegaly which were not frank leukemia. Banti, in 1882 and subsequently, described a form of splenomegaly of unknown etiology associated in its earliest stages with leukopenia, asthenia, and occasional hemorrhagic episodes. In the intermediary stage, hepatic enlargement occurred, as well as urobilinuria and a dirty brown-

ish discoloration of the skin. The final stage consisted of liver atrophy and ascites.

Etiology. Banti described the spleen as being characterized by conspicuous thickening of the fibrillar reticulum in the Malpighian corpuscles and red pulp ("fibro-adenie"). These changes originated around the central artery of the follicle. In his opinion, the spleen was the primary seat of the disease. Later work showed that these changes are not specific and can be encountered particularly when there is increased venous pressure in the portal bed. Thus the designation *chronic congestive splenomegaly* has arisen. Cirrhosis of the liver, cavernous transformation of the portal vein, portal vein and splenic vein thrombosis, or variants in the anatomy of the venous pattern have been found in as many as 60 per cent of the cases. Active congestion in the spleen in the absence of venous obstruction has also been proposed as a cause of this syndrome. This concept depends on the hypothesis that there is primary disease of the splenic arteries with the result that they fail to control the amount of blood entering the spleen, thus permitting congestion to develop.

Pathology. The spleen weighs 600 to 1200 Gm. as a rule, but may weigh as much as 5000 Gm. At first one finds an increase in the reticulum, cellular hyperplastic pulp, degenerative changes in the follicular arterioles, and congestion. Later the follicles become smaller, while fibrosis of the reticulum, trabeculae, and capsule increases. Periarterial hemorrhages, and siderotic nodules deposited in the fibrous tissue around the arterioles, are found in many instances.

Symptoms. Young adults are most frequently affected, but the disease may come on in childhood. The onset is usually insidious. The condition may ultimately attract attention in a variety of ways. There may be gastrointestinal complaints of vague character, probably attributable to the large mass in the left upper quadrant; the mass itself may be noticed accidentally; symptoms of anemia may become prominent; or the disorder may be announced explosively by the occurrence of a gastric hemorrhage. The spleen may extend to the pelvic brim. Ultimately the symptoms and signs of cirrhosis of the liver appear. Obstruction of mesenteric veins may lead to the development of hemorrhoids, while occlusion of the portal vein is followed by the appearance of signs of collateral circulation.

The anemia is normocytic and moderate in degree unless hemorrhage has occurred, when it may be microcytic hypochromic in type. In cases with long-standing and severe liver disease the anemia may be macrocytic. Leukopenia is found consistently and thrombocytopenia is observed frequently. The bone marrow may show no abnormality, or slight myeloid hyperplasia may be present.

Diagnosis. Other conditions leading to pan-cytopenia (p. 1212) must be excluded. Congenital hemolytic jaundice is not associated with leukopenia as a rule, and may be distinguished also by the finding of reticulocytosis, increased hypotonic saline fragility, and the presence of spherocytes. Hookworm infection may produce chronic hypochromic anemia with moderate splenomegaly. Liver function should be studied in suspected cases, and esophageal varices looked for. If liver function is good and other conditions have been excluded, portal or splenic vein thrombosis should be suspected.

Prognosis and Treatment. Unless serious hemorrhage ensues, the course of the disease is slow as a rule and relatively benign. Patients may live for 10 years or longer. The chief nonsurgical procedures are administration of a diet rich in protein, and otherwise complete as well; administration of iron if there has been hemorrhage; and blood transfusion if bleeding has occurred recently. Splenectomy is recommended if the spleen is excessively large. In any event, abdominal exploration is advisable, since some cause for congestion in the portal bed may be discovered and thereupon treated. Splenectomy reduces the likelihood of hemorrhage from varices, especially if combined with an end-to-side anastomosis of the splenic and left renal veins where the splenic vein is intact. Other venous shunts are also receiving trial. The effect of splenectomy on the blood picture is of interest since the leukopenia disappears, sometimes permanently, anemia may be relieved in whole or in part, and the platelet count is also likely to be restored to normal.

GAUCHER'S DISEASE

Definition. This is a rare, chronic familial disorder characterized by marked splenomegaly and often also by skin pigmentation, pingueculae of the scleras, and bone lesions.

Etiology, Morbid Anatomy, and Pathogenesis. The disorder usually is apparent early in life. It

has a predilection for females, and the condition has been observed most often in Jewish families. The characteristic finding is widespread reticulum cell hyperplasia, these cells being filled with kerasin. Consequently, Gaucher's disease is classed as a disturbance of lipoid metabolism. The cause is unknown. The cells are distinctive, being 20 to 80 microns in diameter, round, oval, or spindle-shaped, and possessing one or more small, eccentrically placed nuclei. Appropriately stained, the cytoplasm shows numerous wavy fibrillae. (Plate II, facing p. 1204.) These cells are found in the spleen, bone marrow, lymph nodes, and liver. The spleen may weigh several thousand grams.

Symptoms. The enlargement of the spleen is usually the outstanding manifestation, sometimes the only one. There may be a dragging sensation or pain due to infarction. Pain in the limbs, due to bone involvement, may develop. The liver may be enlarged, but the lymph nodes usually are not palpable. Roentgenograms may reveal osseous changes. Hemorrhage from the nose or gums is relatively common. Light yellowish brown discolorations on the conjunctivas on either side of the cornea, and an ocher to brown hue of the skin, may be present.

As in other splenic disorders, moderate anemia, leukopenia, and thrombocytopenia are the usual blood findings.

Diagnosis. Diagnosis can be made by sternal or splenic puncture which will reveal the characteristic cells.

Treatment and Prognosis. Although the disease coincidentally involves other parts of the reticuloendothelial system, splenectomy is worth while if the spleen is very large and thereby causes discomfort, or if there are serious symptoms attributable to the blood changes. In infants the prognosis is not good, but those who

have survived to adolescence may live for many years even if splenectomy is not performed.

NIEMANN-PICK DISEASE

This is a lipoid disorder of the reticuloendothelial system very similar to Gaucher's disease except that the condition has been observed only in infancy and its course is much more acute, death occurring within a few months after birth. The characteristic cells are filled with small, round, hyaline droplets, grouped in clusters and giving the appearance of a honeycomb. The stored material is a phospholipid, perhaps sphingomyelin.

HAND-SCHÜLLER-CHRISTIAN DISEASE

(Xanthomatosis)

This is another disorder of lipoid metabolism which is characterized especially by exophthalmos, diabetes insipidus, and defects in the membranous bones. These manifestations are produced by the growth of a characteristic type of granulation tissue with cells containing cholesterol and its esters. Unlike Gaucher's disease and Niemann-Pick disease, there is no family predilection, and splenomegaly and hepatomegaly do not always occur and are never conspicuous. The onset often is in the first two years of life or in the first decade. The blood may show pancytopenia. Death may not ensue for many years, but considerable disability may occur in the interval.

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Hodgkin's Disease and Other Conditions Chiefly Affecting Lymph Nodes

M. M. Wintrobe

Definition
History
Classification
Etiology
Symptoms
Blood Picture
Bone Marrow Picture
Diagnosis
Treatment
Prognosis

In an earlier chapter (p. 269) the causes of lymph node enlargement were discussed and their differential diagnosis considered. In this section the clinical manifestations of Hodgkin's disease and of other conditions chiefly affecting lymph nodes, such as lymphosarcoma, will be described. These disorders will be considered under one heading because their clinical manifestations are very similar.

Definition. Hodgkin's disease, lymphosarcoma, giant follicular lymphoblastoma (lymphoma), and reticulum-cell sarcoma are included in this group. They are characterized by painless, progressive enlargement of lymphoid tissue. Lymphadenopathy is a characteristic feature and the spleen is frequently enlarged. Cachexia, anemia, and, in many instances, fever usually are late symptoms.

History. A disorder affecting the "absorbent glands and spleen" was described by Hodgkin in 1832. "Lymphoblastoma," "malignant lymphogranuloma," and many other terms were used in referring to the disease in subsequent descriptions. Jackson and Parker have attempted to classify the disorder in three categories—paragranuloma, granuloma, and Hodgkin's sarcoma. The picture of lymphosarcoma was described by Kundrat in 1893, while Brill, Baehr, and Rosenthal differentiated giant follicular lymphoblastoma in 1925. Roulet (1932) separated reticulum-cell sarcoma from the general group of malignant diseases of lymphoid tissue. Some pathologists differentiate still other groups or call these by other names; others seek to avoid fine separations.

Classification. Clinically these disorders vary considerably in severity. Histologically they show marked differences, but these are not well correlated with the clinical picture. They have been classified in various ways on histologic grounds. One of the most simple is that which differentiates those conditions with a simple histologic pattern from those with more complex patterns. In the first category are reticulum-cell sarcoma and lymphosarcoma. The proliferating cells tend to encroach upon, obscure, and finally replace the architecture of the lymph node. The histologic pattern of Hodgkin's disease is more complex. Lymphocytes, plasma cells, granulocytes (eosinophilic and neutrophilic), monocytes, fibroblasts, and giant cells make up the picture. The giant Reed-Sternberg cells are 10 to 40 microns in diameter and possess abundant cytoplasm, a multilobed nucleus or multiple nuclei, and prominent nucleoli. A variable amount of fibrosis may be present and the lymph node architecture is often lost. In giant follicular lymphoma the histologic pattern is also somewhat complex, but the striking feature is the presence of multiple, follicle-like nodules of various sizes. Other types of "lymphoma" are observed from time to time which are difficult to classify.

Etiology. Hodgkin's disease forms about one third to one half of all cases of this group. It affects a younger age group than the other conditions, being most common in the second and third decades. However, no age is immune. Males are more frequently affected than females.

The cause of these disorders is unknown. There may not even be the common denominator of neoplastic growth to join them, for many consider Hodgkin's disease to be an infectious granuloma. Efforts to transmit the disease to animals have failed, however, and attempts to incriminate various organisms, including the tubercle bacillus, human and avian, diphtheroid bacilli, and *Brucella* organisms, have not succeeded. An

agent in the lymph nodes found to produce encephalitis on inoculation into animals appears to be a nonspecific chemical substance derived most probably from eosinophilic leukocytes. The other disorders in this group are assumed generally to be true neoplasms. This applies even to giant follicular lymphoma, which at first was considered a benign disease.

Symptoms. In most cases lymph node enlargement, usually cervical, is the first symptom to attract attention. This may be bilateral, but is more often unilateral at first. More rarely the axillary or the inguinal nodes are the first to enlarge. The nodes are discrete and movable at first; only later do they become matted together and fixed. They are painless and not tender, and the overlying skin is normal. The size of the nodes ranges from that of a pea to that of a large orange. There is a resilient firmness in most instances, but the growth of connective tissue may make the nodes of Hodgkin's disease harder in the course of time. Occasionally the nodes in the axillary or inguinal regions may become secondarily inflamed and even break down.

After an interval varying from months to years, evidence appears of lymph node involvement elsewhere. This may affect other superficial nodes: supraclavicular, axillary, inguinal, subpectoral, brachial, or femoral. A common site, also, is the mediastinum, to which such symptoms as cough, dyspnea, stridor, or dysphagia should attract attention. Splenoinegaly develops in more than half the cases of Hodgkin's disease and of giant follicular lymphoma; less frequently in the other forms. The liver is often palpable. Ultimately cachexia develops and weight loss occurs.

The mode of onset of these disorders may vary greatly, however. The manifestations may arise first in the mediastinum, the lungs, the digestive tract, the genitourinary tract, the bones, and, rarely, the nervous system. Infiltration of the lungs, atelectasis, or pleural effusion may occur. In the gastrointestinal tract the tumor may be far advanced before it is first discovered. Colicky pain, loss of weight, anemia, a palpable tumor, and obstruction are signs produced by lymphosarcoma of the small intestine. When the retroperitoneal nodes are the chief ones to enlarge, the diagnosis may be very difficult to make and the chief symptoms may be fever, pain, and loss of weight. Hematuria, pyuria, or pain are found when the genitourinary tract is involved. Local-

ized pain and tenderness, spontaneous fractures, and neurologic changes due to extension into the spinal canal from vertebral lesions are the most common manifestations of bone involvement. Areas of rarefaction may be demonstrable in roentgenograms, although symptoms may be present long before roentgenographic signs become evident. Subperiosteal infiltration may occur or the bone marrow involvement may be extensive. Of cutaneous manifestations, pruritus is the most frequent, and this is encountered particularly in Hodgkin's disease. Brownish skin pigmentation, herpes zoster, and nodules produced by infiltration by the specific cells are among other skin manifestations which may be encountered. Symptoms and signs may also develop which are secondary to swellings producing pressure in various areas.

Constitutional symptoms may appear early in Hodgkin's disease, but they occur late in the other lymph node disorders. Hodgkin's disease, in particular, may produce a great variety of manifestations, so that, in addition to the localized form which is much the most common, a generalized type, an acute type with death in a few weeks or months, a "larval" or abdominal form, and a splenomegalic type have been described in addition to those already discussed.

Fever is common in Hodgkin's disease, although the well-known Murchison-Pel-Ebstein type is actually uncommon, appearing no oftener than in 16 per cent of cases. This form of fever consists of febrile periods of several days' to several weeks' duration in which the temperature remains at levels of approximately 102° to 104° F., alternating with periods of weeks to even months during which there is no fever whatever.

BLOOD PICTURE. The greatest degree of variation is found in the blood picture associated with these disorders. There may be no changes whatever. On the other hand, there may be profound anemia as well as striking changes in the leukocytes and platelets. In Hodgkin's disease, changes in the blood occur relatively early. The anemia in Hodgkin's disease is usually only moderate in degree and normocytic in type; very occasionally, hemolytic anemia develops. The total leukocyte count in Hodgkin's disease may be slightly or moderately increased, it may be normal, or there may be leukopenia. Sometimes the leukocyte count may exceed 25,000 per cu. mm. The differential count may show a tendency to neu-

trophilia, relative and absolute lymphocytopenia, monocytosis, or eosinophilia. All of these changes may be present at the same time, or none of them. Eosinophilia, which is mentioned frequently as characteristic of Hodgkin's disease and which may sometimes be very pronounced, is found only in about 20 per cent of cases. An absolute increase in the number of lymphocytes suggests some disease other than Hodgkin's. Neutropenia suggests extensive bone marrow or splenic involvement.

The leukocyte picture in the other forms of disease chiefly affecting lymph nodes is more frequently normal than is the case in Hodgkin's disease. Relative and even absolute lymphocytosis may be seen. The lymphocytes may be of normal types, but unusual forms and "tumor cells" (p. 1218) have been described. Monocytes may be increased in number and young forms may be seen, but a consistent and characteristic picture has not been described.

The platelet count may be increased in Hodgkin's disease, and large, bizarre forms may be seen. It is more common, however, to find the platelet count normal. In some instances thrombocytopenia is present; this usually occurs when leukopenia is found as well. The presence of thrombocytopenia suggests extensive bone marrow or splenic involvement and is usually, although not necessarily, a grave sign.

BONE MARROW PICTURE. As would be expected from this description of the blood findings, changes in the bone marrow are not characteristic and are seldom helpful except in rare cases of so-called "bone marrow Hodgkin's" in which there is extensive involvement of the bone marrow. Reed-Sternberg cells have been demonstrated in the bone marrow in a few cases of Hodgkin's disease. Lymphocytosis may be found in the bone marrow in some cases of lymphosarcoma and of giant follicular lymphoma. Such cases raise serious doubt as to whether there is any true difference between them and chronic lymphocytic leukemia.

Diagnosis. The differential diagnosis of lymph node enlargement was discussed in an earlier chapter (p. 271). Cases in which there is little or no enlargement of the superficial lymph nodes present the most difficult problem in diagnosis, for then a variety of inflammatory and neoplastic disorders of the mediastinum, lungs, gastrointestinal tract, or liver must be considered, and the

possible presence of chronic infections such as brucellosis must be ruled out. Hodgkin's disease, in particular, may produce such varied manifestations that this disorder must be kept in mind almost wherever diagnosis is obscure. This disease is particularly suggested by such symptoms as relapsing fever, loss of weight, and splenic or hepatic enlargement, together with anemia and leukocytosis or leukopenia.

Treatment. Surgical excision, irradiation, and chemotherapy each have their place in the treatment of these disorders. Surgery is useful when the condition is definitely localized, irradiation is effective in the treatment of local manifestations and when the disease is generalized, and chemotherapy is particularly indicated when the disorder is widespread. Sometimes all three forms of therapy can be employed, and frequently there are advantages in using both irradiation and chemotherapy.

Since these conditions, in many instances, appear to arise locally and only disseminate later, surgical excision should be an excellent form of therapy. Unfortunately, correct diagnosis is not often made early. Furthermore, in many instances in which the disease seems to be local, dissemination has already occurred or has been present from the beginning. Nevertheless, this form of therapy, when appropriately applied, offers the only chance of cure. Surgical excision, if undertaken, must be radical and should be followed by irradiation or chemotherapy or both.

Roentgen rays represent the preferred method of irradiation, this apparently being somewhat superior to the use of radioactive phosphorus and more effective than radium. Generally speaking, segmental or localized irradiation is used rather than total irradiation, except in cases in which generalization has taken place. Various areas are treated in succession. The decision as to dosage is the problem of the radiotherapist. The total amount depends on the response of the lesions to therapy, the general effects on the patient, and the effect on the blood. The effect of irradiation may be dramatic, large masses melting away in the course of a week. Pressure symptoms may disappear; fever and pruritus, if present, may be relieved; and pain caused by bone involvement may be alleviated. Pulmonary lesions may decrease in size and pleural effusions may clear. Anemia may disappear and the leukocyte count, if elevated, may drop to normal. In other cases,

irradiation is less effective, in some instances being of scarcely any benefit. Prediction in advance as to the likelihood of benefit from therapy is often difficult. In general, the more chronic and slowly growing forms respond best to therapy. Remission following treatment may last but a few weeks or may persist a year or longer. In some cases such improvement can be reproduced many times by additional therapy.

The action of nitrogen mustard in these disorders is similar to that of irradiation, but in certain cases of Hodgkin's disease this drug seems to be more effective than irradiation. It has been found that, in some cases previously given roentgen therapy and no longer responding to such treatment, nitrogen mustard therapy has been distinctly beneficial. Other cases treated with nitrogen mustard from the beginning have responded well and, in general, in a manner similar to that already described under roentgen therapy. Fever often disappears promptly, and anemia, if present, also is alleviated. Abnormalities in the leukocytes may revert toward normal although the immediate effect, noticeable within 5 to 14 days following the first dose of nitrogen mustard, may be leukopenia and an increase of anemia. Thrombocytopenia, if present at the initiation of therapy, is less likely to be relieved by treatment. The quantity of nitrogen mustard used has ranged from 0.1 mg. per kg. of body weight to 0.8 mg. in a course. This amount can be given in

divided doses or as a single injection of the methyl-*bis* (β -chloroethyl)amine hydrochloride (HN2). The method of administration has been described already (p. 1221).

In addition to these measures, general supportive and symptomatic therapy will be required in individual cases.

Prognosis. The most important factor which seems to determine the course of these disorders is their inherent character. Cases of Hodgkin's disease and of lymphosarcoma are known to have run a very chronic course for many years. In other instances the course is rapid and progress occurs in spite of therapy. In general, cases with the most favorable outlook are those in which only one accessible lymph node group is affected and where evidences of systemic involvement such as fever, loss of weight, increased sedimentation rate, and changes in the blood are lacking. In the last analysis, a therapeutic trial should be attempted, for a prolonged remission may sometimes be encountered even in cases in which the general examination suggests a hopeless prognosis.

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Sarcoidosis

M. M. Wintrobe

Definition
 History
 Etiology
 Morbid Anatomy
 Symptoms

Laboratory Findings
 Diagnosis
 Prognosis
 Treatment

Definition. Sarcoidosis (Boeck's sarcoid, lupus pernio, Besnier-Boeck-Schaumann disease, benign lymphogranulomatosis, uveoparotid fever) is a chronic disease of unknown cause which involves many tissues, particularly the skin, lymph

nodes, eyes, salivary glands, lungs, and bones, especially of the hands and feet.

History. Schaumann, in 1917, showed that the disorder described by Besnier in 1889 (lupus pernio) and the sarcoid of Boeck (1899) were one

and the same and that the process is a generalized one. Since 1936 (LongCOPE and others), Heerfordt's uveoparotid fever has been regarded as one form or phase of this disorder.

Etiology. Those affected are most often between 15 and 40 years of age. Although in certain areas there seems to be a predilection for Negroes, no race seems to be exempt. The majority of cases have been described in the Scandinavian countries, northern Europe, England, and North America. The incidence of the disease does not suggest a familial or communicable basis. Nevertheless, many regard the disorder as infectious in origin, and tuberculosis has been cited as the underlying cause. The evidence for this view is meager, however. It is of interest that patients with sarcoid are more refractory to tuberculin than are normal persons of comparable age, sex, and race. Among other suggested causative agents are the *Mycobacterium leprae* and a virus.

Morbid Anatomy. The characteristic lesion is a granuloma consisting of large, pale, epithelioid cells collected in isolated nests or well-defined nodules, the so-called "hard tubercles." Pale multinucleated giant cells containing peculiar basophilic inclusions may be present. Necrosis or caseation does not occur and there is no inflammatory zone about the clusters of epithelioid cells. The evolution of the lesion is very slow, but fibrosis ultimately develops. Calcification does not take place. The characteristic granulomas may be found in many parts of the body, including the skin, lymph nodes, lungs, bone marrow, spleen, liver, mucous membranes, salivary and lacrimal glands, eye, tonsil, myocardium, nervous system, kidney, prostate, breast, and testis. The manifestations of the disease depend on the location of the lesions and may be those resulting from involvement of the lungs (polycythemia, cor pulmonale), heart (arrhythmia, failure), liver (hyperglobulinemia), thyroid (myxedema), pituitary (diabetes insipidus), kidneys (renal insufficiency), or testes (eunuchoidism).

Symptoms. The onset is insidious, as a rule, and a constitutional reaction is not usually observed. Fever is uncommon except in uveoparotid fever. In that syndrome, after a period of malaise, lassitude, and indefinite gastrointestinal symptoms, intermittent pyrexia of moderate degree may occur. The parotid glands enlarge and are firm but painless. Often one gland is affected later than the other. The mouth may become

very dry. Uveitis usually follows the parotid involvement. Conjunctivitis, keratitis, neuroretinitis, or other types of ocular involvement may occur. Seventh nerve paralysis, unilateral or bilateral, may follow, or there may be other evidences of cranial nerve involvement, or signs of a peripheral neuritis in one of the extremities may appear.

A skin eruption may herald the disease. Boeck described (1) small, firm, brown or blue cutaneous nodules in the butterfly area of the face and on the arms and back; (2) similar, larger nodules; and (3) a diffuse infiltration and thickening of the skin (lupus pernio) over the nose, face, eyelids, and ears. The skin is tense and bluish, but tiny yellow granules are found at the margins. Ulceration never occurs, but atrophic scars may remain when the lesion ultimately subsides.

Firm nodules may appear at the interphalangeal joints of the hands, producing sometimes a knotty appearance. There may be tightness or stiffness of the fingers. Roentgenograms may reveal rarefaction and trabeculation of the medullary portions of the shafts of the phalanges and metacarpal bones, or punched-out areas may be present in the small bones of the hands and feet (osteitis tuberculosa multiplex cystoides).

In other cases, general lymphadenopathy attracts attention first. The cervical, submaxillary, epitrochlear, axillary, and inguinal nodes may be involved, but preauricular, postauricular, and submental involvement are particularly suggestive of sarcoidosis. The individual nodes are usually moderate in size, firm in consistency, discrete, and not tender.

Extensive intrathoracic invasion may be present in the absence of symptoms or signs. The hilar nodes may be massive ("potato nodes"), and the paratracheal nodes are especially prone to be affected. The lesions may be widespread throughout the lungs, even to the extent that they may lead to embarrassment of the right heart. The distribution may be miliary with tiny densities appearing throughout the whole lung field, but more often diffuse or localized nodular parenchymal lesions are discovered to be scattered irregularly through the lung.

The liver or spleen may be enlarged, sometimes greatly. Involvement of the myocardium or pericardium may occur and interfere with the function of the heart. In general, it may be said that symptoms in sarcoidosis are caused prima-

rily by mechanical interference with the function of organs rather than by constitutional effects.

Laboratory Findings. Anemia is unusual. The leukocytes may be normal in number, or there may be slight leukopenia. Eosinophilia (6 to 35 per cent) has been noted in a number of cases. The total plasma proteins are usually increased, as a result of an increase in the plasma globulin. The serum calcium is often above normal, the phosphatase sometimes. Pleocytosis and increased protein in the spinal fluid may be associated with the uveoparotid syndrome.

Diagnosis. The characteristic features of the skin lesions which suggest this disease are their occurrence in groups bilaterally, their persistence and slow extension, and their lack of tendency to ulcerate. The finding or history of parotid swelling and uveal tract involvement, perhaps with facial nerve palsy, the invasion of the lacrimal and salivary glands, the lymph node involvement, and the lesions in the small bones of the hands and feet, offer evidence strongly suggestive of sarcoidosis. Reliance should be placed, however, on biopsy of affected structures whenever possible. Even small lymph nodes which may be thought to be insignificant are likely to show characteristic changes. Hodgkin's disease and tuberculosis, in particular, must be ruled out. In sarcoidosis the constitutional reaction, considering the degree of involvement, is singularly inconspicuous as compared with that expected in Hodgkin's disease or tuberculosis, and the Mantoux reaction and sputum are negative.

Silicosis may be suggested by the pulmonary lesions, syphilis by the bone lesions, and leprosy

by the skin changes. Periosteal changes are found in syphilis, not in sarcoidosis. The benign course and lack of constitutional symptoms rule out leprosy.

Prognosis. Spontaneous recovery may be anticipated in the majority of cases, but the condition is apt to run a long course, during which relapses, with involvement of different organs and tissues, alternate with quiescent or latent periods. Death may result from the accumulation of sarcoids in the mediastinum, lungs, heart, or central nervous system. The uveoparotid syndrome usually disappears, but some thickening of the parotid may persist, and scars, synechias, and even blindness may follow eye involvement. Tuberculosis has been demonstrated in approximately 30 per cent of cases coming to autopsy.

Treatment. A variety of remedies have been tried, including tuberculin, arsenic, gold, ultraviolet rays, roentgen rays, radium, and nitrogen mustard, but their efficacy is yet to be adequately evaluated. General hygienic and symptomatic measures are indicated as the need arises. Sanatorium care is inadvisable, since a tuberculous etiology has not been established.

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Multiple Myeloma

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Definition
Etiology
Symptoms

Diagnosis
Prognosis and Treatment

Definition. Multiple myeloma is a disorder characterized by the development of multiple tumors of bone which produce pain, pathologic

fractures, and anemia. There may be diffuse involvement of the bone marrow, and in the urine or blood a peculiar protein is usually found.

Rarely, a localized tumor is the only manifestation. Tumors composed of other types of cells have been described but the evidence is all in favor of a single type ("myeloma" or plasma cells).

Etiology. The disease appears most commonly after the age of 40 and is twice as frequent in males as in females. The cause is unknown. The true nature of the peculiar protein is not clear. Rather than being a neoplastic growth, it has been suggested that multiple myeloma is due to a derangement in protein metabolism.

Symptoms. Pain is the most frequent complaint and is produced by the tumors which, according to their location, may or may not be discoverable on physical examination. These are confined, for the most part, to the sites of the red marrow: the ribs, sternum, spine, clavicles, skull, or the extremities about the shoulder or pelvic girdle. Deformity, pathologic fractures, and neuralgic or neurologic symptoms may develop. Less frequently, anemia, abnormal bleeding, or symptoms suggesting nephritis are the chief manifestations. The tumors range from the size of a pea to that of a hazelnut.

Anemia is moderate in degree, as a rule, and normocytic, but sometimes it is severe and macrocytic. Enumeration of the cells may be difficult because of clumping, a peculiarity often related to the great quantity of globulin in the plasma. In blood smears there may be a marked tendency to rouleaux formation. Polychromatophilia, stippling, and even normoblasts may be found in the blood smear. The leukocyte count may be normal, slightly increased, or low. Myeloma cells like those seen in the bone marrow may be found. The platelet count is usually normal.

Hyperproteinemia may be present, and sometimes extremely high values are found. The increase is due to the globulin fraction. The nature of the peculiar protein is obscure. When the urine is heated, a white cloudy precipitate appears at temperatures of 50° to 60° C., but when the temperature is raised to near the boiling point the

precipitate redissolves. Such Bence-Jones protein has been observed in nearly 65 per cent of cases. Albumin, casts, and renal epithelial cells may appear in the urine, and evidence of renal functional impairment as well as nitrogen retention may develop.

The bone marrow frequently contains the tumor cells, although their number may range from 3 to 65 per cent. The "myeloma cell" is moderately large (15 to 30 microns), and round or ovoid, and contains a round, eccentrically placed nucleus which may contain one or two nucleoli. The chromatin is moderately coarse. The cytoplasm is bright blue. (Plate II, facing p. 1204.)

Diagnosis. The multiple bone lesions, the excretion of Bence-Jones protein, the hyperproteinemia, and the characteristic cells in the bone marrow form a combination of findings which makes the diagnosis quite evident. Difficulty arises when back pain, obscure anemia, or some complaint of nonspecific character has failed to suggest this disease and the appropriate examinations have not been made. Sometimes the picture may closely simulate hyperparathyroidism (see p. 580).¹

Prognosis and Treatment. The prognosis is unfavorable. The average duration is two years. Great variations occur, however. Roentgen therapy has been of little value. Stilbamidine and urethane have both been reported as being useful in relieving pain in certain cases.

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Section 2—The Cardiovascular System

A. Diseases of the Heart

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Introduction

T. R. Harrison and William H. Resnik

Of the various disorders which afflict mankind, those of the heart and blood vessels assume first rank. In the United States these disorders represent the single greatest cause of chronic disability, and are responsible for more deaths than the next five most common causes combined. As other diseases are conquered by the progress of medical science, the proportion of persons living to the advanced ages at which cardiovascular diseases are most common continually increases. Barring the possibility of as yet unforeseen discoveries leading to more effective prevention and treatment of these disorders, it can be estimated that one fourth or more of the present population of the United States will die of cardiovascular disease. Among males engaged in business and professions, the proportion will perhaps be nearer one half.

Our present knowledge of cardiovascular disease rests upon the solid foundation of clinical physiology. Among those who have contributed most to our understanding of these disorders are William Harvey, who first demonstrated clearly the circulation of the blood after this concept had been suggested by Cesalpino; William Withering, who introduced the use of digitalis into medical practice; René Théophile Hyacinth Laennec, who introduced auscultation, a method so beautifully expounded in heart disease by Pierre Carl E. Potain; William Heberden, who described angina pectoris; James Hope, who described the mechanism of congestive heart failure; Richard Bright, who first clarified the hypertensive and renal disorders; Sir James Mackenzie, who was the first to emphasize that the test of a heart is its response to effort; Ernest Starling, who established the physiologic basis of heart failure; Willem Einthoven, who devised the electrocardiograph; James Herrick, who developed

the modern clinical concept of myocardial infarction; Sir Thomas Lewis, who exemplified the importance of critical investigation in the study of patients with cardiovascular disorders; and Frank N. Wilson, who substituted understanding for confusion in the field of electrocardiography. These men and many who cannot be cited here were the trail blazers, while the roads have been built by the innumerable contributions of others.

The physician who is confronted with a patient presenting evidence of the possible presence of disease of the heart necessarily asks himself certain questions, of which the most important are the following:

1. Is heart disease present?
2. If so, what type of heart disease is it?
3. How serious is it?
4. What should be done about it?

In the sections to follow, an attempt will be made to consider these questions and, accordingly, the diagnostic, etiologic, prognostic, and therapeutic aspects of cardiac disease will be discussed in respective sequence. Since the subjects of senility, arteriosclerosis, hypertension, and rheumatic fever, the most common and important causes of cardiovascular disease, have been considered in previous chapters, the discussion to follow will deal only with such aspects of these topics as are especially pertinent. No attempt will be made to consider all of the less common causes of cardiovascular disease, and the discussion of etiology will be centered on those factors which are especially important, either because of frequency or because of susceptibility to cure.

The arrangement of this section on Diseases of the Heart departs from that traditionally given in discussions of the various types of cardiac disorder. To avoid needless repetition of symptoms,

signs, criteria of prognosis, and methods of treatment that are common to many forms of heart disease regardless of etiology, discussion has been arranged primarily according to the general topics of diagnosis, etiology, etc. The fundamental principles of diagnosis, prognosis, and treatment are, in the main, similar, irrespective of the basic causes of heart disease. To achieve this simplicity of arrangement and avoidance of unnecessary reiteration by rigid adherence to such a program is to introduce certain disadvantages. Thus, angina pectoris would require separate discussions under Pain in the Chest, Etiology, and Treatment; the arrhythmias would need consideration under Diagnosis and Treatment, etc. We believe that a strict pursuit of this plan contains inherent dis-

advantages that tend to nullify whatever logic resides in the approach to heart disease herein employed. Hence, we have finally attempted to resolve this dilemma of presentation by confining the discussion on Treatment chiefly to the treatment of congestive heart failure. The treatment of the manifestations of heart disease other than congestive failure are taken up in those chapters where these disorders seem naturally to fall. Thus, the symptoms, diagnosis, and treatment of the arrhythmias are considered together under Diagnostic Aspects of Heart Disease (Chapter 235); the special problems of symptomatology and treatment of other conditions, in the respective discussions under Etiologic Aspects of Heart Disease (Chapter 236).

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Diagnostic Aspects of Heart Disease (Including a Consideration of the Treatment of the Arrhythmias)

T. R. Harrison and William H. Resnik

Enlargement of the Heart	
Hypertrophy	
Dilatation	
Alterations in Heart Sounds	
Ventricular Volume Curve in Relation to Heart Sounds	
Three-Sound Rhythms	
Heart Murmurs and Diagnosis of Valvular Lesions	
Systolic Murmurs	
Diastolic Murmurs	
Disturbances of Rhythm and Rate of the Heart	
Sinus Arrhythmia	
Premature Beat	
Auricular Fibrillation	
The Less Common Arrhythmias	
Harmful Effects of the Arrhythmias	
Electrocardiography in Relation to Diagnosis of Cardiac Disease	
Cardiac Catheterization and Other Specialized Procedures	
Cardiac Catheterization	
Oximetry	
Angiocardiography	
Electrokymography	
Summary	

Chronic cardiac disease is of two general types, of which one is characterized by pain and the tendency toward sudden death, the other by dyspnea and the tendency toward congestive failure. In the diagnosis of the first type the informa-

tion obtained from the history is all-important as, has been stressed in a previous chapter (p. 21).

It should be emphasized at the outset that persons either do or do not have heart disease, and that, while the decision is at times difficult and rarely may be impossible, there is no intermediate state. Hence such terms as "a heart condition," "a tired heart," "myocardial damage," which are ordinarily used to conceal the physician's uncertainty, have no place in modern medicine. They should be relegated to limbo along with "anginoid," "pseudoangina," etc.

If one omits from consideration those types of cardiac disease related to disturbance of the coronary circulation and characterized by pain as the outstanding manifestation, it may be stated, as a general rule, that the recognition of *heart disease* depends on the objective information obtained by examining the heart, while the recognition of *heart failure* depends either on subjective

information obtained from the story, or objective phenomena to be found by examining the body as a whole rather than the heart. Since the present chapter is concerned with the diagnosis of heart disease rather than of heart failure (which will be considered in a succeeding chapter), the discussion to follow will center around the recognition of those objective findings which afford either suggestive or unequivocal evidence of the presence of structural cardiac change.

ENLARGEMENT OF THE HEART

This is the most common objective manifestation of cardiac disease. Enlargement is of two types—hypertrophy and dilatation. These commonly occur together and are related intimately to each other. However, since they produce somewhat different physical signs, and have somewhat different significance, they will be considered separately.

Hypertrophy. Much has yet to be learned about the exact mechanism responsible for an increase in the cardiac muscle mass. In most cases there is clear evidence that hypertrophy of the individual muscle fiber is related to increase in work, brought about either as the result of an increased load on the particular chamber concerned or as the result of disease of some fibers which become less able to carry their portion of the load, and hence cause the remaining fibers to have an additional burden. However, this explanation does not appear to be entirely valid for all instances, and it may be that, under certain circumstances, conditions other than increase in work may lead to hypertrophy of cardiac muscle fibers.

The clinical recognition of cardiac hypertrophy is not difficult in young, slender individuals, but may be impossible in older subjects with emphysema or obesity. Hypertrophy of the left ventricle ordinarily causes the cardiac impulse to become more forceful, but since the left ventricle makes up only a slight portion (in the region of the apex) of the projection of the heart onto the anterior chest wall, hypertrophy of this chamber does not give rise to a diffuse impulse. In patients with hypertension, aortic valvular lesions, or other causes of left ventricular hypertrophy, the impulse is therefore sharply localized, powerful, thrusting, and heaving.

When, on the other hand, the right ventricle is hypertrophied, the impulse is diffuse, pulsations

are observed over the entire precordial area, and on palpation the beat is found to be tapping rather than thrusting. Since most of the common types of heart disease affect the left side initially, it is common in the earlier stages of cardiac disease to find evidence of hypertrophy of the left ventricle only, but in the later stages both are likely to be hypertrophied and the respective signs may coexist.

When, because of obesity or emphysema, the cardiac impulse is not readily visible or palpable, the electrocardiogram may give useful information as to which ventricle is hypertrophied, provided that one employs multiple precordial leads in addition to the standard limb leads, and provided, moreover, that one bears in mind that confusing alterations of the form of the electrocardiogram are brought about by changes in the position of the heart (Chapter 31). The x-ray may at times yield useful information concerning hypertrophy of the various chambers, but is more apt to be valuable when dilatation coexists (fig. 183).

Dilatation. The mechanisms of cardiac dilatation have already been discussed (Chapter 14), and here it need only be repeated that dilatation results from defective systolic discharge, which tends to occur whenever work is increased in relation to muscle strength. Therefore, dilatation may result from an increase in load or from myocardial disease. It is probable that dilatation of slight degree always precedes hypertrophy, and, indeed, dilatation may be the stimulus which leads to hypertrophy. Under conditions of stress it seems clear that the hypertrophied heart is predisposed to further dilatation, and a vicious cycle tends to occur.

Cardiac dilatation may be diagnosed with confidence in any patient presenting well-marked cardiac enlargement (hypertrophy alone produces only a slight increase in the transverse dimensions of the heart or in the frontal projection of the cardiac area as seen by the x-ray). The decision as to which specific chambers of the heart are dilated is more difficult. When the left ventricle undergoes well-marked dilatation, the sharply localized, thrusting apical impulse becomes somewhat diffuse. In many patients another phenomenon—that of apical gallop—likewise develops. In the presence of a markedly enlarged heart, the decision as to whether the left ventricle is dilated is based to some extent on the

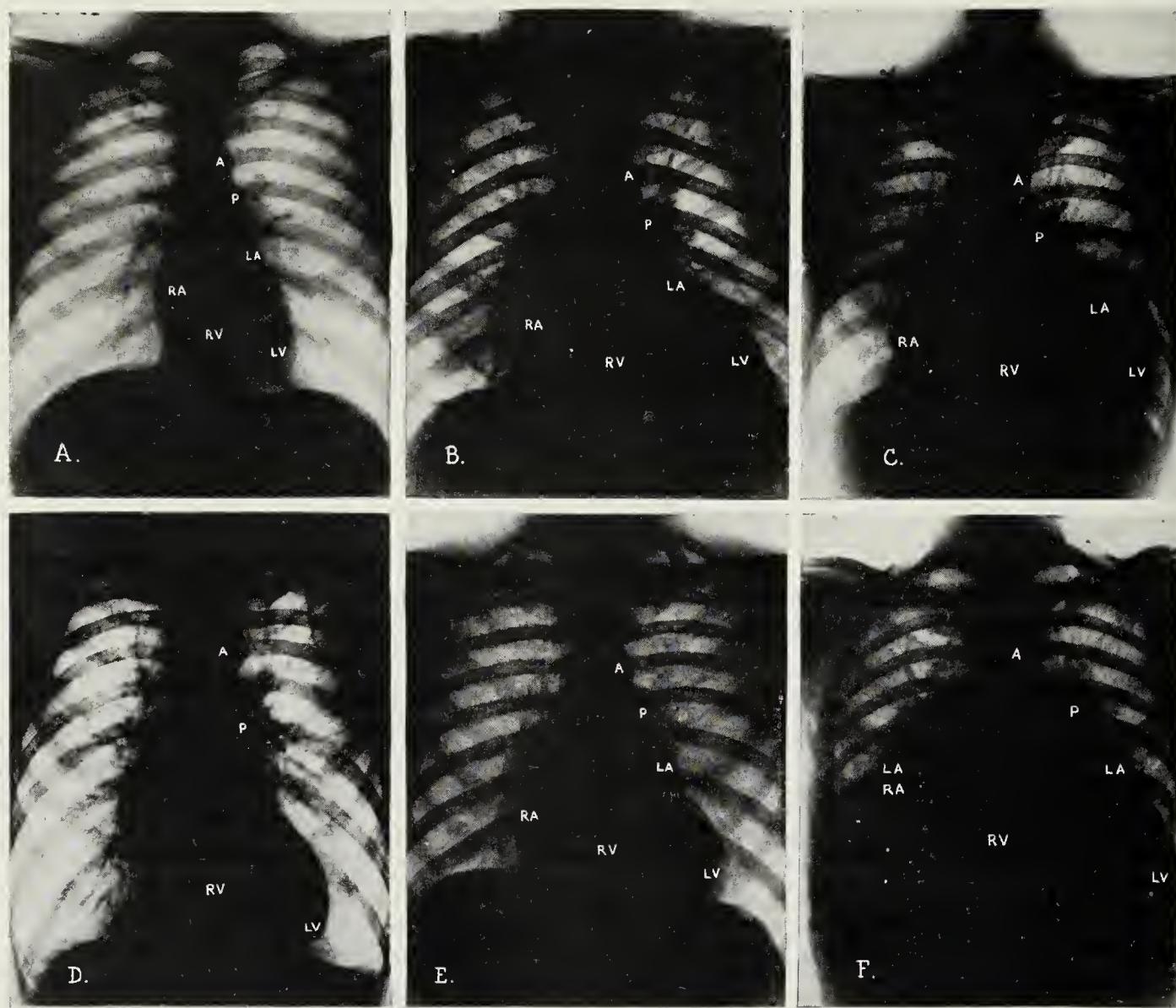


FIG. 183. Some common radiologic configurations of the heart. (H. H. Hecht.)

- (A) A normal heart.
 - (B) Hypertensive heart disease: pulmonary congestion and left ventricular dilatation (prominent LV).
 - (C) Arteriosclerotic heart disease: aneurysm of the left ventricle following myocardial infarction (bulging of LV).
 - (D) Pulmonary heart disease: emphysema, right ventricular hypertrophy with lifting of the apex from the diaphragm and with increase in shadow of pulmonary artery (prominent P, RV).
 - (E) Rheumatic heart disease: mitral stenosis and insufficiency with right and left ventricular enlargement, prominent pulmonary artery, pulmonary congestion, and enlargement of left and right auricle (prominent P, LA, RA, and RV; displacement and slight increase of LV).
 - (F) Rheumatic heart disease: mitral and aortic lesion with "cor bovinum": all chambers are greatly enlarged and show marked encroachment of the lung space. (Decrease in A—rotation; increase in P; enormous increase of LA which forms part of the left and right border of the heart; enlargement of RA, RV, and LV).
- (A) Arch of aorta ("aortic knob"); (P) main stem of pulmonary artery; (LA) left auricle; (RA) right auricle; (RV) right ventricle; (LV) left ventricle. Note: Normal density of lung fields in A; increased vascularity (pulmonary congestion) in B, C, E, and F; increased air content with unusual brightness of the lung fields in D (emphysema).

presence or absence of some lesion, such as hypertension or aortic valvular disease, capable of putting increased strain on the left ventricle. However, the absence of such a lesion does not in any sense preclude the likelihood of left ventricular dilatation, which often exists in senile hearts in the absence of any known cause for increased work of the left ventricle. A more reliable index of left ventricular dilatation is the presence of the clinical manifestations of left-sided failure—i.e., of dyspnea and other results of pulmonary congestion (Chapters 9 and 14).

The diagnosis of left auricular dilatation cannot ordinarily be made by clinical methods but may be presumed from such indirect evidence as the presence of left-sided heart failure, or of mitral stenosis. Similarly, the diagnosis of right ventricular dilatation and right auricular dilatation depends on indirect evidence of right ventricular strain, or the presence of evidence of right-sided heart failure.

The x-ray is of the greatest value in the decision as to the presence or absence of dilatation of the several cardiac chambers. Space does not permit a detailed discussion of this important subject, and the reader is referred to books on radiology. Briefly, it may be said that dilatation of the left ventricle tends to produce some rounding of the apex as seen in the frontal projection, and backward enlargement of the cardiac shadow as observed in the left anterior oblique position. Dilatation of the left auricle produces a convexity of the left portion of the cardiovascular shadow in the region between the pulmonary artery shadow and the ventricular shadow, but a more characteristic sign is the bulging backward of the lower posterior cardiac shadow into the retrocardiac space, with compression of the barium-filled esophagus when the patient is viewed in the right anterior oblique position. This phenomenon is characteristically seen in patients with mitral stenosis. Right ventricular enlargement tends to cause the heart to assume a more anterior position. Right auricular enlargement is usually characterized by increased size to the right. Figure 183 demonstrates some of the common radiologic configurations of the heart when observed in the anterior-posterior position.

It will be apparent, from the foregoing discussion, that the decision as to which chamber of the heart is enlarged is arrived at largely on the basis

of indirect clinical evidence such as the type of valve lesion, the type of heart failure, etc., and of information obtained by the radiologic and electrocardiographic methods. However, physical examination usually yields significant and often decisive information on the all-important question of whether the heart—regarded as a whole—is enlarged or not, and it is on this question that the decision as to the presence or absence of cardiac disease often depends. Once it is known that a person has cardiac enlargement, the question as to how much is dilatation and how much is hypertrophy is difficult to determine, and often cannot be decided with certainty.

In so far as the recognition of cardiac enlargement by physical signs is concerned, palpation assumes the position of first importance. Whether or not the heart is enlarged to the left can usually be determined by palpation of the point of maximum impulse. Unfortunately, the position of the right border cannot be determined with corresponding accuracy by clinical methods, for percussion possesses limited value in the examination of the heart, and does not afford an accurate guide as to the position of the right border in the majority of patients. However, if the point of maximum impulse is outside the midclavicular line, one can be reasonably certain that the heart is either enlarged or displaced. Displacement, usually to the left, may result from lateral curvature of the spine. More commonly, it is due to disorders of the pleural cavity such as hydrothorax, pleural effusion, or pneumothorax, all of which conditions tend to displace the heart toward the opposite side; or to atelectasis and pleural thickening, which tend to displace the heart toward the affected side. Hence, in the absence of lateral curvature of the dorsal spine, the decision as to whether or not there is cardiac displacement can usually be made by examining the lungs. By combining careful physical examination of the lungs with accurate palpation of the heart, cardiac enlargement can be established by clinical methods alone. However, this decision is accurate only when the apical impulse can be felt. When, because of age, obesity, or emphysema, palpation of the apical impulse is impossible, the only satisfactory method for determination of cardiac size is the use of the x-ray. The most commonly used roentgenographic index of cardiac size is the transverse diameter in relation to the total diameter of the chest. This method,

while valuable when marked alterations in cardiac size exist, is of limited value in the detection of the earlier stages of enlargement, and for this purpose other more complicated methods of measurement are considered to be more accurate.

Aside from its great value in affording information concerning the size of the heart, the x-ray is even more useful in revealing alterations in cardiac shape, which, by offering an indication as to the chambers and vessels particularly affected, often furnishes diagnostic clues which cannot be obtained by any other means (see figure 183).

ALTERATIONS IN HEART SOUNDS

Clinical case records and case reports are filled with such terms as "the heart sounds are poor," "the heart sounds are of good quality." Such phrases are seemingly intended to suggest that there are mysterious changes of quality of the heart sounds which reflect the quality of the function of the heart. Actually, such expressions indicate a lack of understanding of the factors concerned in the production of the sounds, and hence are meaningless. Although it is true that under exceptional circumstances changes in the "quality" of the heart sounds may have limited value, it may be stated, as a generalization, that the important things about heart sounds are their timing and their intensity. There are numerous conditions which produce additional sounds, and these will be discussed later. The one most obvious quality of the heart sounds, their intensity, will be discussed first.

Among the extracardiac factors which influence the intensity of the heart sounds are age, body build, and the presence or absence of emphysema. The heart sounds are louder in the young than in the old, in the thin than in the fat, and in individuals with normal lungs than in those with emphysema. In elderly emphysematous patients the heart sounds may be so faint as to be inaudible in the absence of any cardiac disease.

Of the cardiac factors which affect the intensity of the first sound, the most important one is the position of the atrioventricular valves at the onset of ventricular systole. Under ordinary circumstances this position is determined by the length of time which elapses between atrial contraction and the succeeding ventricular contraction. Thus, when the P-R interval is unusually short—i.e., less than .14 second—the atrioven-

tricular valves are widely open at the onset of the succeeding ventricular systole, and an unusually loud sound is produced. Similarly, when the P-R interval is unusually long—i.e., .20 second or more—the atrioventricular valves will have floated back following the atrial contraction to a position of semiclosure, and the sound produced by the ventricular systole is faint. Under ordinary conditions with intermediate durations (.14 to .18 second), the valves occupy an intermediate position, and sounds regarded as of normal intensity are heard. A proper understanding of this general principle is of the greatest importance in auscultation of the heart, as will be apparent from the discussion to follow.

Aside from the position of the atrioventricular valves at the onset of systole, the second factor which influences the intensity of the first heart sound is the work of the heart. The first sound will tend to be louder when the rate of rise of pressure during the onset of systole is great, or when the cardiac output is great. Many of the conditions which alter rate of pressure rise are those which are associated with valve lesions, and these produce characteristic murmurs which affect the intensity of the heart sounds. On the other hand, the conditions which elevate cardiac output are less likely to be associated with valvular lesions, and hence in such states there is usually well-marked exaggeration in the intensity of the heart sounds in the absence of any alteration in the relationship between atrial and ventricular contractions. Loud first heart sounds are characteristically encountered in such conditions as thyrotoxicosis, beriberi, and anemia, which are characterized by increase in the cardiac output. These conditions are of especial importance because they may cause *curable* heart disease.

The influence of valvular lesions has been mentioned. Mitral stenosis is often accompanied by striking accentuation of the first sound, and mitral insufficiency may be associated with replacement of the sound by the systolic murmur.

To summarize: The chief factors which influence the intensity of the first sound are: (1) the position of the valves at the onset of ventricular systole which is usually determined by the length of time elapsing between atrial and ventricular contraction; (2) the cardiac work and especially the cardiac output per minute; (3) the presence

or absence of structural disease of the mitral valve; and (4) the amount of tissue between the heart and the surface. Loudness of the first sound is favored by short conduction time, high cardiac output, mitral stenosis, and thinness; the reverse of these conditions tends to be associated with faintness of the first sound.

Aside from the extracardiac factors which have been mentioned, the intensity and, to some extent, the quality of the second heart sound may be influenced by alterations in the character of the vessel walls. Accentuation of the aortic second sound is a normal phenomenon with age, and occurs in such conditions as arteriosclerosis or syphilitic aortitis, which may cause diffuse change in the physical properties of the wall of the aorta. The other conditions which affect the intensity of the second sound are primarily those which alter the pressures in the aorta and pulmonary artery, increase in pressure tending to be associated with accentuation of the corresponding sounds.

Ventricular Volume Curve in Relation to Heart Sounds. In interpreting the sounds, arrhythmias, and murmurs observed on auscultating the heart, it is helpful to relate these phenomena to the ventricular volume curve. This curve is illustrated in figure 184, and a few of the aspects in which it may be useful are indicated in the accompanying legend. The correlation of mechanical and electrical events is demonstrated in figures 185 and 186, which translate the ventricular volume curve to available observations at the bedside.

Three-Sound Rhythms. Under many different circumstances one hears, upon listening to the heart, not two sounds but three. The proper interpretation of the mechanisms and the significance of the extra sound will often prove of the greatest value in diagnosis. The most common cause of a three-sound rhythm is the presence of a normal third heart sound (LUBB-dup-da, LUBB-dup-da). Here the additional sound occurs during the rapid filling phase of diastole, and apparently is due to the change in tension on the valve cusps which occurs when the intraventricular pressure is suddenly raised and the intraatrial pressure is suddenly lowered as the result of the rapid onrush of blood from atrium to ventricle. This phenomenon is frequently observed in healthy young adults with a slow heart rate. It has no pathologic significance (fig. 187).

Almost equally as frequent as the physiologic third heart sound, and of much greater practical significance, is the gallop rhythm. This term should be limited to a description of an extra

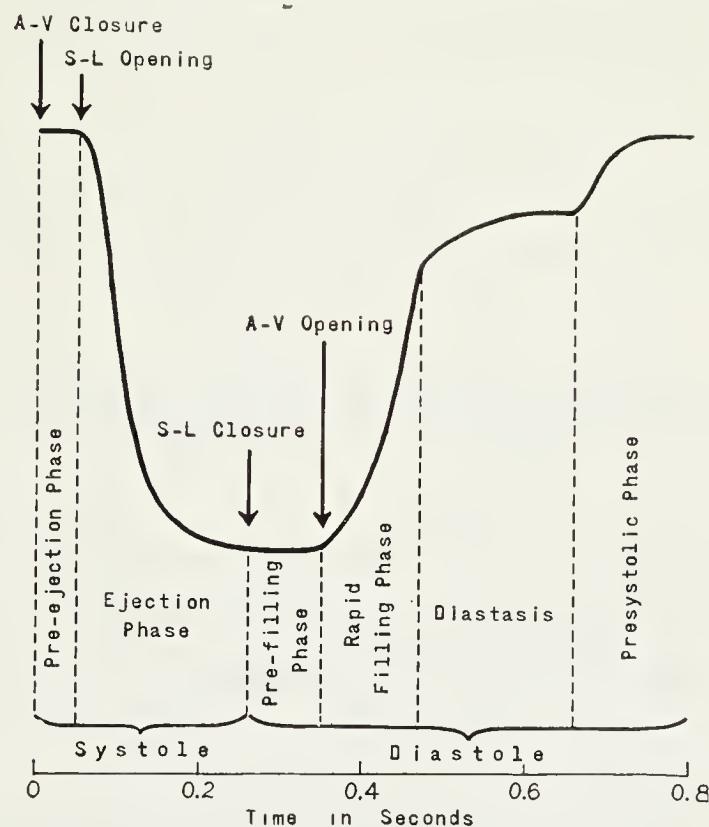


FIG. 184. The ventricular volume curve. At the beginning of systole the atrioventricular valves float into apposition and close at the beginning of ventricular contraction (*A-V closure*: first heart sound). The pressure in the ventricular cavities increases as cardiac muscle compresses the blood contained within them (*pre-ejection phase*, or isometric contraction period: I.M. of figures 185 and 186). The intraventricular pressure rises and, as soon as it exceeds the pressure in the pulmonary artery and aorta, the semilunar valves open (*S-L opening*). Blood is propelled into the periphery (maximum *ejection phase*: Max. E. of figures 185 and 186). The ventricular volume decreases sharply (systole) and the intraventricular pressure declines. When the ventricular pressure falls below that of the major vessels, the semilunar valves close (*S-L closure*: second heart sound). About 0.1 second after the end of the second heart sound the atrioventricular valves open (*A-V opening*). The inflowing blood fills, and in filling distends, the ventricles, first rapidly (rapid filling phase or rapid ventricular filling: R.V.F. of figure 186), then more slowly (diastasis; slow ventricular filling: S.V.F. of figure 186). During the later part of diastole, ventricular filling is further enhanced by the contraction of the atria which initiates the *presystolic phase*.

The heavy line of the diagram represents the volume curve of the ventricles. It illustrates the sharp fall at the beginning of systole, a plateau until the atrioventricular valves open, and a steplike ascent during diastole.

sound occurring in diastole, producing a cadence of sounds resembling that of a galloping horse (da-LUBB-dup, da-LUBB-dup, da-LUBB-dup—presystolic gallop; or LUBB-dup-da, LUBB-dup-da

—protodiastolic gallop) (fig. 188). The protodiastolic gallop of a single cardiac cycle resembles the sequence when a physiologic third sound is present, but the impression conveyed to the ear is quite different because the gallop usually occurs only in the presence of moderate to marked tach-

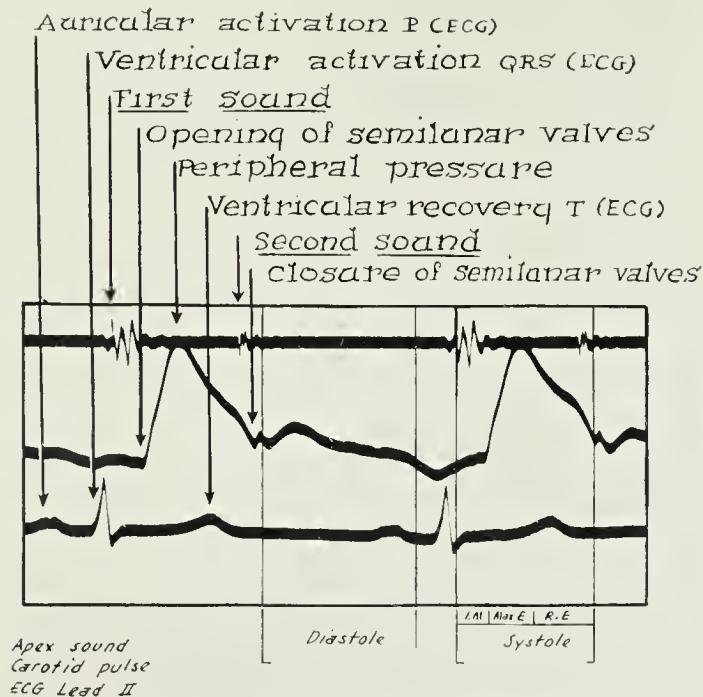


FIG. 185. Mechanical and electrical events during the cardiac cycle (I). (H. H. Hecht.) Apical heart sounds, pulsations of jugular vein, and electrocardiogram (lead II) in a normal 22-year-old male.

Ventricular excitation (QRS) precedes the onset of mechanical systole which is initiated by the first heart sound (closing of atrioventricular valves). All valves are closed and the ventricular tension rises (I.M.: isometric contraction phase). About 0.1 second after the end of the first heart sound the ventricular pressure exceeds the pressure in the base of the large arteries, the semilunar valves open, and blood gushes into the periphery, first rapidly (Max. E: maximum ejection phase), then more slowly (R.E.: reduced ejection phase). Relaxation of ventricular muscle occurs at the beginning of the reduced ejection phase and, when the intraventricular pressure has fallen below the diastolic pressure of the large vessels, the semilunar valves close, producing the second heart sound and characteristic incisure in the carotid pulsation. The T wave of the electrocardiogram is recorded during the later part of systole and is generally completed with the beginning of the second sound.

ycardia, and is not ordinarily observed with slow heart rates. The gallop rhythm is probably brought about by the presence of cardiac dilatation of such a degree that additional sudden filling of the ventricle produces a rise in intraventricular pressure of a magnitude sufficient to cause a change in tension on the valves. In the normal undilated heart, filling produces no significant rise in intraventricular pressure. How-

ever, the dilated ventricle contains a residue of unexpelled blood at the termination of systole. The entrance of additional blood on opening of the atrioventricular valves is sufficient to bring about enough rise in pressure to cause tensing of the cusps, which produces the additional sound.

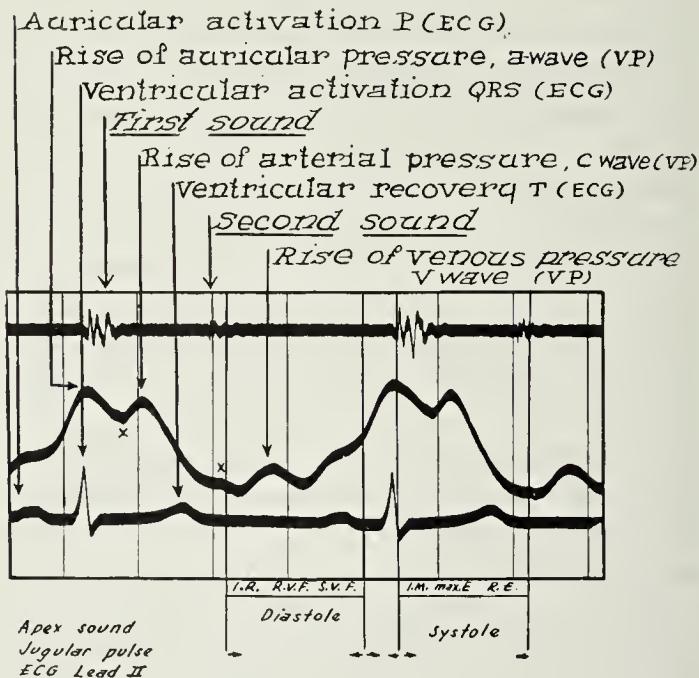


FIG. 186. Mechanical and electrical events during the cardiac cycle (II). (H. H. Hecht.) Apical heart sounds, pulsations of jugular vein, and electrocardiogram (lead II) in the subject of figure 185.

A transmitted pulsation from the adjacent carotid artery is usually observed in the venous pulse curve (c wave of VP). Following the second sound the heart muscle relaxes with all valves closed (I.R.: isometric relaxation). About 0.1 second after the end of the second sound the atrioventricular valves open. Prior to this effect the venous pulse has risen as a result of the slightly increased back pressures in the atria and large veins. As the atrioventricular valves open, the diastolic rise in venous pressure (v wave of VP) falls again. It soon rises anew as the ventricles fill, first rapidly (R.V.F.: rapid ventricular filling), then slowly (S.V.F.: slow ventricular filling). During the latter part of diastole, atrial excitation begins (P wave) and the contracting atria give rise to a sharp increase in back pressure in the large veins (a wave of VP). The onset of the first heart sound marks the end of diastole.

Of all graphic registrations of cardiac activity, the venous pulse curve is the only visible record of events occurring during the diastolic period.

The gallop is, therefore, an important phenomenon because it indicates that the heart is dilated and that heart failure, if not present, is imminent. The peculiar significance of the gallop is, therefore, that this is the only physical sign to be elicited on examining the heart which signifies that heart failure is either present or likely to occur. All of the other manifestations of heart

failure tend to be elicited on examining other parts of the body.

Aside from isolated presystolic and protodiastolic gallops, one may have a summation gallop which occurs when the heart is dilated and the rate is rapid, and since atrial contraction takes

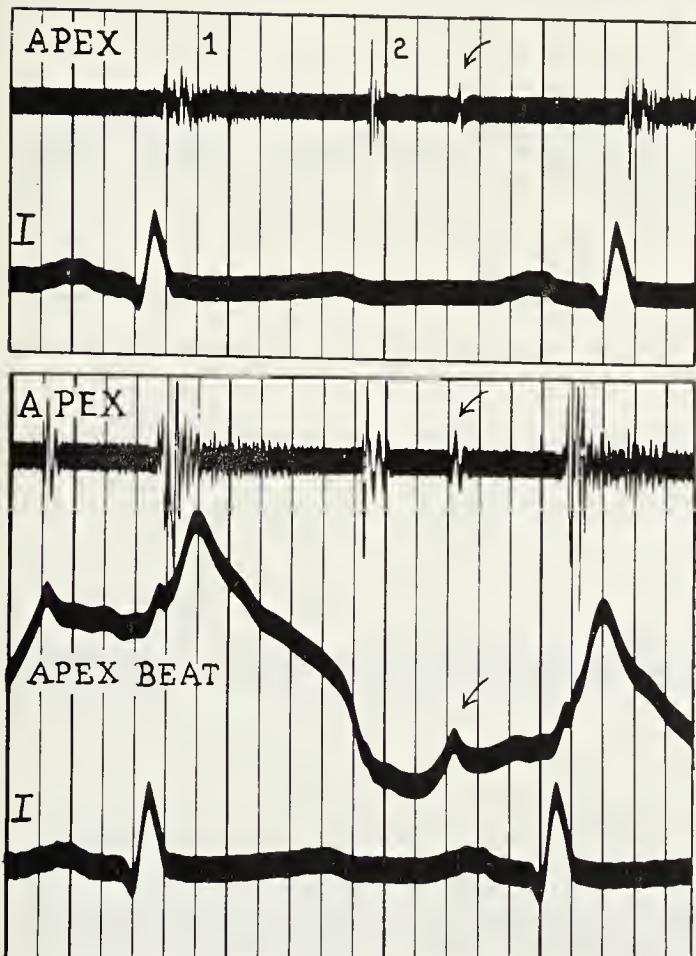


FIG. 187. The physiologic third heart sound. (H. H. Hecht.) In young persons an extra sound in early diastole is often heard. It occurs after the v wave of the venous pulse curve (fig. 186) and is usually accompanied by an outward thrust of the apex beat (arrow in lower tracing).

Record of a nine-year-old child without demonstrable heart disease. Upper tracing: heart sound at apex, lead I of electrocardiogram. Lower tracing: heart sound at apex, apex beat, and lead I of electrocardiogram. Arrows indicate third heart sound and diastolic apical thrust. Time lines: 0.04 second. (A systolic apical murmur follows the first heart sound.)

place very soon after the early rapid filling phase of diastole, the two sounds are superimposed (lubb-dup-DA, lubb-dup-DA) (fig. 189).

Other types of three-sound rhythm are less common, and, although in a given patient the recognition of the type may be of great practical importance, space does not permit a detailed discussion. The more salient points of the three-sound rhythms are summarized in table 97.

HEART MURMURS AND DIAGNOSIS OF VALVULAR LESIONS

Since murmurs constitute the only detectable abnormalities in a large proportion of children and young adults with heart disease, the proper interpretation of these phenomena is of great importance. A significant systolic murmur is not likely to be overlooked, because such murmurs are usually moderately loud to very loud, and barely audible systolic murmurs often have no significance. On the other hand, even the faintest diastolic murmurs practically invariably indicate

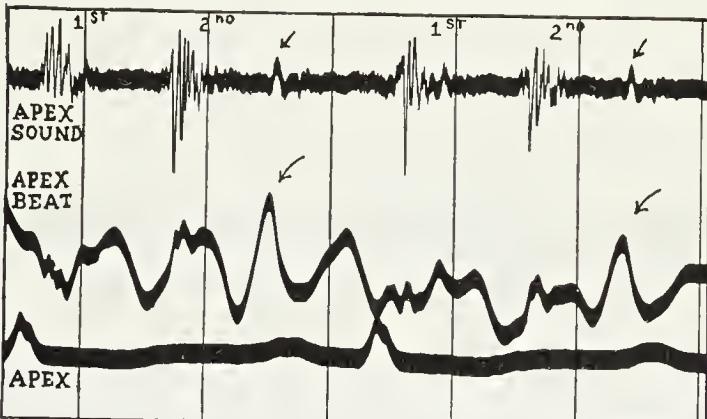


FIG. 188. Protodiastolic gallop rhythm. (H. H. Hecht.) From above downward: heart sounds at apex, apex beat, and lead I of electrocardiogram. Time lines: 0.04 second.

The occurrence of an extra sound in the earlier phase of diastole is accompanied by a diastolic outward thrust of the cardiac impulse (arrows). The protodiastolic gallop sound shares many of the characteristics of the normal third heart sound (fig. 187), but in adults represents a sign of myocardial failure.

organic cardiac disease, even though permanent distortion of the valve leaflets may not be present. The detection of such murmurs is often difficult, and the percentage of errors will be materially reduced if all patients are examined in the left lateral position, and while sitting up and leaning forward during deep expiration. As a rule, the decision as to whether a murmur is systolic or diastolic can be made readily, but occasionally difficulty arises and the decision has to be made by simultaneous auscultation of the heart and palpation of the carotid pulse.

It is to be emphasized at the outset that there is an important difference in the interpretation of diastolic and systolic murmurs. A diastolic murmur, with exceptions so rare that they are negligible, implies the presence of an organic lesion of the heart or a related structure; its meaning is unmistakable and, provided one is certain that the murmur actually occurs in dias-

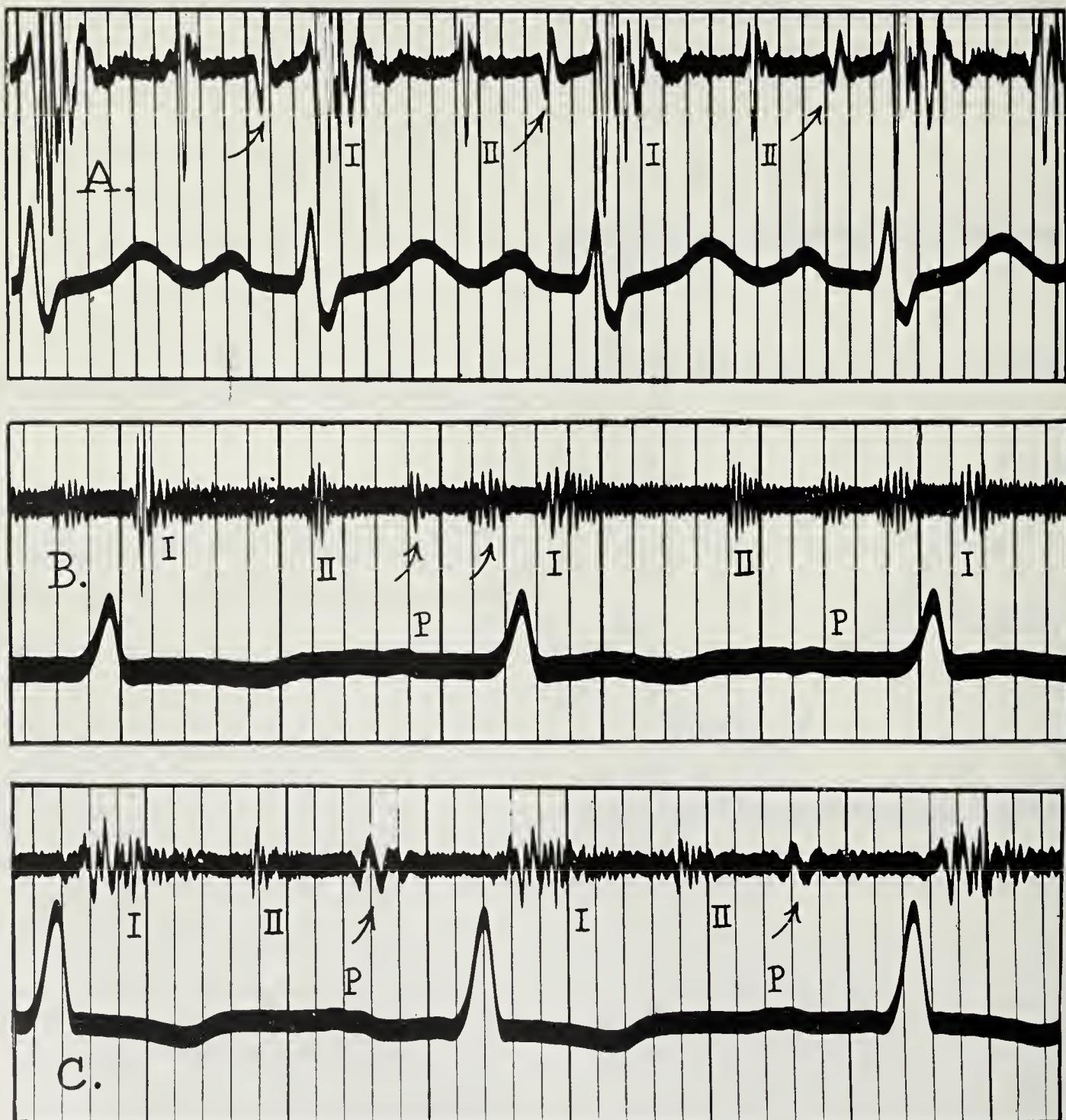


FIG. 189. Gallop rhythms. (H. H. Hecht.) Apical sound records and electrocardiograms (lead I).

(A) *Auricular gallop*: Extra sound preceding the first heart sound and following auricular excitation. Sinus tachycardia (heart rate 123) and relatively prolonged PR interval (0.16 sec.) in a 16-year-old student with acute rheumatic carditis.

(B) *Double diastolic gallop*: Both protodiastolic and auricular gallop sounds are present and separated by a short mid-diastolic interval. Sinus tachycardia (heart rate 115) in a 53-year-old laborer with hypertensive heart disease.

(C) *Summation gallop*: Both diastolic gallop sounds merge into one if rates are rapid and A.V. conduction relatively prolonged. The gallop sound is often louder than either the first or the second heart sound; in this example all three sounds are approximately equal in intensity. The subject is a 35-year-old Negro woman with rheumatic pancarditis and old involvement of mitral and aortic valves.

Table 97

DIFFERENTIAL DIAGNOSIS OF THE MORE COMMON CAUSES OF THREE-SOUND RHYTHMS AT THE APEX*

Condition	Quality of Sound	Time of Cardiac Cycle	Third Sound Ventricular Volume Curve	Associated Conditions	Significance of Sound	Probable Mechanism	Remarks
Physiologic third sound	LUBB-dup-da	Early diastole	Rapid filling phase	Good health	None	Rapid filling	Slow rate, no gallop cadence
Protodiastolic gallop	LUBB-dup-da	Early diastole	Rapid filling phase	Failing heart	Failure present or imminent	Dilatation, rise in pressure during filling	Tachycardia, gallop cadence
Presystolic gallop	Da-LUBB-dup	Presystolic	Atrial contraction	Failing heart	Failure present or imminent	Dilatation, rise in pressure during filling	Tachycardia, gallop cadence
Reduplicated first sound	T'LUBB-dup	Onset of systole	Pre-ejection phase	Good health	None	Asynchronism of ventricles?	
Opening snap	LUBB-dup-tic	Early diastole	Onset of rapid filling phase	Early mitral stenosis	Indicates mitral stenosis	Rigidity of mitral cusps?	Synchronous with onset of descending limb of V wave in jugular pulse
Short early diastolic rumble	LUBB-dup-br	Early diastole	Rapid filling phase	Mitral stenosis, auricular fibrillation	Indicates mitral stenosis	Obstruction at mitral orifice	A murmur of short duration
Audible atrial contraction	LUBB-dup-da	Diastole	Rapid filling phase or diastasis	Fibrosis of mitral annulus, coronary sclerosis	Indicates heart block	Auricular systole	Rate usually very slow
Premature beat causing single sound	LUBB-dup-lubb	Early in rapid filling					Beat very premature, filling not adequate to develop enough energy to open semilunar valves, hence no second sound

* In addition to the above intracardiac causes of three-sound rhythms, there are several extracardiac causes, including mediastinal emphysema, pneumothorax, air in the stomach, and various unknown causes.

tole, one can unhesitatingly assume the presence of organic heart disease regardless of the intensity or quality of the murmur. On the other hand, the presence or absence of valvular disease is rarely established by a systolic murmur alone. Usually its significance depends on the correlation of other data, such as the presence of a thrill or a diastolic murmur, or enlargement of the

heart, or the manifestations of an overactive heart, or a history of rheumatic fever. It is in the light of an evaluation of these various factors that one reaches a decision as to the significance of the systolic murmur. The systolic murmur is then classified as "organic," "relative," or "functional."

A murmur is considered "organic" when it is

the result of structural abnormality of the valve cusps or of the great vessels; "relative" when it is due to regurgitation through one of the atrioventricular orifices as the result of dilatation of the corresponding ventricle without an accompanying valvular lesion; "functional" when it is produced by increased velocity of blood flow or by other mechanisms as yet obscure, and the murmur has no significance as regards heart disease. Although in certain circumstances the diastolic murmur is of the "relative" type (the Austin Flint murmur being the classic example), in the vast majority of cases diastolic murmur indicates valvular disease.

SYSTOLIC MURMURS

Systolic murmurs maximal over the aortic area (i.e., in the right second interspace), loud, rough, and accompanied by a systolic thrill (which should be sought whenever such a loud basal systolic murmur is heard), are due nearly always to stenosis of the aortic valve (see figure 190 C). If the murmur is unaccompanied by a thrill or by a diastolic murmur, one cannot be certain that the aortic valve is the site of an organic lesion. Under such circumstances it will usually be safer to ascribe the murmur to dilatation of the aorta, or overactivity of the heart, or to its conduction from some other site. The commonly expressed view that saccular aneurysms of the aorta frequently produce loud systolic murmurs and systolic thrills is erroneous. Such signs, when present, are usually due to the associated aortic valvular lesion.

Aortic Stenosis. The five classic signs of this disorder are the rough systolic murmur, usually loudest in the right second interspace well transmitted into the neck; the corresponding systolic thrill; the diminished or absent aortic second sound; the slowly rising pulse of low volume (plateau pulse); and the presence of calcification in the region of the aortic cusps as demonstrated by fluoroscopy. The murmur alone does not constitute sufficient grounds for the diagnosis, because faint to moderate systolic murmurs over the base of the heart are commonly found in the absence of valvular lesions. However, the presence of the murmur plus the thrill is sufficient evidence to make the diagnosis, provided syphilitic aortic insufficiency and congenital lesions can be excluded. These various signs are subject to considerable variation. The murmur may not

be loud and rough and it is frequently unaccompanied by a thrill. In some instances the second sound is quite distinct, presumably due to transition of the pulmonic second sound. The character of the pulse may be modified by an associated aortic insufficiency or by rigidity of the aorta. Calcification of the aortic valve is not always visible or recognized. Hence the presence of the classic criteria permits the diagnosis with assurance. The exclusion of aortic stenosis cannot be deduced with equal certainty in the absence of one or more of the traditional features of this lesion.

The problem often arises, in a patient presenting the classic evidence of aortic stenosis, as to whether the lesion is of rheumatic origin. In children and young adults the only other cause which must be considered is the rare congenital lesion which causes stenosis of the aortic outflow tract below the valves (subaortic stenosis). This can be diagnosed with certainty only when the murmur is known to have existed at birth, or when the stenosis is discovered in a very young child. In the absence of such evidence, aortic stenosis in young persons should always be ascribed to rheumatic heart disease.

In older persons, and much more frequently in males than in females, aortic stenosis is usually observed after the age of 60, and under such conditions it may be impossible to decide whether the lesion is rheumatic, is due to senile calcific change of the valves, or is due to the latter process superimposed upon the former. The coexistence of mitral stenosis will settle the question in favor of a rheumatic etiology, but in the absence of this lesion the decision cannot be made with certainty.

Blowing systolic murmurs of all degrees of intensity are frequently heard over the pulmonic area. They are most commonly encountered in young, thin individuals with overactive hearts, but not infrequently these murmurs are heard in older persons as well. In adults, these as well as similar murmurs over the body of the heart are practically always either functional or transmitted from some other site of origin. In very young children, such blowing murmurs may be due to congenital lesions.

Much more infrequently, loud, rough, rumbling murmurs associated with thrills are heard to the left of the sternal border, and these almost always signify the presence of congenital heart

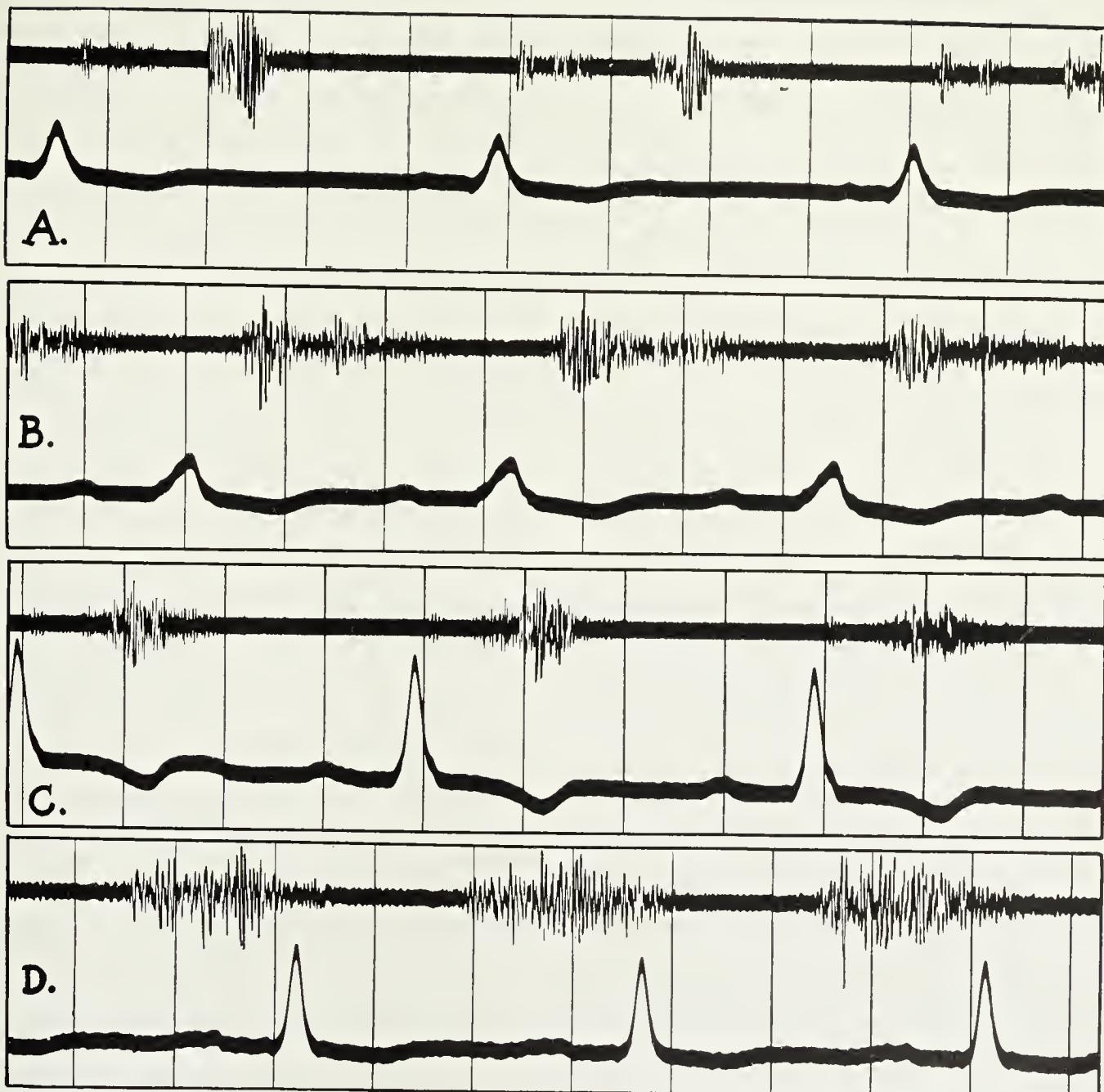


FIG. 190. Murmurs heard over the aortic auscultation points. (H. H. Hecht.)

(A) High-pitched (rapid vibration) systolic murmur of low intensity beginning somewhat after the end of the first heart sound. Its onset coincides with the opening of the semilunar valves (rise of carotid pulse of figure 185). The second sound is replaced by a loud, rapidly fading, early diastolic murmur. The subject is a 58-year-old male laborer with rheumatic aortic stenosis and insufficiency.

(B) Almost continuous murmur with accentuation during systole and replacing the first and the second heart sound. A quiet period is noted during late diastole only. The subject is a 55-year-old mechanic with syphilitic aortitis and syphilitic aortic insufficiency.

(C) A loud, high-pitched (rapid vibrations) systolic murmur beginning 0.08 second after the onset of the first heart sound (opening of semilunar valves) and lasting during the entire ejection phase. There is no discernible second heart sound. The subject is a 70-year-old laborer with calcified aortic valve ring and leaflets.

(D) A quiet systolic period followed by a loud, continuous diastolic murmur which completely replaces second and first heart sounds. The subject is a 25-year-old Negro laborer with syphilitic aortitis and syphilitic aortic insufficiency. The character of the murmur resembled that of C. Proper timing of the murmur was difficult, but essential in establishing a correct diagnosis.

Electrocardiograms (lead I) showed left bundle branch block in A and B, tall deflections with inverted T waves in C and D; all patterns are compatible with left ventricular enlargement. Time lines: 0.04 second.

disease. If such a murmur is continuous throughout systole and diastole ("machinery murmur"), with accentuations during systole, and accompanied by a systolic thrill most pronounced in the second left interspace about 3 to 4 cm. from the left sternal border, it is diagnostic of a patent ductus arteriosus. Murmurs of similar quality but heard only during systole, maximal to the left of the midline in the second, third, or fourth interspaces near the sternal margin, almost always denote the existence of other congenital malformations such as patent atrial septum, tetralogy of Fallot, Eisenmenger's complex, or patent interventricular septum.

Mitral Insufficiency. It is the systolic murmur which is loudest at or near the apex that causes most confusion and difficulty of interpretation. If the characteristic diastolic murmurs of mitral stenosis are heard, the apical systolic blowing murmur which may be present (but which is frequently absent) is, of course, the manifestation of regurgitation through the defective mitral valve. When an apical systolic murmur, soft or loud, is heard in an individual with rheumatic aortic regurgitation, organic or relative mitral insufficiency may be present, but it is unimportant whether the mitral leaflets have been damaged by the rheumatic process; neither prognosis nor treatment is materially altered in either case.

Blowing murmurs of variable intensity are commonly heard at the apex in all forms of cardiac disease associated with cardiac enlargement: aortic regurgitation due to syphilis, and hypertensive, senile, or congenital heart disease; and in these instances the apical systolic murmur is classified as "relative," due to a widening of the mitral ring. If, in a patient with one of these types of cardiac disease, there has been a suggestive or definite history of rheumatic fever in the past and signs of mitral stenosis are lacking, it is again a matter of relatively small importance whether, in a subject known to have one unquestionable form of organic heart disease, structural alteration of the mitral valve is also present. The one possible exception to this latter statement comes from the fact that a mitral valve previously damaged by rheumatic fever is more susceptible to subsequent development of subacute bacterial endocarditis.

Similar loud or soft blowing apical systolic murmurs are also heard in individuals with overactive hearts due to either anemia, thyrotoxicosis,

fever, or any of the rare causes of such a condition. These murmurs usually disappear or become faint and insignificant as the underlying process is corrected, in which case they are considered to have been due to a relative insufficiency. If, however, disappearance of the anemia or hyperthyroidism or fever leaves in its wake a persistently loud systolic murmur at the apex, one is confronted with the problem of whether or not actual organic change in the mitral valve exists.

Up to this point, we have discussed apical systolic murmurs occurring with various forms of cardiac disorder (either unquestionable organic disease or states of overactivity of the heart). In these cases there is adequate explanation for the apical systolic murmur, regardless of whether or not there is coincident structural change in the mitral valve. Moreover, from a practical standpoint, as compared with the primary cause of the cardiac disturbance, the question of a relatively minor organic alteration in the mitral valve is usually a matter of small importance. There remain now for consideration those instances of apical systolic murmur that constitute the chief or the only abnormality in the examination of the heart. A decision that the murmur results from rheumatic disease of the mitral valve may not imply that at the moment the heart is seriously compromised. It does imply that the patient is now, or has been in the past, the victim of a disease process that tends characteristically to cause progressive damage in the valve, with all the serious consequences that may ensue therefrom: cardiac enlargement with ultimate failure, embolism, bacterial endocarditis, etc.

In many young persons, but occasionally in older ones also, a faint or moderately loud apical systolic murmur may be heard. Its characteristics vary: It may be blowing or it may have a more superficial scratchy quality; it may be persistent or transitory; it may be louder in one position and diminish or disappear in another. Usually it is louder when the breath is held in expiration. In the absence of a rheumatic history, or of cardiac enlargement or other positive signs indicative of organic involvement of the heart, these murmurs are considered to be functional, the heart is absolved of any structural damage, and the murmur dismissed as of no significance whatsoever. The origin of these murmurs is not always clear: At times they seem to arise from

the tugging of extracardiac structures; at other times they are so closely related to the respiratory cycle that the murmur seems undoubtedly due to an influence of the cardiac contraction on the vesicular murmur; at other times the cause of the murmur is obscure. In contrast with these are the cases in which the evidence for organic involvement of the mitral valve is equally clear: There is a definite history of rheumatic fever; the heart is enlarged; and the murmur is loud and widely transmitted. The real difficulty of interpretation arises in those patients who have had rheumatic fever but who present no unquestionable signs of cardiac enlargement, and in whom the murmur is of only moderate intensity, such as might be heard in normal young persons. In these, one can only suspect that mitral valvular damage has taken place, a final decision often awaiting years of observation. Even more puzzling are those instances in which even the history of rheumatic fever is doubtful. In children, caution in coming to a conclusive diagnosis is justifiable. In older persons, in the twenties or beyond, without cardiac enlargement, these murmurs of doubtful significance should probably be disregarded.

When in a child or young adult a systolic murmur is heard at any point over the precordium, the possibility of coarctation of the aorta should be entertained. If this condition is present, the murmur will usually be heard well over the upper dorsal spine, and in some patients may be audible only in that region. However, the diagnosis of coarctation depends, in the main, on findings (see p. 1296) other than the murmur.

Needless to say, this brief discussion of systolic murmurs has necessarily been given in rather categoric fashion. Exceptions may be cited to practically all the rules, even those given in the most dogmatic manner. Thus, the systolic murmur of aortic stenosis may not be accompanied by a thrill, and the same is true of the murmurs associated with congenital heart disease. In rare instances, the diastolic murmur has been absent in cases of proved patent ductus arteriosus. Moreover, as has been mentioned previously, a decision as to the meaning of a systolic murmur rarely hangs on the murmur alone. Careful consideration of all the data in the case may lead the experienced observer to a conclusion that differs from the one that is suggested in the foregoing paragraphs.

DIASTOLIC MURMURS

The vast majority of diastolic murmurs are due to either aortic insufficiency or mitral stenosis.

Aortic Insufficiency. The common causes of aortic insufficiency are rheumatic and syphilitic lesions of the aortic cusps; rarer causes include hypertension, congenital lesions of the aortic valve, or rupture of the cusps due to bacterial endocarditis. The diastolic murmur is the sign on which the diagnosis of incompetence of the aortic valve rests. The murmur is blowing, high-pitched, sometimes quite loud, in other cases so faint as to be almost inaudible (fig. 190 A, B, D; see figure 191 B). Occasionally its intensity is maximal over the aortic arca; more frequently it is heard best along the left sternal border at the third and fourth interspaces, and sometimes it is heard only in this region. Detection of the murmur is facilitated when the patient sits up, leans forward, and holds his breath in forced expiration; and not infrequently it is heard only when this maneuver is employed. There is scarcely any other murmur that is sometimes so difficult to hear, that is so likely to arouse differences of opinion even among experienced observers, or that is so capable of exasperating a listener who, because of a clear-cut history of rheumatic fever and the presence of an enlarged heart and the characteristic peripheral signs of aortic regurgitation, feels confident that a murmur should be present but cannot hear it. Regardless of the etiology, a systolic murmur is usually present at the base, giving rise to a to-and-fro murmur. This should not be confused with the continuous murmur of patent ductus arteriosus, in which the pitch is the same during systole and diastole. In cases of rheumatic aortic regurgitation, the systolic murmur cannot be considered evidence of stenosis of the aortic valve unless a systolic thrill is present.

Almost equal in importance with the diastolic murmur in the diagnosis of aortic insufficiency are the peripheral manifestations of the lesion. These consist of the rapidly rising pulse ("water-hammer" pulse), the wide pulse pressure, and the capillary pulse (fig. 191). These various phenomena are due to the combined effect of the regurgitation of blood through the aortic valve into the left ventricle, and the consequent ejection of a large quantity of blood with each contraction of the ventricle; the low diastolic blood

pressure; and the arteriolar relaxation that is present in this condition. Exactly the same peripheral phenomena are encountered whenever there is a leak of blood from the arterial system, as in patent ductus arteriosus or traumatic arteriovenous fistula; and similar peripheral signs, though usually not so well marked, may be seen

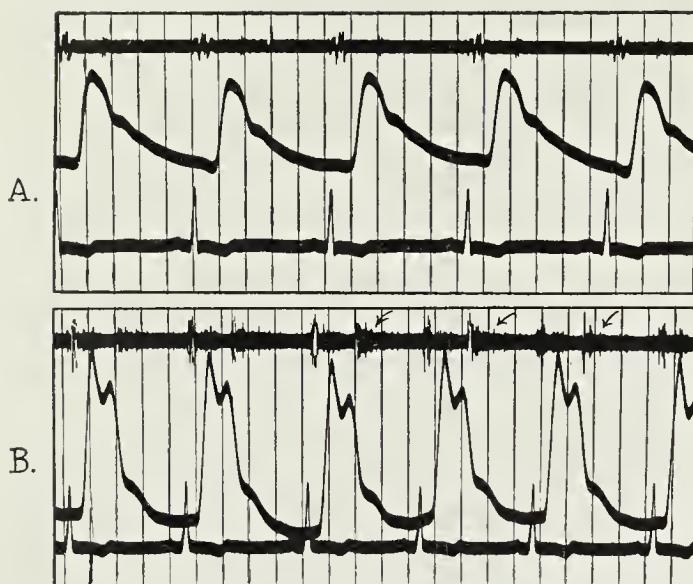


FIG. 191. Murmur and pulse of aortic insufficiency. (H. H. Hecht.)

(A) Heart sounds at apex, carotid pulse, and electrocardiogram (lead I) in a subject without valvular disease but with ventricular enlargement due to hypertensive heart disease.

(B) A subject with syphilitic aortitis and syphilitic aortic insufficiency. The sound records were taken over the second right intercostal space next to the sternal border. Carotid pulse and electrocardiogram are as in A.

A demonstrates normal heart sounds and a normal pulse form characterized by a sharp rise, a plateau, and a gradual fall with the typical incisure closure of the aortic valves. B shows a high-pitched systolic and barely visible (and audible) early decrescendo diastolic murmur (arrows) beginning with the second sound and fading toward the middle of the diastole. The pulse wave is markedly altered and shows high amplitude, steep rise, no plateau, and a rapid fall ("water-hammer" pulse, Corrigan pulse). The electrocardiograms of A and B are almost identical, merely indicating left ventricular enlargement.

in any condition associated with an overactive heart, such as thyrotoxicosis or severe anemia. Whenever these peripheral signs are encountered—and often the examiner's attention is first called to their presence by the relatively high systolic and low diastolic levels obtained in the blood pressure readings—the several possibilities for their cause should be investigated carefully. Not infrequently a faint diastolic murmur will then be heard on closer auscultation of the heart, when this important finding might otherwise have been missed.

Certain points which may be of value in the differential diagnosis of basal diastolic murmurs are presented in table 98.

Mitral Stenosis. The one specific sign of mitral stenosis is the low-pitched, rumbling, apical murmur occurring in diastole. The murmur is loudest in those phases of diastole when the velocity of

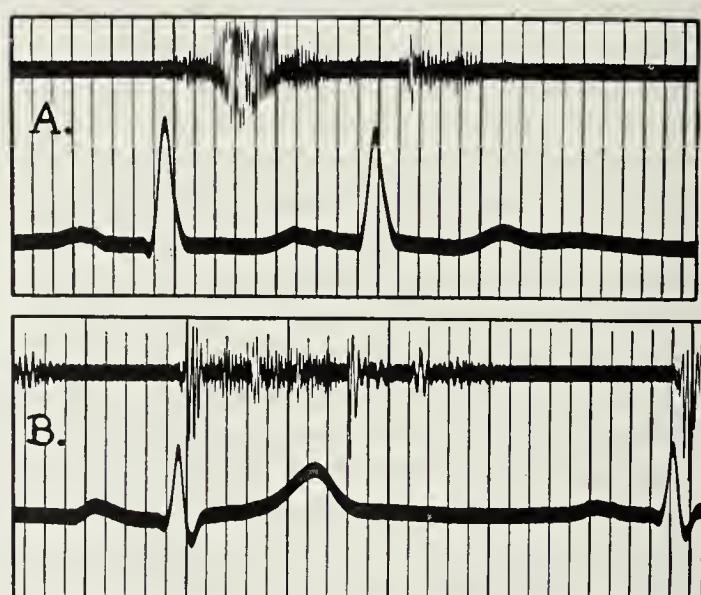


FIG. 192. Murmurs heard over the mitral auscultation points. (H. H. Hecht.)

(A) A loud systolic murmur with maximum intensity during the maximum ejection phase of figure 185 is noted, together with faint first and second heart sounds. The murmur has a musical quality (regular vibrations). The second beat represents an early auricular extrasystole. The murmur is reduced in amplitude, demonstrating that among other factors the intensity of a murmur is proportional to cardiac filling and to the ejection force. The subject is a 65-year-old housewife with rheumatic mitral insufficiency and calcification of the mitral leaflets.

(B) A loud, snapping first heart sound is noted, followed by a high-pitched, long-lasting holosystolic murmur. The second sound is sharp and an early diastolic murmur is seen beginning 0.01 second after the end of the second sound; the murmur is protodiastolic and begins with the opening of the mitral valve (see figure 186). The subject is a 42-year-old housewife with rheumatic mitral insufficiency and stenosis.

In spite of the presence of a normal sinus mechanism and regular atrial contractions, the presystolic period is quiet; a presystolic murmur is not a prerequisite for the diagnosis of mitral stenosis.

blood pouring into the ventricle is greatest: early in diastole immediately after the opening of the mitral valve, and late in diastole when atrial contraction takes place. The exact timing of the murmur depends on the heart rate, the presence or absence of prolongation of the atrioventricular interval (first-degree heart block), and the presence or absence of auricular fibrillation, in which condition there is no effective atrial contraction (figs. 192, 193, 194).

Table 98

DIFFERENTIAL DIAGNOSIS OF THE MORE IMPORTANT CAUSES OF BASAL DIASTOLIC MURMURS

<i>Origin and Cause of Murmur</i>	<i>Important Points in History</i>	<i>Usual Age of Patient</i>	<i>Special Feature of Murmur</i>	<i>Cardiac Enlargement</i>	<i>Peripheral Vascular Signs</i>	<i>Important Associated Findings</i>	<i>Remarks</i>
Rheumatic aortic regurgitation	Rheumatic fever	10-40	Early diastolic blowing Faint or loud	Left ventricular type	Regurgitation or stenosis	Mitral stenosis; auricular fibrillation	Signs frequently modified by coexisting aortic stenosis and mitral lesions
Syphilitic aortic regurgitation	Syphilis	35-60	Blowing, early diastolic, often loud	Left ventricular type	Regurgitation	Positive serologic tests in about 85 per cent	Especially middle-aged Negro males, aorta usually dilated (x-ray) Confusing systolic murmurs common
Hypertension		40+	Very faint	Left ventricular type	Absent	Hypertension (diastolic)	Regurgitation slight
Calcific aortic disease	Syncope Angina pectoris	55+	Diastolic faint Systolic loud, with systolic thrill	Left ventricular type	Stenosis	Calcification of aorta and aortic valves (x-ray)	Signs of stenosis predominate
Bacterial endocarditis	Rheumatic fever	Any	Often intermittent	Left ventricular type	Regurgitation or stenosis	Fever, positive blood culture Embolii Petechiae Hematuria	Usually superimposed on rheumatic lesion; rarely on syphilitic or congenital bicuspid aortic valve
Dissecting aneurysm	Sudden violent pain	35+	Often intermittent	None or left ventricular	Asymmetry in blood pressure	Hypertension	Cardiac tamponade from rupture into pericardium
Pulmonic regurgitation	Graham Steell murmur	10-40	Faint, early blowing	Right ventricular type	P ² ++	Mitral stenosis	Impossible to distinguish from minimal aortic regurgitation
	Overactive heart	Palpitation	Any	Faint, early blowing		Bounding pulse	Anemia, hyperthyroidism
	Congenital lesions	See discussions of patent ductus arteriosus, Eisenmenger's complex, and Lutembacher's syndrome (Chapter 236)					

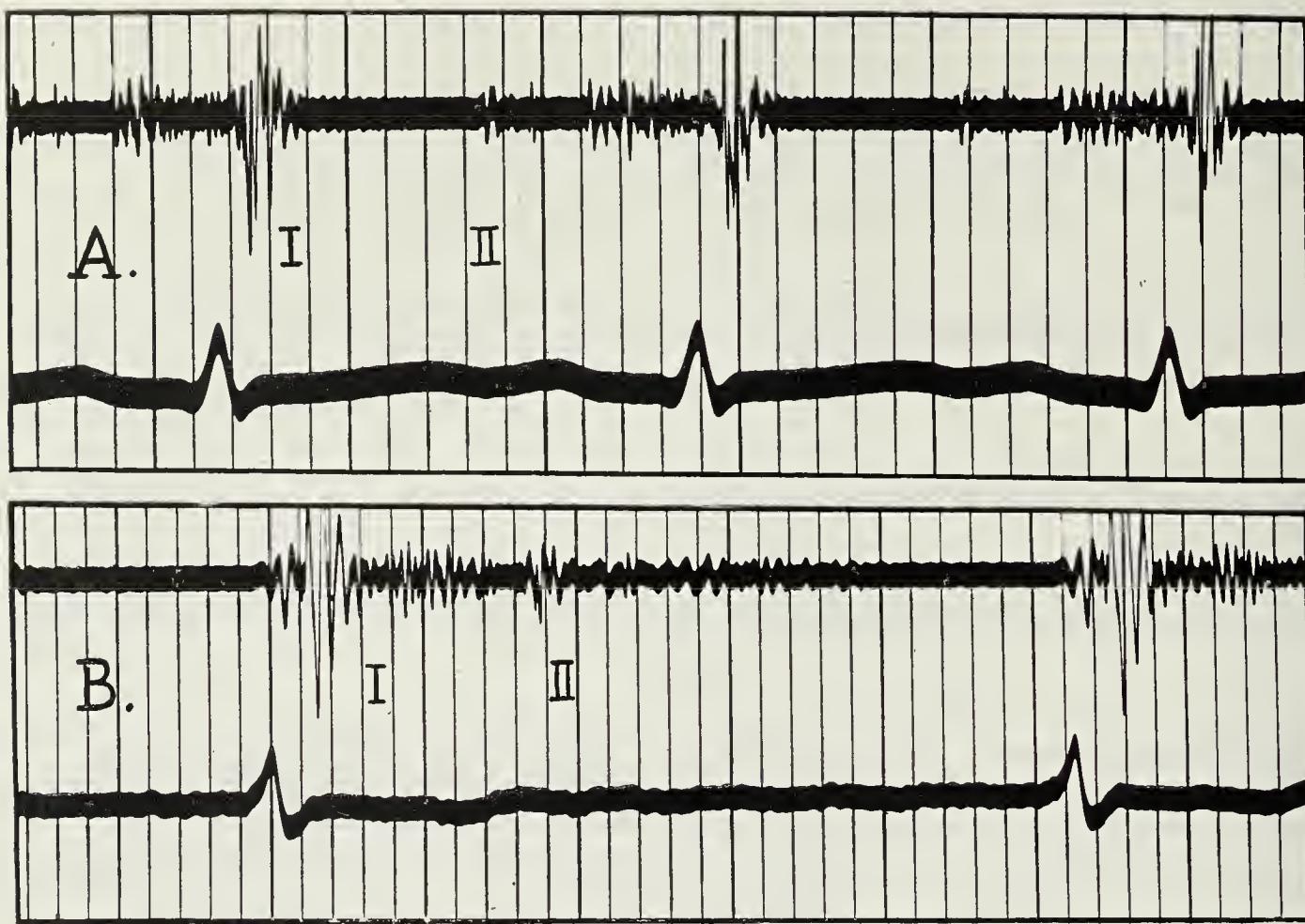


FIG. 193. Murmurs and sounds in mitral stenosis. (H. H. Heeht.) Sound records and electrocardiogram (lead I) of a 42-year-old housewife with rheumatic heart disease.

In the upper record (A) normal sinus rhythm is present and a coarse presystolic murmur ending in a loud and sharp first sound is noted. In the lower record (B), obtained from the same patient, auricular fibrillation was present. First and second sounds are now separated by a loud systolic murmur and the diastolic rumble has shifted from its presystolic to an early diastolic position (absence of distinct presystolic filling phase).

As a rule, in early cases with a normal heart rate and normal rhythm, the murmur is heard only in presystole (corresponding to the time of atrial contraction), terminating in a loud, snapping first sound, the effect being that of R-R-R-R-UP. In some cases, there may be an early diastolic rumble which may be separated from the presystolic murmur by a distinct pause, or which may merge with the presystolic murmur to give a continuous rumble throughout diastole: R-R-R-UP-DUP-R-R-R-R-R-R-UP-DUP. In other cases, only the early diastolic murmur may be heard. When auricular fibrillation is present, that component of the murmur corresponding to atrial contraction disappears, and the result will depend on the heart rate, or, more accurately, on the duration of diastole. When diastole is long, the murmur is heard only in the early phase (fig. 192); when diastole is short, the same murmur fills up the entire diastolic interval and terminates in the loud, sharp first sound. When

there is a well-marked first-degree heart block, the murmur corresponding to atrial contraction is separated from the first sound by an appreciable interval, and instead of occurring in presystole now appears in mid-diastole.

Ordinarily, the murmur has so characteristic a quality that it is readily heard and recognized. Occasionally, it is barely audible and may be easily overlooked unless one takes precautions to listen for it under the most favorable circumstances. In some instances, the murmur is widely transmitted; in others, it may be confined to a small area at or close to the apex. It is heard best when the patient lies on the left side and when the velocity of circulation is increased, as after exercise. Hence, if the mitral stenosis is suspected because of a history of rheumatic fever, or the presence of a loud, snapping first sound, or an accentuated pulmonic second sound, one should never fail to listen to the heart after the

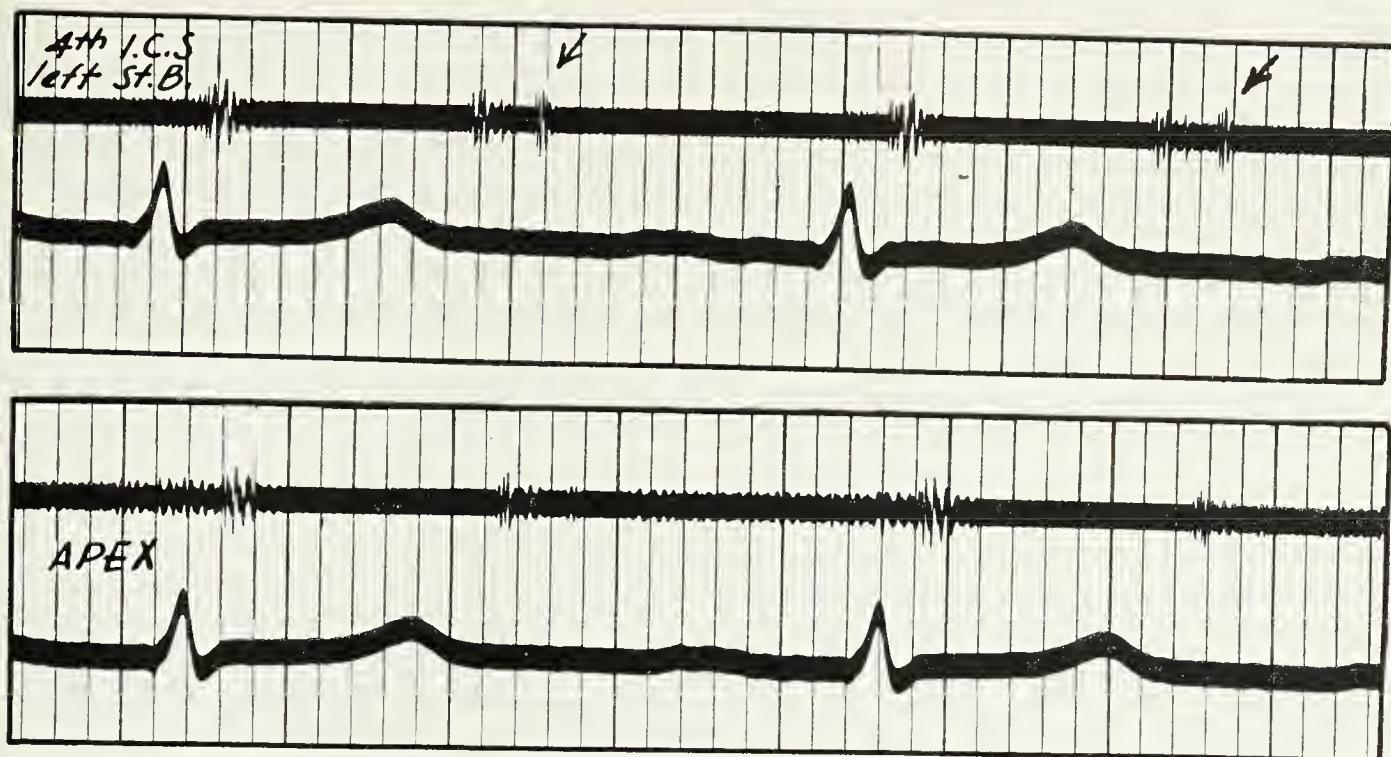


FIG. 194. The opening snap of mitral stenosis. (H. H. Hecht.) In many patients with mitral stenosis an important extra sound occurs in addition to or instead of the rumbling apical murmur. The clicklike character of the sound distinguishes the opening snap from a physiologic third heart sound, although both occur immediately following the opening of the atrioventricular valves (after the peak of the v wave of the venous pulse curve: see figures 186 and 187). The opening snap is best heard along the left sternal border.

The upper tracing shows the heart sounds at the left sternal border (opening snap at arrow), and lead I of the electrocardiogram. The lower tracing shows the apical heart sound obtained immediately following the upper record, and demonstrating a crescendo type of presystolic murmur culminating in a first sound, here not particularly accentuated. The electrocardiogram is as above.

rate has been accelerated by some simple exercise, or, when exercise is not practicable, by placing a nitroglycerin tablet under the tongue. As soon as the heart rate increases appreciably, the patient promptly lies on the left side, and the stethoscope is placed in the immediate vicinity of the apex beat. Frequently, the coexistent mitral regurgitation causes the first sound to be replaced by a blowing murmur, the effect resembling R-R-R-R-SH H H H.

A loud first sound at the apex or an accentuated pulmonic second sound should always arouse the suspicion that mitral stenosis may be present, but the diagnosis should not be made on the basis of these signs alone. They may occur in any condition associated with an overactive heart, such as severe anemia or thyrotoxicosis. Similarly, one should avoid making the diagnosis of mitral stenosis merely through the detection of a thrill at the apex. If the thrill is actually due to mitral stenosis, it will be the palpable equivalent of the diastolic murmur which should then be easily heard. A forcibly beating heart will often induce vibrations in the chest wall difficult to distinguish from the thrill; sometimes the accompany-

ing sounds are readily differentiated from the characteristic murmur of mitral stenosis; at other times the differentiation may be exceedingly difficult. However, there is one valuable differential point. Such individuals, because of the increased stroke volume, exhibit peripheral signs which tend to mimic those of aortic insufficiency—namely, bounding, collapsing pulse, increase in pulse pressure, and pronounced pulsations of the peripheral vessels. This combination of physical findings—namely, signs over the heart resembling those of a mitral lesion, and signs in the periphery suggesting the presence of an aortic lesion (but without the characteristic early blowing diastolic murmur of aortic insufficiency)—is typical of those states in which the cardiac output is increased. In the presence of such signs, and especially if the patient presents evidence of a well-marked anemia or thyrotoxicosis, it is safest to refuse to make a diagnosis of rheumatic disease of the mitral valve until the anemia or the hyperactivity of the thyroid gland has been remedied. If, under such conditions, the signs pointing toward a mitral lesion still persist, the lesion may then be diagnosed with confidence.

The more important features in the differential diagnosis of the commoner apical diastolic murmurs are summarized in table 99.

Tricuspid Lesions. Slight deformities of this valve are fairly common as the result of rheumatic fever, but marked deformities sufficient to produce mechanical consequences are exceptional. The patient with organic disease of the

tricuspid valve practically invariably has mitral stenosis, and the murmurs of the latter lesion plus those of the frequently coexisting aortic lesion usually will effectively obscure the origin of any murmurs arising at the tricuspid orifice. Hence the diagnosis is based on indirect evidence rather than on auscultatory signs. Tricuspid lesions should be suspected in any patient with

Table 99

DIFFERENTIAL DIAGNOSIS OF THE MORE IMPORTANT APICAL DIASTOLIC MURMURS

Origin and Cause of Murmurs		Important Points in History	Special Feature of Murmur	Cardiac Enlargement	Important Associated Findings	Remarks	
Murmurs arising at mitral orifice	With structural mitral disease	Mitral stenosis	Rheumatic fever Chorea	Presystolic (regular rhythm) or early diastole (auricular fibrillation)	Right ventricular type	Loud P ² Loud S ¹ Systolic murmur	Very faint to moderately loud; rumbling (see text) Compression of esophagus by left atrium (x-ray)
		Congenital defects	Murmur since birth	Presystolic rumbling	Right ventricular type Marked enlargement of pulmonary artery (x-ray)	"Hilar dance" (fluoroscopy)	Lutembacher syndrome (interatrial septal defect and mitral stenosis)
	Without structural mitral disease	Rytand's murmur	Syncopal attacks	Blowing, faint, often mid-diastolic	Moderate to marked	Systolic murmur Heart block	Thickening or calcification of mitral annulus, elderly subjects
		Austin Flint murmur	Syphilis or rheumatic fever	Apical, sharply localized	Left ventricular type	Outspoken signs of aortic regurgitation	Rough Presystolic; no compression of esophagus by left atrium (x-ray)
	Murmurs transmitted from other sites	Early left ventricular failure	Palpitation (over-active heart)	Presystolic Faint rumbling	Slight or absent	Loud sounds, systolic murmurs; bounding pulse	Anemia or thyrotoxicosis (presystolic gallop resembling presystolic murmur)
		From aortic valve	Rheumatic fever or syphilis	Loudest at base	Left ventricular type	Signs of aortic insufficiency	Blowing, early diastole

rheumatic disease and mitral stenosis who, despite the presence of well-marked evidences of right-sided heart failure, is able to lie flat in bed without respiratory discomfort. Venous distention is usually striking and does not disappear with treatment. Enlargement of the liver is likewise intractable, and this organ frequently displays systolic pulsation as the result of regurgitation through the tricuspid orifice. Because the patient lies flat in bed, the gravity factor in edema is minimal, and hence edema of the legs is slight in proportion to the rather marked ascites which frequently is present. Many of these patients display slight icterus, brought about by the long-standing hepatic congestion, and this, in conjunction with the cyanosis due to the distention of the small veins, gives a characteristic yellowish blue tint to the skin. These several factors will usually allow one to make the diagnosis of tricuspid lesions, but it should be pointed out that these signs, which are the result of intractable right-sided heart failure, may be induced by another complication of rheumatic heart disease—namely, adhesive mediastinal pericarditis. (This condition will be discussed later in the section dealing with pericarditis.) Hence, in any patient presenting these indirect signs of tricuspid disease, the diagnosis should not be made until adherent pericardium has been sought for and excluded.

Thrills. The significance of thrills at the apex has already been discussed. They have relatively little diagnostic value. On the other hand, the presence of a thrill at the base of the heart or along the left sternal border constitutes practically conclusive evidence that the accompanying murmur is of the organic type. Such thrills are especially important in the diagnosis of aortic stenosis, a lesion which usually cannot be recognized with certainty in the absence of this sign.

DISTURBANCES OF RHYTHM AND RATE OF THE HEART

Certain disorders of the heart action are of importance because they may be responsible for serious consequences: congestive failure, angina pectoris, or even death. Others, such as many of the irregularities, are important because the anxiety they produce is commonly out of all proportion to their seriousness. In exceptional instances the decision as to the type of irregularity has to be made by the electrocardiographic method,

which should be employed in all doubtful cases. However, the physician who has taken the time to study the arrhythmias carefully, and who for a number of years has regularly correlated his clinical observations with electrocardiographic records, can usually recognize the cardiac irregularities by simple auscultation.

Disturbances of rhythm may be conveniently divided into two groups: those which are very common, and those which are less common. The former group includes the sinus arrhythmia, the premature beat, and auricular fibrillation.

Sinus Arrhythmia. Sinus arrhythmia is observed in most healthy young subjects, and consists of quickening of the heart during inspiration, and slowing during expiration. It tends to be intensified by deep breathing, and to disappear when the breath is held or when the heart rate is increased by exercise. This arrhythmia has no significance.

Premature Beat. Premature beats may arise in the atrium, the junctional tissues, or—much more frequently—in the ventricle (figs. 195, 196). They are relatively more common in patients with structural cardiac disease than in healthy subjects, but since they are not rare in such individuals, their presence has no diagnostic significance. When occurring in the absence of organic heart disease, premature beats may be due to emotional stress, hypoglycemia, or the excessive use of tobacco, coffee, or tea. In many instances the cause cannot be determined. The premature beat is usually recognized with ease because it consists of a contraction appearing before the next beat would ordinarily occur, and is usually followed by a pause longer than the usual interval. At times premature beats may occur in groups, one after the other, and under such circumstances the condition may be confused with auricular fibrillation, an error which can be avoided by noting that the rhythm becomes regular when the heart is accelerated by exercise.

One special type of premature beat merits additional comment (fig. 197). This is *bigeminal rhythm*, a state in which every alternate beat is premature. This condition is usually the result of overdosage with digitalis, and disappears within a few days after the drug has been withheld. It should not be confused with *pulsus alternans*, a disorder of rhythm in which every alternate beat is feeble, but in which the rhythm remains regular (Chapter 31, p. 350). In the case of both of

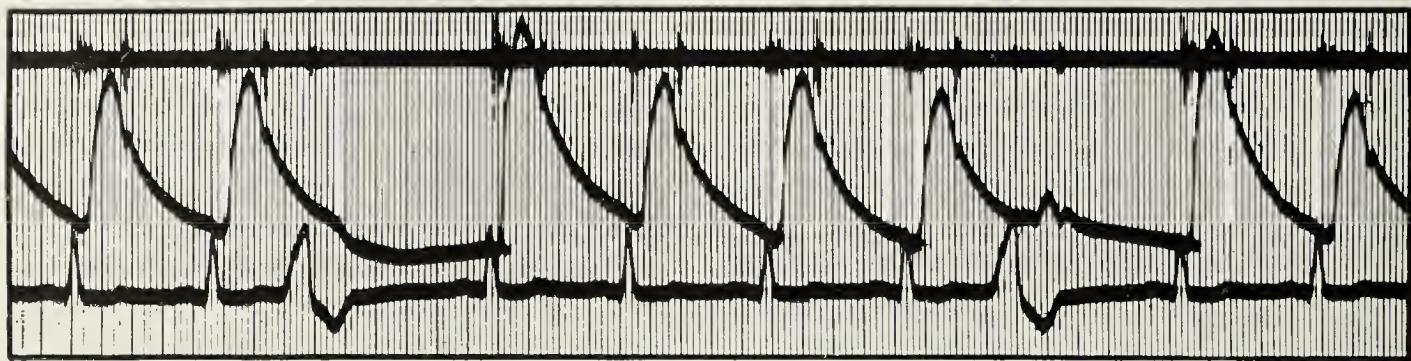


FIG. 195: Premature contractions (I). Ventricular extrasystoles. (H. H. Hecht.) From above downward: apical heart sounds, carotid pulsations, and electrocardiogram (lead II).

The *extrasystolic heart sounds* usually differ in character and intensity from the normal beats because (a) the relation of atrial to ventricular contraction is altered and (b) intraventricular pressures are subnormal. In very early extrasystoles (third beat from left) only one, the first heart sound, may be heard because the intraventricular pressure never exceeds peripheral diastolic pressures and therefore the semilunar valves do not open. The intensity of the first sound of the postextrasystolic beat is often increased.

The *extrasystolic pulse beat* is smaller and the first postextrasystolic beat is usually more forceful than the normal pulse. The size of the pulse wave is related to diastolic ventricular filling and tends to be larger following a long and smaller following a short diastolic interval in a given individual. The size of the pulse wave in extrasystolic disorders is therefore related to the degree of prematurity of the extrasystole. No pulse is recorded when only one heart sound is present.

The *electrocardiogram* of an extrasystolic beat, on the other hand, is not influenced by prematurity as long as the abnormal beat falls outside the refractory period of ventricular muscle. The electrocardiographic configuration is dependent on the site of the abnormal focus. Broad and notched ventricular complexes not preceded by P waves and strikingly different from the nonextrasystolic beats are indicative of asynchronous ventricular contraction and characterize ventricular extrasystoles; QRS complexes generally very similar to the nonextrasystolic beats but preceded by abnormally shaped P waves are indicative of extrasystolic auricular foci (fig. 196).

In the illustration, the first extrasystole occurs 0.51 second, the second 0.60 second, after the beginning of the preceding normal beat. The first extrasystole shows only one heart sound and no pulse beat; the second, following a somewhat longer diastolic period, shows two heart sounds and a definite pulse wave. The mechanical effects of the two extrasystoles are quite different; the electrocardiograms are identical. Time lines: 0.04 second.

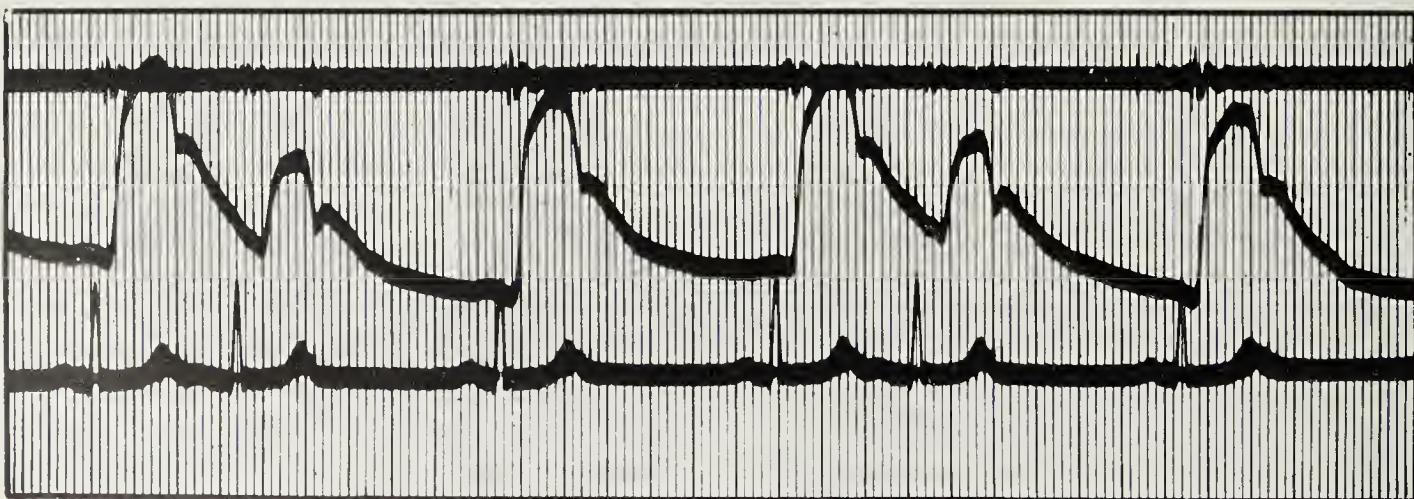


FIG. 196. Premature contractions (II). Auricular extrasystoles. (H. H. Hecht.)

From above downward: heart sound at apex, carotid pulsations, and electrocardiogram (lead II).

The mechanical events in auricular extrasystoles are nearly identical to those observed with ventricular premature beats. The electrocardiogram differs, and is characterized by (1) premature onset of auriculoventricular complexes with visible auricular components, (2) altered shape of P when compared with preceding normal auricular complexes, and (3) none or only slight alteration in the shape of the ventricular complexes.

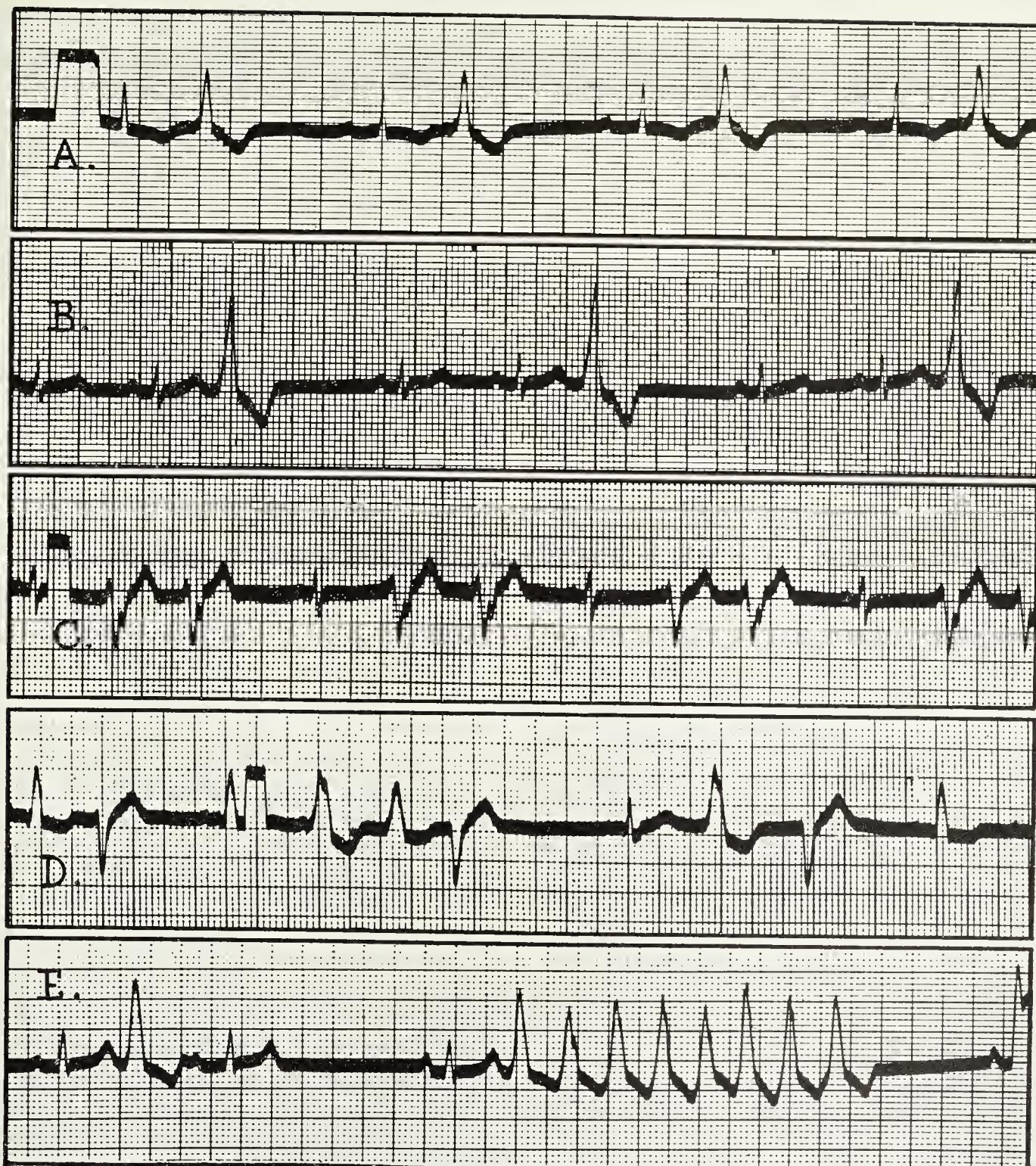


FIG. 197. Multiple extrasystoles. (H. H. Hecht.) Five examples (lead II) of extrasystolic disorders arising within the ventricles, demonstrating rhythmic activity of lower impulse centers (*parasystole*) or repeated *re-entry* (see Chapter 31, figure 50).

(A) *Bigeminus*: Every second beat represents a ventricular extrasystole. The subject is a 61-year-old watchman with arteriosclerotic heart disease who received no digitalis.

(B) *Trigeminus*: Every third beat represents a ventricular extrasystole. The subject is a 22-year-old Negro housewife with no demonstrable heart disease.

(C) *Trigeminus*: Two extrasystolic and one normal beat. The subject is a 26-year-old truck driver with no demonstrable heart disease.

(D) *Multiple extrasystoles* arising from various foci. The subject is a 68-year-old woman with scleroderma, heart failure, and digitalis intoxication.

(E) An "interpolated" ventricular extrasystole occurring between two normal beats and not followed by a compensatory period. (Note: postextrasystolic PR prolongation.) This is followed by a period of rapid firing of eight impulses from the extrasystolic focus representing a short episode of *ventricular paroxysmal tachycardia*. The subject is a 29-year-old housewife with no demonstrable heart disease.

these disturbances one notes, on taking the blood pressure, that every alternate beat comes through at a lower level than the previous one. However, on listening to the heart, the irregularity is readily detected in the case of the bigeminal rhythm, while no irregularity is noted in the case of pulsus alternans. The *paradoxical pulse*, which is sometimes confused with alternation or bigeminy, will be discussed in the section dealing with Pericarditis (p. 1306).

The treatment of premature beats depends on the associated findings. When they occur only occasionally, and evidence of cardiac disease is lacking, no treatment is needed other than correction of hypoglycemia in that small group due to this cause. When a reasonable suspicion exists that tobacco or caffeine is the cause, these drugs should be temporarily withheld. In excitable patients premature beats may disappear following the administration of mild sedatives. Potassium salts may also be effective (6 to 8 Gm. of potassium chloride daily in divided doses, well diluted and suitably flavored). When premature beats occur in a person receiving full doses of digitalis, the drug should be withdrawn for a few days, and if the irregularity is the result of digitalis it will then disappear. Quinidine, in doses of 0.1 to 0.2 Gm. (1.5 to 3 gr.), is a highly effective remedy for premature beats in most patients, but should be given only when the extrasystoles are sufficiently frequent to cause an important mechanical inefficiency of the heart, or occasionally to highly excitable persons who are alarmed by the irregularity.

Auricular Fibrillation. This irregularity has been considered generally to be due to a circus movement—that is to say, a wave of excitation circulating continuously in a short and irregular path about the mouths of the venae cavae (Chapter 31, fig. 50). Recent experimental work suggests that this concept may be erroneous or, at least, not the sole explanation for the irregularity, and that the latter arises from an irritable focus in the auricle. Whichever may ultimately be proved to be the underlying mechanism of auricular fibrillation, the effect is to obliterate the effective contraction of the atria and to bombard the atrioventricular node and the ventricles with a very rapid and irregular series of impulses. Many of these impulses are blocked at the A.V. node, but many pass through, so that the ventricular contractions in the untreated patient are

usually rapid and completely irregular (see figure 198).

Auricular fibrillation may be paroxysmal or persistent. Occasionally, the paroxysmal form occurs in healthy subjects in whom no evidence of structural cardiac disease can be found. It is also encountered in individuals who, otherwise normal, suffer from acute infectious diseases, most commonly in acute lobar pneumonia in the presulfa and prepenicillin era; or in patients who are in the midst of acute illnesses primarily affecting the heart, such as acute rheumatic carditis and acute myocardial infarction. Rarely, paroxysmal auricular fibrillation may be the consequence of digitalis intoxication, or other forms of poisoning. Most frequently, however, paroxysmal auricular fibrillation is seen in thyrotoxicosis, in rheumatic heart disease with mitral stenosis, or in senile heart disease. In the latter two conditions the paroxysmal form not uncommonly occurs from time to time before the arrhythmia becomes permanently established. The paroxysms are of variable duration, lasting from a few seconds to a few days. These attacks have the characteristics of all types of paroxysmal rapid heart action, the onset and offset being sudden; and unless the patient is observed in the midst of the attack, the recognition of the nature of the episode will depend largely on the observation by the patient that the heart action is highly irregular during the attack.

The permanent form of auricular fibrillation is confined almost exclusively to patients with senile heart disease, mitral stenosis, or thyrotoxicosis.

Thus, barring those instances of auricular fibrillation occurring in the midst of acute infectious diseases or in patients with acute rheumatic carditis or myocardial infarction, in all of which cases the cause of the arrhythmia is usually obvious, auricular fibrillation occurring in a patient seen for the first time practically always means that thyrotoxicosis or mitral stenosis or senile heart disease is the underlying cause.

When the rate is rapid—i.e., 120 or more—the diagnosis is made readily, because auricular fibrillation is the only common condition in which one has the combination of a well-marked tachycardia with a gross irregularity. When the rate is normal or only slightly rapid, as in digitalized subjects, the diagnosis is less readily apparent, but the lack of any dominant rhythm or of any rhythmic pattern can usually be demonstrated

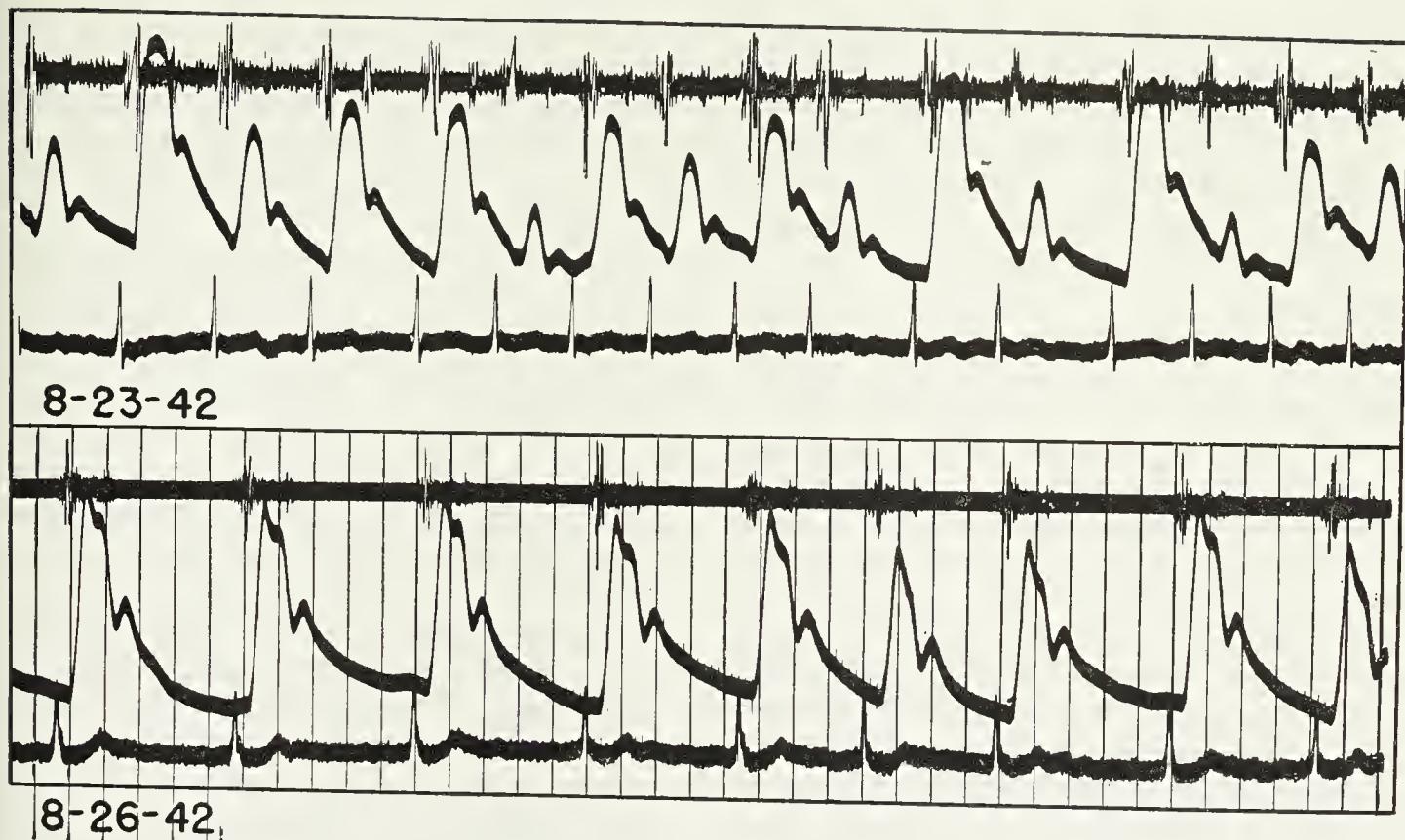


FIG. 198. Auricular fibrillation. (H. H. Hecht.) Apical heart sounds, carotid pulsation, and electrocardiogram (lead II) in a 65-year-old farmer with arteriosclerotic heart disease and congestive failure before (*top*) and after (*bottom*) digitalization.

A complete irregularity of all graphic records is present in both sets of tracings. When the rate is rapid, the irregularity is more readily apparent and the heart is obviously at a mechanical disadvantage (*top*). On "compensation" the heart at rest, though still irregular, appears to be as efficient as when normal sinus rhythm is present (*bottom*).

The varying intensity of the sounds, the irregularity in rate, rhythm, and volume of the pulse curve, and the replacement of coördinated P waves of the electrocardiogram by small undulating movements of the string during diastole characterize auricular fibrillation.

(*Note:* depression of RST segment in lower tracing, caused by digitalis therapy.) (See also Chapter 31, figure 51, and figure 202.)

by simultaneously listening to the heart and flexing one's finger with each beat, in an attempt to determine whether there is predictability to the rhythm. The distinction from numerous extrasystoles can be made by noting that, while in both conditions one has beats of normal interval, followed by groups of beats occurring at shorter intervals, it is only in auricular fibrillation that abnormally long pauses will be noted to occur in groups of two or more. More difficult, and frequently impossible, is the distinction of auricular fibrillation from auricular flutter with varying block, and from a shifting pacemaker in which there are auricular ectopic beats arising from multiple foci. Both of these conditions may produce total irregularity. However, since auricular fibrillation is very common, while the other conditions are rare, it is a safe rule to consider a person with a total irregularity in which the

rhythm has no pattern and no predictability, as having auricular fibrillation.

The untoward effects of auricular fibrillation depend on the rapidity of the ventricular rate and the extent of the pulse deficit (i.e., on the proportion of ineffective and hence wasted ventricular beats), on the prior state of the affected heart, on the duration of the attack, and on the virtual paralysis of auricular contraction. In the paroxysmal attacks, the symptoms are identical with those observed in other forms of paroxysmal rapid heart action: palpitation, weakness, dyspnea, and, in some cases, congestive failure or prolonged anginal pain, depending on the cardiac reserve or the efficiency of the coronary circulation. In the chronic untreated cases, the symptoms are essentially the same. In those cases that are brought under effective control by full doses of digitalis, the symptoms disappear and the ir-

regularity, in itself, has practically no harmful effect on the efficiency of the heart. However, in all cases, paroxysmal or permanent, treated or untreated, the absence of atrial contractions favors the development of mural thrombi in the atria and exposes the patient to the hazards of embolism, either in the lungs or in one or another of the systemic arterial branches.

The effects of auricular fibrillation on the signs of mitral stenosis have already been described. The component of the diastolic murmur due to atrial contraction disappears. What is heard will depend on the ventricular rate: when the rate is slow, only the early diastolic murmur is present; when the rate is rapid, this same murmur fills diastole up to the time of the first sound, and one may gain the impression that the usual presystolic murmur seen in a regular rhythm persists.

It is important to emphasize that when the ventricular rate fails to slow in the usual fashion, in response to full therapeutic doses of digitalis, the presence of thyrotoxicosis should be suspected.

In a patient with auricular fibrillation, one faces the choice between two plans of therapy, that of attempting to control the rate with digitalis, the rhythm remaining irregular; and that of abolishing the arrhythmia by the use of quinidine. When the arrhythmia is of long standing, or when the patient is known to have had congestive failure for several months or longer, or when there is marked cardiac enlargement, digitalis is usually the method of choice; but it should be clearly understood that the drug does not usually abolish the irregularity; it simply reduces the ventricular rate. Under these conditions quinidine may be dangerous, and the drug is also contraindicated when there is marked impairment of intraventricular conduction, because under such circumstances it may lead to fatal standstill or fibrillation of the ventricles. Hence *quinidine should usually be reserved for use in patients with recent auricular fibrillation* who are known to have had no evidences of congestive failure prior to the onset of the arrhythmia. (Others do not consider previous congestive failure a contraindication.) The initial dose of the drug should be small (.1 to .2 Gm.), and followed by a wait of several hours in order to make certain that the patient is not hypersensitive to it (as evidenced by respiratory difficulty, syncope, purpura). Quinidine should then be given in increasing doses, at intervals of two to three hours,

until a dose of approximately 1 Gm. is reached, or until the arrhythmia has been noted to disappear. When large doses are employed, the patient should be seen frequently and the dose reduced as soon as the arrhythmia subsides. The dosage of 1 Gm. every four hours may be maintained for several doses before one decides that the arrhythmia is intractable to the drug. When the rhythm has reverted to normal, maintenance doses of quinidine may be required in some patients, although frequently the normal mechanism persists despite the discontinuance of quinidine. Quinidine therapy should be undertaken only when controlled by frequent electrocardiograms; it should be stopped when evidence of outspoken impairment of conduction appears.

One point needs emphasis: Although there are rare instances of transient auricular fibrillation in which the administration of digitalis is followed shortly by the disappearance of the arrhythmia, when auricular fibrillation is of long duration digitalis does not abolish the arrhythmia, and statements that "the fibrillation is improved" reflect a lack of understanding of the action of digitalis. Following the administration of this drug, the atria continue to fibrillate. However, the ventricular rate diminishes strikingly, and as the rate becomes slower the rhythm becomes less obviously irregular, although careful observation, supported by electrocardiographic tracings, reveals that the ventricular irregularity does actually persist. In some cases, digitalis may cause a complete block at the A.V. node, following which a regular ventricular rhythm may be seen, but even here the atria continue to fibrillate.

The Less Common Arrhythmias. These include the several types of heart block, and the ectopic tachycardias other than auricular fibrillation.

HEART BLOCK. The term *heart block* refers to a condition in which there is impairment of conduction from the atria to the ventricles through the A.V. node and main bundle. *First-degree block* is that state in which all of the atrial beats are followed by ventricular beats, but in which the duration of time for the passage of the impulse from the atria through the A.V. node and main bundle to the ventricles (P-R interval) is prolonged. *Second-degree block* refers to a more advanced disturbance in the conduction system in which atrial impulses are from time to time incapable of penetrating the conduction system

and exciting the ventricle. *Third-degree or complete heart block* describes the condition in which the conduction system is so altered that no atrial impulses reach the ventricles, and the atria and ventricles beat independently at their own rhythms.

FIRST-DEGREE BLOCK (SIMPLE INCREASED P-R INTERVAL). (See figure 199.) First-degree block may be due to increased vagal tone in a perfectly normal individual, or to fatigue in the conduction system as a result of prolonged tachycardia, the action of digitalis, or any of the inflammatory, toxic, degenerative, or vascular processes that may affect the heart. First-degree block is an electrocardiographic diagnosis and produces no characteristic symptoms. It may be suspected when a person suffering from rheumatic fever develops a sudden decline in the intensity of the first heart sound, without any other change in the clinical picture, and without evidence of fluid in the pericardium. Another circumstance under which first-degree heart block may be suspected clinically is when, in the absence of auricular fibrillation, a presystolic murmur becomes mid-diastolic, and ceases prior to the first heart sound (see figure 193). First-degree heart block requires no treatment, the management being that of the underlying condition.

It is generally considered that a P-R interval greater than 0.20 to 0.21 second represents first-degree heart block, and such a prolonged P-R

interval is held by some to be evidence of myocardial disease. However, it is not uncommon to encounter this finding in persons who present no other evidence of cardiac disease, and who give no history of any illness that is known to have a permanent effect on the heart. In the absence of other criteria to indict the heart, this one electrocardiographic deviation from the accepted norm should not in itself be considered indubitable evidence of organic heart disease.

Heart block of a grade higher than simple prolongation of the P-R interval may occur as a transitory or as a permanent condition. It may be the result of digitalis or diphtheritic intoxication, of inflammatory processes such as acute rheumatic fever or syphilis, of coronary occlusion affecting the artery to the A.V. node, of calcification of the annulus fibrosus of the mitral valve with compression of the conduction system, and of congenital anomalies of the interventricular septum. The severity and permanency of the heart block will naturally depend on the extent of the damage to the A.V. node and the bundle of His, and on the completeness of recovery from the damaging process.

SECOND-DEGREE BLOCK. In second-degree block, occasional ventricular beats may be dropped at irregular intervals (fig. 200), or every second or third or fourth beat may fall out, giving rise to 2:1, 3:2 or 4:3 block (fig. 201). In one type, the duration of time between atrial ventricular con-

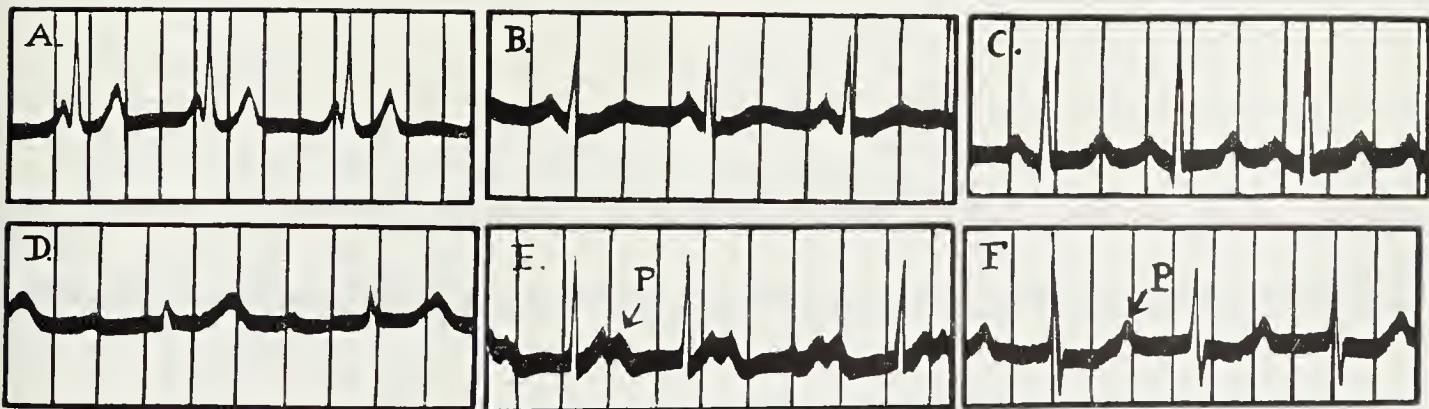


FIG. 199. Normal and impaired atrioventricular conduction (the P-R interval). (H. H. Hecht.)

Normal atrioventricular conduction varies from 0.12 to 0.2 second and is dependent on age and heart rate (see table 36, Chapter 31). Unusually rapid conduction is occasionally seen without evidence of heart disease with and without abnormal ventricular complexes (A). These records are not to be confused with apparent shortening of P-R interval and wide QRS complexes (anomalous atrioventricular conduction, p. 356).

Prolonged A.V. conduction (first-degree heart block) occurs under many circumstances and is usually occasioned by an impairment in conduction through the atrioventricular node. P may occasionally be recorded during a final portion of the preceding T wave, giving the impression of a notched or biphasic T (E, F).

(A-C) No heart disease. (D) Arteriosclerotic heart disease. (E, F) Acute rheumatic fever. P-R interval measures in A 0.1 second (short), in B 0.13 second (normal), in C 0.15 second (normal), in D 0.37 second (long), in E 0.28 second (long), and in F 0.36 second (long). All electrocardiograms, lead II. Time lines: 0.04 and 0.2 second. (See also Chapter 31, figure 48.)

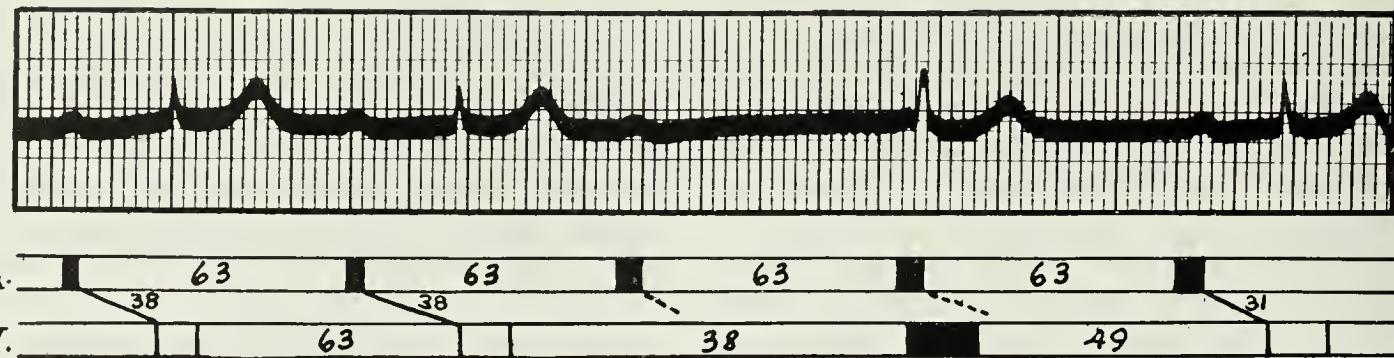


FIG. 200. Impaired atrioventricular conduction with dropped beat and ventricular escape (first- and second-degree heart block). (H. H. Hecht.)

Prolonged atrioventricular conduction is present throughout (P-R interval 0.38 second). The third atrial impulse finds the junctional tissue completely refractory and the impulse is not conducted to the ventricles (*dropped beat*). In this instance, before the next following impulse arrives, an independent beat arises either from junctional tissue or within the neighborhood of the common branch of the bundle of His (*ventricular escape*). The last beat illustrated shows improvement in atrioventricular conduction (P-R interval 0.31 second), presumably because part of the conducting tissue had time to recover.

This is the record (lead II) of a 72-year-old patient with arteriosclerotic heart disease. (A) Atria; (V) ventricles. Time lines: 0.21 second.

traction becomes progressively longer, until finally an atrial beat fails to be followed by a ventricular contraction (Wenckebach's pause). The following atrial impulse gives rise to a ventricular response, the conduction time being much shortened and then increasing with each successive beat until ventricular contraction again fails to take place.

Another type of second-degree heart block is that in which every alternate beat of the atrium fails to be followed by a ventricular beat. Under these circumstances the bradycardia is likely to be marked but the intensity of the first sound may be constant, because the ventricular beats occur in a constant relationship to the preceding

atrial beat. In patients with second-degree heart block, exercise will usually increase the rate, although occasionally, when the ventricles are unable to respond to the increased atrial rate, the paradoxical effect of a slowing of the ventricular rate upon exercise will be observed as the degree of block increases when the atrial rate increases.

THIRD-DEGREE BLOCK (COMPLETE HEART BLOCK). Third-degree block in its permanent form is rarely due to congenital deformity affecting the conduction septum. More commonly, it is due to coronary sclerosis, senile heart disease, or calcification of the mitral annulus. When complete block occurs in diphtheria, the prognosis is exceptionally grave.

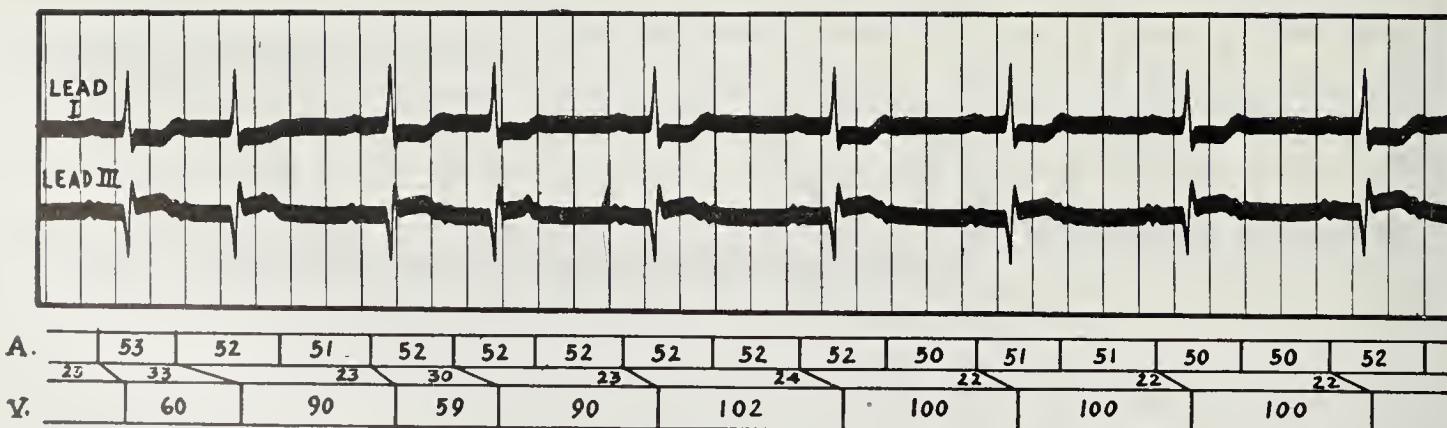


FIG. 201. Partial auriculoventricular heart block (3:2 and 2:1). (H. H. Hecht.)

The left-hand section of the curve shows gradual prolongation of A.V. conduction with eventual failure of conduction (following the second and fourth ventricular beats): *Wenckebach's period*. The right-hand side of the tracing demonstrates failure of conduction following every second atrial impulse (*2:1 block*).

Note QRS and T wave changes characteristic of recent diaphragmatic myocardial infarction (Q_{III}T_{III} pattern).

The subject is a 77-year-old laborer with acute myocardial infarct, admitted on the first day following a coronary occlusion. The figures indicate atrial and ventricular rate and P-R interval. (A) Atria; (V) ventricles. Time lines: 0.2 second.

Complete auriculoventricular dissociation can usually be recognized readily at the bedside without instrumental aid. The heart rate will usually be found to be 45 or less, although exceptionally, and especially following acute posterior infarction or digitalis intoxication, the rate may be as rapid as 65 (fig. 202). The rhythm is regular and the rate does not increase appreciably with exercise. Despite the regular rhythm, the first impression may be that there is an irregularity, because the intensity of the first sound varies markedly from beat to beat. It may occasionally be quite loud when ventricular contractions happen to follow very quickly after the atrial, and at other times it may be almost inaudible (fig. 203).

The slow ventricular rate causes little or no disability. Individuals with congenital complete block but with an otherwise normal heart may lead a normal life and engage in strenuous physical activity without any appreciable disability. In patients with partial or complete block, symptoms referable to the heart are generally due to the underlying heart disease rather than to the slow ventricular rate. Some patients may have the disorder for years, with or without recurrent syncopal attacks of the Adams-Stokes variety. The hazard especially important to patients with organic heart disease and partial or complete block is the sudden slowing or failure of the idioventricular rhythm which results in cessation of effective ventricular contraction for several seconds or longer (fig. 204). This may be due to ventricular standstill or to brief periods of fibrillation or tachycardia of the ventricles. When the ventricular pause lasts 5 to 15 seconds, the patient suffers from an attack of lightheadedness or syncope; in pauses longer than 15 seconds, convulsions may appear; finally, when ventricular arrest lasts more than a minute or two, death ensues. These episodes of syncope and convulsions due to prolonged ventricular pauses are known as Adams-Stokes attacks. In some patients they may occur at long intervals; in others they may develop with great frequency for days, so that death is constantly imminent.

Given a patient with a history of recurrent syncopal attacks, the possibility of heart block should be considered. The more important points in the differential diagnosis of syncope have been discussed in Chapter 7.

The treatment of the more advanced states of heart block is unsatisfactory. During syncopal

seizures recurring in quick succession, epinephrine in 1:1000 aqueous solution, in doses of 0.2 to 0.3 ml. given subcutaneously or intramuscularly every 20 to 30 minutes, may be necessary to prevent fatal asystole. Probably a more effective method would be to administer 1 mg. of epinephrine in oil four to six times a day, with supplementary doses of aqueous epinephrine when necessary. As a heroic emergency measure when death seems almost certain, it has been advocated that aqueous epinephrine be injected directly into the cardiac wall. In other patients whose attacks occur at less frequent intervals, ephedrine given orally three or four times a day appears to be sometimes effective. Success has been reported occasionally with other drugs, but in general they have proved disappointing and can be disregarded. The questions as to whether these measures are contraindicated, and whether quinidine is indicated in patients with syncopal attacks associated with auriculoventricular block and brief periods of ventricular fibrillation or tachycardia, remain unsettled. The problem of the use of digitalis in patients with congestive failure and heart block requires brief comment. Digitalis tends, in itself, to produce impairment of conduction through the atrioventricular node and bundle, and fear may be entertained that the drug may convert a partial block into a complete block with consequent danger of inducing syncopal attacks. Digitalis may be given without hesitation to patients who display merely a prolongation of the P-R interval. When second-degree block is present, digitalis should be given somewhat cautiously: in most instances, either no significant change in the degree of block ensues, or it may actually be lessened by virtue of the preponderant effect of the general improvement of the circulation over the local effect of the drug on the A.V. conduction system; rarely, the reverse may be true and syncopal attacks may be induced. When complete block exists, digitalis can exert no further deleterious effect on A.V. conduction, and it may be administered in the usual manner without reservation.

TACHYCARDIA. Given a patient with a well-marked increase in the heart rate, the first decision to be made is whether one is dealing with sinus tachycardia or with one of the ectopic tachycardias. The latter group of disorders will usually respond to therapy aimed directly at the



FIG. 202. Temporary auriculoventricular dissociation following intravenous administration of ouabain. (H. H. Hecht.)

Following an auricular extrasystole (sixth beat from right), the ventricles assume an independent rhythm of a slightly slower rate than before for a total of four beats; a temporary "unhinging" of A.V. conduction with a high ventricular rate (here 108 beats per minute) is a not uncommon feature of digitalis intoxication. Note the effect of digitalis on RST segment.

The subject is a 65-year-old hospital attendant with hypertensive heart disease and erysipelas of the face. Intensive treatment with sulfonamides and alkali precipitated an episode of acute pulmonary edema for which he received 0.5 mg. of ouabain. The record was obtained 12 hours later.

(A) Atria; (V) ventricles; shaded diagrams indicate independent ventricular beats; black diagrams indicate ectopic auricular beats.

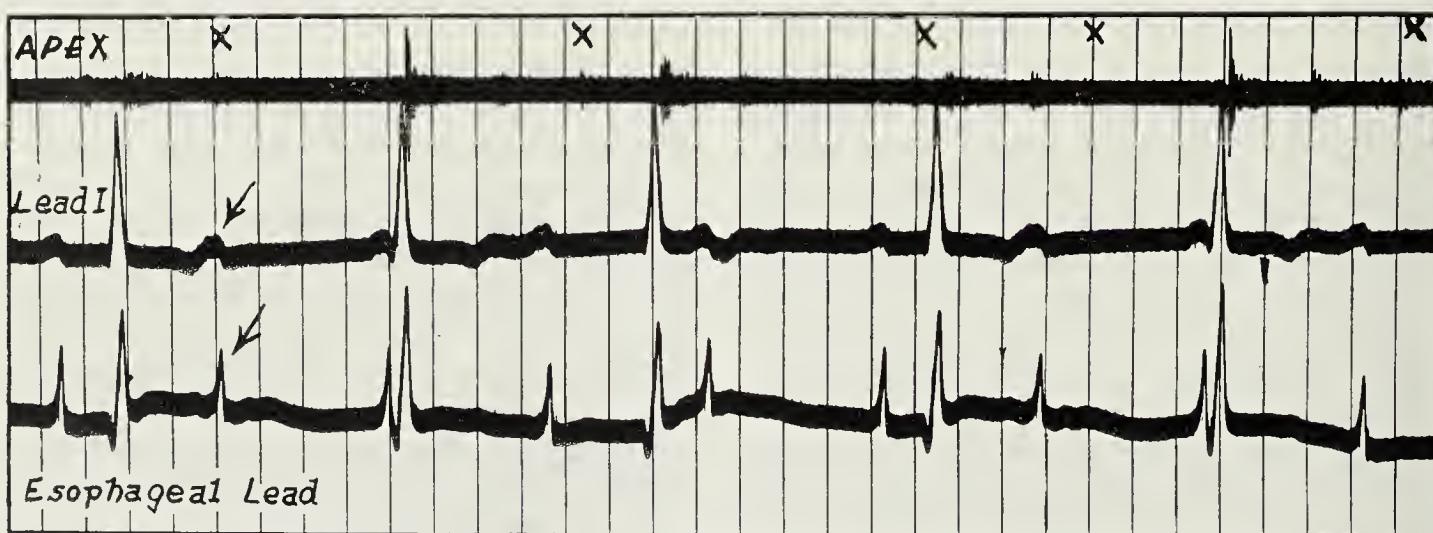


FIG. 203. Complete auriculoventricular dissociation (heart block). (H. H. Hecht.)

From above downward: heart sound at apex, electrocardiogram (lead I), and a lead obtained from the esophagus with the exploring electrode located opposite the left atrium.

A complete independence of atrial from ventricular impulses is noted, the former beating at a rate of 75 beats per minute, the latter at 50 beats per minute. Occasionally atrial and ventricular beats accidentally coincide (third and sixth beats).

The sound records demonstrate (1) a sharp increase in the intensity of the first ventricular heart sound, when atrial and ventricular contractions coincide; and (2) very faint sounds in diastole following atrial excitation ("auricular sounds": marked X).

The subject is a 65-year-old laborer with arteriosclerotic heart disease but without demonstrable evidence of heart failure.

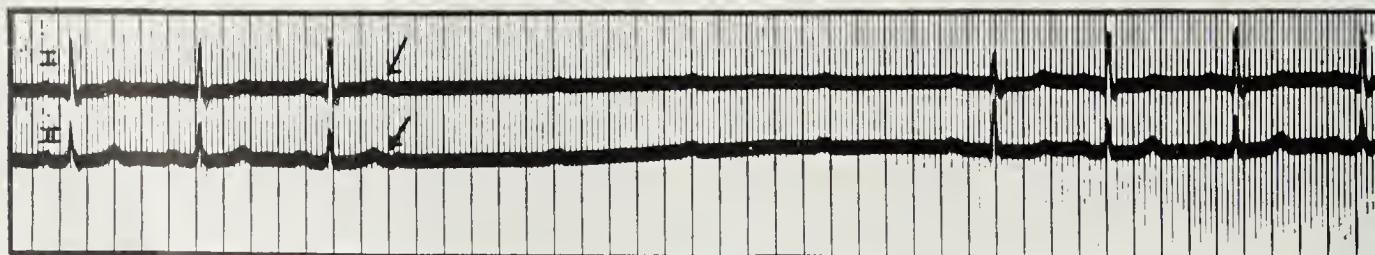


FIG. 204. Spontaneous prolonged cessation of atrioventricular conduction (Adams-Stokes seizure). (H. H. Hecht.)

In this example an extrasystole occurred following the third normal ventricular beat (arrow). The ectopic impulse reaches an unusually refractory conduction system and is therefore not transmitted to the ventricular musculature (*blocked auricular extrasystole*). Following this, the conduction system does not recover and the next three normal atrial impulses are not transmitted. This results in ventricular standstill of 4.8 seconds, after which normal conduction is resumed.

This patient suffered from the terminal stages of arteriosclerotic heart disease and many similar attacks were recorded, during one of which the patient expired.

heart, while in the case of sinus tachycardia the treatment of the rapid rate depends on the management of the underlying condition. The ectopic rhythms set in instantly, and this is usually perceived by the patient. Hence a story of instantaneous onset, if accurate, allows one to know immediately that the rhythm is ectopic. When the rate is less than 140 per minute, the chances are strong that one is dealing with sinus tachycardia. Rates of 170 and more per minute are almost invariably the result of ectopic rhythms, and the difficulty comes chiefly in the group of patients with heart rates between 140 and 170. When the rate is in the general region of 150, ventricular and auricular tachycardia are unlikely, and there is a distinct probability that if the rhythm is ectopic it is auricular flutter.

EXTREME SINUS TACHYCARDIA. The chief causes of extreme sinus tachycardia are marked elevation of the body temperature, severe thyrotoxicosis, and any condition which produces profound circulatory collapse. Occasionally, acute myocardial injury due to infection, infarction, etc., may be the cause, but in most instances sinus tachycardia of severe degree is due to peripheral rather than cardiac causes. Sinus tachycardia does not ordinarily respond significantly to carotid sinus pressure, and in this respect resembles ventricular tachycardia. When slowing does take place, it is usually slight, and neither slowing nor subsequent acceleration occurs with the abruptness observed in patients with auricular flutter. In the absence of marked hyperthermia or severe thyrotoxicosis, a patient with outspoken sinus tachycardia will usually display manifestations of forward failure (see Chapter 14). It should be emphasized again that the decision as to whether one is dealing with sinus tachycardia or with an ectopic rhythm is of the greatest practical importance, because in the latter instance specific therapy aimed toward the heart may have an almost magical effect on the patient. Since sinus tachycardia requires no treatment aside from that directed at its cause, a word may be said regarding the use of digitalis in this condition. Unless there are definite signs of congestive failure, digitalis has no place in the treatment of sinus tachycardia. Not only is this drug valueless under these circumstances, but it probably is harmful and may be dangerous. Digitalis is not indicated merely because the heart rate is accelerated.

ECTOPIC TACHYCARDIAS. The most important of these—auricular fibrillation—has been considered already. *Auricular flutter* is a much rarer but closely allied condition in which the circus movement follows a longer and more regular route; or, as newer observations suggest, a condition fundamentally identical with paroxysmal auricular tachycardia, differing only in that the irritable focus discharges at a much higher rate (fig. 205). When the degree of block between atrium and ventricle is variable, this disorder cannot be distinguished from auricular fibrillation with certainty, except by the electrocardiographic method. As a rule the atria flutter at a rate of approximately 300 per minute, and either 2:1, 3:1 or 4:1 block exists, the corresponding ventricular rates being about 150, 100, or 75. When the block is constant and of high degree, the condition will usually not be suspected; but if it is suspected, its presence can be confirmed by the fact that during exercise the heart rate increases suddenly rather than gradually, and that in the postexercise period slowing occurs suddenly rather than gradually. In an individual with sinus rhythm, exercise causes increase in atrial rate; in an individual with auricular flutter, exercise has little effect on the atrial rate, but the decrease in vagal tone tends to reduce the degree of block, and since the block suddenly changes from the high degree to a lower degree, the acceleration occurs in the space of a single heart beat. More commonly, with auricular flutter, the ventricle responds to every alternate auricular impulse. Under such circumstances the ventricular rate is usually between 140 and 160, and this fact alone should make one suspect the presence of flutter, because the other types of regular tachycardia of ectopic origin are likely to be associated with faster rates. When auricular flutter is suspected, it will usually be found that carotid sinus pressure causes the ventricular rate to slow, but that the slowing is maintained only for the brief period of the pressure, and the heart then returns to the previous rate. Furthermore, the deceleration and the acceleration both occur instantly rather than gradually, as would be the case with sinus tachycardia if there were any response at all to carotid sinus pressure.

Occasionally, the block is so variable that the high degree of ventricular irregularity is virtually identical with that observed in auricular fibrillation. The response to exercise may dis-

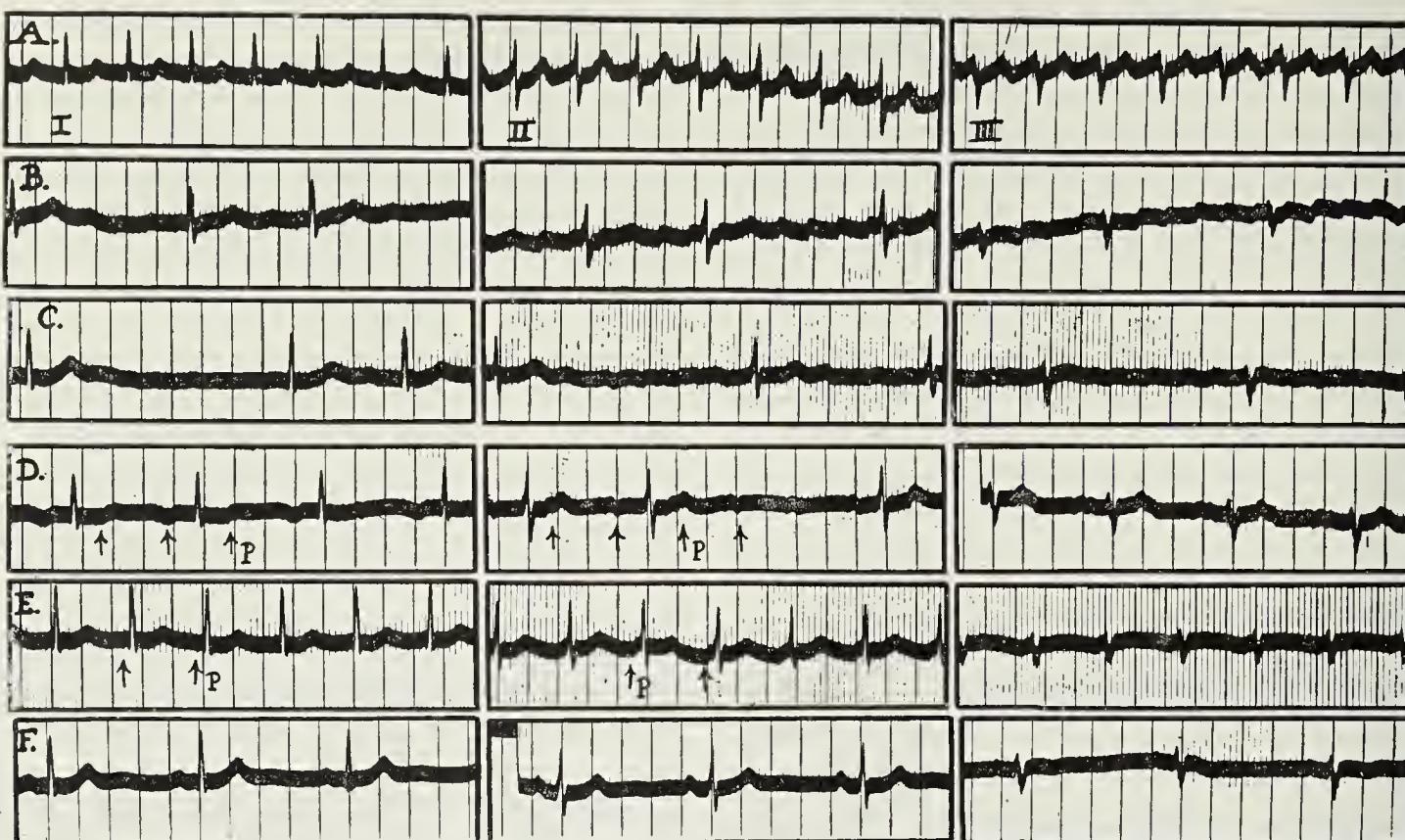


FIG. 205. The interrelationship of auricular flutter, auricular fibrillation, and paroxysmal auricular tachycardia with and without A.V. block. (H. H. Hecht.) Standard bipolar limb leads of a 35-year-old male with rheumatic heart disease.

- (A) Auricular flutter with 2:1 A.V. block, no treatment. Auricular rate 270 per minute.
 - (B) Massive doses of digitalis over two weeks had resulted in depression of A.V. conduction and a slight increase in the flutter rate: auricular flutter with varying ventricular response (4:1, 5:1); auricular rate 310 beats per minute.
 - (C) A week later, following further digitalization, auricular fibrillation was present with a slow irregular ventricular rate.
 - (D) A day later, while still on digitalis, a paroxysmal auricular tachycardia with predominantly 2:1 ventricular response was present. Auricular rate 150 per minute.
 - (E) Two weeks later, after the patient had been switched from digitalis to quinidine, an episode of 1:1 paroxysmal tachycardia was obtained. (A 1:1 flutter with ventricular rates above 300 per minute was observed on other occasions.)
 - (F) Temporary reestablishment of a normal sinus rhythm.
- The fundamental similarity between these auricular disorders, here seen in succession in one patient, is inescapable regardless of the underlying mechanism. (See chapter 31, figure 50.)

tinguish the two arrhythmias: in auricular flutter the irregularity will be abolished with the increased rate; in auricular fibrillation the irregularity will be enhanced.

Careful auscultation will frequently reveal an appreciable difference in the intensity of the first sound in auricular flutter, due to slight variations in the timing of the ventricular contraction in response to the preceding atrial contraction. The principle underlying this variability in the loudness of the first sound has been considered already. This difference in the loudness of the first sound is never present in sinus tachycardia, is rarely found in paroxysmal auricular tachycardia, and is frequently present in ventricular tachycardia. Hence, while this sign is not specific for any one condition, it can serve to limit the

diagnostic possibilities when a tachycardia is first encountered.

Auricular flutter is caused by essentially the same conditions which cause auricular fibrillation, has essentially the same prognostic significance, and is treated in a somewhat similar manner. Although the use of quinidine may occasionally cause auricular flutter to revert to normal rhythm, such an effect is less likely than in the case of auricular fibrillation. The usual method of treatment, therefore, is to administer digitalis, which increases the degree of auriculoventricular block and commonly converts auricular flutter to auricular fibrillation (see figure 205 C). When the drug is withdrawn, such patients frequently will revert spontaneously to normal rhythm, and if this does not occur

quinidine may be employed. Occasionally, it may be impossible to break up the abnormal auricular rhythm, and in such an instance digitalis may be needed to maintain a sufficiently great degree of block to allow the heart rate to remain at relatively normal levels.

Paroxysmal auricular tachycardia is the most common of the ectopic tachycardias, aside from auricular fibrillation (fig. 206). It usually appears first in youth, and attacks may continue to occur throughout life. The majority of subjects with this disorder display no evidence of any other cardiac abnormality. Any patient who has a history of recurrent attacks of rapid, regular heart action setting in instantly, and having been present since childhood or early adulthood, and who displays no evidence of structural heart disease, should be considered as having paroxysmal auricular tachycardia until the nature of the attacks can be established conclusively.

When the patient is seen during the attack, the heart is found to be perfectly regular, and the rate is usually 170 or faster. Procedures which cause vagal stimulation either will have no effect or will cause the attack to cease abruptly. Such procedures include pressure on the carotid sinus, pressure on the eyeballs, the induction of gagging or vomiting, and attempted expiration with the glottis closed (the Valsalva experiment). When these several procedures, attempted singly, are unsuccessful, they may still give a response when utilized in combination with each other.

The causes of auricular tachycardia are unknown, since most of the patients exhibit no signs of structural disease. Prognosis, as a rule, is excellent even in untreated cases, for the attacks tend to subside spontaneously after lasting for periods of minutes to hours. Exceptionally, the attacks may endure for several days, and under such conditions fatigue of the heart muscle, de-

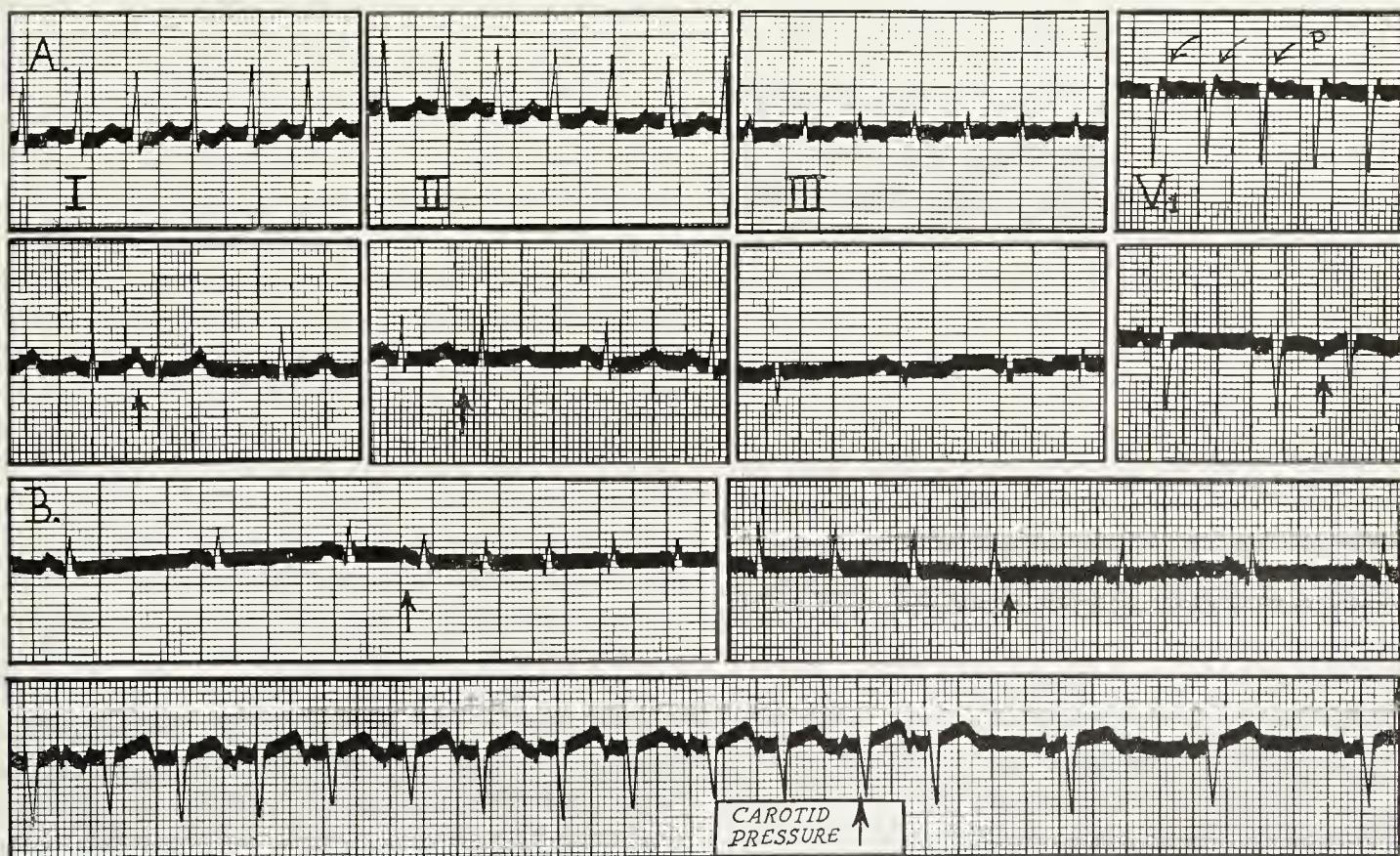


FIG. 206. Paroxysmal auricular tachycardia. (H. H. Hecht.) Two examples of auricular paroxysms are illustrated. The electrocardiographic complexes resemble those of single auricular or nodal extrasystoles.

(A) Leads I, II, III, and V₁ of a 19-year-old nurse before and after termination of an attack precipitated by drinking ice water. The QRS complexes are of normal configuration; P waves are buried in the ventricular complexes but are seen to deform the final portion of QRS in V₁ (arrow). After conversion, a few single auricular extrasystoles are present (arrow). The paroxysm presumably arises from the A.V. node.

(B) Lead II of a 75-year-old laborer at the beginning and at the end of an auricular paroxysm (arrows). The lower record represents lead V₁ before and after conversion by pressure on the carotid sinus. Although P waves were not visible in standard limb leads, the abnormally shaped P in V₁ preceding the normal QRS group indicates auricular paroxysmal tachycardia.

fective systolic discharge, dilatation, and congestive failure may supervene. In the majority of the patients with this disorder the most serious aspect is the psychologic effect on the patient and on the family. The attacks are alarming, and many individuals subject to the disorder develop a secondary anxiety state which causes more suffering than the initiating disorder. Hence the keystone of therapy in such a patient is proper reassurance coupled with attempts to prevent the seizures.

In many patients digitalis is the most effective drug in preventing the attacks. In other patients quinidine will be found to be more useful. Certain patients notice that the attacks are regularly precipitated by certain trigger factors, including anxiety, physical fatigue, abdominal distention, the rapid ingestion of cold drinks, and mild spontaneous hypoglycemia. A careful history in regard to the exact precipitating circumstances will often enable the physician to ferret out these trigger factors, and to instruct the patient as to how to avoid them.

When a patient is seen during an attack of paroxysmal auricular tachycardia, the following plan of procedure will be found to be effective in a considerable proportion of instances:

1. Have the individual take a deep breath and attempt to expire against a closed glottis (the Valsalva experiment).
2. Massage the back of the pharynx with the finger or any convenient instrument, to induce vomiting.
3. Massage the carotid sinus region (first one side, then the other) while listening to the heart, discontinuing the massage if the rate slows abruptly.
4. Press on the eyeballs firmly enough to produce mild but easily tolerable discomfort.
5. With the aid of bystanders, carry out procedures 1, 3, and 4 simultaneously.
6. Induce vomiting either by administering ipecac or by the administration of hot water, followed by the massaging of the pharynx. While the patient is retching, repeat procedures 1, 3 and 4, singly or simultaneously.
7. If the attack persists despite these measures, administer morphine (0.008 to 0.015 Gm.—i.e., $\frac{1}{8}$ to $\frac{1}{4}$ gr.) and digitoxin (1 mg. for an adult who has not received the drug for at least two weeks), and repeat the above procedures four to six hours later.

8. Quinidine sulfate may be administered in increasing doses of 0.2, 0.4, 0.6, 0.8, and 1 Gm., given at two-hour intervals, provided none of the contraindications to the use of the drug is present.

9. If these measures fail, the highly potent but dangerous methacholine chloride may be given. The dose is variable, and it is safest to begin with 2 mg., subcutaneously, and to administer 5 mg., 10 mg., and 20 mg., successively at 30-minute intervals, the site of previous injections being repeatedly massaged before subsequent administration. (The doses mentioned are for young adults.) This drug is especially dangerous in infants, elderly subjects, and severely ill patients. Whenever it is to be used, a syringe containing atropine sulfate (1 mg.) should be at hand for immediate intravenous use, in case alarming symptoms such as collapse or respiratory obstruction occur. Reports on the effect of the intravenous administration of 0.8 to 1.2 mg. of lanatoside C or of the intravenous injection of 0.5 to 1 mg. of "Neo-synephrine Hydrochloride" have been so encouraging that, if they are substantiated, the use of one or the other of these drugs may become the method of choice in the treatment of this disorder. Appropriate reduction in the amount of lanatoside C should be made if digitalis has been administered during the preceding two weeks. Theoretically, there may be some risk in administering "Neo-synephrine Hydrochloride" when there are clinical evidences of impaired coronary flow or if the patient has an appreciable degree of hypertension during the attack.

10. In some instances neostigmine (1 mg. given intramuscularly) has been found to be effective in paroxysmal auricular tachycardia, as well as in other forms of supraventricular tachycardia.

Paroxysmal ventricular tachycardia is a rarer and much more serious disorder than paroxysmal auricular tachycardia (fig. 207). The commonest cause is coronary disease, and this arrhythmia frequently supervenes within a period of a few days following the development of a myocardial infarction. Less commonly, it is induced by the administration of digitalis in excessive amounts, and very rarely the arrhythmia appears spontaneously in healthy individuals presenting no evidence of cardiac disease. The diagnosis can usually be made, without instrumental aid, by the presence of several of the following clinical

K.R., 59 ♂ #107009. LEG AMPUTATED, 3·25·43. SUDDEN COLLAPSE WITHOUT PAIN,
5·26·43 2:30 P.M., DIED 6:25 P.M.

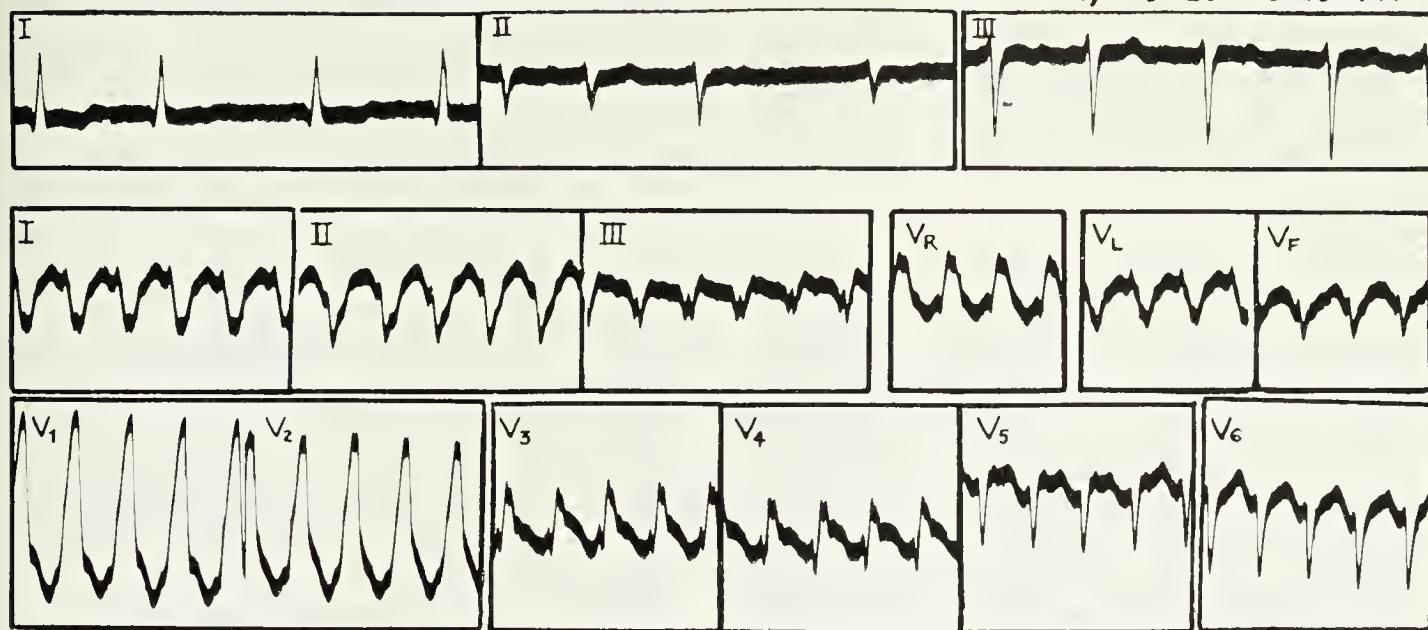


FIG. 207. Paroxysmal ventricular tachycardia. (H. H. Hecht.)

The electrocardiographic complexes resemble those of single ventricular extrasystoles.

The subject was a 59-year-old infirmary inmate with coronary artery disease and angina pectoris. The upper record, taken two days before the onset of the attack, shows auricular fibrillation with left axis deviation of QRS and inversion of T in I suggestive of left ventricular enlargement. Serial precordial leads (not illustrated) were diagnostic of an anterior myocardial scar.

The attack was characterized in the electrocardiogram by broad and notched ventricular complexes following each other at a rate of 220 beats per minute. Autopsy confirmed the diagnosis of severe coronary artery disease with old and recent myocardial infarction.

features: (1) The patient commonly has evidence of coronary artery disease, or has been receiving digitalis in rather large doses; (2) as a rule, there is no history of numerous previous attacks; (3) during the attack the heart rate is usually between 160 and 210, and, although it is essentially regular, there may be slight variations in the regularity of the rhythm and in the intensity of the first sound from beat to beat because the relationship between atrial and ventricular contraction is somewhat variable; and (4) carotid sinus stimulation has no effect on the rate. In doubtful cases electrocardiograms are necessary, but even here the interpretation may be rendered difficult because auricular tachycardia which has endured for several hours often leads to conduction defects which cause the tracing to resemble that of ventricular tachycardia.

Since it is but one step removed from the almost invariably fatal ventricular fibrillation, ventricular tachycardia is the most serious of the ectopic tachycardias. Fortunately, quinidine is an almost specific drug in the treatment of this condition. It may have to be given in heroic doses, and when the patient's condition precludes oral administration the cautious intrave-

nous use of the drug is indicated. In a patient with this arrhythmia, the initial oral dose of quinidine should usually be 0.5 Gm., and increasingly large doses should be given at intervals of three to four hours, until the arrhythmia has broken. In most instances a dose of 1 Gm. will suffice, but occasionally larger doses are required. Since digitalis tends to perpetuate this arrhythmia, it should not be employed. There is some evidence that atropine has a favorable effect, and potassium chloride, papaverine, and magnesium sulfate have occasionally given beneficial results in abolishing the ectopic rhythm. Quinidine, however, remains the drug of choice.

When inability to swallow or a desperate circulatory state makes the oral route inadvisable, intravenous quinidine may be needed. The drug has recently become available in ampuls for such administration, but should be given with great caution and at a rate not exceeding 0.1 Gm., every three minutes, the total single dose being not greater than 1 Gm.

Nodal tachycardia is rare and is usually the result of digitalis therapy. It may be suspected when an individual with a heart rate of 140 or

more, who has been receiving digitalis, is found to have a striking systolic pulsation in the jugular veins as the result of the simultaneous contraction of the atria and ventricles. As a rule the diagnosis can be made only by electrocardiography. The treatment is that of ventricular tachycardia.

The *clinical picture* presented by a patient during an attack of ectopic tachycardia varies with the rapidity of the heart rate, the duration of the attack, the condition of the heart, and the temperament of the patient. In short attacks there may be experienced only a sense of fluttering in the chest or neck, and a mild feeling of faintness; the more stolid person may have no symptoms and remain unaware of the cardiac disturbance. In longer attacks, the characteristic features of forward failure appear: more pronounced weakness and faintness; the skin cool, pallid and moist; the systolic and the pulse pressures diminished. Eventually, after days in a normal person or hours in one already suffering from heart disease, congestive failure may supervene. Angina may appear in persons who have structurally normal hearts, but it occurs more readily in those already suffering from impaired coronary circulation; it is due to the increased energy expenditure of the myocardium and the reduction in coronary flow during the attack. Occasionally, fever may be present, presumably due, in part at least, to the disturbed dissipation of body heat, and when this is associated with leukocytosis, angina, and T wave alterations of the "coronary" type (which may persist for some time following the cessation of the attack), confusion with myocardial infarction is possible.

Some of the more important features of the ectopic tachycardias are summarized in table 100.

The value of electrocardiographic tracings in the differential diagnosis of the tachycardias is obvious, and is illustrated in figure 205. Since registration of atrial activity is particularly desirable, records should be obtained from the right of the sternum, and in many instances while carotid sinus pressure is being applied.

Harmful Effects of the Arrhythmias. The physician will be much aided in management of patients presenting disturbances of the cardiac rhythm if he has a clear comprehension of the

significance of such disorders. When the heart rate is 28 to 30, or more, the bradycardias produce certain changes in the circulation that have little or no clinical significance. Due to the large output of blood with each beat and the long diastolic pause, the systolic blood pressure is elevated and the diastolic pressure is diminished. The low average diastolic pressure tends to diminish coronary blood flow which occurs chiefly in diastole. When the efficiency of the heart is normal or but relatively impaired, patients with this degree of bradycardia carry on a normal or practically normal existence. When the heart rate slows to 15 or less, the circulation to the brain becomes inadequate and Adams-Stokes attacks occur; or complete standstill or fibrillation of the ventricles leads to death.

The tachycardias are important for a number of reasons. Cardiac output and cerebral blood flow are diminished, and, although faintness is usually present, actual unconsciousness rarely occurs unless the patient persists in maintaining the upright posture. The tachycardias also cause marked interference with the coronary blood flow, due to the fact that most of the flow to the subendocardial part of the left ventricle takes place only during diastole. Since the duration of systole is not much shortened with rapid heart rates, the total amount of systole per minute is markedly increased, and the total amount of diastole per minute is correspondingly reduced when the heart rate is excessively rapid. Furthermore, it should be remembered that the energy expended by the heart at each beat consists of two components, of which one fraction—that used in raising the intraventricular pressure sufficiently to open the semilunar valves—is not used for the expulsion of blood. At rapid heart rates the fraction of energy which is thereby wasted is correspondingly increased. For these reasons tachycardia alone, if sufficiently severe and prolonged, may lead an otherwise healthy heart to fail.

Aside from the deleterious effects of alterations in rate in either direction, irregularity of the heart itself may be harmful. This, however, is the case only when the irregularity is of such a nature as to cause a pulse deficit. This occurs when ectopic beats set in so early in diastole that the degree of ventricular filling is slight, and the energy developed at the contraction is not sufficient to expel a significant amount of blood.

Table 100
THE MORE IMPORTANT CLINICAL FEATURES OF THE VARIOUS TYPES OF TACHYCARDIA

Condition	Common Causes		Other Etiologic Data		Rhythm	Effect of Vagal Stimulation*	Effect of Digitalis	Effect of Quinidine	Remarks
	Age at First Attack	Heart Disease	Usual Heart Rate						
Sinus tachycardia	When moderate; exercise, emotion, almost any illness When marked: hyperthermia, thyrotoxicosis, and circulatory failure	Any Adults	Usually absent Nearly always present	100–160 120–160 (Slower when digitalized)	Regular Totally irregular	No effect, or slight temporary slowing Slight temporary slowing	None Rate slowed, irregularity tends to persist	The only common cause of tachycardia with gross irregularity	
Atrial fibrillation	Mitral stenosis, senile heart disease, thyrotoxicosis	Adults	Nearly always present	About 150, 100, or 75 (with 2:1, 3:1, or 4:1 block)	Regular (rarely totally irregular)	May convert to auricular fibrillation	Restores normal rhythm May restore normal rhythm	When rate is normal, exercise causes abrupt acceleration with later abrupt deceleration	
Atrial flutter	Mitral stenosis, senile heart disease, thyrotoxicosis	Adults	Nearly always present	160–220	Regular	Temporary abrupt slowing; abrupt return to rapid rate	May relieve attack. Often prevents attacks	May relieve or prevent seizures	
Paroxysmal auricular tachycardia	Unknown	Childhood or young adulthood	Usually absent	160–220	Regular	Either no effect or abolition of attack	May relieve or prevent seizures	The only common cause of extreme tachycardia in a young adult without evidence of structural heart disease	
Paroxysmal ventricular tachycardia	Coronary disease Digitalis	Usually over 50	Nearly always present	160–220	Essentially regular with occasional slight irregularity	None Likely to be harmful	Relieves and prevents seizures	May terminate fatally	

* Including carotid sinus pressure, ocular pressure, holding breath, Valsalva experiment, induction of gagging, and induction of vomiting.

ELECTROCARDIOGRAPHY IN RELATION TO DIAGNOSIS OF CARDIAC DISEASE

No attempt is made to afford the reader an introduction to electrocardiographic interpretation (see Chapter 31). Dr. Frank Wilson speaks of "the present wretched state of electrocardiographic diagnosis" and "the misery attributable to it." In part, this unfortunate situation is due to the lack of comprehension by many physicians of the kind of information electrocardiography can or cannot bring to them. It is essential that every physician, irrespective of a primary interest in electrocardiography, or in diseases of the heart, or even in the broader field of internal medicine, have a general concept of the functions and limitations of electrocardiographic examination in the diagnosis and management of heart disease. We are aware of no discussion on this subject so lucid, emphatic, and authoritative as that which follows. Electrocardiography serves two purposes:

The first is the recognition and differentiation of the disorders which affect the sequence of auricular and ventricular contractions and the time relations between them; the second, the detection of abnormalities which leave these unchanged but alter the relative order in which the different parts of the ordinary ventricular or auricular muscle pass through the various states of the excitatory and recovery processes.

The disorders first mentioned include the cardiac arrhythmias, the heterogenetic tachycardias, atrioventricular heart block, and the homogenetic ectopic rhythms. In by far the greater number of instances these conditions can be easily identified by inspection, palpation, or auscultation of the heart and accessible blood vessels, by fluoroscopic examination of the chest, by recording the venous and arterial pulses simultaneously, or by taking a phonocardiogram. In this field, electrocardiography is merely a more convenient and more exact, and not a wholly indispensable diagnostic method. . . .

Abnormalities of the form of the ventricular complex belong in an entirely different category. Apart from the slight asynchronism in the contraction of the two ventricles in bundle branch block, there is no correlation between them and the character of the cardiac or vascular pulsations. Since they have no mechanical equivalents they cannot be detected by any means other than an electrocardiographic examination, and there is no reason to suppose that they have any direct bearing upon the ability of the heart to perform its function. Considered as isolated deviations from the normal, distinct from their implications, they have no clinical importance. A physician may find it desirable to relieve a headache, or to

abolish extrasystolic arrhythmia, but inverted T waves do not, of themselves, call for any kind of therapy, or any other interference with the lives of those who display them.

These purely electrocardiographic disorders are significant only because of the inferences which they suggest. Many of them occur under such a great variety of circumstances that they serve merely as evidence that some cardiac abnormality or anomaly is present, and have an important bearing on the clinical diagnosis only when other objective signs of heart disease are lacking. When this is the case, the physician should attempt to ascertain from the history, and such other data as are available, the probable nature of the etiologic factor or factors involved, whether the cardiac reserve is impaired, and, finally, whether he is dealing with (a) a structural or functional alteration in the heart which dates from some long-past illness and has no bearing on the patient's future, (b) an acute condition which may be expected to retrogress within a relatively short period, or (c) a chronic disease or degenerative process which is likely to produce more and more cardiac damage as the years pass. The last of these questions is an important one, for if the myocardial disturbance responsible for the electrocardiographic abnormality is acute it is probably wise to confine the patient to his quarters until it subsides, even when there are no complaints referable to the cardiovascular system. On the other hand, it is seldom desirable in chronic heart disease to restrict an individual's activity to a degree much beyond that required to control symptoms. When there are no other clues, the patient's age and a series of electrocardiograms taken over a period of sufficient length will often make it possible to decide between the three alternatives listed. In the young, chronic progressive heart disease without physical or roentgenographic signs of cardiac abnormality is rare, and abnormalities of the ventricular complex which persist unchanged over two or three weeks usually represent either residues of a previous acute illness or an unusual cardiac anomaly. The form of the T deflection is very labile and may be altered by a great variety of factors, including the tone of the extrinsic cardiac nerves. Therefore, unless the deviations from the normal are pronounced or distinctive, abnormal T waves are less reliable signs of significant myocardial involvement than abnormal QRS deflections.

Some abnormalities of the ventricular complex are encountered only under very special circumstances, so that their occurrence strongly supports some particular clinical diagnosis. Most of these are distinctive electrocardiographic patterns consisting of specific peculiarities in the outline of both the QRS and T complexes in each of several leads. Examples of such patterns are those that occur in preponderant hypertrophy of one ventricle and those characteristic of myocardial infarction affecting various parts of the ventricular walls. They often establish with reasonable certainty a diagnosis which is not inconsistent with the clinical history and other data. A diagnosis which, after careful investigation, is not supported by other

evidence can seldom be made with confidence on the basis of the electrocardiographic data alone. . . .

We shall not attempt a long discussion of the present wretched state of electrocardiographic diagnosis or the misery attributable to it. The errors made in this field are due in large measure to the same human frailties that are responsible for errors in others, medical and nonmedical. We wish, however, to make a few comments which appear to us worthwhile. In our opinion, no physician should refer a patient to another for an electrocardiographic examination and report without giving the referee a résumé of the data which he has collected (if he has any) nor without letting him know exactly what information the electrographic examination is expected to yield.

We think also that there are altogether too many physicians who want to, and try to, read electrocardiograms but are unwilling to go back to the fundamental principles upon which the interpretation of the electrocardiograms must be based. In our opinion, it is impossible to use diagnostic criteria intelligently unless they are fundamentally sound and the foundations on which they rest are clearly understood by the user. . . .

Electrocardiography is one of the most exact of diagnostic methods. Its potential value is great, but it is not being used to the best advantage. Electrocardiographic abnormalities are not diseases. They have no important bearing upon the life expectancy of the patient, or the extent to which his mode of life should be altered when there is a reasonable doubt as to the nature of the factor or factors responsible for them in that particular case.¹

If electrocardiography were practiced according to the philosophy expounded above, and if the medical profession were aware of the limitations as well as the value of electrocardiography, there would be fewer patients leading miserable and unnecessarily restricted lives as the result of harmful and unwarranted interpretations of electrocardiographic records.

CARDIAC CATHETERIZATION AND OTHER SPECIALIZED PROCEDURES

A number of methods have recently been developed which yield important additional information concerning certain aspects of cardiac disease.

Cardiac Catheterization. Of these methods, catheterization of the heart by means of a can-

nula introduced into a peripheral vein has been especially important. This procedure allows measurement of cardiac output according to the Fick principle, because mixed venous blood can be obtained from the right side of the heart. It also permits measurements of pressure in the right atrium, right ventricle, pulmonary artery, and, when a shunt exists, in the left chambers of the heart. Furthermore, the oxygen content of blood from various areas can be compared, and this gives important information concerning the presence and location of shunts between the two sides of the heart. The type of information which can be obtained from cardiac catheterization is illustrated in table 101.

The procedure of cardiac catheterization is of great value in research and in the diagnosis of certain obscure instances of congenital cardiac disease. The method requires practice, skill, and teamwork among a number of highly trained individuals. Even in the most careful hands it has occasionally resulted in a fatality. It cannot be considered as a practical method for general application, and should be employed only by individuals who have had prolonged training and wide experience with it.

Oximetry. The oximetric method allows the continuous measurement of oxygen saturation in the arterial blood. The demonstration that this saturation declines sharply with exercise constitutes important evidence for the presence of a right-to-left shunt.

Exercise in normal persons is accompanied by a rise in oxygen uptake as compared to the ventilation—i.e., by a decline in the oxygen content of expired air. If, because of pulmonic or tricuspid stenosis, the flow of blood through the lungs is sharply limited, the oxygen content of expired air may display a paradoxical rise during exercise.

Angiocardiography. The angiographic procedure, which consists in making rapidly repeated roentgen photographs, following the quick injection of an opaque medium into a large vein, gives important information concerning congenital cardiac disease, and may be valuable in differentiating aneurysms from mediastinal tumors. The procedure requires special and expensive apparatus, technical skill, and wide experience in interpretation of the cardiac shadows. When this is available, the combination of clinical evidence and the angiographic method

¹ Appreciation is expressed to Dr. Frank N. Wilson and the Interscience Publishers, Inc., for permission to quote these passages from Frank N. Wilson *et al.*: Interpretation of the ventricular complex of the electrocardiogram, in W. Dock and I. Snapper, eds.: "Advances in Internal Medicine," New York, Interscience Publishers, Inc., vol. 2, p. 1, 1947.

Table 101
DIAGNOSTIC CRITERIA IN CONGENITAL HEART DISEASE*

	Catheterization and Determination of Pulmonary Capillary Flow†			Exercise Test and Oximetry	
	Pressure, mm. of Mercury	Analysis of Gases in Blood	Flows	Oxygen Consumed per Liter of Ventilation	Oxygen Saturation of Peripheral Arterial Blood
Normal	RA = 5/0 RV = 25/0 PA = 25/8	RA = RV = PA within 0.5 vol. %	S = PA = PC =	Rises	Unchanged
Tetralogy of Fallot Preoperative Postoperative	RV elevated PA lower than RV	O ₂ in RV significantly higher than in RA	S exceeds PA	Falls	Falls
	RV elevated PA lower than RV	O ₂ in RV significantly higher than in RA	Effective and PC increased over Pre-operative	Rises	Falls
Eisenmenger's complex	RV elevated PA systolic and diastolic elevated	O ₂ in RV markedly higher than in RA	S may exceed PA flow or vice versa	Rises	Falls
Pulmonic stenosis	RV elevated PA lower than RV	RA = RV	S = PA; both reduced equally	Falls	Unchanged
Single ventricle with pulmonary stenosis	RA and RV elevated	O ₂ in RV markedly higher than in RA (greatest difference observed)	S exceeds PA	Falls	Falls
Tricuspid stenosis	RA elevated	O ₂ in RA significantly higher than in SVC	S exceeds PA	Falls	Falls
Patent ductus arteriosus	RV = PA = normal	O ₂ in PA significantly higher than in RV	PC exceeds PA	Rises	Unchanged
Isolated septal defects	Normal or elevated	RA significantly exceeds SVC, or RV exceeds RA	PA may exceed S or vice versa	Rises	Falls

* From R. J. Bing, J. C. Handelman, and J. A. Campbell: Physiologic diagnostic tests in congenital heart disease, *Mod. Concepts Cardiovas. Dis.*, vol. 17, no. 3, March 1948, by courtesy of the editor and the authors.

† PA = pulmonary artery; PC = pulmonary capillary; RA = right auricle; RV = right ventricle; S = systemic circulation; SVC = superior vena cava.

yields a high degree of accuracy in the recognition of those congenital anomalies which are amenable to surgical therapy, and cardiac catheterization is rarely necessary for practical purposes but remains a valuable research tool. The angiographic procedure is not without some hazard.

Electrokymography. This is a very promising procedure, the value of which in the diagnosis of congenital lesions and as a research tool is only

beginning to be explored. This procedure, especially when combined with *ballistocardiography*, promises to yield important information, and may at some future date supplant the more hazardous and cumbersome procedures of cardiac catheterization and angiography. The electrokymographic and the ballistocardiographic methods are relatively simple to carry out, require a minimum of additional equipment, and are completely without hazard. Although it is

possible that they will not advance beyond the status of useful research tools, it seems more probable that additional information will place these procedures in the same category as electrocardiography—i.e., as methods of the greatest value when combined with and subordinated to sound clinical judgment, but as yielding misleading half-truths when substituted for such judgment.

SUMMARY

To attempt to summarize all of the important considerations in the diagnosis of heart disease is obviously impossible. However, a few points of especial practical importance may be mentioned:

1. In all cases of congestive failure one should feel the hands carefully. If, in the absence of fever, they are warm, the pulse pressure is large, and the heart sounds are loud, one should think of high output failure, which is often curable and most commonly due to thyrotoxicosis.
2. In every case of hypertension one should palpate the femoral arteries. Feeble or absent pulsations point toward coarctation of the aorta, a curable condition.
3. In every person with peripheral signs suggestive of aortic insufficiency—and the one least likely to be overlooked is a wide pulse pressure—one should make it an invariable rule to have the patient sit up and lean forward. While the breath is held in forced expiration one should listen at the third to fourth left intercostal space for the characteristic murmur of aortic insufficiency.
4. In a person with a previous history suggestive of rheumatic fever, one should never dismiss the heart as normal until one has not only carried out the procedure mentioned, but also has searched carefully for the murmur of mitral stenosis by listening at the exact spot of the maximal impulse with the patient lying on his left side after exercise.
5. In every case of auricular fibrillation one should think of mitral stenosis, senile heart disease, and thyrotoxicosis, but first of all of thyrotoxicosis, because it is curable.

Before terminating the discussion of the diagnosis of structural heart disease, it may be well to summarize certain points concerning the relative value of the various methods of examination. The history is of prime importance in the diagnosis of disturbances of the coronary circulation,

and in the recognition of early congestive heart failure. Palpation is of value in determining the type and degree of cardiac enlargement when the apical impulse can be felt. By establishing the presence of a thrill, palpation is also useful in clarifying the significance of systolic murmurs. Percussion has little place in the diagnosis of heart disease except in so far as it aids in the investigation of the pleural cavities, and thus in differentiating between enlargement and displacement of the heart. Auscultation continues to be the most important method of examination in the diagnosis of heart disease in young persons—i.e., of rheumatic and certain cases of congenital heart disease. The special methods of examination, radiographic and electrocardiographic, are invaluable at times but often reveal little about the earlier stages of heart disease. The radiographic method is especially valuable in congenital heart disease. It should be apparent from the foregoing discussion, as well as from that to follow, that the only way to arrive at a correct diagnosis of the structural and functional disorders of the heart is to take a thorough history and to carry out a meticulous examination of the entire body, utilizing such accessory methods as are necessary. Short cuts are likely to be rewarded by diagnostic errors.

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Etiologic Aspects of Heart Disease (Including Treatment of the Different Etiologic Types)

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More Common Underlying Causes of Heart Disease

- Rheumatic Heart Disease
- Hypertensive Heart Disease
- Arteriosclerotic Heart Disease
- Senile Heart Disease
- Syphilitic Heart Disease

Less Common Underlying Causes of Heart Disease

- Conditions Amenable to Medical Therapy
- Conditions Amenable to Surgical Therapy
- Conditions Not Amenable to Specific Therapy

Rarer Types of Heart Disease

- Pericarditis
 - Etiologic Types of Pericarditis
 - Morphologic Types of Pericarditis
- Endocarditis

The causes of cardiac disease fall into two categories, which may be designated as underlying and as aggravating factors, respectively. The discussion to follow immediately will be concerned with the underlying factors, while the aggravating factors will be considered later.

The more significant underlying causes of heart

disease may be divided into two groups which include, respectively, those causes which are important because of their frequency, and those which are important because of their curability. The recognition of the latter is of especial practical significance, even though they are less commonly encountered than some of the incurable conditions.

In the succeeding discussion heart disease will be classified as follows:

- I. More Common Underlying Causes:
 - A. Rheumatic
 - B. Hypertensive
 - C. Arteriosclerotic
 - D. Senile
 - E. Syphilitic

II. Less Common Underlying Causes:

- A. Conditions amenable to medical therapy:
 - 1. Thyrotoxicosis
 - 2. Thiamine deficiency (beriberi heart disease)
 - 3. Anemia
 - 4. Primary retention of sodium
 - 5. Myxedema
 - 6. Bacterial endocarditis
- B. Conditions amenable to surgical therapy:
 - 1. Thyrotoxicosis
 - 2. Arteriovenous fistula
 - 3. Certain congenital heart lesions
 - 4. Constrictive pericarditis
- C. Conditions not amenable to specific therapy:
 - 1. Cor pulmonale
 - 2. Myocarditis
 - 3. Congenital anomalies of the heart

III. Rarer Types of Heart Disease

- IV. Pericarditis
- V. Endocarditis

The separate consideration of pericarditis, while illogical from the standpoint of etiologic classification, is necessary from a practical point of view.

MORE COMMON UNDERLYING CAUSES OF HEART DISEASE

RHEUMATIC HEART DISEASE

History. Rheumatic fever was first clearly separated from gout by Sydenham (1683). More than 100 years passed before Pitcairn (1788), Edward Jenner (1789), and Wells (1810) emphasized the relationship between rheumatic fever and the subsequent development of cardiac disease. This concept was firmly established by Bouillaud (1834). It was not until 1904 that the specific pathologic lesion characteristic of the disease was described by Aschoff.

Many of the important features of rheumatic heart disease have already been discussed. Thus the pathogenesis of congestive heart failure has been considered in some detail in Chapter 14, while rheumatic fever has been discussed in Chapter 102. Some of the more important aspects of the diagnosis of rheumatic heart disease have

been considered in Chapter 235, dealing with the diagnosis of heart disease in general. Most of the prognostic and therapeutic aspects will be discussed in the sections to follow. The present discussion of rheumatic heart disease will, therefore, be limited largely to such aspects of the disorder as are not applicable to heart disease in general, and are not adequately covered elsewhere in the book.

Etiologic Considerations. In the United States rheumatic heart disease has now assumed first rank as a cause of death among children of school age, and is second only to tuberculosis as a cause of death in young adults.

The disease appears to be distributed on a world-wide basis, but is most frequent in damp, cold climates such as prevail in the British Isles, northern Europe, and the northern and western plateau portions of the United States. The frequency in the tropics is much less. In the southern part of the United States the disease is rarer than in the northeastern states, but is more common than was formerly believed to be the case. The available statistics indicate that in different parts of the United States the frequency of rheumatic heart disease varies between 0.5 and 2 per cent of the population.

The disease is rare in children below the age of two years, reaches its greatest incidence in older children and young adults, and is not uncommon in older individuals in whom senile heart disease is frequently superimposed on an old nonprogressive rheumatic valvular lesion.

Both sexes are affected, with a slight tendency toward predominance in females. Mitral lesions are decidedly more common in women than in men, while aortic lesions are more common in males. Involvement of the aortic valve, without coexistent mitral disease, is quite rare in women but is frequently observed in men.

Racial predisposition for individuals of northern European descent has been suggested but not proved. The disease is somewhat more frequent in the urban than in the rural population, and is decidedly more common in the lower income groups than in the well-to-do. Familial predisposition occurs and does not appear to be a simple matter of contagion, but rather to be related to increased susceptibility on the part of certain families.

Rheumatic heart disease refers either to the

active form commonly designated as acute carditis, in which acute inflammatory lesions are developing or regressing, or to the inactive form in which the rheumatic process has spent itself and has left behind as a residue a permanently damaged heart. The two forms may occur simultaneously when an acute exacerbation of rheumatic fever takes place in an individual who already has undergone permanent structural alteration in the heart as the result of past episodes of rheumatic fever.

It is now generally accepted that involvement of the heart is a practically universal phenomenon of all cases of rheumatic fever. If this view is correct, the concern is not whether the heart has been affected in rheumatic fever, for the decision is implicit in the diagnosis. The more relevant question is how seriously the heart has been affected. The grades may vary from the mildest subclinical forms in which minimal lesions are present which reveal no definite clinical signs that point specifically to cardiac involvement, to the types in which extensive and severe pathologic changes in the heart are unmistakably manifested by abnormal clinical signs. Through common usage, the term *acute carditis* is generally limited to those cases in which the clinical signs of impairment of the heart are more or less definite.

MANIFESTATIONS OF ACUTE CARDITIS

Congestive Failure. This is the most serious evidence of acute carditis, and implies extensive myocardial involvement. The gravity of congestive failure is witnessed by the fact that about 75 per cent of the children who display it in the course of an attack of rheumatic fever die before they reach 20 years of age; the average duration of life after its onset is about three years. Acute inflammatory lesions characteristic of rheumatic fever are found in so high a percentage of adults under the age of 40 with rheumatic heart disease who die of congestive failure, that it is considered probable that the precipitating cause of the failure in the majority, if not all of such cases, is an acute exacerbation of the rheumatic fever rather than the mechanical effects of the valvular disease.

Pericarditis. This occurs clinically in a small to moderate percentage of cases, and almost invariably accompanies the severer forms of carditis. It is recognized by the appearance of a pericar-

dial friction rub, or of the signs of pericardial effusion (p. 1306).

Cardiac Enlargement. The lesser degrees of enlargement may not be detected by physical examination or by the conventional x-ray examination in the frontal view. More accurate estimation of the size of the individual chambers is afforded by x-ray investigation in the oblique position.

Diastolic Murmurs. These constitute unequivocal evidence of cardiac damage, but when occurring during the course of acute or subacute rheumatic carditis do not invariably indicate permanent valvular damage. The acute process may lead to dilatation of the cardiac chambers or of the valve rings, or possibly to edema of the cusps with the production of characteristic apical rumble or of basal blows which subsequently disappear.

The above signs, appearing during an attack of rheumatic fever, are certain evidence of acute carditis of undoubted severity. There are other signs that indicate the presence of acute carditis of a lesser degree. Systolic murmurs at the apex are commonly heard. When they are faint, it is hardly possible to assess their significance: they may represent the unimportant systolic murmurs that appear in any febrile condition, or they may be the earliest evidence of damage in the mitral ring. When loud, they bespeak more surely of relative mitral insufficiency due to myocardial damage, but in these cases cardiac enlargement is usually present and is the more decisive finding. Sudden decline in the intensity of the first sound, without evidence of pericardial effusion, should lead to the suspicion of first-degree heart block (p. 1238). When serial electrocardiograms have been secured at very frequent intervals, prolongation of the P-R interval has been demonstrated in so high a percentage of all cases of acute rheumatic fever, that it is doubtful whether this finding alone can be considered proof of anything more than the presumption that some involvement of the heart is a practically constant phenomenon in acute rheumatic fever. Since other febrile disorders occasionally may cause first-degree heart block, the finding of P-R prolongation constitutes suggestive rather than conclusive evidence of rheumatic carditis.

More severe degrees of heart block, transient auricular fibrillation, and probably prolongation of the Q-T interval must be considered signs of

more than minimal impairment of cardiac integrity—their meaning must be judged in the light of the whole clinical picture. A heart rate that is rapid in relation to the temperature is suggestive that the heart is undergoing more mischief than may be apparent by physical examination. Gallop rhythm should be considered here, as in most other circumstances, a sign of impending myocardial failure when actual congestive failure is not manifest. Numerous subcutaneous nodules are often found in conjunction with the severer forms of carditis, but the association is not a common one. Precordial pain is frequently present and, except when due to pericarditis, its mechanism is obscure.

The ultimate effect on the heart is inextricably bound with the variable and unpredictable course of rheumatic fever. Prophecy in the individual case is uncertain. Whether the initial attack begins in childhood when carditis is common, or after puberty, or in adult life when serious involvement of the heart is less common; whether the patient has but one attack or a number of recrudescences which increase the opportunity for cardiac damage; whether outspoken involvement of the heart occurs in one or in several of the attacks—all these factors have an important bearing on the probabilities as to the final result, and at any one point in the course of the disease it is not possible to foresee what the future will hold. The more severe the carditis and the more frequent the number of attacks of carditis, the graver the outlook for life and for the likelihood of permanent structural damage in the heart. Of those who suffer from rheumatic fever before puberty, and who display definite evidences of acute carditis, a small percentage succumb to an overwhelming infection within the first year after onset; about 10 per cent die within 5 years; and about 20 per cent die within 10 years after the initial attack. Of the survivors, about 75 per cent develop permanent valvular damage. These figures are rough approximations, and vary somewhat in different series of reported cases. An appreciable number go on to complete recovery, and this fortunate outcome may take place even in children who, during the acute illness, have displayed diastolic murmurs considered characteristic of mitral stenosis or aortic insufficiency. The disappearance of these, as well as the systolic murmurs that develop during the early weeks of rheumatic fever, suggests that they are due to

transitory myocardial damage or edema of the valves rather than to actual scarring of the leaflets. Scarring of the valves sufficient to produce malfunction and the corresponding murmurs of permanently damaged valves requires months to a few years.

Unfortunately, absence of definite clinical manifestations of acute carditis does not signify that the patient will escape unscathed. About 10 to 20 per cent of the cases of mitral disease encountered in childhood occur in individuals who give no history suggestive of rheumatic fever; the percentage is considerably higher in adults. Of those children with recognized rheumatic fever but without clear-cut manifestations of acute carditis, one third to one half eventually present signs of permanent valvular damage. When chorea is the only manifestation of acute rheumatic fever, the outlook is much brighter. Only a small percentage develop permanent valvular disease.

It is well to emphasize again the striking difference between the effect of rheumatic fever in children and in adults. In the former, the evidences of cardiac involvement are frequently severe; and whether or not the signs of acute damage are manifest, a high percentage of these young patients eventually reveal manifestations of permanent structural alterations of the valves. In adults, the rheumatic process in the heart tends to assume a more benign form. Only infrequently is the heart gravely involved in the acute stage, and in only a relatively small percentage is the heart left with significant organic lesions.

CHRONIC (INACTIVE) RHEUMATIC HEART DISEASE

Diagnosis. The diagnosis of chronic rheumatic heart disease rests on the recognition of the various valvular lesions that have been discussed in detail in Chapter 235. In this disorder the patient's future depends on several factors: recrudescence of the active rheumatic process; the type of valve lesion; and the presence of the four cardinal complications—congestive heart failure, bacterial endocarditis, angina pectoris, and embolic phenomena. The clinical phenomena indicative of active rheumatic carditis which have just been discussed are more commonly found in children. In adults with established rheumatic heart disease, the manifestations of acute carditis

are rarely so pronounced, and in the absence of polyarthritis the decision as to whether or not the rheumatic infection is active is based largely on the presence or absence of fever, leukocytosis, elevation of the sedimentation rate, or a persistent tachycardia. In a young adult the presence of congestive failure constitutes strong evidence that the process is active. From a practical standpoint the importance of the decision as to whether or not rheumatic fever is active cannot be overemphasized, because the presence of rheumatic activity constitutes an important indication for prolonged rest.

One of the problems presented by a young individual with a rheumatic valvular lesion and fever is the differential diagnosis between active rheumatic infection and subacute bacterial endocarditis. The presence of fever and a heart murmur is compatible with either condition. Prompt and dramatic response of the fever to salicylates points toward rheumatic infection as the cause, but a failure to respond to salicylates does not entirely exclude this disorder. Rheumatic infection, when persistent and unassociated with joint pains, is likely to be associated with minimal elevation of temperature, while bacterial endocarditis is frequently associated with a higher fever and with chills, which are very rare in rheumatic infections. Enlargement of the spleen, which is common in bacterial endocarditis, is very exceptional during episodes of rheumatic fever. Slight clubbing of the fingers does not occur in rheumatic infection except when complicated by bacterial endocarditis, but this sign is absent in about half of the patients with the latter disorder. As a rule the differential diagnosis will depend upon the appearance of petechiae or other evidences of embolism (Chapter 239), or upon obtaining a positive blood culture.

Clinical Course. The clinical course of rheumatic heart disease varies markedly in relation to the presence or absence of repeated or persistent activity of the rheumatic process. At one extreme we have the child, or young adult, with persistent active infection; and the development within a few months of evidence of myocardial, pericardial, and endocardial damage, with the appearance at an early stage of intractable and progressive congestive heart failure, and death within a year or two after the onset of the initial attack. At the other extreme we have the middle-

aged person, in perfect health, with or without a story of fever and joint pains in youth, who is discovered to have a valvular lesion (most commonly mitral regurgitation, but occasionally mitral stenosis or aortic valvular disease), but without any symptoms either at rest or upon strenuous effort. In such individuals the minimal valvular damage has usually resulted from a single rheumatic episode. The heart has adjusted to the mechanical defect, and health may remain entirely unimpaired and the patient may eventually die of some entirely unrelated process; or, not rarely, he may develop congestive failure after the age of 60, as senile myocardial degeneration sets in. Between those two extremes there is every intermediate gradation.

It is of importance to note that the patients with minimal valve lesions and without symptoms of congestive failure or diminished cardiac reserve are those who are peculiarly susceptible to the development of bacterial endocarditis, a complication which rarely occurs in the presence of lesions so far advanced as to cause congestive failure.

CLINICAL COURSE IN RELATION TO DIFFERENT TYPES OF VALVE LESIONS. Patients with mitral regurgitation and no other lesion usually remain free of evidences of congestive failure, but are particularly susceptible to bacterial endocarditis. Patients with well-marked mitral stenosis develop dyspnea early, because left-sided heart failure and consequent congestion of the lungs occur primarily as the direct mechanical result of the valve lesion and, therefore, are not delayed until left ventricular dilatation and failure take place. However, paroxysmal nocturnal dyspnea is rare in such subjects, and, even after dyspnea at rest has appeared, life may go on at a lower level of activity for many years, progression being slow. Hemoptysis is common in patients with mitral stenosis, and appears to result from the bronchial varicosities induced by enlargement of the collateral channels between the pulmonary and bronchial systems as a consequence of the increased pressure in the pulmonary veins.

Patients with aortic stenosis frequently suffer from syncopal attacks and from angina pectoris, and are particularly liable to sudden death, but are unlikely to develop congestive failure until late in life. Rheumatic aortic insufficiency remains asymptomatic for a long period. Once

dyspnea upon mild effort begins, seizures of paroxysmal nocturnal dyspnea are common, and from this point on congestive failure tends to supervene and to progress rapidly. Angina pectoris is not rare in such patients, but is less common than in those with aortic stenosis. As has been stated, rheumatic tricuspid lesions are characterized by intractable but nonprogressive right-sided heart failure, lasting for years with relatively little dyspnea.

The relation of auricular fibrillation to rheumatic heart disease is of interest. This complication practically never occurs in patients with involvement of the aortic valve alone. It is likewise rare when mitral regurgitation without stenosis exists. However, it is very common in persons with mitral stenosis, and in such patients the onset of auricular fibrillation frequently converts a previously asymptomatic state into congestive failure. Since digitalis produces dramatic benefit when it slows the rate, even though the total irregularity persists, it is clear that the harmful effects of the arrhythmia are, in the main, the result of the tachycardia and of the pulse deficit rather than of the irregularity. Embolic phenomena appearing in patients with rheumatic heart disease may occur as the result of infected valvular thrombi when bacterial endocarditis coexists, or as the result of sterile thrombi arising in the left atrial appendage in patients with mitral stenosis. The likelihood of the development of atrial thrombi and consequent embolism is much greater in subjects with auricular fibrillation than in those with regular rhythm. The seriousness of embolism depends on the size and location of the occluded artery.

Rheumatic heart disease, like all other forms of chronic heart disease, produces pronounced emotional effects in a large percentage of the patients. Physicians are partly responsible for this situation because, in their eagerness to enforce rest during the stages of rheumatic activity, they often inadvertently convey to the patient and the family an unduly grave picture of the future. In many instances the harmful psychic effects of excessive restriction more than counterbalance the beneficial physical results of such a regime (p. 1320).

PROGNOSIS

The essential points on which judgment as to the future must be based have already been men-

tioned. The first of these is the persistence or recurrence of active rheumatic infection. The second is the type of valve lesion, and it can be stated as a general rule that the duration of life tends to be longer after onset of symptoms in patients with mitral and tricuspid lesions than in patients with aortic lesions, who are particularly likely to encounter angina pectoris, sudden death, or rapidly progressive congestive failure. Obviously, the prognosis is completely uncertain in patients who have angina pectoris. The presence of syncopal attacks in persons with aortic stenosis, likewise, indicates liability to sudden death, even though there may be no attacks of anginal pain. The prognosis formerly was hopeless when subacute bacterial endocarditis developed, but with modern penicillin therapy this complication can be cured in the majority of patients, although many unfortunately are left with an exaggeration of the valve lesion.

MANAGEMENT

The problems may be divided into: (1) the treatment of acute rheumatic carditis; (2) the prevention of recurrences (as discussed in Chapter 102, dealing with acute rheumatic fever), and (3) the management of chronic inactive rheumatic heart disease. The third problem concerns the management of heart disease in general, including the treatment of the arrhythmias, which have been considered, and the treatment of chronic congestive failure and of angina pectoris, which will be discussed later. The present discussion will, therefore, be centered upon the treatment of those cardiac complications which occur as the result of active rheumatic infection.

Congestive failure should be managed in the usual way (rest, diuretic drugs, sodium restriction, etc.). Digitalis is relatively ineffective in the presence of acute carditis. It should be tried when congestive failure supervenes, and will occasionally prove beneficial, but will usually be disappointing.

Auricular fibrillation, when appearing during acute rheumatic carditis, is likewise relatively resistant to digitalis. Quinidine is the treatment of choice, provided the contraindications which have been discussed are not present.

Acute rheumatic pericarditis, whether of the fibrinous (dry) or serofibrinous (wet) type, will usually be strikingly benefited by salicylates, which are so much more effective in combating

the exudative than the proliferative lesions, and which are ordinarily useless in rheumatic myocarditis. Six to 10 Gm. per 24 hours, administered in four oral, or two rectal, doses will usually be adequate. When edema is present or imminent, acetylsalicylic acid (aspirin) is preferable to sodium salicylate. Increasing evidence of cardiac tamponade, as defined later in the discussion of pericarditis, constitutes an urgent indication for paracentesis of the pericardium.

The question of the duration and rigidity of restriction of activity in patients with recent rheumatic infection is controversial. Pending information based on carefully controlled studies of several hundred cases, the following principles appear reasonable:

1. Fever and leukocytosis constitute indications for marked restriction of activity—i.e., rest in bed with, at most, a few hours daily in a chair, and no walking other than to the toilet. However, when minimal temperature elevation (maximum less than 100° F., orally) persists for several months, a gradual increase in activity may be allowed, with reimposed restriction if this causes additional fever.

2. Persistence of a rapid sedimentation rate without other evidence of active infection does not constitute sufficient evidence to justify rigid restriction, but does justify limitation of activity to slow walking for short distances. The same applies to tachycardia present in the sleeping as well as in the resting state. Tachycardia which disappears during sleep may be disregarded.

3. After signs of active rheumatic infection and all evidence of carditis have disappeared, physical activity may be increased gradually during a period of two to three months, with frequent evaluation of the clinical state. If after such time no evidence of diminished cardiac reserve or of recrudescence of rheumatic infection appears, the patient may be allowed freedom to do as he pleases, provided he lives below the symptom threshold—i.e., does not perform activities which induce dyspnea or fatigue.

4. In an individual with chronic rheumatic heart disease who is under the age of 35, the development of congestive failure constitutes presumptive evidence of recurrent activity, and both conditions should be treated.

5. Constant attention to the problem of the prevention of bacterial endocarditis is essential (see Chapter 239).

6. It cannot be stated too strongly that, in rheumatic as in other types of heart disease, tactful psychologic management is of the utmost importance, and will serve to prevent the development of that anxiety state which is such a common and tragic occurrence in many patients with chronic heart disease.

7. The plan of management discussed is fundamentally palliative rather than curative. Preliminary reports on the use of cortisone (compound E, not vitamin E) and ACTH (the adrenotrophic hormone of the anterior pituitary) suggest that these substances may have a strikingly curative action. If so, the palliative treatment which has been considered will obviously undergo important modifications.

Surgical procedures have yielded encouraging results in certain subjects with rheumatic heart disease. Thus, patients with severe pulmonary hypertension and intractable pulmonary edema consequent to mitral stenosis may be benefited by anastomosis of pulmonary veins to the azygos vein. Although this procedure and various others should be regarded as experimental at the present time, they offer promise for the future.

HYPERTENSIVE HEART DISEASE

The discussion to follow will not deal with the question of hypertension in general, which has been discussed in Chapter 13, but only with heart disease resulting from hypertension.

Elevation of blood pressure is the most common cause of congestive heart failure among patients in the 40- to 55-year age group; it accounts for a minority of the instances under the age of 40 and, when coupled with senile change, is frequently an important factor in the production of congestive failure in patients in the seventh and eighth decades. About one half of the individuals with hypertension will eventually develop congestive failure, although this complication usually does not occur for many years.

Hypertension is also an important etiologic factor in relation to angina pectoris, as will be discussed later.

Hypertensive heart disease is that form of heart disease that is associated with long-continued increased arteriolar resistance and is presumably due largely, if not entirely, to the increased work of the left ventricle contracting against a permanently increased peripheral re-

sistance. There are no clearly defined limits that mark off hypertension from normal pressure levels. It is generally accepted that a diastolic pressure of 90 mm. Hg or more, usually accompanied by a systolic level of 150 or more, indicates the presence of a peripheral resistance sufficient to be designated as hypertensive. Certain precautions in accepting increased pressure levels as evidence of hypertensive heart disease are to be noted. Patients with aortic insufficiency, complete heart block, and arteriosclerosis of the aorta and large vessels, as well as those with increased cardiac output (e.g., thyrotoxicosis, severe anemia, beriberi), have for a variety of reasons an increased systolic pressure; but the lower-than-normal diastolic pressure eliminates them from the category of hypertensives. Transitory elevations of both systolic and diastolic levels occur in acute nephritis, prostatic obstruction, acute increase in intracranial pressure, and adrenal medullary tumors, and sometimes during congestive failure. Permanent elevations of both systolic and diastolic pressures are produced by a multitude of conditions: coarctation of the aorta, rare cases of adrenal medullary tumor, Cushing's syndrome, and certain affections of the kidney such as chronic glomerulonephritis, chronic pyelonephritis, and polycystic kidneys. (Adrenal medullary tumors, although a very rare cause of hypertension, are, like coarctation of the aorta, important because of their curability by operative removal. The value of the histamine and benzodioxane tests in their recognition has been mentioned in Chapters 13 and 58.) By virtue of its frequency, however, essential hypertension (i.e., hypertension of unknown etiology) is by far the most important cause of permanent elevation of the blood pressure.

Practically invariably a sustained increase in the blood pressure leads to cardiac enlargement, in some cases so slight as to be clinically undetectable and insignificant. Cardiac enlargement is the sole manifestation of early hypertensive heart disease.

Clinical Course. Following the discovery of the hypertension a number of years may elapse, 10 or 20 or even 30, before symptoms referable to the heart develop, if they develop at all. This may be true even though levels as high as 240 systolic and 120 diastolic have been obtained during a large part of this time. In some, the clinical picture is that of coronary disease: angina pectoris

or myocardial infarction. In others, a much larger group, congestive failure ensues. Because the strain is primarily on the left ventricle, left-sided failure, with rise in pressure in the left atrium and consequent pulmonary engorgement, may set in suddenly and produce attacks of paroxysmal nocturnal dyspnea or of acute pulmonary edema. These attacks may appear as the first manifestation of congestive failure; more frequently they occur after appreciable exertional dyspnea has become evident. Gallop rhythm and pulsus alternans are observed with especial frequency, and when they occur they are ominous signs, for they indicate not merely disease but impending or actual myocardial failure. Eventually, provided the patient does not succumb to an attack of acute pulmonary edema, left ventricular failure is followed by failure of the right ventricle, and the complete picture of congestive failure is apparent.

Treatment. The treatment of hypertensive heart disease consists essentially of the treatment of the hypertension, plus the management of congestive failure or of angina pectoris, according to which of these conditions exists.

ARTERIOSCLEROTIC HEART DISEASE

Arteriosclerotic heart disease, as here defined, refers to those cardiac disorders that are due to atherosclerosis of the main coronary branches. The distinguishing clinical features of sclerosis of the coronary arteries are evidence of past or present myocardial infarction or a history of pain of the anginal type. The undesirability of applying the term *arteriosclerotic heart disease* to patients who lack these features will be discussed later. Occasionally, a patient may suffer a painless infarction of the myocardium, initiating cardiac symptoms whose origin is clarified by serial electrocardiograms that leave little doubt that coronary disease is present; or an electrocardiogram may reveal such characteristic changes in the QRS complexes as could have resulted from an infarction for which the patient can give no equivalent history. Electrokymographic investigation may occasionally reveal an old infarct when both the history and the electrocardiograms are negative or equivocal. Barring these exceptions, the diagnosis of coronary sclerosis cannot be made in the absence of a history of anginal pain or of myocardial infarction, and it is

only to patients with the manifestations just described that the term *arteriosclerotic heart disease* can properly be applied. The common use of this diagnosis in elderly subjects with cardiac enlargement and congestive failure, in the absence of hypertensive or valvular disease or anginal pain, is an error unsupported by anatomic studies. These latter individuals should be designated as suffering from senile heart disease, as described on pages 1289-1291.

Another common mistake is the assumption that, in an individual presenting evidence of heart disease, the finding of thickening of the radial and brachial arteries justifies the conclusion that sclerosis of the coronary arteries is present and that a diagnosis of arteriosclerotic heart disease is warranted. Actually, there is no parallelism between the two processes.

Etiology. Coronary arteriosclerosis is far more common in men than in women. The cause of this sex discrepancy has been obscure, although recent work indicates that the difference in susceptibility may be related to the greater thickness of the intima in males as compared with females, a difference that is already manifest at birth.

Aside from the experimental observations that suggest the concept that atherosclerosis represents a disorder of cholesterol metabolism, there is an impressive body of clinical evidence that points in the same direction. This evidence has been considered in Chapter 240.

Many believe that this disorder is more frequent in individuals who carry on sedentary occupations, associated with relatively great emotional tension. Thus there is some evidence that the disease is more common in business executives, physicians, and the like, as compared with laborers, but this prevalence in the former group may be largely a reflection of a higher standard of living, with consequent higher intake of cholesterol, of fat, or of total calories in relation to caloric need.

Clinical Picture. The clinical pictures induced by coronary arteriosclerosis are variable. In a large percentage of instances no manifestations of illness occur, despite extensive disease of the coronary arteries. In other individuals relatively slight disease may be associated with severe anginal attacks and sudden death. It is apparent that the degree of arteriosclerosis is less important than its rate of development, especially in relation to the rate of development of collateral

circulation through other channels. When coronary sclerosis does induce clinical manifestations, either angina pectoris or myocardial infarction may occur. As the result of repeated infarction, with loss of functioning heart muscle, dilatation and congestive failure may supervene. However, the cardinal clinical pictures associated with coronary arteriosclerosis are those of angina pectoris and of myocardial infarction, and these conditions will, therefore, be discussed in some detail.

ANGINA PECTORIS

This disorder may be defined as a clinical syndrome brought about by a temporary discrepancy between oxygen supply and oxygen need in the heart, and characterized by a particular type of pain as well as by the likelihood of sudden death. Angina pectoris is not a disease in the sense of an etiologic or morphologic entity, but, like diabetes, represents a clinical and physiologic entity. The disorder was first clearly delineated in 1768 by William Heberden, whose classic description represents a model of astute observation and clear expression.

The restriction of the term *angina pectoris* to indicate the pain alone rather than the total syndrome, of which the pain is one important feature, is justified on neither historical nor clinical grounds.

Etiologic Factors. Age and sex are important, the disease being most common in males beyond the fiftieth year, but being observed sometimes as early as the second or third decade. In the absence of hypertension or diabetes, angina pectoris is rare in women below the age of 60. The other predisposing factors are those which have been mentioned as tending to produce coronary arteriosclerosis—namely, obesity, diabetes, myxedema, xanthomatosis, and other hypercholesteremic states, and the disorders which tend to affect the aortic valve, including rheumatic fever and syphilis.

¶ The relation of hypertension to angina pectoris is of interest. There is ample evidence that hypertension favors the development of coronary arteriosclerosis. The increased work of the heart tends to increase the oxygen needs of the myocardium. The increased intramural pressure during systole tends to diminish the systolic coronary flow to the subendocardial portions of the left ventricle, and this mechanism may be related to the alterations in the S-T segment of the electro-

cardiogram that are frequently observed in hypertensive subjects. On the other hand, the higher head of pressure in the aorta tends to increase the systolic flow to the outer portions of the left ventricle, and the flow during diastole to the whole heart tends to be elevated as the result of the rise in diastolic blood pressure. The overall result of these opposing factors is that angina pectoris is considerably more likely to occur in hypertensive subjects than in individuals with normal blood pressure.

Other etiologic aspects of angina pectoris have been considered in Chapter 3.

The precipitating causes (i.e., the conditions which tend to induce an attack in persons with one of the underlying disorders which have been mentioned) include exercise, emotion, eating, and cold as the most common agents. When attacks occur at rest in the absence of these factors, they are much more likely to appear in the recumbent rather than in the sitting or standing postures. Hypoglycemia, either induced by insulin or of the spontaneous type, is a less frequent precipitating factor, but is of considerable practical importance. The various types of ectopic tachycardia may induce attacks in predisposed subjects and, less commonly, may cause anginal seizures in individuals without disease of the coronary arteries and with structurally normal hearts. Since the duration of systole is relatively constant and varies only slightly with variations in heart rate, the total amount of systole per minute is increased, and the total duration of diastole per minute correspondingly decreased during tachycardia. The coronary flow to the fibers of the inner part of the left ventricle tends to be shut off during systole. This factor, when added to the factor of increased energy expenditure by the heart, probably accounts for the occasional occurrence of anginal attacks during seizures of paroxysmal tachycardia in individuals with structurally normal hearts.

Diagnosis and Symptomatology. The majority of patients with angina pectoris give histories that conform closely to the classic picture originally described so vividly and precisely by William Heberden. The deviations from this pattern are rather infrequent, but they are frequent enough so that some of the more important ones deserve mention.

The characteristic description of the pain is that it is squeezing and viselike. Rather rarely,

the patient will insist that the pain is "burning," not constrictive, although all other features of the history are typical of angina and subsequent events may prove beyond question that angina pectoris has been present. It is very common for anginal pain to seem to be related primarily to eating, when actually the pain is precipitated by exercise which happens to be taken immediately after a meal. Here, the most important factor is the exercise.

Occasionally, a patient will suffer his only anginal attack of the day after he first begins to walk in the morning. On resting, the pain disappears and will not return, even though the individual may walk long distances at his usual pace.

In a small group of patients the first appearance of the pain is not on effort but rather in direct relation to meals. In some instances angina occurs shortly after a meal, even though the patient remains at complete rest. In other cases, two or three hours after eating, when the patient is sitting or standing quietly, he may experience a typical substernal pain that is promptly relieved by eating or by an alkali. In other words, the quality and distribution of the pain are that of angina; the time of its appearance and its mode of relief are suggestive of peptic ulcer. In some of these, the cause is hypoglycemia; in others, the cause is obscure, for no ulcer can be demonstrated, and, without any treatment for ulcer, the peculiar timing of the symptoms disappears spontaneously and the usual angina of effort may make its appearance. When attacks occur after meals (either soon or late), and without exercise, the development of myocardial infarction within a few weeks is a likely event. Occasionally, a chest pain suggestive of angina may develop without reference to effort, to meals, or to excitement. The electrocardiogram not only may be normal but will not show the slightest evidence of coronary insufficiency after vigorous exercise. After an interval of time, the classic angina of effort clarifies the diagnosis. Some patients experience their initial attacks only on assuming the recumbent position, especially on retiring; only later does the angina of effort appear.

Finally, the location of the anginal pain may differ from the usual site and offer some difficulty of interpretation. Radiation into the neck and to the angles of the lower jaw is not uncommon, and the pain may be felt only here. In some cases the pain may be experienced only in the

back of the neck at about the level of the lower cervical vertebrae, or in the left supraspinous fossa, or in the left shoulder.

The differential diagnosis of angina pectoris, as well as the mechanism of the pain, has been discussed in detail in a preceding chapter (p. 38), and need not be discussed here.

Prognosis. Prognosis is more uncertain in this disorder than in any other chronic disease. Attacks may cease either following myocardial infarction with destruction of the area responsible for the pain, or spontaneously as the result of the development of collateral circulation. Apparent recovery may also occur when the individual learns to avoid the precipitating factors. In some patients the disorder persists in an essentially static stage for many years, the exercise tolerance remaining almost unchanged. Increase in severity and frequency of the attacks may follow myocardial infarction, and in such individuals it is presumed that the coronary branches are diffusely affected, and that the increase in work of the remaining myocardium, following destruction of one portion by the disease, causes the aggravation. The important point is that even in patients with an apparently mild form of the disease—i.e., mild in the sense that the pain is minimal and the attacks infrequent—sudden death may occur at any time. In general, however, the prognosis is worse when the pain sets in frequently or is of great severity and long duration, and is particularly bad when the attacks occur at rest, independently of any known precipitating factor.

The exact relationship of the cholesterol level of the serum in the development of atherosclerosis, and of the effect of diet on the cholesterol level, has long been a matter of dispute. Although there tends to be a parallelism between the height of the cholesterol concentration of the serum and the tendency to develop coronary disease, notable exceptions are frequently found. The work of Gofman *et al.* may prove to be of great importance in clarifying many of the problems relating to the development of atherosclerosis. These workers have found that cholesterol is transported in the serum in the form of large complex lipids and lipoproteins of low density. Some of these giant molecules are of a lower density than the major group of lipoproteins carrying cholesterol, and it is these particular molecules of lower density that appear to bear a relationship to the development of atherosclerosis. Generally, the

higher the serum concentration of cholesterol, the higher is the concentration of these apparently significant lower-density molecules, but the parallelism is not exact. The lower-density molecules may be present in serums with cholesterol concentrations of 120 to 140 mg. %. They tend to be present in greater quantities in young males as compared with females, in diabetics, and particularly in those who have sustained a myocardial infarct. In other words, the findings are consistent with the expected incidence of atherosclerosis in these groups. The evidence seems to indicate that the intake of cholesterol may have an influence on the serum concentration of these significant lower-density molecules, but that it is not the only factor concerned.

Even if one accepts the thesis that atherosclerosis represents a form of disturbed cholesterol metabolism, our knowledge regarding the factors instrumental in influencing the cholesterol content of the blood and the deposition of cholesterol in the intima of the arteries is meager. The fragmentary evidence available at the present time suggests that the following measures may be important in effecting a reduction in the blood cholesterol level:

1. Restriction of total caloric intake sufficient to maintain the body weight at a figure considered normal for the individual aged 20 to 25.
2. Restriction of all fats (vegetable as well as animal).
3. Restriction of animal foods especially rich in cholesterol (brain, yolk of egg, butter and other milk products rich in butterfat, liver, kidney, sweetbread, roe, shellfish).

This type of dietary management should be prescribed for patients with angina pectoris due to coronary sclerosis, with the hope that it may tend to prevent or delay further progression of the disease, thus affording more time and greater opportunity for the development of an effective collateral circulation to the involved areas of the heart. As a preventive measure, similar dietary restrictions should be advised for persons with a pronounced family history of coronary sclerosis, or for those who display an elevation of the blood cholesterol. There is no clear evidence that the administration of choline, methionine, or other lipotropic substances is of benefit in the management of patients who have coronary arteriosclerosis.

Treatment. The treatment of angina pectoris consists, first, of the application of those general principles of management of heart disease which will be discussed in a subsequent section; and, second, of the avoidance of the circumstances which induce attacks. The remaining therapeutic problems may be divided as follows: (1) treatment of the disease; (2) prevention of attacks; (3) treatment of attacks.

The treatment of the underlying disease rarely is completely successful.

There is no evidence that exercise below the threshold of pain is harmful, and there is some evidence that exercise in moderation and always kept below the degree of effort which induces attacks may have a beneficial effect. Many patients with angina pectoris seem to improve when they begin to take a short walk at a slow rate twice daily, after first taking a nitroglycerin tablet. The distance of the walk should be increased gradually as the exercise tolerance rises. Whether the benefits apparently sometimes observed from such a regime are to be attributed to the development of increased collateral circulation in the coronary system, or are of psychic origin due to restoration of confidence in a previously frightened patient, remains uncertain.

The role of anemia, thyrotoxicosis, hypoglycemia, and paroxysmal tachycardia as possible etiologic factors should be kept in mind, for these conditions, though rather uncommon in patients with angina pectoris, are readily amenable to treatment.

Reduction of weight sometimes results in striking benefit in obese patients with angina pectoris.

Attacks are best prevented by avoiding precipitating factors. In addition, patients should be instructed to use nitroglycerin, 0.3 to 0.4 mg. ($\frac{1}{200}$ to $\frac{1}{150}$ gr.), prophylactically, in an attempt to prevent attacks when conditions arise which are likely to lead to seizures. Thus the lawyer suffering from angina pectoris may wisely take a nitroglycerin tablet under the tongue before making an important speech to a jury, the minister before addressing his congregation, and the business man before a tense and argumentative conference.

The treatment of the attack consists essentially of having the patient stand or sit still (these postures being preferable to the recumbent posture) and take a nitroglycerin tablet under the tongue. The dose of nitroglycerin should be

slightly less than that which induces flushing of the face and headache. In most patients 0.3 mg. ($\frac{1}{200}$ gr.) is sufficient, although an occasional patient may require twice this dose. The individual who is unusually susceptible to headache from this drug may achieve excellent results by reducing the dose to as little as 0.15 mg. ($\frac{1}{400}$ gr.). Compared to nitroglycerin, other drugs have relatively little value in the relief of anginal attacks. Papaverine, theobromine and theophylline may be given to increase the exercise tolerance; rarely is the improvement striking.

Anginal pain may be relieved by interruption of appropriate nerve pathways. This may be accomplished either by resection of the upper four dorsal roots, bilaterally, or by injection of alcohol into the corresponding sympathetic ganglions. These procedures should be reserved for those rare instances in which the pain remains intractable or intolerable, despite the conservative plan of management which has been described. For such patients who are considered to be fair surgical risks, resection is preferable; for those with the most advanced coronary disease, injection is the procedure of choice.

To summarize: The management of angina pectoris consists in the recognition and treatment of known aggravating and precipitating factors. Reduction of weight in obese subjects is particularly important and the taking of a low-cholesterol diet may also be advantageous, although this latter is still a matter of dispute. Nitroglycerin should be used when attacks occur or are expected. In view of the wide margin of safety of this drug, it also seems wise to administer it routinely after meals and at additional intervals throughout the day.

MYOCARDIAL INFARCTION

Although partial descriptions of the clinical picture of this disorder had appeared in the literature from time to time for many years, it was not until the clear discussions of James B. Herrick, in 1912 and 1919, that the condition began to be recognized generally.

The terms *coronary occlusion*, *coronary thrombosis*, and *myocardial infarction* are often used synonymously. Actually, coronary occlusion may be the result of embolism or, more commonly, may be the consequence of gradual arteriosclerotic narrowing without actual thrombosis. Coronary

occlusion with or without thrombosis may lead to infarction when the occlusion develops rapidly, and may be associated with no infarction when the process proceeds slowly. Gradual progressive narrowing of coronary vessels, resulting in partial occlusion, may be associated with anginal attacks of progressively increasing severity and duration (*status anginosus*, coronary insufficiency), and such attacks may persist over a period of several weeks without the development of myocardial infarction if an adequate collateral circulation develops and terminates the attacks. Under certain circumstances, such as prolonged paroxysmal tachycardia, myocardial infarction may develop without actual structural occlusion of the coronary vessels. Such considerations make it clear that the interrelationship between coronary occlusion, coronary thrombosis, and myocardial infarction is not a simple one. Actually, coronary thrombosis and coronary occlusion are often recognizable only by post-mortem examination. On the other hand, myocardial infarction produces a characteristic clinical picture which will usually lead readily to the correct diagnosis.

Etiology. The etiologic factors concerned are essentially those already discussed in regard to coronary arteriosclerosis and angina pectoris. The fundamental pathologic process in the great majority of instances is an atheromatous change, and myocardial infarction may result from gradual narrowing of the lumen due to such atherosclerosis, or from the development of a blood clot at the site of the atheroma. A less common cause of acute myocardial infarction is a subendothelial hemorrhage in the wall of a coronary vessel.

Clinical Picture. The clinical picture and the differential diagnosis of myocardial infarction have already been discussed in the chapter dealing with chest pain. Here it will be sufficient to summarize briefly the clinical picture. In typical cases the combination of prolonged substernal pain, with development of signs of forward and backward failure, followed in a day or two by evidence of tissue destruction (fever, leukocytosis, elevation of sedimentation rate), plus characteristic electrocardiographic changes (Chapter 31), will make the diagnosis clear. When the pain is absent and the patient notices only dyspnea or nausea, or when the pain is atypical, and when electrocardiographic changes are minimal or atypical, the diagnosis may be obscure. The cases more difficult to recognize are those that

occur without pain. In some the onset may be characterized only by a brief period of faintness. In others (rare instances) the patient may exhibit evidences of profound shock without any clinical manifestations indicative of a disorder of the heart. In most of the cases of acute painless myocardial infarction, however, the initial symptom is severe dyspnea sometimes associated with acute pulmonary edema. In doubtful cases it may be necessary to treat the patient as an instance of myocardial infarction, pending the development of further characteristic manifestations of this disorder, or of some disorder such as dissecting aneurysm, pulmonary embolism, mediastinal emphysema, etc., which may simulate it.

The most serious manifestations of myocardial infarction are those simulating shock as well as those of congestive failure, and frequently both types of symptoms coexist. Next in frequency are transitory disturbances of rhythm, which may be of almost any type, and which are of especial practical significance because they often constitute a serious but remediable additional hazard. Another frequent complication is the development of an additional myocardial infarction while the patient is recovering from the first. Pulmonary embolism and infarction are common; cerebral embolism is not infrequent. Since infarction of the right ventricle with consequent mural thrombosis is very rare, such pulmonary emboli usually arise in the deep veins of the legs. Their prevention is one of the important problems in management of patients with myocardial infarction, as in other individuals who are kept in bed because of cardiac disorders. Systemic embolism consequent to the left ventricular mural thrombi is a less frequent complication, and may lead to gangrene of the legs, hemiplegia, occlusion of abdominal vessels, etc. Rupture of the heart is a rather rare complication, but is always fatal. There is some evidence which suggests that it is more prone to occur when the previous diet has been deficient in vitamin C. Thinning of the ventricular wall, with the development of ventricular aneurysm, is compatible with a duration of life of many years.

Prognosis. In this condition, as in the case of angina pectoris, prognosis is always uncertain. There is perhaps no other disorder in which a patient, apparently progressing favorably, is so likely to die unexpectedly. Likewise, there are few conditions in which a patient so seemingly

moribund may recover to assume eventually a life of relatively normal activity. In general, the prognosis is better in middle-aged than in elderly patients, because the younger individuals are less apt to have advanced sclerotic changes throughout the coronary tree, and perhaps especially because the older patients are more apt to have serious concurrent disease, such as latent senile heart disease, prostatic enlargement, emphysema, etc. The prognosis is likely to be better when the infarction sets in suddenly than when it is preceded by prolonged and severe attacks of angina pectoris (coronary insufficiency). The appearance of severe congestive failure adds to the gravity of the outlook, as does persistence of the pain beyond a period of one or two days. A well-marked decline in arterial pressure, even to systolic levels of less than 100 mm., is not necessarily serious, provided that the other signs of forward failure, such as clouding of the sensorium, clamminess of the skin, and marked decline in pulse pressure, do not appear. However, prognosis is grave when these manifestations of forward failure are obvious, and is especially grave when well-marked manifestations of forward and backward failure coexist.

The serious arrhythmias which may develop have important prognostic significance. Auricular fibrillation exerts its harmful influence through acceleration of the ventricular rate. Frequent ventricular premature beats sometimes precede the development of ventricular tachycardia and hence should be viewed as an unfavorable sign, particularly so if they do not disappear on administration of quinidine. Ventricular tachycardia, when setting in after infarction, is a serious complication, not only because of the harmful effects of the tachycardia superimposed on an already gravely compromised myocardium, but also because it is a frequent forerunner of ventricular fibrillation. Nevertheless, the prognosis in a given case is not necessarily poor, since the disturbance is often amenable to treatment by quinidine administration. The danger arises from the fact that, even after one paroxysm has been stopped, another may start and progress into fatal ventricular fibrillation despite the use of quinidine in the usual prophylactic doses. Heart block, of either second or third degree, is also a serious complication, since it may culminate fatally in ventricular standstill or ventricular fibrillation.

Treatment. During the acute and painful stage, complete rest is indicated, and sufficient opiates or other analgesics should be used to relieve the pain. Food may be restricted to fruit juices for the first 24 to 48 hours, and water given in amounts of 1000 to 1500 ml., or more, if sweating is profuse. The intravenous route for administration of fluids and drugs should be avoided except when imperative.

If there are numerous rales in the lungs, or if cyanosis is present, oxygen is urgently needed. Even in the absence of these signs, oxygen is probably of value, as the elevation of arterial oxygen content, although small in degree, will allow a given level of tissue oxygen tension to be achieved at a lower level of cardiac output and may, therefore, rest the heart.

Atropine, 0.3 to 0.4 mg. ($\frac{1}{200}$ to $\frac{1}{150}$ gr.), subcutaneously, has been advocated at six-hour intervals during the first two days to relieve reflex spasm of the coronary vessels, although the value of this procedure has been questioned. Papaverine, 0.1 to 0.2 Gm. ($1\frac{1}{2}$ to 3 gr.), should be administered subcutaneously at four- to six-hour intervals for several days because of its effects in dilating the coronary arteries and in preventing ectopic rhythms. Unless nausea is present, the oral route should be utilized after the first day or two. Nitroglycerin, 0.15 to 0.3 mg. ($\frac{1}{400}$ to $\frac{1}{200}$ gr.), at intervals of two to four hours, may be substituted for papaverine after the first week. Since this drug is the most effective coronary dilator and in proper dosage may produce this effect without lowering blood pressure, it is probable that nitroglycerin may eventually supplant the other drugs used for the purpose of ensuring maximal blood flow to the injured area.

The available evidence indicates that anticoagulant therapy may be of great value in the management of patients with myocardial infarction. The purposes of such therapy are to prevent phlebothrombosis and hence reduce the likelihood of pulmonary embolism and infarction, to prevent further thrombosis in the coronary vessels, and to prevent mural thrombosis. Anticoagulant therapy may increase the gravity of cerebral or other embolism, if such complications should occur. The available evidence suggests that anticoagulant therapy should be used routinely, provided adequate laboratory control is available and important contraindications such as disease of the liver and kidney are not present.

After the initial stage has passed and the pain has ceased, the problem of therapy changes somewhat. The diet should be low in calories (800 to 1000 calories), low in cholesterol, and generous in ascorbic acid, which may perhaps have a favorable effect on the healing of the infarct. Pending more complete knowledge, it would seem wise to administer ascorbic acid in oral doses of about 300 mg. per day for the first three weeks.

Rigid restriction of sodium should be the mainstay in the treatment if congestive failure appears. Digitalis should be used cautiously because of the potentially serious consequences of ventricular premature beats in this condition. Dyspnea, whether or not associated with Cheyne-Stokes breathing, will usually be benefited by theophylline ethylenediamine (aminophylline), 0.5 Gm. ($7\frac{1}{2}$ gr.), administered rectally at six-hour intervals.

The question as to the wisest management of individuals with striking evidence of forward failure—i.e., with a shocklike picture—is a difficult one. The intravenous administration of blood or other fluids may tend to raise the blood pressure, but may also tend to produce pulmonary edema and other evidences of backward failure. Theoretically, when the dynamic state of the heart is on the ascending limb of the Starling curve (p. 153), transfusion would be expected to benefit the manifestations of forward failure and to aggravate the phenomena of backward failure, while venesection would have the reverse effects. On the other hand, in the case of a heart on the descending limb of the Starling curve, transfusion should aggravate and venesection should benefit both groups of manifestations. Unfortunately, there is at present no reliable method of estimating the dynamic state of the heart in a given patient. In the absence of definite knowledge on this point, it would seem wise to withhold transfusion unless the patient's life seems to be threatened by the shocklike state; and, under such conditions, to administer the blood with caution, stopping in case dyspnea or other evidence of pulmonary edema develops. Similarly, when dyspnea and venous distension are prominent, it may be wise to withdraw blood cautiously, provided a significant decline in arterial pressure is not produced thereby.

Arrhythmias, which frequently make their appearance during the first and second weeks following the onset, are of great practical impor-

tance, and should be treated along the lines already discussed.

In order to avoid straining at stool, intestinal lubricants such as mineral oil should be utilized, by either oral or rectal routes.

It is possibly useful to administer coronary dilator drugs in the hope of dilating collateral channels and minimizing the size of the infarct. For such a purpose nitroglycerin, given in amounts of 0.15 to 0.3 mg. ($\frac{1}{400}$ to $\frac{1}{200}$ gr.) every 2 to 3 hours, provided it does not lower the blood pressure significantly, is probably the drug of choice, and should replace papaverine after the first week. However, there is no certainty concerning the value of this procedure.

A large percentage of the patients with myocardial infarction who are doing well from a physical standpoint suffer from marked apprehension and restlessness. In such individuals mild sedatives of the barbiturate group are likely to be useful.

One of the major problems in the management of patients with myocardial infarction involves the decision concerning the duration and rigidity of restriction of activity. During the acute phase the patient should be kept in bed and should remain in the position which is most comfortable. Ordinarily, the semirecumbent posture will be preferable when there is slight dyspnea, the sitting position when dyspnea is marked, and the recumbent position when dyspnea is absent or a shocklike state exists. The idea that in order to achieve maximal rest for the heart it is necessary to have the patient lie flat in bed is based on unsound concepts. Actually, the work of the heart per minute is rarely greater and is frequently less in the sitting position than in the recumbent posture. The decision as to whether the patient should use the bedpan or be allowed to walk to the toilet can usually be resolved by adopting the middle course of a bedside commode when the use of the bedpan is attended by discomfort.

As a rule, the patient should be kept in bed, except for bowel movements, for a period of two to three weeks after pain and shock have subsided, and then allowed a little more activity each day, with gradually increasing walking about the room. During the period of bed rest *it is important that the legs be massaged, and that first passive, and later active, movements be initiated* in order to minimize the likelihood of phlebothrombosis. In the case of elderly patients who are predisposed

to thrombosis and infection, it is probably wise to utilize a shorter period of strict bed rest than in the case of younger subjects in whom the possible advantages of strict rest may outweigh the disadvantages. The present evidence, which is decidedly incomplete, would seem to indicate that there is every advantage in prolonged restriction of activity, but little advantage in prolonged rigid rest in bed.

Emphasis has been directed repeatedly at the importance of psychologic management in all cases of disorders of the heart. In none is sympathetic understanding and insight into the emotional problems of the patient more necessary than when dealing with individuals who have suffered a myocardial infarct. Most of these patients are stricken when they are at the height of their business or professional careers and of their responsibility to family and colleagues. The ominous significance of "heart attack" and "coronary thrombosis" has attained such wide diffusion among the laity and especially through reports of the unexpected deaths of friends who but a few days before had seemed so robust and well, that hardly any person who has sustained such an attack can fail to ponder anxiously on what the future will hold for him. Aside from the immediate threat to his life, the questions of his capacity to carry on his business, job, or profession, and of the far-reaching influence this illness will have on the lives of his wife and children, must obtrude on his thoughts. It is not necessary to discuss the innumerable anxieties that inevitably attend the convalescence of the person who lies in bed or leads the restricted life following the acute attack. Suffice it to say that these ideas do preoccupy a large part of his thought, and recognition of their existence must not be overlooked by the physician, however impassive and philosophic the patient may seem to be. It is during these days that the physician must exert his utmost skill in restoring confidence, in explaining in simple terms the significance of the illness, and in allaying fears and anxieties. The task is not easy, for the physician cannot forget that behind the apprehensions of the patient there is a core of truth that can never be dissipated. He can, however, come to a reasonably accurate estimate as to the degree of activity in which the patient may ultimately participate; and he can, within the limitations imposed by a malady of such uncertain course, encourage a life that will often be

more active and useful than the patient had imagined. He can point out the many useful and productive years that others suffering from the same disorder have experienced. The details and intricacies of this complex psychologic problem will be as varied as the temperaments and the circumstances surrounding each individual patient. The administration of drugs and the supervision of strictly medical measures constitute a progressively diminishing part of the total management as the days of the acute attack recede and the days of convalescence and resumption of more or less normal life progress.

SENILE HEART DISEASE

For years there has existed the problem of the correct designation of that form of heart disease that occurs in elderly persons which is unaccompanied by anginal pain and for which there is no obvious cause. The term *chronic myocarditis*, formerly applied to this group, has now been largely abandoned since histologic examination rarely reveals evidence of inflammatory lesions in the myocardium. At the present time, *arteriosclerotic heart disease* is the name commonly applied to these cases, presumably based on two assumptions: (1) Even though no gross atheromatous lesions may be present in the larger branches of the coronary arterial system, sclerotic changes in the finer branches not visible to the naked eye have compromised the blood supply to the myocardium to such a degree that myocardial failure ensues. (2) Sclerotic changes in the smaller branches of the coronary arteries may progress to the point of causing myocardial failure by virtue of the reduction of blood supply to the myocardium, and yet fail to cause the one characteristic manifestation of myocardial ischemia—angina pectoris (or myocardial infarction).

Regarding the absence of anginal pain, it is well known, of course, that this pain may occasionally be absent in the presence of narrowing or complete obstruction of a coronary artery. Anginal pain fails to appear under two conditions: (1) When the collateral blood supply to the area nourished by the sclerotic coronary becomes sufficiently abundant to prevent myocardial ischemia. Under these circumstances, we are no longer dealing with myocardial tissue devoid of an adequate blood supply. The structural defect in the artery exists, but the physiologic integrity of the myocardium is maintained. (2) In a minority of

cases, impairment of coronary flow to the myocardium may lead to unquestionable disturbance in the heart muscle, both structural and functional. These are the cases of painless myocardial infarction. The reason for the absence of pain of the anginal type in this group is not altogether clear; it is probably due to the localized destruction of the afferent pain fibers in the periarterial plexuses of the coronary artery supplying the ischemic area of the myocardium. Thus an undoubtedly myocardial ischemia may exist and may effect the characteristic structural and functional consequences of such a defect in coronary blood supply without evoking the pain of angina pectoris or of myocardial infarction; but these cases are the exception, not the rule. There is no valid basis for the assumption that sclerosis of the finer microscopic coronary arteries should lead to a reduction in the supply of blood to the myocardium and consistently, not exceptionally, fail to produce the pain of angina pectoris.

Careful quantitative observations on the perfusibility of the aging heart have demonstrated that, aside from diminution in the blood supply to the myocardium due to gross narrowing of the larger branches of the coronary system, there is no reduction in the vascular bed that can afford a satisfactory basis for the congestive failure that may have been present during life. Consequently, the term *arteriosclerotic heart disease* should be restricted to patients with angina pectoris or demonstrable myocardial infarction. This term should not be applied to elderly persons suffering from heart disease and congestive failure without obvious cause. Just as *chronic myocarditis* was cast aside as the proper designation of this form of heart disease since the concept on which the term rested was proved to be fallacious, it now seems desirable to abandon the term *arteriosclerotic heart disease*, as applied to the particular cases under discussion, for exactly the same reason: the concept is equally unfounded.

Intimately related to this question of the nature and classification of heart failure in elderly patients in whom, during life, no recognizable basis for the heart disease and failure of the myocardium exists, is the long-recognized fact that disorders that are known to place an unquestionable handicap on the heart may precipitate congestive failure in a patient 45 years of age or older, even though the same burden may be tolerated without difficulty by a younger person.

Thus slight elevations of arterial pressure, mild forms of thyrotoxicosis, and paroxysmal tachycardias of relatively moderate duration may be associated with congestive failure in elderly subjects, although much more intense examples of the same disorders rarely bring about failure of the myocardium in young individuals. The diminishing capacity of the myocardium to cope with these various burdens—organic, metabolic, or peripheral vascular—as the patient reaches the fifth or sixth decade of life, is not due to a reduction in the blood supply to the myocardium when the coronary arterial system is not grossly involved. This loss of adaptive capacity of the aging myocardium is due to involutionary changes for which there is no recognized histologic basis, and the biochemical defect is as yet unknown. When these involutionary changes have progressed to the point where they cause or contribute in a significant degree to the appearance of heart failure, we believe that the most appropriate designation for the condition is *senile heart disease*.

This discussion is concerned primarily with those cases of heart failure in elderly persons for which no cause can be found. In some, continued investigation during life may reveal a structural lesion hitherto undetected. Thus, electrokymographic studies may uncover a healed myocardial infarct previously unrecognized. In others, careful autopsy examination will disclose scars of healed infarcts or valvular and other lesions that had been unsuspected during life. In other words, a great many of these patients harbor cardiac lesions that are not recognized during life or that are not even recognizable. The authors do not consider these lesions, even when present, the sole cause of the heart failure ultimately causing death. They believe that senile heart disease, superimposed on these various other lesions, has converted them from tolerable into intolerable burdens on the heart. Whether myocardial involution alone—pure senile heart disease—ever causes heart failure remains to be determined. It is the authors' objective here to emphasize that *the absence of an obvious etiologic basis for heart disease in an elderly person does not, ipso facto, warrant the diagnosis of arteriosclerotic heart disease*. It is equally important to appreciate the role that involutionary changes in the myocardium—senile heart disease—play in reducing the adaptive capacity of the aging heart in cop-

ing with the various handicaps to which it is subjected.

Etiology. Concerning the possible significance of race, sex, diet, climate, and occupation, little is known. Heredity probably plays an important part in determining whether an individual will wear out first in his heart, his brain, or some other organ.

Senile myocardial degeneration frequently occurs in individuals with preexisting but asymptomatic cardiac disease due to some other cause such as rheumatic lesions of the mitral valve. It is often associated with elevation of systolic blood pressure due to the associated rigidity of the aorta, and in many such individuals true (i.e., diastolic) hypertension coexists.

Diagnosis. The diagnosis of senile heart disease depends essentially on the demonstration of evidence of impaired cardiac function, either in the form of frank congestive failure or of diminished cardiac reserve in an individual beyond the age of 50, presenting no evidence of any other etiologic factor. This type of cardiac disease is the most common cause of rapidly increasing dyspnea on effort in elderly individuals who lack evidence of chronic disorders of the lungs. Dyspnea, cardiac enlargement, and gallop rhythm may constitute the only clinical manifestations in the early stages. As the disorder progresses, evidence of failure of the left side of the heart, with congestion of the lungs, becomes manifest, and at a later date signs of right-sided failure appear.

Prognosis. The process probably exists for many years in an asymptomatic state, but cannot usually be diagnosed with certainty prior to the onset of diminished reserve, which persists for years before symptoms occur at rest. The prognosis after the onset of frank congestive failure is often relatively good, because the condition is especially responsive to digitalis. However, in view of the advanced age of most of the patients, death from intercurrent disorders is common.

Treatment. The treatment of senile myocardial degeneration is essentially that of congestive heart failure in general, as discussed later.

SYPHILITIC HEART DISEASE

With rare exceptions, syphilitic disorders of the heart are secondary to involvement of the aorta. Syphilitic aortitis will be discussed in Chapter 241, and the discussion here will be concerned only with such aspects as affect the heart

directly. These include the problems of angina pectoris and aortic insufficiency.

Diagnosis. Syphilitic aortic insufficiency should be suspected when a middle-aged individual, usually a male, lacking a story of rheumatic fever, presents the classic manifestations of aortic regurgitation. The suspicion is strengthened when there is a history of a primary lesion or of anti-syphilitic treatment in the past, and when the serologic tests for syphilis are positive (about 85 per cent).

Although syphilis does not produce deformity of the mitral valve, the dilatation of the mitral ring consequent to aortic regurgitation frequently causes an apical systolic murmur. Furthermore, the Austin Flint murmur ("relative mitral stenosis") is frequently heard in patients with syphilitic aortic regurgitation, and this murmur cannot be differentiated with certainty from the similar murmur of mitral stenosis. Rough basal systolic murmurs are commonly present and, rarely, a systolic thrill is felt, but other evidence of aortic stenosis is not encountered. Hence the decision as to whether, in a given individual presenting aortic insufficiency, there is syphilitic disease involving the aortic valve only, or rheumatic disease involving either the aortic valve only or both the aortic and mitral valves, cannot be made by auscultation alone. The presence of chronic auricular fibrillation constitutes almost conclusive evidence that the lesion is rheumatic, as does the presence of peripheral signs of aortic stenosis, or x-ray evidence of compression of the esophagus by an enlarged left atrium. In the absence of such differential points the decision as to whether the lesion is syphilitic or rheumatic has to be made on the basis of the history, the serologic reactions, etc.

Clinical Course. The clinical course of syphilitic aortic insufficiency is often rather rapid, once symptoms have begun to develop. Many such individuals develop acute left-sided heart failure, soon followed by evidence of right-sided failure. At first the usual methods of management for congestive failure are effective, but within a year or two intractable heart failure tends to supervene. The prognosis is not so grave as this in all instances, but in the majority of patients the length of time from the onset of evidence of diminished cardiac reserve to intractable failure and death is shorter than in most of the other types of chronic heart disease.

Management. The management of syphilitic aortic insufficiency is similar in most respects to the management of congestive heart failure in general, as discussed in Chapter 238.

Coronary Ostial Stenosis as the Result of Syphilis. This condition is especially frequent when the coronary arteries take their origin somewhat distal to the usual site, and slightly above the sinus of Valsalva. In the chronic form which develops slowly, the condition may produce no symptoms if the collateral circulation is adequate. However, the picture may be that of angina pectoris in a relatively young patient with syphilis, of unexplained rapidly progressive congestive failure, of syncopal attacks (rarely), or of a combination of these states. The acute form occurs as the result of sudden swelling of the aortic wall, leading to partial or complete occlusion of one of the coronary ostiums as a manifestation of the Herxheimer reaction which occurs when a previously untreated patient with tertiary syphilis is administered a strongly spirochetocidal drug. Here the picture tends to resemble that of myocardial infarction, and the condition can be fatal within a few days. The prevention of such reactions will be discussed later when the treatment of syphilitic aortitis is considered (Chapter 241).

Syphilitic Myocarditis. In the secondary stage of syphilis the myocardium may be affected, although clinical manifestations are rarely if ever induced. Whether there is a true chronic syphilitic myocarditis occurring in tertiary syphilis is a disputed question. On the other hand, there can be no doubt that focal myocarditis in the form of local gummas does occur, and may cause heart block if the gummas are located in suitable areas of the myocardium. Such cases are very rare.

LESS COMMON UNDERLYING CAUSES OF HEART DISEASE CONDITIONS AMENABLE TO MEDICAL THERAPY

There are certain conditions which are preventable, but which cannot usually be cured once the heart has been involved. Among such conditions are syphilis, pulmonary embolism, and diphtheria. Since the present discussion is concerned with disorders which are curable even after the heart has become affected, the preventable but noncurable causes of heart disease will not be considered in the present discussion.

Although some forms of heart failure associated with low cardiac output are curable, whereas others with high output are not, the majority of the curable types of heart failure fall into the high-output group. Since high-output failure is characterized by certain common clinical features, regardless of the etiologic basis, a short description of the chief manifestations may be summarized briefly. In general, they are similar to those observed in normal individuals immediately following vigorous exercise: moderate tachycardia (100 to 130 beats per minute); warm hands; strong, bounding pulse; and increased pulse pressure. In addition, the first sound at the apex and the second sound at the pulmonic area tend to be loud, and frequently systolic murmurs of variable intensity, from faint to quite loud, may be heard in the same regions. Exceptionally, faint diastolic blows may be present, or rumbling sounds may be audible at the apex in diastole. Hence almost any valvular lesion may be mimicked. The important point to be emphasized is that the presence of conspicuous limitation of cardiac reserve or outspoken congestive failure, in an individual manifesting clinical evidence of increased cardiac output, should immediately arouse the suspicion that a curable form of heart disease may be present.

THYROTOXICOSIS

Thyrotoxicosis of itself does not cause angina pectoris, but when it occurs in an individual with coronary arteriosclerosis the increased oxygen needs of the heart may precipitate this disorder. Thyrotoxicosis may also lead to congestive failure. This complication is uncommon before the age of 40 and usually occurs in individuals who already suffer from some other form of heart disease, although occasionally congestive failure may appear in persons who, after cure of the hyperthyroidism, present no recognizable cardiac abnormalities. In some older patients, the characteristic features of thyrotoxicosis may continue to be so conspicuous, even after the development of congestive failure, that the diagnosis is simple. However, in other individuals, the recognition of the underlying thyrotoxicosis as the cause of the heart failure may not be made so readily. The eye phenomena and the enlargement of the thyroid gland may be absent, but these difficulties are not peculiar to the problem of conjoined cardiac failure. When, in addition, the

tachycardia is reasonably attributable to the condition of the heart, the increased appetite is diminished by the passive congestion of the viscera, the loss of weight obscured by the gain due to edema, and the warmth and flushing of the skin and the sensitivity to heat modified by the antagonistic effects of cardiac failure, it is not surprising that the basic overactivity of the thyroid is hardly discernible.

Despite these difficulties, thyrotoxicosis should nevertheless be recognized or suspected as an underlying etiologic factor in patients with cardiac disease when any of the following phenomena occur: persistent tachycardia that endures after prolonged rest; attacks of paroxysmal auricular fibrillation, especially in the absence of mitral disease; auricular fibrillation in which the ventricular rate is resistant to the slowing effect of full doses of digitalis; high-output failure in the absence of any other recognizable cause.

Even when thyrotoxicosis is suspected as the cause of congestive heart failure, the firm establishment of the diagnosis is confronted with additional difficulties. Measurement of the basal metabolic rate becomes unreliable in the presence of heart failure which, in itself, tends to bring about an increase in oxygen consumption because of the increased respiratory effort incident to dyspnea. Hence, in a patient with heart failure, a moderate increase in the basal metabolic rate (up to +25 to +30 per cent) cannot be taken as proof of the existence of overactivity of the thyroid. In such cases of heart failure where the role of thyrotoxicosis is in doubt, determination of the level of precipitable iodine in the serum is of value in arriving at a decision. Unfortunately, this laboratory procedure is not yet readily available. Some help may be obtained from estimation of the circulation time, but the most practicable and important clinical method of establishing the presence of thyrotoxicosis in such cases is the favorable response to the administration of iodine or one of the thiouracil compounds.

The treatment of thyrotoxic cardiac disease is essentially a combination of the management of thyrotoxicosis (Chapter 55) and that of heart failure, as will be discussed later.

THIAMINE DEFICIENCY (BERIBERI HEART DISEASE)

A careful history as regards dietary habits and alcoholism should be obtained from all patients

with congestive heart failure. Elderly males who live alone are particularly likely to have dietary deficiency states.

The classic full-blown picture of beriberi heart failure is characterized by cardiac dilatation, passive congestion, and the presence of high-output failure. Various nonspecific electrocardiographic changes may be present. When these findings occur in an individual who gives a history of prolonged dietary insufficiency, and who presents other manifestations of vitamin or other nutritional defects, and in whom no other cause for the heart failure can be ascertained; and when digitalis confers no benefit, whereas thiamine brings about a dramatic response, the heart becoming smaller and the congestive phenomena disappearing, the diagnosis may be considered to be clearly established. Recent studies suggest that all cases do not conform completely to this pattern. Probably the most important deviation lies in the response to thiamine. Not all patients respond quickly, spectacularly, and completely to the administration of this vitamin. In some, the improvement takes place slowly over the course of several weeks; in others, an apparent cure may be followed by recurrent bouts of congestive failure, indicating that in them the vitamin deficiency has culminated in irreversible changes in the myocardium that have permanently impaired its efficiency. In the favorable cases, enlargement of the heart and nonspecific electrocardiographic changes disappear.

Clinical and experimental evidence indicates that cardiac involvement is more likely to develop when partial rather than complete thiamine deficiency has been present for a long period of time, when the individual has participated in prolonged strenuous labor, and when the metabolism and carbohydrate intake have been elevated, thus increasing the thiamine requirement.

In the United States, primary thiamine deficiency is an uncommon cause of congestive failure; nevertheless, in any individual suffering from myocardial failure, the possibility of beriberi heart disease should be considered when the diet has been grossly defective. Thiamine deficiency should also be considered as a possible contributing factor in patients with any of the more common primary causes of congestive failure, when there is reason to believe that anorexia has been responsible for an inadequate diet. Hence all patients with congestive failure, whose

response to the usual measures is unsatisfactory, should be given a trial with thiamine therapy, especially important in hyperthyroidism.

In recent years another type of cardiac disease has been ascribed to deficiency of thiamine. This is the condition characterized by diffuse endocardial and subendocardial fibrosis with mural thrombosis, the process involving the left ventricle predominantly and the other chambers of the heart to a lesser degree. This disorder should be suspected in an individual presenting heart failure refractory to digitalis, with systemic embolic manifestations and a story of an inadequate diet. It is believed by some that the type of thiamine deficiency associated with the overactive heart, and mentioned in a preceding paragraph, is due to severe deficiency of short duration; while a more moderate deficiency of longer duration may produce the picture of endocardial fibrosis with mural thrombosis. However, the lesions of the latter disorder have not been reproduced in experimental animals. Its relationship to thiamine deficiency is also made questionable by the fact that therapy with thiamine does not result in dramatic improvement, which, however, could hardly be expected even if thiamine were responsible, in view of the nature of the structural change. Conclusive proof that subendocardial fibrosis is due to deficiency of thiamine or other dietary factors is lacking at present.

ANEMIA

In many patients with the commoner types of heart disease, anemia, as the result of intercurrent disorders, constitutes an important aggravating factor. However, severe anemia may in itself produce congestive heart failure, especially in elderly persons.

Such a condition should be suspected when a patient with severe anemia presents the manifestations of high-output failure for which no other obvious cause can be found. The diagnosis in such instances is difficult because severe anemia commonly produces systolic murmurs, which may be loud enough to mimic closely the murmurs of organic valvular damage. Less commonly, anemia induces diastolic murmurs. As a general rule, it is wise to withhold judgment concerning the presence or absence of organic valvular disease in any patient presenting striking anemia. This is particularly true in patients with sickle-cell anemia in whom the associated fever

and joint pains may lead to confusion with acute rheumatic fever.

In these patients, digitalis is usually ineffective, and there is some evidence that it may be harmful. Therefore, the treatment of a patient presenting congestive heart failure as the result of severe anemia consists essentially of the other usual management of congestive heart failure, plus the treatment of anemia, which naturally depends upon the cause (Chapter 22). At times the question of transfusion presents a difficult problem, this procedure being needed from the standpoint of the relief of the underlying cause of the cardiac condition, and yet offering the threat of making the congestive failure worse. Under such circumstances the proper procedure may be to administer erythrocytes, free from plasma, in small daily doses, in the hope of alleviating the anemia without aggravating congestive failure. However, such treatment is rarely needed, as the patient is usually adjusted to the anemic state, and management of the cause of the anemia alone will permit a gradual readjustment to the increasing blood volume.

PRIMARY RETENTION OF SODIUM

Retention of sodium plays an important role in all forms of congestive heart failure, regardless of the cause. In relatively rare instances, acute sodium retention may be a primary cause of cardiac failure. Such a mechanism is probably the basis of the heart failure which frequently complicates acute nephritis, and also that which occasionally results from the excessive administration of desoxycorticosterone acetate. Under these conditions the blood pressure increases rapidly, and at the same time the clinical features of increased cardiac output make their appearance.

Regardless of the cause, patients with congestive heart failure should be treated with low-sodium diets, and, when necessary, with diuretic drugs to facilitate the excretion of sodium.

MYXEDEMA

This disorder may affect the heart in a number of different ways. First, the associated hypercholesterolemia favors the development of coronary arteriosclerosis and angina pectoris. Second, myxedema may be complicated by pericardial effusion. Finally, some hold that even in the absence of these factors myxedema may lead to a

state of myocardial failure. In a given patient presenting evidence of myxedema and congestive failure, the decision as to whether the mechanism is that of myocardial failure or of pericardial effusion may be very difficult, as the usual signs of effusion may be lacking. Fundamentally, the diagnosis of the myxedema heart depends on the demonstration of cardiac disease of the anginal or congestive type, in an individual presenting the clinical evidence of myxedema (Chapter 55). Among the cardiac findings which should lead to a suspicion of myxedema as a possible cause of the cardiac manifestations are: bradycardia despite heart failure, low voltage of all waves in the electrocardiogram (fig. 208), and dramatic improvement of the cardiac status upon the administration of desiccated thyroid gland. This improvement is not likely to be observed when the cardiac disease is of the anginal type, because under such circumstances the increase in metabolic rate, with the consequent augmentation of the oxygen need of the myocardium, may lead to an increase in the frequency and severity of the attacks. When, on the other hand, either pericardial effusion or myocardial failure due to myxedema exists, thyroid administration is indicated. Since coronary and cerebral arterio-

sclerosis are common in persons with myxedema, either anginal attacks or psychic disorders may be induced by rapid elevation of metabolic rate. Hence thyroid should be administered with great caution.

It is noteworthy that the myxedema heart constitutes an exception to the general rule that most of medically curable types of heart disease are associated with the clinical manifestations of increased cardiac output. Here, the signs are quite the reverse, the heart sounds tending to be faint and the pulse pressure low.

BACTERIAL ENDOCARDITIS

This condition will be considered in detail in Chapter 239, and need not be discussed here.

CONDITIONS AMENABLE TO SURGICAL THERAPY

THYROTOXICOSIS

Thyrotoxicosis has already been discussed, and is mentioned again because operative treatment still constitutes an important method of treatment, despite the recent advances in medical management.

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5·9·41

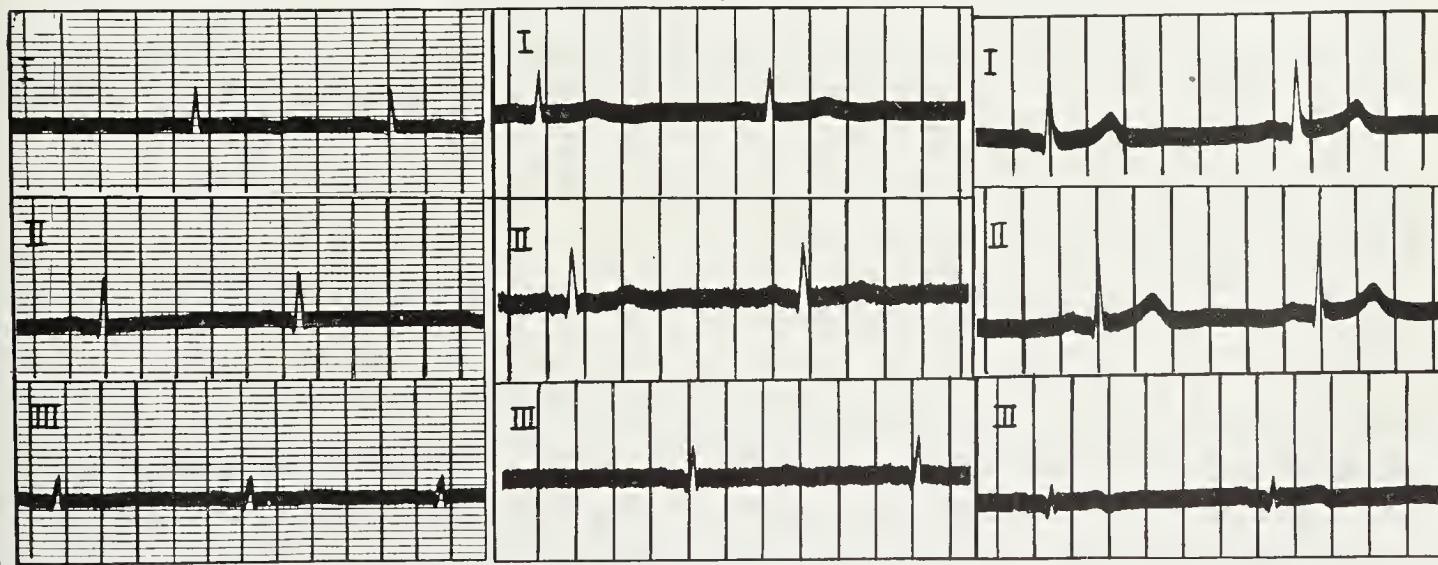


FIG. 208. The electrocardiogram in myxedema. The usual electrocardiographic findings consist of bradycardia and low voltage of all atrial and ventricular components. These alterations are present in this patient, the changes in P and T being more pronounced than those involving the QRS complex. They were readily corrected by thyroid medication.

In some myxedematous patients the electrocardiogram displays changes reflecting coronary insufficiency which is often associated with myxedema.

In many cases, it is believed that the probable cause of the enlargement of the heart shadow and the electrocardiographic changes in patients with myxedema is pericardial effusion.

ARTERIOVENOUS FISTULA

This condition is a rare cause of heart failure, but should be suspected when a patient has unexplained cardiac enlargement with or without congestive failure, plus a story of a penetrating injury such as a knife wound or a bullet wound. The diagnosis depends on searching for and finding the characteristic signs of an arteriovenous communication in the region of the injury. These signs include a continuous murmur with systolic intensification, a thrill, a bounding pulse, a high pulse pressure, slowing of the heart when the fistula is compressed, etc. Successful surgical removal of the fistula may lead to dramatic improvement in the manifestations referable to the heart.

In certain patients with Paget's disease, the extensive development of new vascular channels in bones may induce a circulatory state fundamentally similar to that caused by an arteriovenous fistula. There is some evidence that x-ray therapy may be of value under these circumstances.

CERTAIN CONGENITAL HEART LESIONS

At the present time the congenital lesions amenable to surgical treatment include the patent ductus arteriosus, coarctation of the aorta, and the tetralogy of Fallot. The two former conditions may be cured entirely, while the latter—although not curable—may be benefited strikingly by operative treatment.

Patent Ductus Arteriosus. This condition should be suspected in any individual presenting a continuous murmur with a systolic intensification heard best in the second or third left inter-spaces near the sternal margin. This is the cardinal physical sign, and its presence is practically pathognomonic of the condition, provided intra-thoracic arteriovenous fistula can be excluded. Suggestive but less characteristic signs include a systolic thrill, accentuation of the pulmonic second sound, bounding pulse with elevation of pulse pressure and lowering of the diastolic pressure, and prominence of the pulmonary artery segment of the cardiovascular shadow as seen under the fluoroscope (see figure 210). These findings are also of value in differentiating the condition from combined lesions (stenosis and insufficiency) of the aortic valve, but the differentiation of such a combined lesion from patent

ductus arteriosus depends, in the main, on the decision as to whether the murmur is continuous or has distinctive diastolic and systolic components (fig. 209).

Coarctation of Aorta. The characteristic feature of this condition is the hypertension in the upper extremities and the hypotension in the lower extremities. In addition, there may be large dilated arteries in the chest wall. X-ray examination of the chest presents important evidence in confirmation of the diagnosis: "scalloping" of the lower borders of the ribs (erosions produced by the dilated intercostal arteries), and prominence of the aortic arch to the right of the midline and absence of the aortic knob on the left (fig. 210).

Systolic murmurs are usually present. They may be heard at any point over the precordium, but are likely to be loudest in the middorsal area. Diastolic murmurs due to the commonly associated bicuspid aortic valve, and continuous murmurs due to a coexistent patent ductus arteriosus, may be present. The diagnosis of coarctation will usually depend, however, not on the murmurs but on the other findings. Systolic murmurs may be present at the apex or base, but are often absent. Since congenital bicuspid aortic valves (with or without regurgitation) and patent ductus arteriosus are often associated lesions, the characteristic murmurs of these conditions may be noted.

The characteristic changes in the ribs develop slowly and, while nearly always present in adults, are frequently absent in children. These various manifestations become quite obvious when the diagnosis of coarctation is established, although they are not infrequently missed before the nature of the disorder is suspected. Such an error can be avoided if it is made an invariable rule in all cases of hypertension (and this is especially important in younger persons) to palpate the femoral arteries, which will show an absent or strikingly diminished and delayed pulsation when coarctation of the aorta is present. (In children the blood pressure may not be elevated, and hence the condition will usually be overlooked unless the femoral arteries are palpated routinely.) Although surgical treatment of this condition is a relatively new procedure, it has already yielded strikingly beneficial results.

Tetralogy of Fallot. The cardinal features of the tetralogy of Fallot consist of an interven-

tricular septal defect, dextraposition of the aorta which overrides the defect, stenosis of the pulmonary artery, and hypertrophy of the right ventricle. This condition is the most common cause of severely cyanotic heart disease in a patient who survives the first year or two of life. In an individual presenting the characteristic evidences of a right-to-left shunt, with by-passage of the pulmonary circulation, the condition should be suspected when there is a rough systolic murmur in the second and third interspaces, associated with an abnormally small shadow of the pulmonary artery as seen under the fluoroscope (see figure 210). In atypical instances the diagnosis may be very difficult, and special procedures such as catheterization of the right side of the heart, electrokymographic tracings, etc., may be needed before the diagnosis can be established. The operative procedure for this condition con-

sists in shunting an additional amount of blood to the lungs by anastomosis of one of the major systemic arteries with the pulmonary artery, or by producing an artificial communication between the pulmonary artery and the aorta.

Congenital Pulmonary Arteriovenous Aneurysm. This is a rare disorder which may mimic the tetralogy of Fallot. This condition should be suspected when the physical examination of the heart is negative despite cyanosis, clubbing, and polycythemia, and when one or more rounded, discrete shadows can be visualized in the lungs by x-ray. Amenability to surgical cure depends on whether only a few such arteriovenous anastomoses exist, or whether they are too numerous to make operative treatment practicable. Although the condition is rare, it is mentioned because it may be curable.

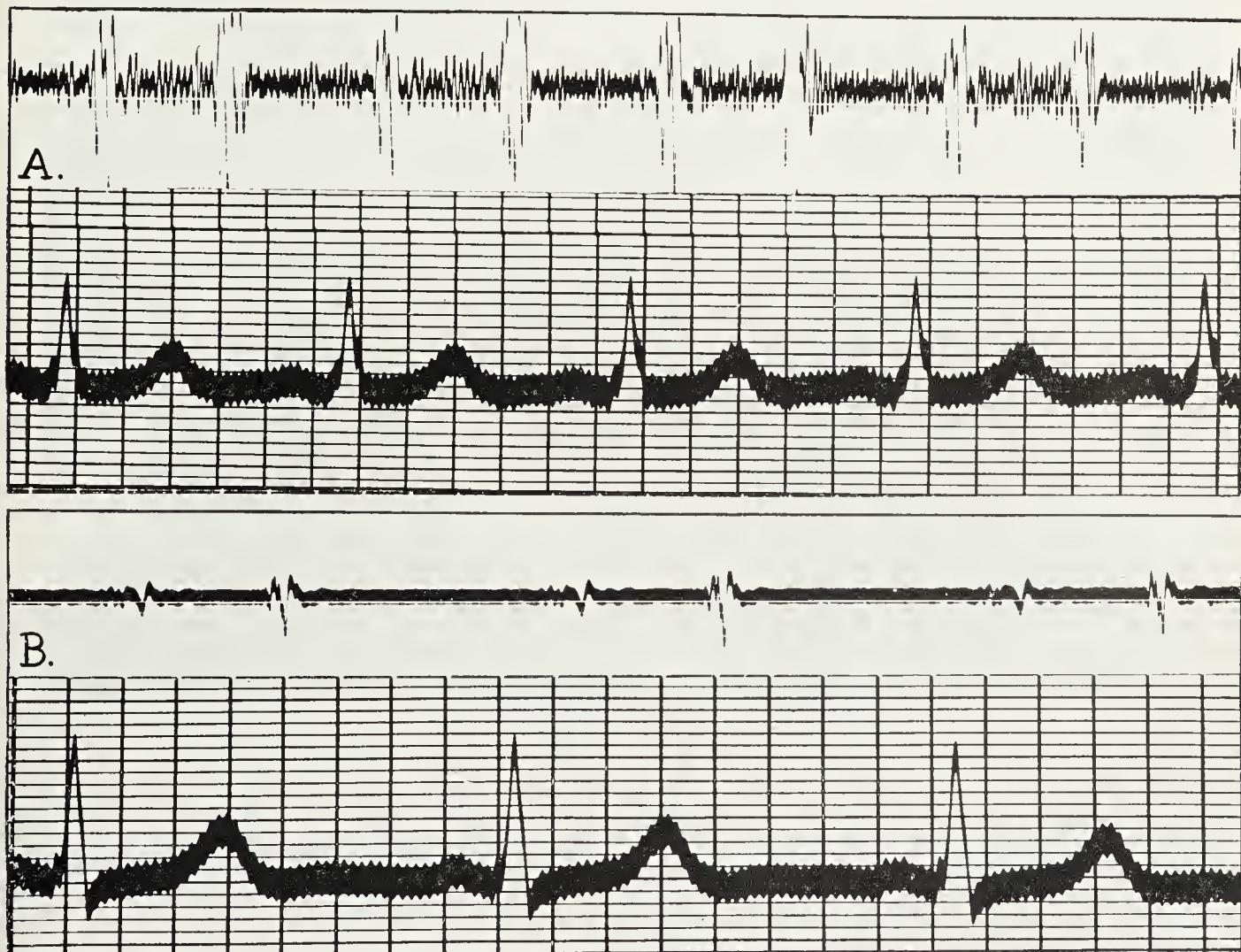


FIG. 209. The murmur of patent ductus arteriosus. (H. H. Hecht.) In this 40-year-old Italian watchmaker a continuous murmur was audible over the pulmonary auscultation points (A: 4-1-49). The murmur was transmitted into the shoulder and posteriorly to the left scapular region. It was louder in the recumbent position and showed systolic accentuation. Record B (5-2-49), taken over the same region and with equal sensitivity, demonstrates that the murmur had completely disappeared after the ductus had been ligated and divided.

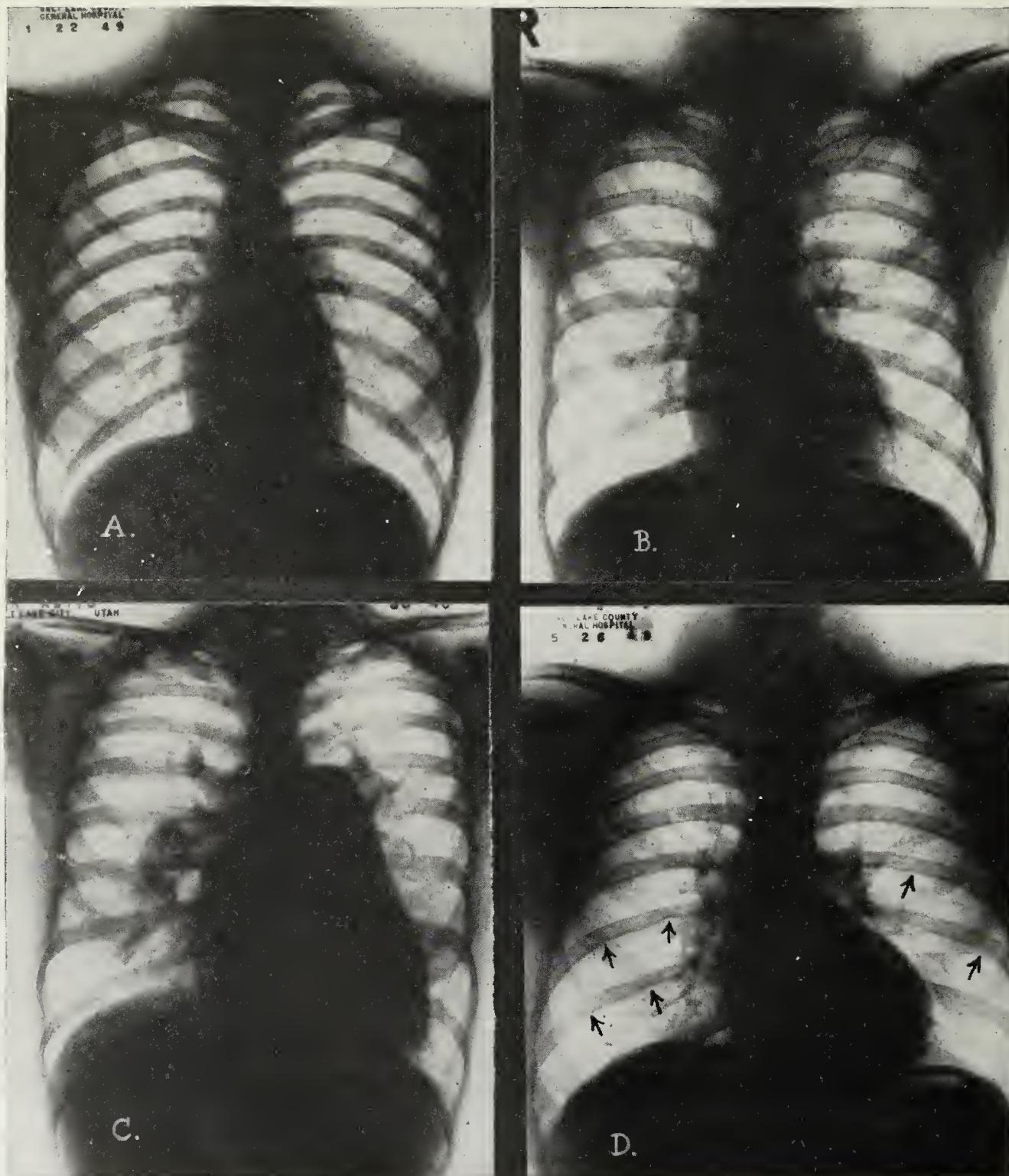


FIG. 210. X-ray configuration in certain congenital abnormalities of the heart and great vessels. (H. H. Hecht.)

(A) Patent ductus arteriosus: Heart size normal, slight bulging of pulmonary artery and increase in pulmonary vascular markings. In this subject the presence of a patent ductus arteriosus had not interfered with cardiac function. In others enlargement and hypertrophy of both ventricles with sharp increase in pulmonary vascularity may be noted. Fluoroscopy may reveal "dancing hilar shadows" characteristic of a large pulmonary pulse pressure.

(B) Tetralogy of Fallot: X-rays are often not informative but this example reveals (a) absence of pulmonary conus, (b) right ventricular hypertrophy with lifting of the cardiac apex upward, and (c) some decrease in pulmonary vascularity with increased brightness of the pulmonary field.

(C) Intraatrial septal defect: Marked increase in the shadow of the pulmonary artery with aneurysmal dilatation of the main pulmonary vessels and increased vascularity of the pulmonary field. The x-ray findings are usually similar to those observed in subjects with patent ductus arteriosus, but are in general more striking.

(D) Coarctation of the aorta: Left ventricular hypertrophy with (1) absence of "aortic knob" and (2) evidence of collateral circulation through greatly enlarged intercostal arteries, causing erosion of ribs ("notching": see arrows).

The decision as to whether or not surgical treatment should be undertaken in a patient presenting one of these types of congenital heart disease may present considerable difficulty. In general, patients with the tetralogy of Fallot have a poor prognosis and a poor life expectancy. Hence, if the diagnosis is reasonably assured, operative management will usually be indicated. In regard to patients with patent ductus arteriosus, the indications for surgical intervention are becoming clearer as the operative technic has been perfected to the point where operative mortality has reached a very low figure. Although the immediate and near-term prognosis for such patients is generally good, the average life span is undoubtedly shortened by the frequent development of congestive failure or of bacterial endocarditis. It seems probable that operative management will eventually be deemed advisable in all children suffering from this condition in order to obviate the risks of these complications, and in adults on the earliest evidence that either of these complications has supervened. The operative treatment of coarctation is so new a procedure that the indications for it have not yet become clearly established.

CONSTRICITIVE PERICARDITIS

This condition, which is readily amenable to surgical therapy, will be discussed later in this chapter when pericarditis in general is considered.

CONDITIONS NOT AMENABLE TO SPECIFIC THERAPY

COR PULMONALE

A wide variety of circumstances may produce a state of hypertension in the pulmonary artery with consequent right ventricular strain and eventual right ventricular failure. Such a sequence of events may set in acutely, following pulmonary embolism of sufficient grade to cause serious interference with the circulation through the lungs, but not of sufficient grade to lead to almost immediate death. The subacute type which endures for a few weeks or, at most, a few months may be due to recurrent embolism or may be the result of extensive miliary carcinomatosis of the lungs, of miliary tuberculosis, of widespread pyogenic or fungous infections, or of extensive fibrosis from any cause. However, the more common and important type is chronic cor

pulmonale, which may be considered in somewhat more detail.

The most common causes of chronic cor pulmonale are asthma, emphysema, and bronchiectasis, which frequently appear in combination with each other. Other causes include pneumoconiosis; pulmonary fibrosis due to any chronic infection; well-marked chest deformities of the scoliotic or funnel-breast type; and primary disease of the pulmonary blood vessels, either of the atheromatous or the syphilitic types (Ayerza's disease).

Diagnosis. Cor pulmonale should be suspected in an individual presenting evidence of any of the above etiologic factors, and in all persons with evidence of right-sided heart failure, plus a story of long-standing, chronic cough. A few of the patients with chronic cor pulmonale have a special type of substernal pain (Chapter 3) brought on by effort and relieved by rest, or brought on whenever there is aggravation of the underlying pulmonary condition. This type of pain bears a close resemblance to angina pectoris, but differs in the tendency toward longer duration, the relative or complete ineffectiveness of nitroglycerin, the more striking cyanosis, and a tendency to be alleviated by measures which benefit the pulmonary condition. Cyanosis and polycythemia are common in individuals with chronic cor pulmonale, and clubbing of the fingers is not rare. In addition, such individuals present clinical, electrocardiographic, and radiologic evidence of right ventricular hypertrophy. The dyspnea in these patients is of the pulmonary rather than the cardiac type (Chapter 9), and is relatively slight in the resting state as compared to such prominent manifestations of right ventricular failure as distention of the veins and enlargement of the liver.

Certain patients with chronic cor pulmonale may exhibit the clinical signs of the overactive heart, and actual measurements of cardiac output per minute have demonstrated normal or high values despite the presence of congestive failure. Such high outputs are presumably due to anoxia.

Treatment. The management of cor pulmonale consists of the treatment of the underlying disease process, plus the usual management of congestive heart failure. Digitalis is often ineffective and some believe it to be harmful in this and other types of high-output failure. Amino-

phylline may be useful. Many such patients will be benefited by oxygen therapy, and, when circumstances permit, there is value in having the individual utilize an oxygen mask or an oxygen tent during sleep, in order to minimize the arterial anoxia which is an almost constant feature of the disorder.

MYOCARDITIS

Formerly, many conditions of noninflammatory nature, including enlargement secondary to hypertension or to valve lesions, and senile myocardial degeneration, were grouped together under the term *chronic myocarditis*. A reaction against such terminology led to an almost complete abandonment of the term *myocarditis* as a diagnosis; but in recent years, with a better recognition of its limitations, the term is again, and more properly, being used.

Acute myocarditis may be due to rheumatic fever, diphtheria, scrub typhus, or almost any acute infectious process. The diagnosis is justified when evidence of heart disease, and more especially gallop rhythm, increase in size, conduction defects, and other electrocardiographic changes, set in during or following acute infection. The prognosis is usually good, except for the types complicating diphtheria and rheumatic fever. Diphtheritic myocarditis commonly is fatal, and although immediate recovery from rheumatic myocarditis usually takes place, long-term impairment of the heart is the rule. The management is that of the underlying disease process, plus that of congestive failure, when this complication supervenes. Digitalis rarely has a dramatically beneficial effect on any type of acute myocarditis, and may be harmful in the diphtheritic type.

Chronic myocarditis may be of known or unknown cause. The former group includes such rare disorders as tuberculous myocarditis, and trichinosis and sarcoidosis of the myocardium. Chronic myocarditis of unknown etiology includes a group of conditions, some of which produce granulomatous changes, and others non-granulomatous changes, in the myocardium. To this group of conditions the term *Fiedler's myocarditis* is sometimes applied. As more is learned about etiologic factors in the rarer types of heart disease, various conditions are gradually being separated from this general category. Thus the condition of subendocardial fibrosis with mural

thrombosis, which has already been discussed, is an example, as is scleroderma with myocardial fibrosis (p. 470). Chronic myocarditis of unknown etiology should be suspected when a young adult, without evidence of valvular lesion, rheumatic fever, or hypertension, develops cardiac enlargement and failure, associated in most instances with pronounced electrocardiographic changes, and in the absence of any known etiologic factor. The treatment is that of congestive heart failure, and the prognosis usually is poor.

CONGENITAL ANOMALIES OF THE HEART

The types of anomalies which are of the greatest practical importance, in that they may be benefited or cured by surgical therapy, include patent ductus arteriosus, coarctation of the aorta, and the tetralogy of Fallot, as well as instances of pulmonary arteriovenous shunts mimicking congenital heart disease. These conditions have been discussed already. The types of congenital heart disease which are not curable at the present time include a wide variety of conditions which may exist in numerous and frequently confusing combinations. Space does not permit a detailed discussion. A few pertinent points will be mentioned, and the more important features of some of the less uncommon varieties will be summarized in the accompanying tables.

There is now much evidence which suggests that certain congenital anomalies are brought about in the fetus as the result of infections occurring in the mother during the early phase of pregnancy. Strong evidence implicating German measles as one possible cause of congenital heart disease has recently been forthcoming. Whether other infections in the mother are capable of having a similar effect is unknown.

Diagnosis. In deciding whether an individual has congenital heart disease, two points are of cardinal importance. The first is to establish the age at which evidence of heart disease—usually in the form of murmurs or cyanosis—was first noted. The second is to determine the presence or absence of rheumatic infection in the past, because the various rheumatic valve lesions may simulate congenital heart disease.

Maude Abbott's original separation of congenital heart disease into the persistently cyanotic, intermittently cyanotic, and noncyanotic groups is of great value in approaching the decision as to which type of congenital heart disease

exists. The persistently cyanotic type, with polycythemia and marked clubbing of the fingers, is usually recognizable at a glance, but must be differentiated from polycythemia vera, cor pulmonale, and pulmonary arteriovenous fistula. The decision as to whether a person has one of the intermittently cyanotic types is more difficult, and usually needs to be based not only on the history but on observation of the patient under varying conditions. The noncyanotic types of congenital heart disease have to be differentiated from each other and from valvular lesions due to rheumatic endocarditis.

Within recent years, rapid strides have been made in the diagnosis of the specific types of congenital lesions. These advances have come about as the result of the interest aroused when it was demonstrated that certain types are amenable to surgical therapy. With the increasing use of cardiac catheterization, and the study of oxygen content of blood in various cardiac chambers, as well as measurements of intracardiac pressures, and with a more widespread use of angiocardiography and the electrokymograph, it appears likely that most of the hitherto baffling problems of diagnosis in this field will soon begin to approach solution. When these special methods of examination are not available, accurate diagnosis still can usually be made by clinical methods supplemented by fluoroscopic studies of the size of the various chambers, plus electrocardiographic evidence as to the type of ventricular enlargement (see figure 210).

Interauricular septal defects are of several types. The most common is the *patent foramen ovale*, in which case a valvelike membrane allows blood to pass from the right to the left atrium, but not in the reverse direction. Under ordinary circumstances this defect is of no significance because the slightly higher pressure in the left atrium keeps the orifice closed. However, conditions which raise right atrial pressure may permit the shunt to take place, and hence this condition may be the cause of cyanosis occurring during exercise, or of excessive cyanosis during crying in a child. In adults its chief significance is the possibility of paradoxical embolism—i.e., embolism in a systemic artery as the result of a thrombus arising in a systemic vein.

The *Lutembacher syndrome* is the condition which arises when a large auricular septal defect is associated with a lesion of the mitral valve—

thought by some to be congenital, by others to be due to superimposed rheumatic infection which seems to be common in this disorder. In infancy the shunt may be from right to left, and cyanosis may occur. With the progress of the mitral lesion, left atrial pressure is raised, the shunt is reversed, cyanosis disappears, and the pulmonary artery enlarges as the result of the great increase in right ventricular output. This condition produces physical signs resembling those of mitral stenosis or insufficiency, and is the only congenital lesion which causes a murmur loudest at the apex. The diagnosis is made by the characteristic x-ray findings (fig. 210), which consist of very marked enlargement of the pulmonary artery associated with striking pulsations of its major branches (the "hilar dance"). Auricular flutter and fibrillation, rare in other forms of congenital heart disease, are not uncommon in the Lutembacher syndrome.

Large auricular septal defects without an associated mitral lesion are, for the reasons mentioned, accompanied by constant cyanosis at birth which later becomes inconstant. The patients frequently have congenital cataracts and long, tapering extremities (arachnodactylly, "spider fingers," Marfan's disease), and confusing basal systolic murmurs may be present.

The *Eisenmenger complex* (dextraposition of the aorta which overrides the associated interventricular septal defect) is the only congenital lesion in which cyanosis, absent during infancy, tends to develop in later years. As the result of the initially left-to-right shunt, the pulmonary blood flow is increased and the pulmonary artery tends to enlarge, although to a lesser degree than in the case of the Lutembacher syndrome. The pulmonary pressure tends to rise progressively, so that eventually the right ventricle discharges a considerable portion of its blood into the aorta, and cyanosis then becomes apparent but may vary markedly in degree from time to time. A systolic murmur along the left sternal border is usually but not invariably present. Hemoptysis is frequent. The Eisenmenger complex is one of the most difficult of the congenital lesions to diagnose with certainty by the usual methods, but can be detected readily by the method of cardiac catheterization and by the demonstration that the oxygen content of blood from the right ventricle is higher than that of the blood from the right atrium.

Prognosis. In view of the fact that accurate diagnosis has only recently become possible, and that recent advances in surgical treatment modify the outlook in several of the common types, few generalizations about prognosis are justifiable. Of the cyanotic types (tables 102 and 103), the only conditions in which survival to adulthood is common are the tetralogy of Fallot and the Eisenmenger complex. Of the common acyanotic types (table 104), the uncomplicated intraventricular septal defect is the most benign, and coarctation of the aorta is likely to be the most serious, with the patent ductus arteriosus and the Lutembacher syndrome occupying an intermediate position. The outlook is usually excellent in patients with dextrocardia or complete block when no other anomaly coexists. In general, infectious disorders, especially bacterial endocarditis and cerebral abscess, are more prone to occur than is congestive failure.

Treatment. In addition to surgical therapy, when indicated, the management of congenital heart disease consists of the application of the general principles of prevention and treatment of congestive failure, which will be discussed in a separate section. Other therapeutic considerations include the prevention and treatment of bacterial endocarditis; the protection of the patient in so far as is possible against respiratory and other infections, and hence against brain abscess; adequate attention to physical and mental development; and the use of oxygen in suitable cases. Perhaps the most important therapeutic aspect presented by such patients is that of the proper psychologic management, not only of the patient but also of his parents and other members of the family.

Somewhat more detailed information concerning some of the various types of congenital heart disease are presented in tables 102, 103, and 104.

Table 102

CLINICAL FEATURES OF SOME OF THE MORE IMPORTANT TYPES OF CONGENITAL HEART DISEASE WITH CONSTANT CYANOSIS

Condition	Important Points in History	Murmurs	Other Physical Findings	X-ray Findings	Common Complications*	Remarks
Tetralogy of Fallot (interventricular septal defect, dextrorotation of aorta, pulmonary stenosis, hypertrophied right ventricle)	Murmur from birth	Systolic at base with thrill	Often none except murmur, cyanosis, and clubbing	No transverse enlargement Right ventricle enlarged forward Clear "pulmonary window"	Intercurrent disease Tuberculosis	Amenable to operation. The common cyanotic congenital lesion in adults Right axis deviation
Pulmonary stenosis with patent foramen ovale	Murmur from birth	Systolic at base	Systolic thrill	Enlarged right ventricle	Right-sided failure Early death Tuberculosis	Right axis deviation
Transposition of great vessels	Cyanosis varies from time to time	Variable, evanescent (direction of shunt varies)	Cyanosis more marked in arms than legs, which receive oxygenated blood via patent ductus arteriosus	Vascular shadows narrow in anteroposterior view; wide in left oblique Both ventricles enlarged	Left- and right-sided failure may alternate or coexist	Cyclic shrinkage and dilatation of right atrium as foramen ovale opens and closes
Persistent truncus arteriosus	Cyanosis progressive if pulmonary circulation is via bronchial arteries	Systolic at base Rarely continuous (dilated collaterals)	Loud second sound, never reduplicated	Diagnostic Enlarged aorta Clear "pulmonary window" Enlarged ventricles	Early death usually	Pulmonary circulation may come from bronchial arteries. Right ventricular shadow extends from aorta to chest wall
Cava draining into left ventricle		Only if other lesions present	Depend on associated lesions	Angiocardiography	Early death	Altered circulation time
Tricuspid atresia with hypoplasia of right ventricle and auricular septal defect		Absent or dependent on associated lesions	Enlarged, pulsatile liver Venous distension	Small right ventricle and small pulmonary conus	Early death	Left axis deviation in ECG Either ventricular septal defect or patent ductus arteriosus
Pulmonary arteriovenous fistula		Faint, continuous; over lungs	Cyanosis Clubbing	Heart negative Shadows in lung fields	Hemoptysis	Amenable to surgical cure

* Brain abscess is common in these disorders with right-to-left shunt.

Table 103

CLINICAL FEATURES OF SOME OF THE TYPES OF CONGENITAL HEART DISEASE ASSOCIATED WITH TRANSIENT, VARIABLE, OR LATE CYANOSIS

Condition	Important Points in History	Murmurs	Other Physical Findings	X-ray Findings	Common Complications	Remarks
Eisenmenger complex (Tetralogy of Fallot without pulmonary stenosis)	Cyanosis develops late, as pulmonary pressure rises, and is variable in degree	Systolic (may be absent)	Clubbing develops late Loud P ²	Enlargement of both ventricles; enlarged pulmonary artery; "hilar dance"	Hemoptysis; congestive failure Brain abscess	Distortion of aortic valve with insufficiency frequent; pulmonary artery usually dilated <i>Cyanosis may first appear during adolescence</i> Angioardiography
Patent foramen ovale	History of cyanosis during crying or exercise	None	None	Normal	Paradoxical embolism Cerebral abscess	Valvelike membrane allowing right-to-left shunt when right atrial pressure is elevated
Auricular septal defect	Cyanosis constant at birth, later disappearing or becoming inconsistent	None or systolic at left sternal margin in 3d and 4th interspaces	Arachnodactyl (spider fingers) and congenital ectaracts are common	Right auricular enlargement	Paradoxical embolism Cerebral abscess Pneumonia	Right atrial pressure higher than left at birth; later left becomes higher and shunt reverses
Lutembacher syndrome (auricular septal defect, mitral lesion, dilated pulmonary artery)	Cyanosis at birth; disappears later	None or systolic at left sternal margin in 3d and 4th interspaces Plus apical presystolic or diastolic	No clubbing Loud P ²	Very marked enlargement of pulmonary artery Marked "hilar dance"; enlarged auricle and right ventricle	Rheumatic infection Various arrhythmias Pneumonia	<i>The only congenital lesion with predominantly apical murmur</i> Excessive pulmonary artery enlargement; other features suggest rheumatic mitral disease Right axis deviation

Table 104

CLINICAL FEATURES OF SOME OF THE MORE IMPORTANT TYPES OF CONGENITAL HEART DISEASE WITHOUT CYANOSIS

Condition	Important Points in History	Murmurs	Other Physical Findings	X-ray Findings	Common Complications	Remarks
Patent ductus arteriosus	Murmur since birth	Continuous with systolic intensification	High pulse pressure Loud P ²	Enlarged pulmonary artery and conus	Bacterial endocarditis; congestive failure	Curable by operation
Patent ductus arteriosus with pulmonary stenosis	Dyspnea, delayed growth	Continuous with systolic intensification	Faint or absent P ²	Enlarged pulmonary artery and conus Enlarged right ventricle	Right-sided failure; right axis deviation	Operation contraindicated Ductus necessary for pulmonary blood flow
Intraventricular septal defect	Normal health	Systolic, harsh, left 4th interspace	None	Normal size and shape	Bacterial endocarditis	Diagnosis suggested by loud murmur with normal health
Coarctation of aorta	Good health in youth Symptoms of hypertension in adulthood	None or systolic	Hypertension in arms; hypotension in legs Collaterals	Notched ribs Absent aortic knob	Bacterial endocarditis; dissecting aneurysm; congestive failure; apoplexy	Femoral pulse should be palpated in all hypertensive subjects. Freeness suggests coarctation
Subaortic stenosis	Murmur since birth Fair general health	Systolic murmur and thrill at aortic area and in neck	Low pulse pressure	Left ventricular enlargement	Bacterial endocarditis; left-sided failure	Left axis deviation. <i>Aortic stenosis without insufficiency or mitral lesion in young person</i>
Bicuspid aortic valve	Normal health	None	None	Normal size and shape	Bacterial endocarditis; calcification of valve	Usually an incidental autopsy finding
Origin of left coronary artery from pulmonary artery	Normal at birth; anginal pain (?)	None	Progressive enlargement	Dilated left ventricle	Progressive congestive failure	Inversion of T waves; low voltage of QRS. Simulates primary myocardial disease
Right aortic arch	Dysphagia Cough	None	None	Displacement of esophagus to left and of cava to right Right aortic knob	Respiratory infections	Often associated with tetralogy of Fallot

RARER TYPES OF HEART DISEASE

Space does not permit a detailed discussion of these conditions. Almost any serious disease of the body may at times affect the heart. Table 105 is, therefore, not comprehensive, but simply lists

a few of the conditions in which the manifestations of cardiac disease may be outstanding and dominate the clinical picture. The rare disorders which are curable have been discussed already and are not included in the table.

Table 105

CHIEF CLINICAL FEATURES OF SOME OF THE RARER CARDIAC DISORDERS*

Etiologic Group	Specific Disorder	Important Clinical Features			Accessory Features	Remarks
		Cardiac	Noncardiac			
Infections	Scrub typhus	Enlargement Gallop	Eschar, fever	ECG Nonspecific changes		Orient and tropics
	Diphtheria	Arrhythmias Failure	Nasopharyngitis Ulcers of skin	Klebs-Loeffler bacillus		Grave prognosis
	Chagas' disease	Enlargement	Anemia Debility	Antibodies to <i>Trypanosoma cruzi</i>		Sudden death frequent
	Trichinosis	Enlargement	Muscle pains	Eosinophilia		Ingestion of raw pork
Metabolic	Xanthomatosis	Angina pectoris	Xanthomas Xanthelasma	Hyperecholes-teremia		Family history
	Von Gierke's disease	Enlargement	Enlarged liver	Hypoglycemia		Infants
	Cardiac amyloidosis	Enlargement Failure	Often none	Congo red test		Other features of amyloidosis may be absent
Therapeutic	Excessive intravenous fluids	Dilatation Failure	Evidence of the primary disease	Hemodilution		Especially elderly subjects
	Emetine	Tachycardia Hypotension	Evidence of the primary disease	T wave inversion		
	Desoxycorticosterone	Enlargement	Hypertension Edema	Hemodilution		
Miscellaneous	Acute nephritis	Enlargement Gallop	Hypertension Edema	Hematuria Proteinuria		
	Polyarteritis	Enlargement Pericarditis	Fever Arthritis	Leukocytosis Eosinophilia		Bizarre clinical picture
	Libman-Sacks disease	Enlargement Pericarditis	Fever, arthritis, lupus of face	Leukopenia		Young females, atypical verrucous endocarditis
	Post-partum heart failure	Enlargement Failure	Recent delivery			
	Myocardial sarcoidosis	Enlargement Failure	Enlarged spleen, liver, nodes	Hilar shadows Bone lesions Increased globulin		Slight fever, cutaneous lesions

* The list is not comprehensive, as many disorders are omitted. None of the types due to curable causes are listed, since these have been considered in the text.

PERICARDITIS

Certain types of pericarditis are curable, and hence should logically have been discussed when curable types of heart disease were considered. However, in order to avoid repetition, all types of pericarditis are considered in the discussion to follow.

Pericarditis may be classified according to two different methods, both of which are of practical importance.

I. Etiologic and Prognostic Classification:

A. Infectious:

1. Grave types (including rheumatic, tuberculous and pyogenic)
2. Mild type (benign pericarditis)

B. Noninfectious:

1. Uremic (prognosis usually grave)
2. Ischemic (myocardial infarction)
3. Neoplastic (rare)

C. Uncertain etiology:

1. Polyarteritis
2. Collagen diseases (disseminated lupus, etc.)

II. Morphologic and Clinical Classification:

A. Acute:

1. Fibrinous (without significant effusion)
2. Serofibrinous (with significant effusion)

B. Chronic:

1. Constrictive (usually due to tuberculous or pyogenic infection)
2. Adhesive mediastinopericarditis (usually rheumatic)

ETIOLOGIC TYPES OF PERICARDITIS

Infectious Pericarditis. Infectious pericarditis may be divided into two groups, according to the gravity of the condition. The more serious group includes the rheumatic, tuberculous, and pyogenic types. All of these are likely to induce severe pain at the onset, and to be followed by an effusion. The rheumatic type, which is commonly associated with other evidences of severe rheumatic infection, and usually preceded or followed by valvular damage, often responds dramatically to salicylate therapy. It sometimes leads to chronic adhesive mediastinopericarditis. The tu-

berculous type may occur in an individual with obvious pulmonary, pleural, or peritoneal tuberculosis, but not infrequently occurs when evidence of tuberculosis elsewhere is absent. It probably reaches the pericardium by way of the mediastinal lymph nodes, and it commonly terminates in chronic constrictive pericarditis. Acute pericarditis due to the pyogenic cocci is less common than it was before the advent of effective antibiotics. It may follow pneumonia, empyema, trauma, or myocardial abscess, and may lead to constrictive pericarditis. Once pyogenic pericarditis has been recognized, surgical intervention should be undertaken unless antibiotic therapy is rapidly effective.

Benign infectious pericarditis is a common disorder of unknown etiology. It usually complicates a mild respiratory infection and is possibly the result of spread from mediastinal lymph nodes. The pain is of variable severity, and is usually associated with breathing. In an occasional case both the pain and the electrocardiographic changes bear close similarity to those occurring in certain instances of myocardial infarction. Differential diagnosis between these conditions has already been discussed in some detail (Chapter 3). In many instances of benign pericarditis the only clinical manifestations are slight fever, vague substernal or precordial distress, a pericardial friction rub, and minimal or borderline electrocardiographic changes. When the characteristic friction rub is absent, the condition cannot be diagnosed with certainty. Benign pericarditis, unlike the rheumatic tuberculous and pyogenic types, only rarely leads to pericardial effusion of significant degree. The condition is not serious and requires no particular therapy, but is important in that it is likely to be confused with more dangerous conditions, such as myocardial infarction or the more serious types of infectious pericarditis.

Noninfectious Pericarditis. The two common causes of noninfectious pericarditis are uremia and myocardial infarction. In both instances the diagnosis of pericarditis depends upon the demonstration of the characteristic friction rub, and the decision as to the underlying condition is based on the general clinical picture. The treatment is that of the underlying disease process, the involvement of the pericardium being a relatively unimportant part of the picture.

Neoplastic pericarditis occasionally occurs as

the result of invasion of the pericardium by malignant tumors of adjacent structures. The condition is rare and has little practical significance.

Pericarditis of Uncertain Etiology. The most important types of pericarditis of unknown etiology are those associated with the arteritic and collagen diseases. In these disorders pericarditis is rarely severe enough to produce important clinical consequences, and its chief significance lies in the fact that its presence may furnish a clue as to the existence of arteritis or disseminated lupus.

MORPHOLOGIC TYPES OF PERICARDITIS

Since, in some instances, the underlying cause of the pericarditis may not be readily amenable to therapy, while treatment of the mechanical effects of the process may be a lifesaving procedure, the morphologic classification of pericarditis is important. From the standpoint of the mechanical alterations induced by the disease, three general types of pericarditis are recognized.

Acute Fibrinous Pericarditis. This is the name given to the type which does not lead to a significant amount of fluid in the pericardial sac. Any of the conditions mentioned above may cause this type of pericarditis. The characteristic symptom is pain, usually precordial but not infrequently in the region of the left shoulder or in the epigastrium. The pain is likely to be absent in the cases due to myocardial infarction or uremia. The cardinal clinical manifestation of this type of pericarditis is the friction rub, and the condition cannot be recognized with certainty in the absence of this physical sign. Electrocardiographic changes consisting of initial elevation of the S-T segment in the limb leads, followed by inversion of the T waves, are frequently encountered, and must be differentiated sharply from the somewhat similar changes commonly observed in patients with myocardial infarction. This type of pericarditis must be differentiated not only from myocardial infarction but also from acute pleurisy, with which it is frequently associated. The problems involved in such differentiation have been discussed in Chapter 3. The treatment of acute fibrinous pericarditis is that of the underlying cause. Of special importance is the recognition of the pyogenic type in the early stages and the administration of antibiotics. It is likewise important to administer

salicylates when rheumatic infection is suspected as the cause.

When a pericardial friction rub has been detected, it is important to make careful daily observations in order to discover a developing effusion.

Acute Serofibrinous Pericarditis. This condition is usually due to rheumatic fever, tuberculosis, or pyogenic infection, although it may result occasionally from the other etiologic agents which have been mentioned. As the effusion develops, the pain may diminish, but evidence of congestive failure associated with tachycardia and diminution in pulse pressure may appear. These signs, when associated with fever, venous distention, and a pulse of small volume which can be demonstrated to be paradoxical by the blood pressure apparatus, will usually indicate the diagnosis clearly, and the suspicion will become stronger when the cardiac impulse is found to be feeble or absent, and percussion demonstrates marked increase in size, not only to the left but also to the right. One should not be misled into an incorrect diagnosis of pneumonia by signs of consolidation of the left lower lobe, as these are not infrequent in the presence of massive pericardial effusions (Ewart's sign).

In an occasional patient the decision as to whether heart failure is the result of cardiac tamponade (i.e., interference with filling and consequent venous congestion) from fluid in the pericardium, or of myocardial failure, may present difficulties, and especially so when fever and pain are absent or minimal and no friction rub has been heard. The decision is a matter of great practical importance because digitalis has no beneficial effect in instances of tamponade, and may even be harmful, while lessening of the intrapericardial pressure by thoracentesis may be a lifesaving procedure. Feebleness of the cardiac pulsation, as viewed under the fluoroscope, may be present in either condition, but complete absence of visible pulsation points toward pericardial effusion. Pronounced alteration in the shape of the cardiac shadow on the roentgen film, with change from the sitting to the recumbent posture, also points to pericardial effusion.

PARADOXIC PULSE. Since the paradoxical pulse is a phenomenon of considerable importance in the diagnosis of the cardiac tamponade, a brief discussion of this phenomenon may be in order.

The term *pulsus paradoxus* refers to a condition in which there is a pronounced decline in blood pressure during inspiration, without changes in rate or rhythm. Normal subjects will frequently display a decrease of a few millimeters, but an alteration of more than 10 ml. is abnormal. The paradoxical pulse is seen occasionally in persons with peripheral circulatory failure and is the rule when there is obstruction to breathing or when dyspnea is pronounced from any cause. In the absence of such conditions the phenomenon indicates cardiac compression as the result either of thickening of the pericardium, or of fluid in the sac. The paradoxical pulse resembles *pulsus alternans*, certain instances of slow auricular fibrillation, and certain instances of second-degree heart block, in being more readily detected by measurement of the blood pressure during a series of cardiac cycles than by auscultation of the heart.

The differentiation of serofibrinous pericarditis from hydropericardium due to heart failure, or from serous effusion due to myxedema, depends on the total clinical picture and on the character of the fluid rather than on the cardiac findings alone.

The treatment of pericardial effusion consists first of all of the management of the underlying condition; penicillin, streptomycin, and salicylates are indicated in the pyogenic, tuberculous, and rheumatic types, respectively. When a significant degree of tamponade exists, as shown by evidences of congestive failure and diminished pulse pressure, striking benefit may follow paracentesis, with reduction of intrapericardial pressure. Therefore, patients with pericardial effusion should be followed with extreme care, the blood pressure being measured at hourly intervals. Either a progressive decline in blood pressure or a steady increase in dyspnea indicates that the degree of interference with filling is beginning to threaten life, and that paracentesis should be instituted immediately. Of the several methods of approach to the pericardium, the authors prefer the one just lateral to the apex.

When pericardial effusion is of obscure cause and long duration, exploration may be justifiable for the purpose of determining etiology and instituting specific therapy.

Chronic Adhesive Pericarditis. In many instances, adhesions between the two layers of the

pericardium, or between the parietal pericardium and the surrounding structures, are encountered at autopsy as incidental findings. Such asymptomatic instances are of no clinical importance. When important mechanical results occur from adhesive pericarditis, two different pictures may be encountered—the constrictive and the adhesive mediastinopericardial types, respectively.

CONSTRICITIVE PERICARDITIS. This is the disorder which results when the healing of acute fibrinous or serofibrinous pericarditis results in obliteration of the cavity of the sac, with the formation of granulation tissue which gradually contracts, forming a firm scar encasing the heart and interfering with filling. The condition is usually the result of tuberculous, staphylococcal, or pneumococcal infection, but less commonly other organisms may produce it. The clinical picture is characterized by dyspnea on exertion which, however, is relatively slight at rest, while orthopnea may be entirely absent; pronounced enlargement of the liver; distention of the cervical veins; ascites; and peripheral edema. The heart is usually normal in size or only slightly enlarged; occasionally, a moderately enlarged heart is present. A paradoxical pulse is frequently encountered. Both by palpation and by x-ray, marked diminution in cardiac pulsation is noted. A very important finding is the presence of calcification of the pericardium, visible by x-ray in about one-half the cases. The spleen is sometimes palpable, and, in the absence of evidence of bacterial endocarditis, splenomegaly in a patient with congestive heart failure should arouse suspicion of constrictive pericarditis. The electrocardiogram frequently displays low voltage and flattening or inversion of the T waves in all three limb leads. Auricular fibrillation is often present in this condition.

Inasmuch as the usual physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or entirely lacking, the presence of hepatic enlargement and intractable ascites may lead to a mistaken diagnosis of cirrhosis of the liver. This error should be avoided if the veins of the neck are inspected carefully in all patients with ascites and hepatomegaly. Given a clinical picture resembling cirrhosis but with the added feature of distended cervical veins, careful search for calcification of the pericardium by x-ray examination and detection of the electrocardiographic signs described above may disclose a

curable or remediable form of heart disease that might otherwise be overlooked.

In the treatment of constrictive pericarditis, digitalis is of no value, but diuretic drugs and sodium restriction are useful. The benefits derived from the delicate operation of cardiac decortication are often striking, and frequently the improvement, while slight at first, is progressive over a period of many months. The patient may be restored from a state of invalidism to something approaching normal activity. The operation should be performed as soon as the causative infection has become relatively inactive, as indicated by the temperature and sedimentation rate, in order that the scar tissue will not have become too dense. Since hypoproteinemia is common, the preoperative use of human serum albumin may be of value.

CHRONIC ADHESIVE MEDIASTINOPERICARDITIS. This condition is usually the result of rheumatic infection. Here the heart is bound to the surrounding structures by dense adhesions, and the primary difficulty is in emptying rather than in filling, as is the case with constrictive pericarditis. The condition is practically invariably associated with rheumatic lesions of the mitral valve, and often with lesions of the aortic and tricuspid valves. Among the findings which should lead to a suspicion of this condition are (1) striking cardiac enlargement; (2) pronounced periapical systolic retraction; (3) the presence of the Broadbent phenomenon, which consists of systolic retraction of the left lower interspaces, posteriorly; (4) the failure of the area of absolute cardiac dullness to change with deep inspiration; and (5) the presence of a pendulum motion on inspiration, both the left and the right sides of the chest tending to move to the right, presumably because of the extensive adhesions between the heart and chest wall. The pulse is usually paradoxical, but this may be difficult to demonstrate because auricular fibrillation frequently coexists. The type of heart failure tends to resemble that found in constrictive pericarditis, but dyspnea is likely to be more marked because the lungs are usually congested as the result of coexistent mitral stenosis. The intense congestion of the liver which frequently occurs may give rise to slight jaundice, and the coexistent venous distention may cause slight cyanosis. The bluish yellow tint of the skin in this condition, therefore, resembles that seen in patients with organic le-

sion of the tricuspid valve. Fluoroscopic examination will usually reveal diminished pulsations.

The diagnosis of chronic adhesive mediastinopericarditis is frequently very difficult, because most of the physical signs associated with this disorder may be either masked or produced by the associated valvular lesions. The treatment is essentially that of rheumatic heart disease with congestive failure. Favorable results have been reported in a few instances following removal of ribs in the precordial and left axillary regions, in order to allow the heart to pull against soft tissue rather than bone.

ENDOCARDITIS

Diseases of the endocardium present four different types of clinical problems. On the one hand, there are the types which produce little or no deformity of the valves, and which are part of a diffuse collagen disorder (Libman-Sacks disease, Chapter 38). At the other end of the spectrum there is the acute bacterial endocarditis occurring as part of an overwhelming septicemia, the clinical pattern being essentially that of the primary disease. The commoner varieties of acute endocarditis are discussed in the appropriate chapters dealing with the specific infections. Third, and most important, are those common forms of chronic endocarditis, due to rheumatic fever or syphilis, which produce mechanical deformities of the valves and eventually lead to congestive heart failure. These have been considered in the earlier portions of this chapter.

Finally, there is a rather unique disorder, subacute bacterial endocarditis, which, because of its frequency and importance, is considered in the following separate chapter.

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Natural History and Prognostic Aspects of Heart Disease

T. R. Harrison and William H. Resnik

Stages of Heart Disease

- Potential Cardiac Disease
 - Asymptomatic Cardiac Disease
 - Diminished Cardiac Reserve
 - Left-Sided Congestive Failure
 - Right-Sided Congestive Failure
- Evaluation of Congestive Heart Failure
- Aggravating Causes of Heart Disease
- Infection
 - Exertion
 - Cough

Tachycardia

- Obesity
- Pregnancy
- Dietary Deficiency
- Anemia
- Emotional Stress
- Pulmonary Infarction
- Intercurrent Disorders
- Complications of Cardiac Disease
- Causes and Mechanisms of Sudden Death
- Summary

A number of important prognostic problems have already been considered in the preceding chapter dealing with the various etiologic types of heart disease. The discussion to follow will, therefore, be concerned mainly with prognostic problems encountered in relation to congestive heart failure.

STAGES OF HEART DISEASE

It has been pointed out that in the case of those disorders characterized by myocardial anoxia as the fundamental functional disturbance, and by pain as the chief clinical manifestation, the progress is uncertain and unpredictable. However, in the types of heart disease which

tend to lead to congestive failure, the progression follows a more clearly defined pattern, and ordinarily proceeds through a number of stages.

1. Potential Cardiac Disease. This term describes the state of an individual who has no subjective or objective manifestations referable to the heart, but who has suffered, or is suffering, from some disorder which predisposes to heart disease. The classic examples are individuals who recently have had rheumatic fever and have made an apparently satisfactory recovery, and individuals with early hypertension or untreated syphilis.

2. Asymptomatic Cardiac Disease. This term refers to individuals who present objective evidence (such as enlargement or a diastolic murmur) of cardiac disease, but who are entirely free from symptoms, even when leading a vigorous, active life. In the case of rheumatic heart disease the asymptomatic stage is common, but it is rarely seen in persons with senile myocardial degeneration, in whom subjective manifestations frequently antedate objective evidence of cardiac disease.

3. Diminished Cardiac Reserve. This term applies to individuals who are entirely free from symptoms at rest but who, as the result of disease of the heart, suffer from dyspnea upon the performance of an effort which would not ordinarily produce dyspnea in an individual of similar age, sex, race, weight, and habits of living.

4. Left-Sided Congestive Failure. This term designates the state of a patient with passive congestion of the lungs, and is characterized by increasing exertional dyspnea and especially by dyspnea at rest (usually in the form of orthopnea or of paroxysmal seizures), rales at the lung bases, decline in vital capacity, and prolongation of the pulmonary circulation time. The restriction of the term *congestive heart failure* to persons with venous engorgement and edema (right-sided heart failure) is entirely unjustifiable. Actually, left-sided heart failure frequently occurs in pure forms and may antedate right-sided failure by months or years. Another common error is the assumption that the absence of rales indicates that the lungs are not congested. Actually, rales are a sign of pulmonary edema, and a high degree of congestion, as indicated by decline in vital capacity and prolongation of circulation time, may exist in the absence of rales. *Dyspnea*

occurring in the resting state, when due to cardiac disease, is a clear indication of congestive heart failure even though evidence of systemic engorgement may be completely lacking.

In patients in whom the burden on the heart is thrown particularly on the left ventricle (those with hypertension, lesions of the aortic valve, and coronary artery disease), the initial manifestation of left-sided heart failure may occur dramatically in the form of paroxysmal nocturnal dyspnea. Several hours after falling asleep, the patient is awakened by severe dyspnea, and sits at the side of the bed, or beside an open window, usually leaning forward. There is a persistent, annoying cough, at first nonproductive. Within the course of 15 to 30 minutes the dyspnea becomes progressively worse; the cough becomes productive of a thin, frothy, faintly blood-tinged sputum; cyanosis becomes evident; and apprehension and distress are written on the countenance of the patient, who is all too aware of the desperate state into which he has suddenly been precipitated. On examination at this stage, numerous moist rales are audible at the lung bases, wheezing sounds are present throughout the chest, and superimposed on these findings are loud, bubbling rales that may obscure the other physical signs. The heart rate is moderately increased, usually the blood pressure is elevated over its previous level (unless the attack is due to an acute myocardial infarction), the skin is covered with sweat, and distinct cyanosis may be evident. As the result of energetic treatment, occasionally as the result of the spontaneous subsidence of the attack, the symptoms abate, and within a brief period the patient is comfortable and an onlooker would hardly suspect that this patient had but a short time ago been in the grip of a well-nigh fatal disorder.

Such attacks of acute pulmonary edema may be the first sign of congestive failure in a patient who previously has had no symptoms other than mild exertional dyspnea.

The initial acute attack may terminate fatally, but this is exceptional if vigorous therapy is applied immediately (see p. 1329). As a rule the patient has subsequent attacks which can be lessened in intensity and frequency by proper management.

Aside from such dramatic episodes of acute pulmonary edema, milder attacks of nocturnal dyspnea are common. These are often spoken of

as cardiac asthma because of the wheezing rales which are frequently present, and which may be so pronounced as to lead to an erroneous diagnosis of bronchial asthma. The milder attacks are the result of acute pulmonary congestion without much edema; in the severe attacks the congestion is of such high degree that well-marked edema is produced.

5. Right-Sided Congestive Failure. This term designates systemic congestion as the result of cardiac disease, and is manifested by venous distention, increased venous pressure, and enlargement of the liver, as well as a tendency toward edema formation. Since most types of cardiac disease are of such a nature as to put the primary strain on the left side of the heart, right-sided failure is, in most instances, the consequence of increased pressure in the pulmonary circuit as the result of left-sided failure; and it is, therefore, exceptional to observe failure of the right side of the heart without the manifestations of left-sided failure. However, the reverse is not true, and many patients have left-sided failure, as manifested by dyspnea at rest, without clinical evidence of failure of the right side of the heart.

The separation of these stages from each other is of practical importance, because prognosis and management differ in the different stages. The transition from one stage to the next may be gradual, but is often abrupt and induced by one of the aggravating factors which will be discussed later.

EVALUATION OF CONGESTIVE HEART FAILURE

The recognition of heart *disease* has already been considered and, aside from the disorders of the coronary circulation, is based primarily upon examination of the heart. The recognition of heart *failure* is, on the other hand, mainly dependent upon the examination of the patient as a whole, and especially upon the evaluation of dyspnea and edema. These problems have already been discussed in considerable detail (Chapters 9, 14, and 20), but some of the more important features will now be reemphasized:

1. In a young individual, heart failure will almost invariably be associated with outspoken evidence of cardiac disease ("organic" murmurs, enlargement, etc.).
2. In an elderly individual, the evidence of

cardiac disease is often equivocal, and the decision may be difficult. The following considerations, while not applicable in every instance, will be useful as a general guide:

- a. If outspoken cardiac enlargement exists, it is highly probable that coexistent dyspnea and/or edema are of cardiac origin.
- b. If the heart is within normal limits in size, and if constrictive pericarditis can be excluded, it is improbable that dyspnea and edema are of cardiac origin.
- c. If the heart is intermediate in size—i.e., if enlargement is questionable or slight, the decision as to whether dyspnea and/or edema are of cardiac origin may be difficult. The presence of a normal or rapid arm-to-tongue circulation time practically excludes cardiac failure due to the common causes, but does not exclude cardiac failure of the high-output type due to thyrotoxicosis, thiamine deficiency, etc. A diminished vital capacity, which may be due to almost any type of extensive pulmonary disease as well as to congestion, does not constitute proof that dyspnea is of cardiac origin. When edema is increasing or is stationary, a normal level of venous pressure makes it unlikely that cardiac failure is the cause. Venous pressure elevation which is generalized (i.e., present both in arms and in legs) indicates that edema is of cardiac origin, provided renal disease and excessive sodium intake can be excluded as possible causes. Normal levels of venous pressure do not exclude heart failure (left-sided) as the cause of dyspnea.

- d. In doubtful instances, the demonstration that digitalization causes rise in vital capacity or reduction in pulmonary circulation time indicates that dyspnea is of cardiac origin.

- e. Enlargement of the liver can be considered as due to cardiac failure only when there is co-existent increase in venous pressure.

- f. The presence of gallop rhythm or pulsus alternans indicates that heart failure is imminent, if not already present.

Aside from those cardinal manifestations of heart failure such as dyspnea and edema, which have been discussed in detail, certain other manifestations are frequently important.

Fever of slight degree is often present and is probably related to disturbed dissipation of heat. A rise in body temperature of more than 1° C. (2° F.) should lead to the suspicion of *thrombosis*,

infarction (pulmonary or myocardial), or *infection*. The most common infections are those of the respiratory tract, but in persons with rheumatic heart disease both recrudescence of the rheumatic process and bacterial endocarditis are common causes of fever. In the absence of intravenous therapy the presence of *chills* nearly always indicates a blood stream infection. Excessive sweating may be due to infarction, infection, severe forward failure, or thyrotoxicosis.

Cough is most commonly the result of pulmonary congestion or edema, but may result from pulmonary infarction or infection. Pressure on the recurrent laryngeal nerve by an enlarged left auricle, or a saccular aneurysm, is a less common cause. *Hemoptysis* in a patient with congestive failure is usually the result of infarction or edema of the lungs. In patients with asymptomatic mitral stenosis, hemoptysis is common and is to be ascribed to bronchial varicosities as the result of dilated collateral channels between the pulmonary and bronchial veins.

Nausea and vomiting may be so striking as to suggest a primary disorder of the gastrointestinal tract. Congestion of abdominal viscera is frequently responsible, but drugs such as digitalis and opiates are an even more common cause. Persistent nausea and vomiting are frequently due to renal insufficiency which is not rarely precipitated by heart failure. Painless myocardial infarction is occasionally responsible for vomiting.

Palpitation is relatively rare in persons with congestive failure, and its presence in a patient without premature beats or ectopic tachycardia should lead to the suspicion of a coexistent emotional disturbance.

In evaluating the future of a patient with congestive failure, the size of the heart and the stage of the process are usually more important than the nature of the underlying process. Above all else, *the response to treatment is the best guide to prognosis in a patient with congestive failure*. The individual who responds quickly to a few days of rest, plus digitalis, will usually live for at least several years, and, not too rarely, for longer than a decade, depending on the natural history of the specific type of heart disease. On the other hand, the patient who, despite these measures, plus drastic sodium restriction and diuretic drugs, improves very slowly or not at all, will rarely sur-

vive longer than a few months. An intermediate response indicates an intermediate prognosis.

The onset of auricular fibrillation will usually tend to cause congestive failure, but in two undigitalized patients with congestive failure—one with and one without auricular fibrillation—the prognosis is better in the subject with the arrhythmia because a better response to therapy will usually be obtained. When congestive failure appears in a well-digitalized patient, the prognosis is not materially altered by the presence of the arrhythmia, except for the greater likelihood of embolism.

Electrocardiographic tracings, while often of diagnostic aid, are of little prognostic value in patients with chronic congestive failure. Unfortunately, the widespread tendency to attempt to predict the patient's future—on the basis of such records—constitutes an abuse of a valuable tool, often leads to unnecessary restrictions and psychic invalidism, and cannot be too strongly deprecated.

AGGRAVATING CAUSES OF HEART DISEASE

Patients suffering from those types of heart disease which are likely to lead to congestive failure commonly pass through the several stages which have been mentioned. The transition from one stage to another may be gradual but is frequently abrupt, and in many instances is precipitated by certain disorders which are of considerable practical importance, since they are often amenable to therapy.

1. Infection. Almost any type of febrile illness is likely to aggravate cardiac disease, and to bring on the next most advanced stage. Because of their frequency, infections of the respiratory tract assume first rank.

2. Exertion. This factor is of especial significance in individuals who perform manual labor, and, even in sedentary individuals, is second in importance only to the various infections.

3. Cough. This is a common symptom, and may be brought about by congestion of the lungs, or by various complicating disorders. It is a factor of importance in many patients because of the severity of the effort associated with coughing, and because of the effect on circulatory dynamics.

4. Tachycardia. The untoward effects have been discussed in a previous section. Any condi-

tion, whether it be infection, exertion, emotional upset, or an abnormal rhythm, which produces prolonged and sustained tachycardia, may aggravate the cardiac status. The ectopic tachycardias are particularly important because of the very rapid rate with which they are frequently associated, and because the most common of them—auricular fibrillation—tends to produce not only tachycardia but also a pulse deficit. When a heart beat fails to produce an effective peripheral pulse, the energy expended in opening the aortic valves is wasted. Many patients with chronic cardiac disease progress favorably until the onset of auricular fibrillation precipitates congestive phenomena.

5. Obesity. This condition increases the work somewhat at rest, and even more so upon effort. It is one of the commonest aggravating factors of cardiac disease, and is readily amenable to therapy in coöperative patients.

6. Pregnancy. During the latter months of pregnancy the output and work of the heart are considerably increased, and, in persons predisposed, cardiac failure may occur either before or after delivery. Unlike muscular effort, pregnancy imposes a strain which is continuous rather than intermittent.

7. Dietary Deficiency. Under exceptional conditions, pronounced deficit of thiamine in the diet may be a primary cause of cardiac disease. This is a rare occurrence. However, cardiac disease due to any of the primary causes may, in its later stages, lead to anorexia and secondary dietary deficiency, which further aggravates the underlying state.

8. Anemia. When of sufficient severity and duration, anemia may likewise be a primary cause of cardiac disease; but here, as in the case of dietary deficiency, such a sequence of events is rare. On the other hand, moderately severe anemia tends to produce compensatory increase in cardiac output, and, when present in patients with any of the commoner primary causes of cardiac disease, may be an additional factor of some importance. In this regard it should be remembered that too hasty treatment of the anemia by transfusion of large amounts of blood may precipitate congestive failure.

9. Emotional Stress. The physiologic effects of emotion on the heart are as yet poorly understood. In normal individuals emotion has been shown to increase the output of the heart per

unit of time, and there may likewise be an elevation of blood pressure associated with an acceleration of the rate of the heart. It is probable, but unproved, that emotional stress tends to cause coronary constriction. Clinical experience indicates that anxiety, worry, and stress from any cause are potent factors in the aggravation of cardiac disease.

10. Pulmonary Infarction. This is a common and important aggravating factor but, since it is usually a complication of congestive failure, it will be considered later.

11. Intercurrent Disorders. In many instances patients with chronic cardiac disease progress favorably, with no exacerbation of symptoms until some other disorder supervenes. Aside from the conditions already mentioned, such as obesity and infections, prostatic enlargement and neoplastic diseases are among the most common of such intercurrent disorders which aggravate preexisting cardiac disease.

These aggravating factors frequently cause an abrupt intensification of the symptoms. Following the removal of such aggravating factors, the patient usually improves, but often does not return to his former state of health.

Quite aside from the importance of these various factors in relation to congestive failure, they are also important in regard to aggravation of angina pectoris, and, in many instances, in regard to precipitation of myocardial infarction in persons with disease of the coronary arteries. Hence one of the most significant of all principles of therapy in an individual with chronic cardiac disease is proper attention to prevention of these aggravating factors, and to their management when they occur.

COMPLICATIONS OF CARDIAC DISEASE

The complications which occur in persons with chronic heart disease fall into two general groups. The first includes disorders directly referable to the heart, such as recrudescence of rheumatic infection, bacterial endocarditis, congestive failure, myocardial infarction, and the onset of various disturbances of rate and rhythm. These disorders have already been discussed in previous chapters.

Of the various extracardiac complications which commonly appear in persons with chronic

heart disease, embolism, infarction, uremia, and pneumonia assume first rank. The various hypertensive disorders which are common causes of cardiac disease are also frequent causes of uremia. The congested lungs are particularly susceptible to infection, and hence pneumonia is common. Since, however, the problems of uremia and pneumonia, when developing in persons with cardiac disease, do not differ in essential principles from those which occur under other conditions, these conditions need not be discussed further here.

Embolism and infarction, which are perhaps the most common of all the serious complications of chronic heart disease, may be divided into three general groups, according to whether these disorders involve the pulmonary, the coronary, or the systemic circulation. Pulmonary embolism commonly results from phlebothrombosis of the deep vessels of the calves, but may be secondary to thrombosis in the dilated right auricle. Pulmonary embolism, with consequent infarction, is perhaps the most serious and common complication occurring in patients with congestive failure, and should be suspected not only when the classic manifestations of pleural pain, hemoptysis, and fever occur, but also in any patient with congestive failure who takes an unexplained turn for the worse or fails to show a satisfactory response to management. When liver function is already impaired by congestion and the amount of blood extravasated into the infarcted area is large, jaundice may result.

The problems of thrombosis and infarction in relation to the coronary circulation have been considered already.

Systemic embolism, with consequent infarction, in the brain, kidneys, spleen, intestinal tract, or extremities is commonly observed as the result of: (1) auricular thrombi in patients with mitral stenosis or auricular fibrillation; (2) valvular thrombi in individuals with bacterial endocarditis; and (3) ventricular thrombi following myocardial infarction, or in the rarer condition of subendocardial fibrosis, which has been discussed already. Systemic embolism is a frequent complication in patients with cardiac disease, but is less common than pulmonary embolism.

In view of the rapid progress being made in the use of anticoagulant drugs, the problems of thrombosis, embolism, and infarction can no longer be considered as being of only academic

interest, but are now of great practical significance. Their prevention and management will be discussed in Chapter 242.

CAUSES AND MECHANISMS OF SUDDEN DEATH

Aside from trauma, which is outside the scope of this volume, diseases of the cardiovascular system are the most common causes of sudden death. There are degrees of suddenness.

Instantaneous death is almost invariably the result of ventricular fibrillation or standstill, and, when it occurs in an apparently healthy individual, is nearly always due to a disturbance of the coronary circulation.

Death occurring within *a few minutes* of the onset of symptoms is usually due to massive pulmonary embolism; less often, to rupture of the heart or aorta.

Death occurring within *several hours* after the beginning of symptoms is, likewise, usually referable to internal hemorrhage. When abrupt loss of consciousness is the initial manifestation, intracerebral bleeding is the likely cause; when severe headache precedes more gradual loss of consciousness, subarachnoid hemorrhage should be suspected. Progressive decline in blood pressure, associated with increasing distention of the cervical veins and terminating in death within a few hours, suggests seepage of blood into the pericardium; while a similar sequence, with collapse of the neck veins, points toward hemorrhage within the abdominal cavity.

SUMMARY

The clinical course of cardiac disease is notoriously uncertain, and dogmatic opinions concerning the future frequently prove to be erroneous. In general, however, a fair estimate as to the likely course of events can be arrived at by a judicious assessment of the following factors:

1. The nature of the underlying disease process, including the decision as to whether it is curable or incurable, progressive or stationary.
2. The stage of the cardiac disorder, whether asymptomatic or not; and, if symptomatic, whether symptoms appear only upon effort or in the resting stage also.
3. The significance of the various aggravating factors, including their response to attempts to prevent or combat them.
4. The general state of health as determined

by thorough examination of the entire body, in order that various associated disorders may be detected.

5. The likelihood of complications.
6. The patient's emotional state and his willingness to coöperate.
7. Perhaps most important of all, observation of the response of an individual to treatment.

Due consideration of these factors will usually allow for a reasonably accurate prognosis in the majority of patients.

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Therapeutic Aspects of Heart Disease

T. R. Harrison and William H. Resnik

Principles of Therapy in Patients with Chronic Cardiac Disease	
Psychologic Management	
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A number of problems in treatment, including management of the arrhythmias, of angina pectoris, of myocardial infarction, and of the specific etiologic factors causing heart disease, have already been considered. The discussion to follow will, therefore, center about two general matters—namely, principles of management of patients with chronic cardiac disease, and treatment of diminished reserve and congestive heart failure.

PRINCIPLES OF THERAPY IN PATIENTS WITH CHRONIC CARDIAC DISEASE

Psychologic Management. This is of the utmost importance. The number of man-hours of suffering caused by anxiety concerning the heart is perhaps as great as the number caused by structural disease of the heart. When the anxiety state exists in the absence of structural disease, thorough examination, coupled with tactful and time-consuming reassurance, plus the use of specialized psychiatric therapy when needed, will usually yield strikingly gratifying results. The problem becomes more difficult when, as is so often the case, the anxiety state occurs in a patient presenting clear evidence of a structural cardiac disorder. Here again, psychic invalidism can usually be avoided if the physician will refrain from frightening the patient, and will take sufficient time to discuss the problem and to explain the significance, or in many cases the

insignificance, of various findings. It should be realized that the source of the greatest anxiety to patients is usually either the sensation of palpitation or the knowledge of the presence of objective findings with which they are unfamiliar, such as murmurs, enlargement, and arrhythmias; while patients are less likely to be concerned about the important subjective manifestations such as pain and dyspnea. The physician, realizing that it is only the latter which are apt to have serious prognostic import, can conscientiously and truthfully minimize to the patient the significance of palpitation and of the objective findings which inspire fright. He is justified in pointing out that, so long as a person is free of the important subjective manifestations, the presence of these objective findings does not constitute a serious hazard, and need not interfere with an essentially normal life.

It is especially important that unnecessary restrictions not be imposed on patients, for there is no evidence that physical activity which does not induce pain or dyspnea is harmful to the person with chronic cardiac disease. On the other hand, there is strong evidence that anxiety, worry, and emotional stress not only make the patient unhappy but may actually tend to aggravate the structural disorder; and hence one of the prime principles in management is to attempt to remove all sources of psychic stress, whether these be related to anxiety about the heart, or to environmental factors concerning family, business, etc. In the patient with cardiac as with most other chronic diseases, there are many situations in which the physician himself becomes the treatment, and in which happiness depends mainly, and health partly, on the physician's wisdom, optimism, and tact, and perhaps above all else on his willingness to devote as much time as may be required to listening to the patient's troubles, and to alleviating his anxiety.

Treatment of Underlying Disease Process. Throughout the preceding pages emphasis has been placed on the fact that certain causes of

cardiac disease, unfortunately not the most common ones, are amenable to cure. Hence one of the primary therapeutic principles is to search constantly for such causes. It should be reëmphasized that in the majority of instances these curable conditions are those which are associated with the clinical manifestations of high-output failure (p. 159)—i.e., the signs of congestive failure occurring in association with the signs of the overactive heart. When, as in the great majority of patients with congestive failure, such manifestations are absent, one should think first of all of constrictive pericarditis and of myxedema as possible causes. In an individual with congenital heart disease the first thoughts should concern patent ductus arteriosus, coarctation of the aorta, and the tetralogy of Fallot, because these conditions, likewise, are completely or partially curable. The preliminary investigations with cortisone (compound E) and with ACTH (the adrenocorticotropic hormone of the anterior pituitary) have yielded very favorable results in persons with acute rheumatic carditis, and have suggested that this common and fearsome disorder may eventually become amenable to cure or control.

Prevention and Management of Aggravating Factors. As has been pointed out, the clinical state of the patients with chronic cardiac disease is not steadily downward but tends to remain stationary or to improve slightly for long periods of time, with sudden aggravation as the result of various secondary factors. These have already been discussed in some detail, but it should be emphasized at this point that the prevention and management of these factors is, in many patients, the most important of all therapeutic considerations.

First consideration should be given to prevention of respiratory infections, and patients with chronic cardiac disease should be advised to isolate themselves from members of the family with acute respiratory infections, and to avoid public gathering places, such as the theater and the church, during the winter months. However, periods of isolation should be brief in order to prevent psychic invalidism. When economic conditions permit, a sojourn of several weeks in a warm climate during the winter is advisable.

Coughing is harmful to the patient with congestive heart failure because: (1) it constitutes muscular effort; (2) it raises intrathoracic pres-

sure and alters circulatory dynamics; and (3) it interferes with sleep. Hence cough should be controlled by the use of codeine, dihydrocodeine none bitartrate ("Hycodan"), and allied drugs.

Ectopic tachycardias, especially auricular fibrillation, are common and, when prolonged, may cause serious aggravation of the cardiac status. Hence the patient should be instructed to seek medical advice immediately, if he notes attacks of palpitation associated with tachycardia.

Thorough general physical examinations at intervals of six months to a year are indicated, in order that the progress of the disease may be evaluated and the intercurrent disorders may be detected and corrected at an early stage. Such examinations also furnish an opportunity for reassurance and for combating a tendency toward introspection.

Since pregnancy represents a common aggravating factor which calls for difficult decisions, it may be discussed in some detail. Pregnancy throws an added burden on the heart for several reasons: (1) The dilated vessels of the uterus have an effect similar to that of an arteriovenous fistula in increasing venous return and inflow load. (2) The retention of sodium and water, which is characteristic of the pregnant state, tends to cause hypervolemia and to cause further increase in inflow load. (3) The increase in cardiac work persists throughout the 24-hour period, and in this way differs from muscular exercise which places an intermittent strain on the heart.

The chief practical problems presented by pregnancy in relation to cardiac disease are as follows: (1) Should the woman with cardiac disease marry? (2) Should a married woman with cardiac disease be advised against pregnancy? (3) What should be done about a woman already pregnant, who presents evidence of cardiac disease?

When a patient, whether male or female, who presents clear evidence of structural disease of the heart desires to marry, the physician's responsibility is to explain to both parties the problems involved. As a general rule, to which there will obviously be exceptions, it may be stated that persons presenting evidence of congestive failure (i.e., of symptoms at rest) should be advised against marriage, and that the same advice is usually applicable to individuals with

marked limitation of cardiac reserve (i.e., with dyspnea or pain on undertaking slight muscular activity). Such instances rarely constitute a serious problem, as the patients themselves will usually make the decision against marriage. The difficulty comes in individuals with asymptomatic cardiac disease (usually rheumatic or congenital). Here, the physician should explain the facts and the probable diagnosis to both parties, withholding from the patient only such information as is likely to create an anxiety state, but explaining the situation with complete frankness to the prospective spouse. The decision then has to be made by the individuals concerned.

The problem of the woman who, having clear evidence of structural cardiac disease, desires to undergo pregnancy must be viewed in the light of the economic and environmental conditions, the nature of the underlying disease, and, above all else, the functional state of the circulation. When economic circumstances are such that household work and responsibilities can largely be removed from the patient, the likelihood of her tolerating pregnancy without deleterious effect on the heart is decidedly greater. Women with hypertension, and with the cyanotic types of congenital cardiac disease, are more likely to be adversely affected by pregnancy than are women with rheumatic and the noncyanotic types of congenital heart disease. When, however, there has been a recent episode of rheumatic activity, pregnancy is contraindicated. A woman who has had congestive failure should not become pregnant. A patient with asymptomatic cardiac disease of the rheumatic or the acyanotic congenital type will usually tolerate pregnancy without serious difficulty. In the patient with rheumatic heart disease and diminished reserve, but no symptoms at rest, the decision is more difficult; but, in general, pregnancy should be undertaken by such women only when the desire for offspring is very strong, and when economic and environmental circumstances are favorable.

The problem is somewhat different in a patient who, having structural cardiac disease, is already pregnant. Here, the presence of mild hypertension constitutes an indication for early interruption of the pregnancy only when there is evidence that previous pregnancies have caused aggravation of the hypertensive state. The development of evidences of congestive failure during the first trimester constitutes a clear indica-

tion for the interruption of pregnancy, regardless of the underlying types of cardiac disease. However, since therapeutic abortion is a more hazardous procedure when performed after the first three months of pregnancy, congestive failure which develops during the last three months or even during the second trimester will usually be best managed conservatively, the patient being treated by the usual methods employed for heart failure, and the pregnancy interrupted only in case the situation becomes alarming. In such a patient the decision as to route of delivery should be made by the obstetrician, but, in general, it would appear that Cesarean section is undesirable and that the induction of labor during the eighth month, at a time when the fetus is still small and yet mature enough so that the likelihood of survival is great, is the procedure of choice. After delivery, precautions against the development of thromboembolic disease should be employed.

When cardiac disease is asymptomatic and remains so throughout pregnancy, no special treatment directed toward the heart is indicated other than repeated examinations and careful evaluation of the cardiac status. The pregnant patient with diminished cardiac reserve should, in general, be managed conservatively, subject to the conditions already mentioned, in case congestive failure supervenes.

Physical Activity. A sharp distinction must be made between those patients presenting evidence of recent myocardial injury, and those in whom no such evidence exists. In general, patients with subacute rheumatic carditis should be kept at complete rest, and allowed out of bed only for purposes of bowel movement. Following myocardial infarction, temporary complete rest is indicated, according to the principles already discussed, and with the realization that prolonged bed rest carries serious hazards.

In the absence of evidence of recent or progressive myocardial injury, the problem of physical activity is different. It is here that overzealous insistence by the physician on unnecessary restrictions so often creates a state of anxiety and psychic invalidism which is more disabling to the patient than the underlying structural disease. In the absence of acute or recent myocardial injury, there is no evidence that physical activity which can be tolerated by the patient without symptoms is harmful. Hence the rule of living for

such patients is a simple one, and consists of living below the symptom threshold. In other words, *the patient should not do anything which induces pain of the anginal type, or dyspnea, but may carry on physical exertion which does not cause these symptoms.* This principle of management is probably the single most important feature of the treatment of chronic cardiac disease, for adherence to it will automatically adjust the patient's activities to things which can be done without overburdening the heart, and at the same time allow all the leeway which the cardiac condition permits. Moreover, it will tend to prevent the development of that anxiety state which is so commonly the most important feature of the disease in so far as the happiness of the patient and his family is concerned. For the appropriate patient the knowledge that he is permitted to participate in a game of golf, or some other moderate form of physical exertion, has a greater psychotherapeutic value than verbal assurances that have no concrete meaning to him.

Diet. The problem of diet has already been discussed in some detail in relation to the management of arteriosclerotic heart disease. The same general principles apply to the earlier—i.e., asymptomatic—stages of all types of cardiac disease. Here, the primary dietary problem is the prevention and control of obesity. The obese patient with any type of chronic cardiac disease should be subjected to weight reduction, which should usually be carried out slowly, and at a rate of about 5 pounds per month. During starvation the blood cholesterol rises before it declines, and it is theoretically possible that rapid reduction of weight may favor atherosclerosis.

Restriction of cholesterol and of fat, which is probably important in the prevention of coronary disease, is of little significance in regard to the common types of cardiac disease in young persons, but is probably of preventive value in subjects with hypertension, which predisposes to coronary disease. Cholesterol restriction causes a decline in blood cholesterol in some patients but not in others. Adequate protein intake is necessary to avoid tissue protein depletion in patients who are forming plasma protein rapidly, as the blood volume increases during congestive failure.

In the earlier stages of cardiac disease, vitamin therapy has no place, provided the patient is taking a normal and adequate diet. Individuals with prolonged congestive failure, or with pro-

longed anorexia from any cause, should have vitamin supplements with particular emphasis on thiamine.

In the advanced stages of cardiac disease when reserve is diminished, and especially when congestive failure is present, restriction of sodium is indicated, as will be considered later. The only indication for such dietary management in the early and asymptomatic stages of cardiac disease is the presence of hypertension in a relatively young patient. A fair percentage of such individuals will display dramatic reduction in blood pressure when sufficiently drastic sodium restriction is instituted. On the other hand, many patients with hypertension exhibit no favorable response to such a dietary regime, and the reasons for the success in some individuals and the failure in others are unknown at present.

MANAGEMENT OF DIMINISHED CARDIAC RESERVE AND OF CONGESTIVE FAILURE

The general principles which have just been discussed are of prime importance, and especially the considerations which apply to the recognition of the curable types of heart disease, the prevention and management of the various aggravating factors, and the rule as regards living below the threshold of symptoms. Since it is in respect to the latter principle that much confusion exists, this problem will be discussed first.

Use and Abuse of Rest as a Therapeutic Measure. The idea that the best way to reduce the work of the heart is to keep an individual in bed in the recumbent position is based on a mistaken comprehension of circulatory physiology. The work of the heart per unit of time depends almost entirely on the peripheral resistance and the cardiac output. The blood pressure in young subjects is somewhat lower in the recumbent than in the sitting position, but in elderly patients who often have a tendency toward postural hypotension, the reverse is frequently true. The cardiac output is somewhat greater in the recumbent position. The result is that the work of the heart in the young subject tends to be about the same in the two positions, and, in the elderly subject, tends to be somewhat less in the sitting posture.

There is another and even more important factor. In the case of the individual with congested lungs, orthopnea is usually present, and the

breathing is more labored in the recumbent than in the sitting position. Labored breathing increases the oxygen consumption of the body, and this function may be elevated by more than 50 per cent when dyspnea is severe. Hence the first consideration in the management of the patient with congestive failure is that of placing him in a position in which dyspnea and the consequent metabolic demand on the heart are minimal. In most patients the semirecumbent position in bed meets these requirements, but when dyspnea is pronounced the sitting position is preferable, and when dyspnea is very pronounced sitting in a chair is often better than sitting in a bed. The upright posture favors edema formation in the dependent portions of the body but tends to diminish pulmonary edema, a far more serious condition than peripheral edema. Hence, when the physician is forced to choose between increased peripheral edema, with diminished dyspnea as the result of the sitting posture, or diminished peripheral edema, with increased dyspnea as the result of the recumbent posture, he should choose the former.

The bedpan has been termed, not without some justification, an "invention of the devil." It is doubtful whether the energy expended in achieving a bowel movement on a bedpan is less than that required to get out of bed and walk to a near-by commode or toilet. Hence, unless the patient is incapacitated by severe dyspnea or weakness, he may be permitted to walk to a commode or toilet, if necessary with the assistance of an attendant. This permission may be granted to persons suffering from myocardial infarction, provided the stage of shock has disappeared. Mild laxatives, such as mineral oil or cascara, may be administered to avoid straining at stool.

The available evidence, while not conclusive, suggests that inactivity of the leg muscles favors the development of thrombosis in the deep veins of the calves. Consequently, the patient with congestive failure should be encouraged to walk slowly a few steps several times a day, unless the dyspnea is very severe. All patients confined to bed, whether due to myocardial infarction or congestive failure, should be instructed to flex the feet on the legs a number of times each day. If the condition is such that even this mild exercise is impossible, passive movements and massage of the legs are desirable. Elastic bandages may be

valuable in tending to limit venous stasis. The available evidence suggests that the anticoagulant drugs are effective in lowering appreciably the incidence of phlebothrombosis and pulmonary embolism in patients with congestive failure. Experience with this type of therapy is not yet sufficiently extensive to warrant specific rules regarding its use; anticoagulant drugs will probably be most useful in patients with myocardial failure so severe that strict bed rest for the patient is obligatory.

Pneumonia is one of the commonest complications of congestive heart failure. Since the advent of antibiotic drugs this hazard has been reduced. It is probable that recumbency for a number of days favors the development of pneumonia, and this fact constitutes another reason for keeping the patient with congestive failure out of bed during part of each day. Pneumonia frequently complicates pulmonary infarction.

The great advantages of the recumbent position are in lessening fatigue and in combating peripheral edema and the subsequent rapid resorption of fluid during the night, with the danger of inducing paroxysmal nocturnal dyspnea. Hence, there is some advantage for the patient in lying flat in bed for several hours a day, preferably in the late afternoon or early evening. This daily rest should be carried out indefinitely, so long as myocardial function is impaired to such a degree that the activities of the day in the upright position result in the development of more than a slight amount of edema of the lower extremities. How rigorously the rule of lying flat in bed for several hours a day will be enforced must depend on individual circumstances. Essentially the same purpose is accomplished by administration of mercurial diuretics. Whether the one or the other method is used will depend on the severity of the myocardial failure and the consequent tendency for edema to develop, the economic circumstances, and the preferences of the patient.

The time is past when it was considered desirable to confine the patient with congestive failure to an arbitrary regime of strict bed rest for a given number of weeks. There is no magic virtue and there is almost certainly a great deal of potential harm in "six weeks of strict bed rest." The duration and kind of rest must be planned according to the individual problems of each patient.

Diet and Fluids. The importance of reduction in weight, with restriction of total calories, and of the use of a diet low in cholesterol in suitable cases, has been discussed, as has the desirability of ensuring an adequate vitamin intake (especially thiamine) in all patients with chronic cardiac disease and long-standing anorexia. Studies of the past few years have indicated clearly that the kidneys of patients with congestive failure do not excrete sodium normally. Concerning the exact renal mechanism responsible for this, there is a difference of opinion, but the fact remains that diminished excretion of sodium is a factor of fundamental importance in the production of cardiac and other generalized edema. Hence, when the output of this element is defective, restriction of intake becomes a matter of prime importance.

All patients with diminished cardiac reserve, or with congestive failure, should be placed on a low-sodium diet, the extent of the sodium restriction depending on the severity of the cardiac failure. With the elimination of salted foods; the use of sodium-free milk, bread, and butter; and the avoidance of canned vegetables and prepared condiments, diets containing not more than 200 to 400 mg. of sodium per day can be administered. At the same time it is important to be certain that the water ingested (especially if it is water that has been softened) is poor in sodium, and that drugs containing sodium are avoided. It is possible that further experience with the ion-exchange resins may make it possible to administer almost unrestricted diets to these patients with comfort and safety.

When the patient with congestive failure is first seen, anorexia may be so severe as to preclude a reasonably well-balanced diet. Under these circumstances sodium-free milk ("Lanolac") or fruit juices alone, containing only minute quantities of sodium, are preferable to the traditional Karell diet (800 ml. of milk per day, containing about 400 mg. of sodium) for the first two or three days. At the end of this time, and as the result of this regime and other therapeutic measures simultaneously instituted, it is usually possible to administer a balanced diet containing not more than 200 to 400 mg. of sodium (equivalent to about 0.5 to 1 Gm. of sodium chloride). When compensation is fully restored or when the maximum therapeutic effect has been achieved, some of the dietary restrictions may be lifted.

However, it is preferable to insist that the patient remain permanently on a diet containing not more than 1000 mg. of sodium, and considerably less in the case of those individuals whose myocardial efficiency is markedly impaired. The less the sodium intake, the less the tendency for outspoken congestive failure to recur, and the less the need for mercurial diuretics. The definitive proof of the value of sodium restriction constitutes the most important therapeutic advance of the last decade in regard to the management of congestive failure. Such restriction is of especial value in preventing edema, but it is less rapidly effective than diuretic drugs in treating edema.

The opinion formerly held, that the defect in excretion chiefly responsible for edema concerned water rather than sodium, can no longer be regarded as valid; and, indeed, many patients can take water freely if sodium is restricted. On the other hand, impairment of excretion of water can be demonstrated readily in most patients with cardiac failure, and it is well to prescribe water according to the patient's thirst rather than to attempt to force it. There is no advantage in restricting water intake sufficiently to make the patient thirsty.

~~X~~ The importance of sodium restriction has been stressed. It should also be emphasized that such restriction, when prolonged, may lead to depletion of the sodium stores of the body, and a clinical state resembling that of Addison's disease. Furthermore, there is evidence that chloride restriction may also be important, and that sodium salts of other ions may actually have diuretic properties. It appears likely that much progress will be made in the general field in the near future, and that corresponding changes will need to be made in the concepts expressed in the preceding paragraphs.

Digitalis. Since this drug constitutes one of the cornerstones of management, it will be discussed in some detail.

CERTAIN MISCONCEPTIONS IN REGARD TO USE OF DIGITALIS. One of the most important of these misconceptions is the idea that the drug is valuable in the treatment of any type of tachycardia. Actually, there is no evidence that the drug has value in any type of tachycardia other than (1) the ectopic tachycardias of auricular origin, and (2) that minority of cases of sinus tachycardia in which congestive failure is present or imminent.

Another misconception is that the drug is con-

Digitalis
contraindicated in persons with hypertension because of its tendency to raise blood pressure, and in patients with aortic insufficiency because the slowing of the heart might lead to increased regurgitation. Actually, the drug causes a rise in blood pressure only when this function is already abnormally low as the result of acute heart failure, and frequently causes a slight to moderate decline in blood pressure when this function is elevated as the result of chronic congestive failure. Likewise, in persons with aortic insufficiency, the slowing of the rate is usually slight. Hence the indications in these conditions are the same as in other conditions—namely, the presence or imminence of congestive heart failure.

A third misconception—i.e., that the drug ordinarily abolishes the arrhythmia in persons with auricular fibrillation—has been commented upon already, and need not be discussed again.

The idea that digitalis is useless in rheumatic heart disease except when auricular fibrillation is present is likewise not valid. It is true that the most dramatic benefit occurs in patients with auricular fibrillation, because here the slowing of the rate and the increase in mechanical efficiency is greatest. It is also true that in patients with mitral stenosis and pulmonary congestion the drug may have little effect upon the dyspnea, because in such instances this phenomenon is the result of the congestion brought about by the mechanical narrowing of the valve, and digitalis cannot affect the stenotic valve. Similarly, it may bring little benefit to the exceptional patient with mitral and tricuspid stenosis, regular rhythm, and right-sided and left-sided heart failure. On the other hand, patients with right-sided heart failure as the result of hypertension in the pulmonary circuit secondary to mitral stenosis are often benefited; and patients with rheumatic aortic lesions are likewise benefited. Under such circumstances the drug is acting on the myocardium and producing the usual effect. Naturally it cannot be expected to have a beneficial action when the congestive phenomena are the direct results of a stenotic valve rather than of myocardial failure.

It has been stated that the drug is of no value in patients with failure of the high-output type. Some of the conditions associated with high-output failure are the result of processes which tend to reduce the oxygen tension in the tissues. Common examples are cor pulmonale with ar-

terial anoxia, severe anemia, and thyrotoxicosis. Under such circumstances the anoxic tendency affects the heart, likewise. Recent evidence concerning the fundamental chemical defects in the failing myocardium suggests that the metabolic dislocations caused by anoxia are different from those induced by the usual types of heart failure. Clinical evidence would suggest that digitalis has little, if any, effect in restoring the defective energetic mechanisms when these are the result of anoxia. Such a conception explains the ineffectiveness of the drug in persons with congestive failure associated with arterial anoxia, anemia, and thyrotoxicosis. The conception likewise explains the absence of beneficial effects in individuals with thiamine deficiency, which, although not associated with defective tissue oxygen tension, nevertheless leads to disordered tissue oxidation. Since these conditions are the classic causes of high-output failure, and since in them little or no benefit is observed following the administration of digitalis, the conclusion has been drawn that the drug is useless in all instances of high-output failure. However, such does not appear to be the case in the heart failure which follows the excessive intravenous administration of fluids to patients with preexisting heart disease. Likewise, the drug is frequently valuable in patients with cardiac failure complicating acute nephritis. Clinical observations make it probable that in at least some of these patients the failure is of the high-output type, although this point has not yet been demonstrated conclusively.

It has been suggested that, when the rhythm is regular, digitalis is of value only in persons with senile cardiac disease. It is true that, aside from instances of auricular fibrillation, it is in the senile heart with regular rhythm that one most frequently sees dramatically beneficial results. However, this is to be expected because this is the most common type of heart failure in which there is no irreducible mechanical load on the heart. Since the drug acts on the myocardium, one would expect it to be particularly effective when the circulatory defect is entirely the result of myocardial dysfunction. However, the dramatically beneficial results observed in children with heart failure due to such conditions as acute nephritis, or certain congenital lesions, point out clearly that the indications for digitalis are not limited to the senile heart and to auricular fibrillation.

Another misconception is that which holds that the drug is valuable in all types of cardiac failure, regardless of the cause. The classic exception to such an idea is constrictive pericarditis, in which digitalis has been demonstrated to exert harmful effects, because any slowing of the rate will reduce the output per minute when, as in this condition, the capacity of the stroke volume to increase is mechanically limited. Likewise, there appears to be clear evidence that the drug is useless in acute diphtheritic myocarditis. This disorder tends to produce the more serious types of ectopic rhythm, such as ventricular tachycardia, ventricular fibrillation, and the advanced degrees of heart block. All of these effects may be enhanced by digitalis. Even in the absence of such arrhythmias, the considerations which have been mentioned in relation to the lack of effectiveness of the drug when tissue oxidation is disturbed will tend to account for the ineffectiveness of digitalis in acute diphtheritic myocarditis, when one recalls the recent evidence which indicates that the diphtheria toxin exerts its baneful effect by interfering with the cytochrome system. Other types of acute myocarditis, of which rheumatic infection is the most common, are also relatively or completely resistant to the beneficial action of the drug.

~~X MODE OF ACTION.~~ The reduction of responsiveness of the junctional tissues to the barrage of impulses arriving from the fibrillating auricle, with consequent slowing of rate and increase in myocardial efficiency, explains the dramatically beneficial results in persons with ~~l~~ auricular fibrillation.

~~l~~ The benefit in individuals with regular rhythm, in whom the slowing is vagal in type and exerted through the sinoatrial node, but only slight in degree, has been the subject of considerable discussion. The available evidence appears to indicate that benefit in such patients over and beyond that which can be ascribed to the slight reduction in heart rate is due to two effects, the one cardiac and the other peripheral. The cardiac effect is that of a strengthening of the myocardium, with augmented mechanical efficiency and more nearly complete systolic emptying. Therefore, the ventricular diastolic pressure declines, and the sequence of events responsible for heart failure (Chapter 14) tends to be reversed.

The peripheral effect is that of decline in venous pressure and in blood volume. The concept

has been advanced that the alteration in venous pressure is the direct result of action of the drug on venous tone. An additional and possibly an alternative explanation of these peripheral effects is as follows:

It has long been known that transfusion of blood into a normal subject is followed by a rapid decline in the excess blood volume, with a restoration toward the normal level. It has been demonstrated that digitalis causes decline in blood volume not only in patients with heart failure but also in normal persons and in normal animals. The possibility that the foregoing effects of transfusion and of digitalis on the blood volume are mediated through somewhat similar mechanisms has not been explored. Transfusion obviously tends to produce plethora which presumably affects such tissues as the bone marrow, brain, or other organs concerned in the regulation of blood volume. Digitalis lowers ventricular diastolic pressure and therefore initiates alterations in blood distribution which are the opposite of those occurring during the development of heart failure (Chapter 14). The decline in the size of the central venous stream bed would be expected to result in distribution of blood away from the thorax and toward the periphery. In this sense—i.e., increased blood in the periphery—the effect of digitalis may be not unlike that of transfusion. It is, therefore, possible that the drug may cause decline in blood volume as a consequence of plethora in the brain, bone marrow, or some other region. According to this concept, which is entirely speculative, the decline in venous pressure would be regarded as secondary to alterations in blood distribution or blood volume.

~~X INDICATIONS.~~ ~~l~~ Auricular fibrillation, with a rapid ventricular rate, constitutes the classic indication for use of digitalis. ~~l~~ Attacks of paroxysmal auricular tachycardia, when occurring at frequent intervals, may be prevented or reduced in frequency and duration by digitalis. In some instances the drug tends to end an attack already present.

Subject to the exceptions which have been mentioned, the most common indication is the presence of ~~l~~ congestive heart failure, even when the rhythm is regular. In advanced cases the drug alone is often ineffective and other measures such as diuretics are needed. However, in the earlier cases, and especially in those having attacks of paroxysmal nocturnal dyspnea, the effect of digi-

talism in preventing the seizures may be almost magical.

In the absence of frank congestive failure the drug should be used ~~when the cardiac reserve is diminishing~~, as indicated by increasing dyspnea for a given effort, or by well-marked gallop rhythm. In doubtful instances the value of the drug can usually be tested by measurements of vital capacity and circulation time, before and after digitalization. This procedure is occasionally of value in differentiating dyspnea due to cardiac disease from that due to emphysema.

Some believe that digitalis should be utilized in patients with asymptomatic cardiac disease, and in those with only slight diminution of reserve, as indicated by dyspnea on the performance of moderately severe exertion. Convincing evidence concerning the value of the drug in such instances has yet to be presented. In the absence of definite information it is perhaps wise to take the position that a patient should be given digitalis when the minimal exertion which can be carried on while leading a happy and economically useful life begins to induce dyspnea.

Once digitalis has been administered, the patient will usually need it either continuously or for long intervals throughout most of his life. The practice, frequently followed, of discontinuing the drug as soon as the overt manifestations of congestive failure have disappeared is not sound.

~~X~~ **CONTRAINDICATIONS.** This drug, like any other, is contraindicated under conditions where there is no clear indication for its use. It should not be given to people with sinus tachycardia except when clear evidences of congestive failure, either actual or imminent, are present. It should be withheld in individuals with peripheral circulatory failure unless evidence of congestive heart failure as the result of prolonged decline in coronary blood flow supervenes, as happens occasionally. When, on the other hand, a patient displays congestive failure after receiving fluids intravenously, digitalis is indicated. Types of heart failure in which the drug is harmful, or relatively useless, have been discussed.

Digitalis may cause nodal or ventricular tachycardia, and most instances of fatal digitalis intoxication arise from the mistaken assumption that the presence of tachycardia in such a patient constitutes an indication for larger doses. Bradycardia of moderate degree is often a desir-

able effect, and the common practice of discontinuing the drug when the heart rate is less than 70 per minute is unsound. In some patients maximal benefit is achieved at rates between 50 and 60.

~~X~~ **PREPARATIONS AND DOSAGE.** The most widely used preparation is the powdered leaf, which should usually be given in divided doses of about 4 digitalis units each, at six-hour intervals, until a total of 12 to 16 digitalis units has been administered. This should be followed by the daily administration of 2 to 3 digitalis units until the desired effect has been obtained, or until toxic effects are observed. Once a maximum therapeutic effect has been achieved, a daily maintenance dose of 1 or 2 digitalis units is utilized. Toxic effects are an indication to discontinue the drug until these have disappeared, and then to institute the maintenance dose or to reduce the maintenance dose if intoxication has occurred under its administration.

Excellent results are also obtained from the use ~~of purified digitoxin~~, the initial total digitalizing dose usually ranging between 1.2 and 2.5 mg. within a 48-hour period. The size of the optimal maintenance dose of digitoxin is the subject of some difference of opinion. Good effects are usually obtained with doses varying between 0.05 and 0.3 mg. daily. In the final analysis, dosage must be determined not by rule but by observation of the maximal therapeutic response of the individual patient.

~~X~~ **When a rapidly acting digitalis is desired**, or when one is uncertain as to whether the drug should be given and wishes to use a preparation the effect of which will wear off within a few days, either strophanthin (ouabain) or Digitalis lanata may be employed. The most satisfactory preparation of *Digitalis lanata* is lanatoside C ("Cedilanid"). Its quick onset of action makes it especially useful in the management of such emergencies as acute pulmonary edema. Its rapid disappearance from the body makes it useful in patients who need digitalis but who are particularly susceptible to its untoward effects. Hence, in a person with myocardial infarction and increasing congestive failure, in whom digitalization may precipitate a serious disturbance of rhythm, this drug is probably preferable to digitoxin. On the other hand, the rapidity of elimination makes it less desirable than digitoxin for use in the management of the usual patient with

congestive failure. For adults of average size the initial digitalization dose of lanatoside C is 1 to 1.6 mg., by the parenteral route. In patients with acute pulmonary edema not due to myocardial infarction, the intravenous route should be utilized; in other subjects the intramuscular route is preferable.

X MANIFESTATIONS OF DIGITALIS INTOXICATION. The most important of these include gastrointestinal disturbances—i.e., anorexia, nausea, and vomiting, developing in that order—and disturbances of the cardiac rhythm, of which premature beats, usually in the form of bigeminal rhythm, are the most common. Inversion of the T waves and slight increase in the P-R interval are normal effects of the drug. Severe degrees of heart block due to digitalis intoxication are very exceptional in man, although these occur frequently in animals when excessive doses are administered. In an occasional patient the drug converts sinus rhythm into auricular fibrillation. Nodal rhythm with moderate to marked tachycardia occasionally occurs, and ventricular tachycardia may develop, with danger of ventricular fibrillation if the administration is continued. Less common toxic effects include diarrhea and xanthopsia (yellow vision). When doses within the therapeutic range are employed, the only common toxic effects are anorexia, nausea, and bigeminal rhythm, all of which disappear within a few days after withdrawal of the drug. However, it is important to remember that the more serious toxic effects may supervene without the preliminary appearance of the usual warning signals in the form of the milder manifestations of toxic action.

Venesection and Venostasis. Theoretically, these procedures should be valuable in all patients with heart failure of such great severity that increasing inflow load leads to diminished output response—i.e., in all patients whose cardiac status corresponds to the descending slope of the Starling curve (Chapter 14). In such patients venesection or venostasis (trapping of blood in the legs by appropriate tourniquets on the thighs) should not only lessen congestion but also increase output. When heart failure is of lesser degree and when increasing inflow load leads to increase in output response—i.e., when the cardiac status corresponds to the ascending limb of Starling's curve—venesection should ben-

efit backward failure but augment forward failure. Unfortunately, there is no method of evaluating in a given patient the condition of the heart in relation to the Starling curve. Hence the decision concerning vēnesection has to be made on clinical grounds.

Seizures of acute pulmonary edema constitute the most important indication for vēnesection, which is a rapidly effective and often a lifesaving procedure under these circumstances (p. 1330). Painful congestion of the liver may likewise be benefited. Venesection may be employed in all patients with intractable heart failure, but under such circumstances lasting benefit is rarely produced. Ordinarily, the amount of blood removed should be 300 to 500 ml. for an adult patient of average size without anemia.

Diuretic Drugs. These are of great value. All patients who have ever suffered from edema of cardiac origin and who have a tendency toward recurrence should weigh themselves each day under standard conditions. (As a rule, this means weighing in the morning immediately after rising and emptying the bladder, with no clothes on other than slippers and pajamas.) The written record of such daily weighings constitutes the best single guide to the frequency of the need for diuretic drugs and to their effectiveness.

X The mercurial diuretics are the most effective, and their administration often results in dramatic improvement. There is now convincing evidence indicating that these drugs act by diminishing the reabsorption of sodium in the renal tubules, such an effect being brought about as the result of temporary depression of renal enzyme systems. The volume of diuresis is usually greater if these drugs are given to patients who are receiving ammonium chloride, 1 Gm. (15 gr.) three times daily, concurrently. In the presence of impaired renal function, the ammonium salts may produce acidosis if employed for more than a few days at a time. The mercurials that are combined with theophylline are most effective. The size of the dose and the frequency of administration are governed by the severity of the congestive failure, the rapidity with which its manifestations recur, and the response in the individual case. The initial dose should be 1 ml.; if no untoward symptoms are produced and a loss of two or three pounds in the course of 24 hours is effected, the same dose may be given daily for a few days or at longer intervals, depending on the

urgency of the case. If a satisfactory diuresis is not produced by 1 ml., 2 ml. is given, and this dose may be repeated after several days. The mercurial is administered until all evidences of passive congestion have disappeared and the weight becomes stabilized at a steady level. When compensation has been restored, a maintenance dose of the mercurial is administered at varying intervals, using the weight curve as the guide. The patient should be instructed to report to the physician whenever the weight increases by as much as 5 pounds within a period of one or two weeks.

Toxic effects

In general, the mercurial diuretics may be considered to be relatively free of serious harmful effects. Numerous patients have received hundreds of injections over a period of several years, without any detectable harmful effects. Toxic manifestations do occur, and they fall into two main groups: (1) Immediate reaction. The symptoms occur within a few minutes after the drug is administered, and consist of pallor, weakness, substernal distress, dyspnea, various arrhythmias, and electrocardiographic changes. This type of reaction is apparently caused by a direct toxic effect of the drug on the myocardium, and it occurs only when the drug is given by the intravenous route. (2) Delayed reaction. The symptoms occur after the peak of the diuresis, usually 6 to 24 hours after the injection. They resemble those of Addison's disease, and consist of lassitude, faintness, and occasionally apathy and mental confusion. These symptoms are due primarily to excessive loss of water and sodium, which may induce a state of severe extracellular fluid deficit in certain portions of the body, even though other portions are still edematous. Aside from the specific effects of excessive loss of water and sodium, which are rarely serious if recognized promptly, it is possible that some of these symptoms may be explained by the decline in blood volume and consequently in inflow load, with subsequent decline in cardiac output in an individual whose heart is functionally on the ascending limb of the Starling curve (Chapter 14). In the instances of heart failure so advanced that the heart is functionally on the descending limb, the manifestations of both backward and forward failure may be improved by diuresis. When the heart is functionally near the peak of the curve, the manifestations of forward failure will remain relatively unaffected, while the mani-

festations of backward failure are improved as diuresis occurs.

Both the immediate and the delayed reactions may terminate fatally. Since the former seems to be due to a direct toxic effect of the drug on the myocardium, the risk of this type of reaction may be minimized when the mercurial is given intravenously by injecting the drug slowly and intermittently; the risk may be avoided completely by employing the intramuscular route, which is now entirely practicable when a relatively painless preparation such as "Mercuhydrin" is mixed with an equal quantity of 1 to 2 per cent procaine, or a subcutaneous injection may be given when "Thiomerin" is employed. The delayed reaction may be avoided by giving doses that will ensure satisfactory (2 or 3 pounds) weight loss in 24 hours, but not excessive diuresis. When a delayed reaction does occur, sodium salts should be given promptly. Water should be administered likewise, unless, as occasionally occurs, there is evidence of diminished osmolar concentration (Chapter 28).

A more common and insidious form of the delayed reaction is observed in patients who are ingesting minimal amounts of sodium, and receiving vigorous and repeated mercurial therapy. The symptoms, which are the result of sodium depletion, vary from minimal lassitude to profound asthenia resembling that of Addison's disease. In order to protect the patient against the serious consequences of sodium depletion, it is important to determine the nitrogenous constituents of the blood at frequent intervals. Oral administration of sodium salts is indicated when these symptoms are outspoken, and is imperative when nitrogen retention is outspoken.

There are other less common reactions to the mercurials. Occasionally an allergic type of response will cause the appearance of various types of skin eruptions. Changing the mercurial will usually permit the continuation of diuretic therapy. Rarely, true mercurial intoxication with severe renal injury may develop. For this condition BAL is a useful antidote. Finally, it has been suggested that in some instances symptoms due to digitalis intoxication have appeared, apparently the result of mobilization of digitalis from the extracellular fluid removed on diuresis. This must be an exceedingly rare phenomenon.

Toxic reactions to mercurial diuretics can largely be prevented by measuring, at frequent

intervals, the urea content of the blood, and by careful clinical observations, especially in relation to the early symptoms (lassitude, apathy, etc.) of sodium depletion.

The contraindication to the use of mercurial diuretics is the presence of serious impairment of renal function, as indicated by marked elevation of blood urea, by fixation of specific gravity of the urine, or by the appearance of red blood corpuscles in the urine in large numbers. A few red blood corpuscles do not constitute a contraindication, and neither does proteinuria. When, in a patient prepared properly by sodium restriction and by the administration of acidifying salts, the mercurial diuretics are ineffective upon several trials, their further use is interdicted.

Preliminary reports indicate that ~~X~~ "Thiomerin," a new mercurial diuretic containing sulfur, may be more effective and much less toxic than the compounds previously available. Should further experience confirm the earlier results, one might expect this new compound to supplant the others in the future.

The xanthine diuretics which were used formerly are now seldom employed, because they frequently induce nausea. A more recently introduced xanthine, sodium theophylline glycinate ("Glytheonate") appears to be less open to this objection, and to have a more favorable therapeutic:toxic ratio. In general, the magnitude of the diuretic response to the xanthines is decidedly less than that to the mercurials.

Sedatives. The judicious administration of sedatives is helpful, especially in the early days of severe congestive failure. For dyspnea, morphine (10 to 20 mg.) or "Pantopon" (10 to 20 mg.) administered parenterally is usually effective in affording some degree of comfort and in ensuring sleep. These are best given in the evening and, after four or more hours, repeated during the night if necessary, but always with due regard for the caution that is necessary in the use of these drugs in the aged, and for the dangers of habituation if they are used for more than a few days. After the first few days, when congestive failure has been considerably alleviated, moderate amounts of barbiturates may be substituted. During the day small doses of phenobarbital (15 to 30 mg.) two or three times daily may diminish undue restlessness and apprehension. *It is most important, however, that one be particularly careful to avoid excessive sedation*, not only because of the

risk of precipitating toxic manifestations which are particularly prone to occur in patients with heart failure, but also because of the possibility of rendering the patient so lethargic that he is unwilling or unable to participate in sufficient activity to minimize the danger of phlebothrombosis, and because of the undesirability of excessive respiratory depression in a patient with lowered vital capacity.

Oxygen. Administration of oxygen is indicated: (1) in any patient with evidence of outspoken arterial anoxia; (2) when dyspnea is severe; and possibly (3) in any patient with intractable congestive failure. The possibility that oxygen may tend to rest the heart by reducing cardiac output as the result of elevation of tissue oxygen pressure has already been mentioned. However, this hypothesis remains unproved. When oxygen is needed for several days, the tent is the most useful method of administration; for periods of a few hours the mask is convenient, effective, and relatively inexpensive.

Thoracentesis. This is a valuable procedure in many patients with congestive failure. It should be employed in all severely dyspneic patients who present evidence of hydrothorax, which is frequently bilateral but often confined to the right pleural cavity. Abdominal paracentesis is indicated whenever ascites is prominent and fails to respond promptly to sodium restriction and diuretics. Massive hydropericardium is a rare complication, but is of great practical importance and usually calls for paracentesis. Southeby-Leech tubes are often extremely effective in the treatment of massive, soft, pitting edema, and occasionally may initiate a progressive elimination of edema and subsequent improvement in myocardial function when all other measures have failed. Penicillin should be administered as long as the tubes are inserted, to prevent infections.

MANAGEMENT OF ACUTE PULMONARY EDEMA

Because of its frequency, seriousness, and amenability to therapy, the type of congestive failure which is manifested by acute attacks of congestion and edema of the lungs merits special comment. Proper management is dependent on a clear understanding of the mechanism (Chapter 14) which is essentially that of sudden increase in pulmonary congestion as the result of aug-

mented inflow load in an individual who has a disproportionate inability of the left ventricle (as compared to the right) to respond.

When the seizures are relatively mild, no treatment is required other than the assumption of the upright position and the administration of codeine to control cough. The presence of wheezing (cardiac asthma) is usually an indication for aminophylline, which may lessen dyspnea even when the obstructive component is not obvious. The usual dose is 0.5 Gm. (7½ gr.) administered either intravenously over a five-minute period or by rectum when dyspnea is mild. When the rectal route is employed, sodium theophylline glycinate ("Glytheonate") appears to be more effective and better tolerated, the usual dose being 0.8 Gm. (12 gr.) as a suppository.

Morphine In the case of a severe seizure, energetic therapy is lifesaving. Morphine should be employed in large doses (15 to 30 mg.) in young and middle-aged adults, but should be used with caution in the elderly, and in persons with impairment of hepatic function. In the younger subjects with very severe dyspnea, the intravenous route is to be preferred. ~~Venesection (about 500 ml.) should be carried out immediately~~, and may need to be repeated in desperate cases. Venostasis (trapping blood in the legs by the application of pressure cuffs to the thighs) is likewise useful. Oxygen is urgently indicated. Digitalis in the form of the rapidly-acting *Digitalis lanata* ("Cedilanid," 0.8 to 1.2 mg.) or strophanthin (ouabain) should be administered intravenously to previously undigitalized patients. (For subsequent maintenance effects, either digitoxin or the powdered leaf is preferable.)

~~X~~ For the prevention of attacks in susceptible patients, two measures are of cardinal importance. These are adequate digitalization and control of peripheral edema by restriction of sodium and the use of diuretics. The most important "trigger" factors which may require management are cough, nightmares, excessive bedclothes, overeating, tympanites, and hypoglycemia.

It will be noted that the therapeutic measures which are effective in combating acute pulmonary edema fall into two groups: ~~X~~ 1) Those which act by diminishing inflow load: These include the sitting position, which tends to distribute blood to the periphery and away from the heart, as well as venostasis, venesection, and diuretic drugs, which tend to diminish the circulatory

blood volume and hence the size of the stream bed (Chapter 14). ~~II~~ Morphine, by lessening the labored breathing, tends to raise the mean intra-thoracic pressure and hence to diminish venous return. Oxygen reduces anoxia which causes increased venous return. ~~X~~ 2) Those which increase the capacity of the heart to respond to a given inflow load: These include digitalis, which has a direct effect on the heart, and aminophylline, which acts through mechanisms as yet poorly understood. Each of these therapeutic measures tends to restore the unfavorable balance between the inflow load in the left ventricle and the capacity of this chamber to empty itself in normal fashion.

One final therapeutic principle may be stated. The condition of a patient with congestive failure is never hopeless so long as life remains. Vigorous, and judicious treatment will save the lives of many patients who are desperately ill and almost moribund. This happens more frequently at present than a decade ago, and there is every reason to believe that, with increasing knowledge of the energetic mechanisms of heart failure, further therapeutic advances will be forthcoming.

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Bacterial Endocarditis

Paul B. Beeson

- Subacute Bacterial Endocarditis Due to *Viridans Streptococci*
 Definition
 Etiology
 Pathogenesis
 Manifestations
 Laboratory Findings
 Differential Diagnosis
 Treatment
 Other Etiologic Agents in Bacterial Endocarditis

Under the term *bacterial endocarditis* are included a variety of clinical syndromes, some of which pursue a rapid and acute course, whereas others evolve slowly over a period of many months. By far the commonest type of bacterial endocarditis is the subacute variety caused by streptococci of the *viridans* group.

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO VIRIDANS STREPTOCOCCI

Definition. This is a prolonged, febrile, often fatal disease, resulting from streptococcal infection of a heart valve, characterized by fever,

heart murmur, splenomegaly, embolic phenomena, and bacteremia.

Etiology. The *viridans* group of streptococci includes several different strains. Those which are important causes of subacute bacterial endocarditis are: *Streptococcus mitis* and *Streptococcus bovis*, normally present in the mouth; the *Streptococcus faecalis*, or enterococcus, normally present in the intestinal tract; and a newly recognized type, *Streptococcus s.b.e.*, whose normal habitat is not known and which has been isolated only from cases of bacterial endocarditis.

Pathogenesis. In the great majority of cases, bacterial infection is established on a valve which has been previously damaged by rheumatic fever. Changes caused by congenital heart disease, or rarely by arteriosclerosis or syphilis, may also provide the foundation for this infection. The mitral is the valve most frequently involved; the aortic is second. Both valves may be affected at the same time. The tricuspid and pulmonic valves

are affected in only about 15 per cent of cases, including those in which the mitral and aortic are also involved. It is often said that slightly damaged valves are more likely to be the seat of bacterial endocarditis than extensively scarred valves. This is partly attributable to the fact that people live longer with slightly damaged than with severely damaged valves, and hence have more opportunity to contract the infection. Several experienced clinicians have commented on the infrequency of bacterial endocarditis in patients with auricular fibrillation.

A similar process may become established on a patent ductus arteriosus, at the site of coarctation of the aorta, or in an arteriovenous fistula. These infections are called *subacute bacterial endarteritis*.

Bacteria must reach the heart valves by way of the blood stream. There is abundant evidence to show that the entrance of bacteria into the circulation is not infrequent. For example, it is a common occurrence in minor surgical procedures such as tooth extraction and tonsillectomy. Bacteremia can occur, in persons with periapical dental infection, simply as a result of grinding the teeth together. Ordinarily such brief episodes of bacteremia are not serious because the organisms are quickly phagocytized by the reticuloendothelial system. If, however, living bacteria happen to lodge in or on a damaged heart valve, the stage has been set for the establishment of a grave infection. The manner in which a colony of bacteria becomes established in such a location is not known with certainty. It is possible that intravascular clumping of bacteria by antibody favors their lodgment in this location. The fact that preexisting deformity of the valve is usually a requirement brings up the possibility that roughening of the endocardial surface or some change in blood supply to a valve may predispose to implantation of the infection. Possibly the bacteria become lodged beneath small platelet thrombi on the surface of a valve. Possibly they are carried into a valve through its blood supply and are deposited beneath the endothelium. In any event the primary site of bacterial growth is usually near the free edge of the valve at the line of closure. This growth stimulates the deposition of platelets and fibrin and leads to the formation of a "vegetation." This structure increases in size and may extend onto the adjacent endocardium. Meanwhile, the valve leaflet is under-

going gradual necrosis. Granulation tissue grows into the vegetation from the valve, but capillaries seldom reach the periphery of the infected necrotic area. Nests of growing bacteria are scattered through the vegetation; those which are in the avascular outer portion of the vegetation are protected from phagocytosis since leukocytes do not seem able to penetrate the area. This protection from phagocytosis may be the principal factor which permits survival of bacteria and persistence of the infection.

Organisms are constantly shed into the blood, but their stay in the circulation is very short, since studies have shown that one half to one-third of the organisms entering the arterial blood are removed during each circuit of the body. The principal sites of removal are organs rich in reticuloendothelial elements—i.e., liver, spleen, and bone marrow.

Vegetations of bacterial endocarditis are friable and fragments are occasionally broken off by motion and the current of blood passing over them. These particles are carried in the arterial blood to all parts of the body, where they eventually lodge as arterial emboli. The damage produced by embolus depends principally on its size and on the artery which happens to receive it; additional factors are the amount of associated vascular spasm, the collateral circulation, and the tissue affected. Emboli which lodge in the brain, in the mesentery, or in arteries of the extremities are most likely to have serious effects. Those carried into the walls of large arteries by vasa vasorum may cause the formation of mycotic aneurysms which may rupture at a later time.

It should be noted that the infected emboli and the free bacteria which are constantly disseminated throughout the body very seldom create metastatic abscesses. The infecting organisms are usually of low pathogenicity and when separated from the protection of the vegetation they are readily phagocytized.

The *myocardium* may be the site of a low-grade inflammatory process which is probably an embolic myocarditis. The *spleen* is nearly always enlarged, and in most instances shows areas of infarction. The *kidneys*, which, because of their rich blood supply, constantly receive small emboli, show changes of focal embolic nephritis. In addition, a diffuse type of low-grade glomerulitis is commonly encountered. These processes may

result in renal decompensation, which can be the cause of death.

Manifestations. In about one third of cases the symptoms of this disease begin one to three weeks after some other illness such as a respiratory or post-partum infection, or some procedure such as tooth extraction or tonsillectomy.

The symptoms and course of subacute bacterial endocarditis do not conform to any single typical picture, since they depend upon variable factors such as the extent of the preexisting valve damage and the chance distribution of emboli. The symptoms of congestive failure may appear at any time during the course of the disease.

In only about 25 per cent of cases is the onset of symptoms of subacute bacterial endocarditis sufficiently dramatic that it can be recalled with certainty by the patient. More often, the illness begins very insidiously and the patient cannot name the exact time of onset. The principal *symptoms* are weakness, malaise, feverishness, chills (occasionally), sweating, weight loss, joint pains, paresthesias, and paralyses.

The patient usually appears chronically ill. The skin is pale and sometimes has a tan color, the so-called *café au lait* appearance. The skin may be flushed and hot or it may be wet with perspiration. Tiny *petechial hemorrhages* may be visible in any part of the body; they are particularly evident on mucous surfaces: the conjunctiva, the palate, or the buccal mucosa. Some of the petechiae in the conjunctiva have white or gray centers; these are considered by many to be of diagnostic significance but are occasionally seen in other conditions. Petechiae in the skin may be less obvious, and also more difficult to distinguish from other lesions, such as small angiomas. The latter usually blanch when pressed with a glass slide. It is sometimes helpful to circle all suspicious lesions with ink, and re-examine them later. Old petechiae fade in a day or two, and new ones appear in other areas, whereas angiomas do not change. Petechial hemorrhages in the nail beds usually are located near the distal margin and have a linear shape resembling embedded splinters; hence the name *splinter hemorrhages*. Small, painful, reddish or purplish areas in the pulps of the fingers (*Osler's nodes*) may develop during the course of the disease; they usually disappear within a day or two. Larger painful erythematous areas may appear from time to time on the palms of the hands or soles of

the feet. Embolization of small arteries as in the digits or in the nose occasionally produces a local area of gangrene. In cases of long duration, *clubbing of the fingers* is likely to be present. Examination of the *heart* reveals the signs of the preexisting valvular defect. Changing murmurs have often been mentioned as helpful in diagnosis, but too much stress should not be given this sign. The changes which do occur are most often due to the circulatory effects of anemia and fever. Occasionally, however, there are rather striking fluctuations; these are especially likely to occur in patent ductus endarteritis. The *spleen* is palpable in more than one half of all cases; following an infarction there may be severe pain and tenderness in the left upper quadrant, and a friction rub may be audible over the left lower costal margin. Inflammation of *joints* occurs in about one fourth of all cases and may simulate acute rheumatic fever. The pathogenesis of these arthritides is not clear.

Symptoms and signs of congestive heart failure may be present from the onset or may appear at any time during the course of subacute bacterial endocarditis. There may be orthopnea, distension of the neck veins, peripheral edema, rales in the lungs, pleural effusion, and large, tender, swollen liver. When present, these manifestations may dominate the clinical picture, and may in fact obscure the diagnosis.

The *manifestations of embolic phenomena* depend upon the tissues involved. There may be hemiplegia; meningeal inflammation; infarction of lung, myocardium, mesentery, spleen, or kidney; or occlusion of peripheral arteries. In right-sided endocarditis or patent ductus endarteritis, emboli are carried to the lungs; these may lead to erroneous diagnosis of pneumonia.

The *course* of subacute bacterial endocarditis is variable and may last from one month to two years. Before effective methods of treatment were available, the majority of patients died within nine months of the onset.

Intercurrent infections are not very common, although bronchopneumonia occurs occasionally. In rheumatic subjects the development of arthritis produces a clinical picture which may be indistinguishable from acute rheumatic fever.

Since the introduction of penicillin therapy, the principle *cause of death* in subacute bacterial endocarditis is progressive, intractable cardiac decompensation. This is probably the result of

valvular damage which renders the heart mechanically less efficient, together with myocarditis and increased demand for cardiac work occasioned by fever and anemia. Some patients die following cerebral, myocardial or mesenteric embolism, while others succumb to a progressive "toxemia" of infection without localizing manifestations. Rarely, death is due to uremia caused by a progression of the nephritis; this is more likely to occur in the relatively inactive cases. Sometimes coma and death are the result of multiple small cerebral emboli which do not give localizing signs.

Laboratory Findings. The *leukocyte count* in the peripheral blood is usually moderately elevated but may be within the normal range. *Circulating macrophages* may be found in smears of the peripheral blood. These are thought by some hematologists to be of diagnostic value. In cases of long standing, a moderately severe normochromic anemia may be present.

The erythrocyte sedimentation rate is elevated. Microscopic hematuria is very common, and is helpful in diagnosis. Albumin may also be found in the urine. The *blood culture* is positive for *viridans streptococcus* in 80 to 90 per cent of cases. In these cases the number of colonies of bacteria per milliliter of blood is usually approximately the same from day to day. In a minority of instances the blood culture is consistently negative, for reasons which are not clear. It may be that in these cases the bacteria grow more deeply in the vegetations and hence do not have free access to the circulating blood. It is often said that bacterial endocarditis located on the right side of the heart is more likely to be associated with negative blood cultures, but there is little foundation for this assertion, since it is not known that the lungs serve as bacterial "filters" in man. Actually it is not at all uncommon for bacteremia to be present in cases of right-sided bacterial endocarditis.

Differential Diagnosis. The diagnosis of subacute bacterial endocarditis may be very easy or may be extremely difficult, depending on the prominence of the various manifestations. In patients with the cardinal manifestations of fever, heart murmur, splenomegaly, petechiae, and clubbing of the fingers, the diagnosis is obvious. On the other hand, subacute bacterial endocarditis can be a most difficult diagnostic problem since it can simulate a variety of diseases. The

possibility of subacute bacterial endocarditis should be considered in every patient with fever and heart murmur. The diagnosis is missed most often in elderly patients, especially those whose presenting complaint is the result of a cerebral embolic accident; in such individuals a diagnosis of cerebral thrombosis or hemorrhage is likely to be made and little consideration given to the presence of a systolic murmur or low-grade fever. Heart murmur is so constantly present (99.2 per cent of Kelson and White's series of 250 cases) that the diagnosis of subacute bacterial endocarditis can be excluded fairly safely in patients without murmurs.

This disease is one of the classic causes of "fever of undetermined origin"; many of the foremost clinicians in the early part of the twentieth century established their reputations in part by being familiar with its manifestations. *Lymphomas* may have fever, anemia, splenomegaly, and even petechiae. Diagnosis is usually established by biopsy of a lymph node. *Periarteritis nodosa* can cause fever, anemia, hematuria, and vascular accidents, but heart murmurs may not be present. Here again the best diagnostic procedure is biopsy. *Disseminated lupus erythematosus*, in the absence of characteristic skin eruption, may show fever, arthritis, hematuria, splenomegaly, and heart murmur. There may also be petechiae. This disease should be thought of when blood cultures are negative, especially in women between the ages of 15 and 45. *Hematologic diseases* (leukemia, thrombocytopenia), particularly if associated with anemia and petechiae, splenomegaly, and fever, may resemble bacterial endocarditis. Careful blood examination should rule them out. *Brucellosis* is also manifested by prolonged fever, splenomegaly, and anemia. The differential diagnosis will depend principally on positive blood culture or on high and changing agglutination titer. It is to be remembered, of course, that endocarditis due to *Brucella* occurs. *Acute rheumatic fever* may present anemia, arthritis, heart murmur, and (very rarely) petechiae and splenomegaly. The differential diagnosis between active rheumatic fever and subacute bacterial endocarditis may be very difficult. Abatement of all symptoms with salicylate therapy and repeated negative blood cultures points to rheumatic fever. It should be remembered, however, that the majority of patients with bacterial endocarditis are rheumatic pa-

tients, and in the course of bacterial endocarditis an arthritis resembling that of rheumatic fever may occur. *Typhoid fever*, with its splenomegaly, may also resemble bacterial endocarditis. Cultures of the blood and feces and positive Widal test should differentiate this disease. *Tuberculosis*, particularly when extrapulmonary, may create a diagnostic problem. In the early stage, miliary tuberculosis may be particularly difficult to differentiate. Repeated careful physical and laboratory examinations may be required to distinguish between these types of infection.

Treatment. Various forms of therapy which have been tried in bacterial endocarditis include radiation of the heart valves, transfusions from immunized donors, vaccines, and the use of a variety of antiseptic drugs such as arsenicals, merbromin, and acriflavine. These are now of historical interest only. The introduction of penicillin in 1943 altered the prognosis of subacute bacterial endocarditis and reduced the fatality rate from more than 95 per cent to approximately 30 per cent. With the addition of streptomycin and other antibiotics it is likely that the results will be even better in the future. Fortunately, most of the strains of *Streptococcus viridans* which cause subacute bacterial endocarditis are sensitive to penicillin within ranges which can be achieved therapeutically. Somewhat more than half of all cases of subacute bacterial endocarditis are caused by strains which will yield to therapeutic doses of 500,000 units of penicillin daily. *Streptococcus mitis* and *Streptococcus bovis* are usually inhibited by from 0.01 to 0.1 unit of penicillin per ml. *Streptococcus faecalis*, however, is relatively resistant, the majority of strains being resistant to 5 or more units per ml. The sensitivity of *Streptococcus s.b.e.* usually lies between these values.

It is of the greatest importance in the therapy of this disease to have an accurate bacteriologic diagnosis, including test of the sensitivity of the infecting organism. A question which frequently arises is whether penicillin therapy should be initiated as soon as the diagnosis is made or whether therapy should be withheld until laboratory studies on the infecting organism have been completed. In favor of beginning therapy immediately is the fact that embolic accidents are a constant threat and that progressive destruction of the valve is taking place. On the other hand, the advantage in waiting is that the

dose can be estimated more accurately. There is a possible disadvantage in beginning therapy with a dose which is too small, since the organism may be rendered even less susceptible than before any therapy was given.

It is generally believed that a fairly good correlation exists between the dose of penicillin, the in vitro susceptibility of the organisms, and the clinical response. A practice which is usually satisfactory is to establish an average blood concentration of penicillin which is three to five times the in vitro susceptibility of the organism. For example, if the infecting organism is inhibited by 0.04 unit of penicillin per ml., a dosage of 25,000 units every two hours should be adequate, since it could be expected to give an average blood level of 0.2 unit per ml. Most authorities maintain, however, that no patient should receive less than 500,000 units per day.

Enormous quantities of penicillin may have to be given in the treatment of infections caused by relatively resistant organisms. Doses of as high as 75,000,000 units per day for a period of several weeks have been employed with good results. The administration of such quantities of penicillin is not only expensive but is technically difficult, since large doses are likely to be painful when given intramuscularly, and their intravenous injection may cause chemical phlebitis and thrombosis. In order to administer very large doses of penicillin it is usually necessary to employ a variety of methods such as continuous intravenous, continuous intramuscular, and intermittent intravenous and intramuscular injections. Adjuvants such as caronamide may be advantageous by reducing the rate of excretion of penicillin by the kidney. Rapid intravenous injection of large booster doses in conjunction with caronamide has been urged in order to produce high blood levels. Ingenuity, technical skill, and stubborn persistence on the part of the doctor may be lifesaving.

Penicillin therapy of subacute bacterial endocarditis should be continued for at least four weeks. Some clinicians advise six and even eight weeks of continuous therapy in all cases. The likelihood of relapse is certainly very great if therapy is discontinued after only two or three weeks. Presumably the drug merely causes bacteriostasis, and eradication of the infection must await the gradual removal of the vegetation, liberating those organisms protected in it so that

they can be destroyed by phagocytes. This process requires time. Complete healing at the site of the vegetation probably does not occur in less than three to six months, as judged by autopsy observations in patients who have succumbed to heart failure or other disease.

Emolic manifestations may occur during penicillin therapy, even when an apparently good effect on the infection has been achieved. These include hemiplegia, mesenteric infarction, and occlusion of a peripheral artery.

The effect of penicillin on the fever is variable. In some instances the temperature falls to normal within two or three days of the beginning of therapy and does not rise thereafter. In other cases where the end result is satisfactory, a low-grade fever may persist for two or three weeks.

Relapse may occur after the cessation of penicillin therapy, especially when the period of treatment has been short. The great majority of relapses occur within the first four weeks after cessation of treatment. It is usually safe to consider a patient's infection eradicated if he is free of symptoms and signs of the disease and if his blood cultures show no growth six weeks after the conclusion of therapy. A rerudescence after that time may be due to a new infection rather than to persistence of the initial one.

In the event of relapse, additional chemotherapy is indicated. It is particularly important to check the sensitivity of the infecting organism and to adjust the dose of penicillin accordingly.

Patients who have recovered from subacute bacterial endocarditis should be given prophylactic penicillin therapy before any operative procedure in an infected area, such as tonsillectomy or tooth extraction. It is advisable to administer penicillin in a dosage of 300,000 units daily for two days prior to the procedure and for one day afterward.

It has been suggested that the administration of an anticoagulant drug such as heparin or dicumarol is advisable as an adjunct to the antibacterial chemotherapy of subacute bacterial endocarditis. There is no convincing evidence that this facilitates healing of the infectious process; on the other hand, anticoagulant therapy carries with it an extra hazard of bleeding, particularly at sites of cerebral emboli.

In infections located on patent ductus arteriosus or arteriovenous fistula, cure can sometimes be achieved by surgical excision or ob-

literation of the fistulous tract. Such operative therapy can be carried out during, or at the conclusion of, a course of chemotherapy, as just outlined.

The chief causes of failure to achieve a cure in penicillin therapy of subacute bacterial endocarditis are: (1) insensitive organism, (2) valvular damage so severe that intractable heart failure occurs (see figure 211), (3) embolus, and (4) progressive renal failure.

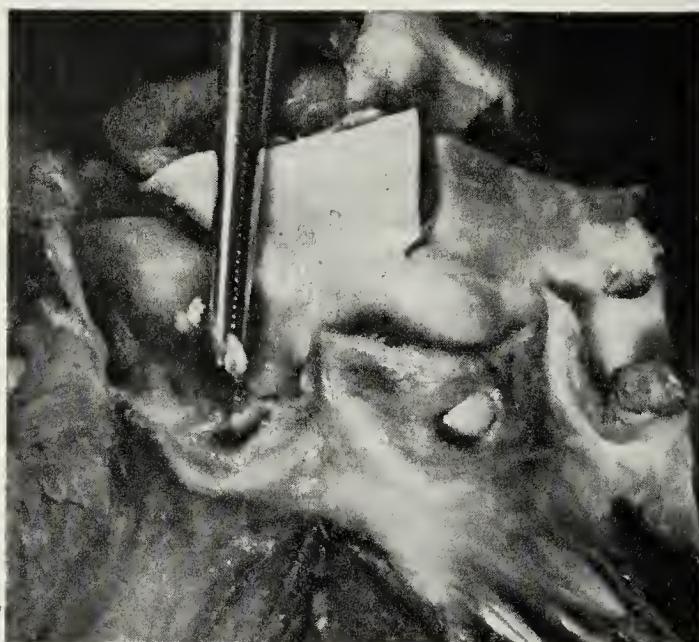


FIG. 211. Photograph of the aortic valve area from the heart of a patient who died in congestive heart failure two months after the conclusion of penicillin therapy for subacute bacterial endocarditis. The extensive damage to the three aortic cusps is easily seen. (Courtesy, Dr. J. C. Massee.)

Streptomycin therapy has been successful in the treatment of a small number of cases of bacterial endocarditis caused by organisms not susceptible to penicillin. Experience with this agent is limited, but the recovery rate, even with susceptible organisms, will probably be less than 10 per cent, because of the development of streptomycin resistance by the infecting organisms. Streptomycin is of great value as an adjunct to penicillin in endocarditis due to *Streptococcus faecalis*. This organism is usually comparatively insensitive to penicillin, yet results of treatment with a combination of *streptomycin* and *penicillin* have been very good.

Aureomycin and "Chloromycetin" should be effective in certain instances where penicillin, or penicillin plus streptomycin, are not helpful. The sensitivity of *Streptococcus faecalis* to aureomycin

is especially promising, since that form of bacterial endocarditis has been difficult to control.

Previous to the introduction of the antibiotics there were occasional reports of cure of subacute bacterial endocarditis with the *sulfonamide compounds*. The over-all recovery rate with this therapy was, however, probably not greater than 5 per cent. Although they are still used occasionally as adjuvants to penicillin or to streptomycin, they have comparatively little value in bacterial endocarditis. In desperate situations, however, it is reasonable to try the effect of maintaining a high blood sulfonamide level—i.e., above 20 mg. per 100 ml. This can be achieved with the least risk of renal complications by giving several different compounds—for example, sulfadiazine, sulfamerazine, and sulfathiazole, each in a dose of 6 Gm. daily. The use of mixtures reduces the risk of renal complications, although it slightly increases the danger of toxic manifestations due to hypersensitivity.

The therapy of congestive failure in bacterial endocarditis does not differ from that of other kinds of congestive heart failure.

OTHER ETIOLOGIC AGENTS IN BACTERIAL ENDOCARDITIS

Although streptococci of the *viridans* type are by far the commonest cause of bacterial endocarditis, accounting for approximately 90 per cent of all cases, a wide variety of other microorganisms may be the cause of subacute or acute bacterial endocarditis. These include nonpathogenic bacteria, such as *Staphylococcus albus*, *Haemophilus parainfluenzae*, and many genuinely pathogenic organisms, such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Brucella*, and the

gonococcus, meningococcus, and pneumococcus. In addition to bacteria, certain of the fungi, such as *Histoplasma capsulatum*, have been shown to cause bacterial endocarditis.

The term *acute bacterial endocarditis* is usually given to those cases in which the etiologic organism is a true pathogen, such as *Staphylococcus aureus* or the pneumococcus, and in which the course is relatively rapid—i.e., a few weeks. This type of infection may involve previously normal valves. The clinical picture is characterized not only by a short course, but also by high fever, multiple petechial hemorrhages and other embolic manifestations, development of metastatic abscesses in other parts of the body, and rapid destruction of the heart valve.

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Section 2—The Cardiovascular System—(Continued)

B. Diseases of the Vascular System

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Arteriosclerosis

William Dock

Atherosclerosis: Metabolic Basis for the Disease

Hypertension and Arteriosclerosis

Study and Management of Arteriosclerotic Patient

Appendix: Technic of Measurement of Arterial Blood Pressure

The human arteries and veins become altered in their gross and microscopic structure soon after maturity, and in certain parts of the body these aging changes lead to clinical disorders. Similar aging changes occur in many mammalian species, but in the quadrupeds, varicose veins and hemorrhoids, the common clinical sequelae of human vascular aging, are unusual, so that vascular aging has no serious sequelae in these species. The *arterial* changes due to involution and aging in man *do not occlude the lumen*, nor do they lead to arterial dilatation of clinical importance.

Several types of vascular aging are known, the commonest being fibrosis with ectasia, in which collagen replaces muscle and elastin in the media. This is diffuse and bilaterally symmetric, involves the vessel uniformly over long distances, and is the basis for the tortuous temporal arteries, the elongation and widening of the aorta, and the dilatations of veins in the hands, feet, and anal ring. All these may have been apparent by the age of 30 in people who yet lived well beyond 80 without vascular accidents.

Medial calcification is less frequent in man, but common in some mammals. It never affects arteries at points of flexion, as in the coronaries, or the limb vessels at elbows, knees, or groins. It involves fixed large arteries, like the femorals and radials, and smaller ones in the atrophic sex organs of the aged. The disease is bilaterally symmetric, but often occurs in discontinuous bands or rings. It rarely is present before the age of 40, and can be demonstrated by x-ray or by palpation.

These changes may predispose to atherosclerosis, and even to various forms of inflammatory disease, such as periarteritis nodosa and throm-

boangiitis obliterans, but proof of this is not convincing. True vascular aging seems to be an unimportant factor in clinical arteriosclerosis.

Atherosclerosis: Metabolic Basis for the Disease. The patchy cholesterolosis and scarring of the intima, so familiar to all observers of autopsies in America, are not seen in any wild animals, but occur in domestic fowl, and in rabbits fed cholesterol, as well as in hypothyroid dogs fed this animal wax. The blood cholesterol of most animals and birds ranges from 50 to 150 mg. %; the levels in birds or mammals developing atheroma usually are over 400 mg. %. Mongoloid races, on diets low in meat and eggs, and free of dairy products, have blood cholesterol levels of 100 to 140, and have a striking freedom from atheroma and clinical evidence of arteriosclerosis. In Occidental countries, blood cholesterol levels from 200 to 400 mg. % are often noted in the absence of endocrine disorder. The highest levels are found in those with diets rich in butter and eggs, and these may fall over 100 mg. % in three to six months on low-cholesterol diets with adequate protein content. Cholesterol, constantly formed by the liver, secreted into the bile, and reabsorbed from the bowel, does not fluctuate in the blood from day to day. The levels rise and fall slowly when cholesterol intake is varied. Vegetable sterols are not absorbed and have no effect on the blood levels.

All the diets low in cholesterol are also low in fat, and there is very strong evidence that high-fat diets, low in cholesterol, markedly alter the levels of cholesterol in the blood and tissues of experimental animals, and that blood levels of cholesterol rise in obesity, together with acceleration of atheroma formation. There is also evidence that the cholesterol-phospholipid ratio, rather than absolute levels of blood cholesterol, determines the rate of atherosclerosis, and that

certain fractions of cholesterol, presumably those not conjugated as lipoprotein molecules, are particularly important and especially labile in relation to diet. Finally, it has been shown that on a synthetic fat-free diet normal subjects exhibit an average fall of 85 mg. % in plasma cholesterol within a few weeks, with return to normal levels on normal diets. There is evidence that the body reacts to detergents by marked rise in all plasma lipids, and that the level in the blood may represent a protective system against soaps formed from neutral fats. The clinical fact is that diets high in protein and low in fat and cholesterol seem to retard atherosclerosis. Whether pure cholesterol, fed to patients on low-fat diets, will elevate cholesterol levels has not been tested.

In families, as in species, the cholesterol levels vary widely even on a uniform diet. In families with congenital xanthomatosis (yellow granulomas of the tendons and skin), blood levels over 1000 mg. % occur on cholesterol-free diets. These individuals may die of arteriosclerosis before the age of 20, and nearly all of them suffer from biliary cholesterolosis and atheroma before they are 50. Other families, on cholesterol-rich diets, may have blood levels under 200 mg. %. Those with gout often have higher levels, while myxedema and diabetes are regularly associated with levels above 250 mg. % and up to 600 mg. %, even without diabetic acidosis, in which the level may rise over 1000. Precocious arteriosclerosis is the rule in diabetics, and is not infrequent in myxedema.

In summary, the tendency to widespread arteriosclerosis depends on such inherent factors as the endocrine and hepatic control of cholesterol, but can be profoundly altered by a diet rich in calories and cholesterol. Pathologists in Germany and America have offered convincing proof that, in certain types of wasting disease and under-nutrition, atheroma may be reabsorbed. Yet in India and South Africa, where dairy products are a regular part of a diet low in protein, calories, and vitamins, precocious arteriosclerosis is not uncommon. Thus, a diet must be well balanced and low in cholesterol and fat in order to retard, or reverse, the formation of atheromas.

Intimal thickening, whether innate, as in the epicardial branches of the coronary system, or acquired, as in syphilitic mesaortitis, predisposes to rapid local arteriosclerosis. This is the appar-

ent basis of predilection for the coronaries, where numerous and fatal lesions are often seen in men under 35 years old when all other vessels are faultless, and for the male sex, in whom even at birth the intimal lining of the coronaries is thicker than in females, and much thicker than in any other part of the body.

Hypertension and Arteriosclerosis. There is one school of students of hypertension and arterial disease who regard the disorders as unrelated results of hereditary abiotrophies, like freckles, white scalp hair, achylia gastrica, and pernicious anemia. Such stigmas may be inherited together, none having a causal relation to the other. Thus hypertension would be neither a cause nor a result of arteriosclerosis. For the following reasons we believe that hypertension plays an important part in accelerating the development of atherosomas, and in the vascular accidents which lead to lesions of the heart, brain, retina, and lower extremities.

As the pulse wave goes toward the legs, it becomes steeper and the systolic peak is higher at the bifurcation of the aorta and in the femoral arteries than it is in the arch of the aorta. Because of this and the erect posture which adds the weight of a column of blood, the leg vessels have a pressure 80 to 120 mm. Hg higher than that in the arms. These differences in pressure seem not unrelated to the fact that for every arm amputated for arteriosclerotic gangrene, over a thousand legs are sacrificed. The pressure difference explains the equally obvious fact that severe atherosomas in old people are far more numerous and advanced in the abdominal aorta and iliac arteries than in the arch and the subclavians.

In most bodies, arteriosclerosis of the abdominal aorta and systemic arteries is far more striking than in the pulmonary arteries, where pressure is one sixth as high. In mitral stenosis, asthma, and pulmonary fibrosis, where pulmonary hypertension is evidenced by right ventricular hypertrophy, severe pulmonary arteriosclerosis is not uncommon. Experimental renal hypertension in rabbits accelerates experimental arteriosclerosis due to cholesterol feeding. Neither of these facts can be accounted for by chance relations of blood pressure elevation and rapid evolution of arteriosclerosis.

While it is true that some people have hypertension for decades and do not show much arteriosclerosis, there is a very high statistical corre-

lation of retinal vascular disease and severe renal atherosclerosis with hypertension. In the retina the course of the disease can be followed; hypertension precedes vascular change, and progressive disease not infrequently is arrested when pressure falls to normal after a myocardial infarct or a sympathectomy. Next to the level of blood cholesterol, the level of arterial pressure is apparently the most important factor in determining the *rate* of atherosclerosis; next to intimal thickness, the level of pressure is the most important factor in determining the *site* of atherosclerosis.

Neither vascular aging nor atherosclerosis of the great vessels causes hypertension, although increased velocity and amplitude of the pulse wave are the regular sequelae of "hardening" of the arteries. Narrowing of the smaller renal arteries may, and in elderly patients probably does, lead to renal hypertension of arteriosclerotic origin. How often this occurs is problematic, because widespread lesions of small arteries in the kidneys, retina, adrenals, and pancreas are usually seen only in cases where hypertension has existed for years or decades before the first retinal lesion was demonstrable. Exceptions are not rare in diabetics, whose proteinuria and retinal lesions may precede the development of hypertension by many months or years; but in other patients, hypertension preceding arterial disease is far more frequent than the reverse. In cases of pheochromocytoma in young people, severe vascular disease may develop within six months of the initial rise in blood pressure, but usually the pace is much slower.

There is no good proof that restriction of coronary or cerebral blood flow is a cause of hypertension or tends to further aggravation of the disorder. On the contrary, the establishment of a much lower level of pressure not infrequently occurs after a cerebral vascular accident. This is also seen in cases recovering from myocardial infarction. Transient rise in pressure with these accidents seems to be due to apprehension and pain, and not to a pressor mechanism in the ischemic tissue.

Study and Management of Arteriosclerotic Patient. The presence of clinically important atherosclerosis can be proved only by detecting functional impairment of legs, kidneys, heart, splanchnic viscera, retina, or brain, and ruling out arteritis, Buerger's disease, syphilis, and other diseases as an alternative basis for the diag-

nosis. In the brain, arteriosclerotic disease cannot safely be diagnosed on the basis of personality changes; focal lesions affecting sensation, motion, or some other function must be observed. In the heart, angina (in the absence of aortic valve lesion or paroxysmal hypertension) or myocardial infarction is associated with severe atherosclerosis in nearly 90 per cent of cases; in the legs, intermittent claudication and gangrene in more than half the cases are arteriosclerotic in origin.

When the question of severity and extent of this disorder is raised, careful history and examination suffice to indicate degree of damage done in various regions, and x-rays may show calcific lesions in the aorta and the legs. But no degree of care in scrutiny can detect any large proportion of the coronary arteries which will become occluded in a few hours or years. It can, however, be predicted that those with bad family records of vascular accident, those with high blood cholesterol, and those with hypertension will, in any given decade, have far more vascular accidents than those without these signs. This fact is of importance to insurers, but when the doctor talks to a patient no good is done by stressing bad prognosis unless it leads the patient to accept effective therapy or prophylaxis. The patient may live in comfort for years, or survive a series of severe vascular accidents with unimpaired earning power and morale; he may become depressed and disabled by the thought of imminent death or invalidism if risk of arterial disease is described to him.

The patient touched by arteriosclerosis, or threatened by it, may be benefited not at all by drugs, diet, or surgery, nor by a combination of all three. A diet free of cholesterol, adequate in protein, and low in calories if the patient is at all plump, is advisable for those whose diets have been otherwise in the past. If cholesterol falls in three months, continuation of the regime for life can be urged for those who would prefer long life to rich fare. Low-salt diet can, on the same grounds, be recommended for trial by the hypertensive person, and more drastic therapeutic endeavors when the threat to life or vision becomes more apparent. Lecithin, inositol, choline, potassium iodide, all have been used to lower cholesterol levels, or to moderate cerebral symptoms. Their value in lowering cholesterol, in any given case, can be determined only if the diet and weight are kept constant while the agent is being

tested. There is a little evidence that they lower plasma lipids in man, but suggestive evidence that large doses (6 Gm. of choline per day) may retard or reverse atheroma formation even at constant levels of cholesterol. Unfortunately, many patients develop digestive distress with these high doses, and while there are some enthusiastic reports of their value in postponing subsequent infarcts, their true value remains to be proved.

In the hypothyroid person, specific therapy postpones vascular disease; in the diabetic patient, neglect or obesity hastens its evolution.

Arteriosclerosis, removing people from active life when the period of maximum fertility has passed, is of benefit to the young if it relieves them of the care of parents, or brings them an inheritance as they enter adult life. But this biologic blessing must be paid for later, for the way to avoid the disease is to have, and to be responsible for, long-lived ancestors. In an urban society, this means to marry late and to have few or no children. The high incidence of arteriosclerosis in the social group which has longest urban existence—the Jews—is to be correlated with their maintaining the dietary taste for dairy products, and with the biologic advantage of losing the parents between the ages of 45 and 60 years. Any attempts to eradicate such a disease from an urban population will be frustrated by natural selection and the survival of more grandchildren in families with few grandparents. Those best fitted to survive in a world growing more urban are those who cease to require support as soon as their roles as parents have been completed. Atherosclerosis and hypertension are now the chief factors in determining that we do not overstay our allotted span of life too long.

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APPENDIX: TECHNIC OF MEASUREMENT OF ARTERIAL BLOOD PRESSURE

The following lines are quoted from the joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland.

1. Blood Pressure Equipment. The blood pressure equipment to be used, whether mercurial or aneroid, should be in good condition and calibrated at yearly intervals—more often if defects are suspected. (Mercurial preferred—British Committee.)

2. The Patient. The patient should be comfortably seated (or lying—British Committee), with the arms slightly flexed and the whole forearm supported at heart level on a smooth surface. If readings are taken in any other position, a notation of that fact should be made. The patient should be allowed time to recover from any recent exercise or excitement. There should be no constriction of the arm by clothes, etc.

3. Position and Method of Application of the Cuff. A standard-sized cuff containing a rubber bag 12 to 13 cm. in width should be used. A completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about 1 inch above the antecubital space and with the rubber bag applied over the inner aspect of the arm. The cuff should be of such a type and applied in such a manner that inflation causes neither bulging nor displacement.

4. Significance of Palpatory and Auscultatory Levels. In all cases palpation should be used as a check on auscultatory readings. The pressure in the cuff should be quickly increased in steps of 10 mm. Hg until the radial pulse disappears, and then allowed to fall rapidly. If the radial pulse returns at a higher level than that at which the first sound is heard, the palpatory reading should be accepted as the systolic pressure; otherwise the auscultatory reading should be accepted.

5. Position and Method of Application of Stethoscope. The stethoscope should be placed over the previously palpated brachial artery in the antecubital space, not in contact with the cuff. No opening should exist between the lip of the stethoscope and the skin; this should be accomplished with the minimum pressure possible. The hand may be pronated or supinated, depending on which position yields the clearest brachial pulse sounds.

6. Determination of the Systolic Pressure. The cuff should be rapidly inflated to a pressure about 30 mm. above the level at which the radial pulse can be palpated. The cuff should then be deflated *at a rate of 2 to 3 mm. Hg per second*. The level at which the first sound regularly appears should be considered the systolic pressure, unless, as pointed out above, the palpable level is higher, in which event the palpable level should be accepted. This should be noted.

7. Determination of the Diastolic Pressure and the Pulse Pressure. With continued deflation of the cuff, the point at which the sounds suddenly become dull and muffled should be known as the diastolic pressure. If

there is a difference between that point and the level at which the sounds completely disappear, the American Committee recommends that the latter reading should be regarded also as the diastolic pressure. This should then be recorded in the following form: RT* (or LT†) 140/80-70; or 140/70-0. If these two levels are identical the blood pressure should be recorded as follows: 140/70-70. The cuff should be completely deflated before any further determinations are made.

* RT = right arm.

† LT = left arm.

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Diseases of the Aorta

Ben Friedman

Congenital Anomalies of the Aorta

- Obstruction or Limitation of the Blood Stream
- Admixture with Unoxygenated Blood
- Compression or Displacement of Mediastinal Structures
- Syphilis of the Aorta
- Arteriosclerosis of the Aorta
- Dissecting Aneurysm

CONGENITAL ANOMALIES OF THE AORTA

Some congenital malformations of the aorta are entirely benign; others are incompatible with life beyond the intrauterine stage. Symptoms can be due to three fundamental defects:

1. Obstruction or limitation of the blood stream due to atresia, stenosis, and coarctation. They have been discussed in Chapter 236.

2. Admixture with unoxygenated blood resulting in cyanosis and anoxia. This may arise from a persistent truncus arteriosus, from aortic atresia with a patent ductus arteriosus, and from partial or complete transposition of the aorta. The tetralogy of Fallot and the Eisenmenger complex are the only conditions in this group likely to permit life to adult age (see Chapter 236).

3. Compression or displacement of mediastinal structures by "vascular rings." These anomalies of the aortic arch may occur as isolated defects or in combination with other malforma-

tions. They derive from the embryonic aortic arch pattern which encircles the primitive foregut. Complete and incomplete forms are observed with the descending aorta lying either to the right or to the left of the midline. In the complete type a functional double aortic arch encircles the esophagus and trachea. Variations occur in which portions of the right or left arch atrophy, resulting in unusual origin and position of the major branches. Most of these malformations are asymptomatic. Dysphagia (dysphagia lusoria) and respiratory distress occasionally result from compression of the esophagus, trachea, or recurrent laryngeal nerve by an anomalous subclavian artery which courses behind the esophagus, by undue tension of the ductus arteriosus and pulmonary trunks, or by a double aortic arch. The abnormal position of the aorta and the anterior displacement of the esophagus and trachea can be detected readily by means of the fluoroscope. The symptoms can be relieved surgically.

SYPHILIS OF THE AORTA

The *Treponema pallidum* is unique among parasites in its predilection for the aorta. The incidence of aortic involvement in large groups of untreated or poorly treated syphilitics has been estimated to be between 70 and 95 per cent. The

earliest lesions consist of perivascular inflammation and endarteritis of the *vasa vasorum* in the adventitia and media. Medial necrosis, fragmentation of elastic and muscle tissue, and scarring follow. The loss of elastic tissue results in dilatation varying from slight localized or diffuse widening to huge aneurysms. Gummatous aortic lesions are rare.

Clinically demonstrable syphilitic cardiovascular disease rarely occurs in individuals who have had syphilis for less than 10 years, or in those who have had even moderate antisyphilitic treatment in the early phase of the infection. Its incidence is highest in the fourth and fifth decades of life, in males, and in Negroes.

The clinical manifestations are determined in part by the localization of the lesions. Angina pectoris and aortic insufficiency arise as the result of involvement of the root of the aorta, at the site of the coronary ostiums, and at the insertions of the valves. Both of these crippling lesions may be influenced by congenital anatomic peculiarities: the first, by an abnormally high location of the coronary orifices above the sinuses of Valsalva; and the second, by extension of elastic tissue into the commissures below the upper level of the cusps. The clinical pictures of aortic insufficiency and coronary ostial stenosis have been described in Chapters 235 and 236.

Uncomplicated aortitis is the commonest manifestation of cardiovascular syphilis and the most difficult to diagnose. In its early phase it is indeed a pathologic and not a clinical entity. Symptoms are singularly absent and myocardial function is never embarrassed. A vague nondescript type of retrosternal pain occurs rarely, and is attributed to periaortitis or mediastinitis. The presence of angina pectoris, paroxysmal dyspnea or cardiac enlargement denotes either a syphilitic lesion involving the valves or the coronary orifices, or else an independent complicating disease. The two most reliable signs of uncomplicated aortitis are aortic dilatation and the presence of a ringing, tambour-like second aortic sound with or without a systolic murmur. Both signs are found in other conditions, such as hypertension and arteriosclerosis, and hence have little diagnostic significance unless these disorders are absent. Dilatation becomes apparent only when a sufficient amount of elastic tissue has been destroyed. Aortic widening occurs with advancing age, in arteriosclerosis, and to some extent in hyperten-

sion. The auscultatory signs are heard frequently in hypertension, advanced arteriosclerosis, fever, hyperthyroidism, anemia, emotional stress, or in any condition giving rise to an overactive circulation.

Uncomplicated syphilitic aortitis may be diagnosed in a known syphilitic who has had little or no treatment in the early phase of his infection, and who presents the auscultatory signs or widening of the aorta, especially in the ascending portion, in the absence of the disturbing complications listed above. It is the exceptional patient who meets these criteria. The vast majority of cases of uncomplicated syphilitic aortitis cannot be recognized clinically by the methods available at present.

Syphilitic aneurysms, like aortitis, occur with diminishing frequency from the ascending aorta distally toward the abdominal aorta. They may be single or multiple, diffuse or sharply localized, fusiform or saccular, smooth-walled or filled with large organizing thrombi. Aortic aneurysms rarely burden the myocardium, and then only secondarily as the result of abnormal communications subsequent to rupture into the pulmonary artery or, as in the case of aneurysms of the sinuses of Valsalva, into the right ventricle or atrium. Sudden death usually follows rupture with bleeding into the pericardium, bronchi, esophagus, or mediastinum. Many large aneurysms are surprisingly symptomless. In most instances, chronic disabilities develop due to compression, displacement, erosion, and interference with the circulation in neighboring structures.

The clinical picture is dependent on the size and site of the aneurysm and the direction in which it projects. Aneurysms which bulge anteriorly, particularly those located in the ascending aorta, are relatively asymptomatic. The prominent signs are related to the mass itself—i.e., visible pulsations or pulsating tumors, widening of the area of percussion dullness, localized shocks, thrills, and systolic murmurs at the base of the heart. In advanced cases the anterior chest wall may be eroded and deformed. Aneurysms of the arch, and those pointing posteriorly and medially, are more likely to give symptoms and signs due to impingement on neighboring structures, and little or no clinical evidence of the mass itself. The structures encroached on, and the ensuing symptoms and signs, may be tabulated in order of frequency as follows:

Structure	Symptoms	Signs
Periaortic or mediastinal tissues	Pain	X-ray appearance of widening of mediastinal shadow
Trachea or bronchi	Cough; dyspnea; hemoptysis; recurrent bouts of "pneumonia" with fever and pleural pain	Tracheal tug Atelectasis Pneumonitis Bronchopneumonia Bronchiectasis
Recurrent laryngeal nerve	Hoarseness; brassy quality to cough Aphonia rarely	Paresis or paralysis of left vocal cord
Superior vena cava	Edema in head, neck, and arms	Venous distention in neck, upper chest, and arms
Esophagus	Dysphagia	Esophageal displacement on barium swallow
Interference with blood flow in arterial branches:		
1 Innominate common carotid or subclavian	Generally none	Difference in blood pressure in arms Asymmetry in carotid pulsations
2 Intercostal arteries	Neuritic pains	Evidence of myelitis or neuritis
3 Renal arteries	May have symptoms of uremia	Hypertension and renal failure
Spine	Severe boring pains in back	Erosion of bone Horner's syndrome if in cervical region Neuritis or radiculitis

Aneurysms may occasionally be due to arteriosclerosis, rheumatic fever, or congenital anomalies. With rare exceptions, patients with syphilitic cardiovascular disease will have corroborative evidence of syphilis, either by history or serologic tests in blood or spinal fluid, or by physical signs apart from the cardiovascular system. Arteriosclerotic, unlike syphilitic, aneurysms involve the descending more often than the ascending aorta, and seldom erode bone. Advanced syphilitic aortitis is frequently accompanied by extensive atherosclerosis which may be reflected radioscopically in disproportionate calcification in the

ascending aorta. Arteriosclerotic aneurysms of the abdominal aorta usually occur below the renal arteries, while syphilitic aneurysms occur generally at or above the renal arteries.

Widening of the aorta is often impossible to demonstrate without the aid of the x-ray. For this reason examination in every known syphilitic case should include fluoroscopy and x-ray of the aorta in posteroanterior and left oblique or lateral views. Expansile pulsation is sometimes damped by intraluminal clots and periaortic inflammation, thus presenting an appearance which simulates a nonvascular tumor. Visualization of the aorta with "Diodrast" can be of great help in differential diagnosis. When this procedure is not feasible, a brief course of antisyphilitic therapy will sometimes reduce periaortic inflammation and thus enhance pulsations. Conversely, in the case of radiosensitive mediastinal tumors, a therapeutic trial of radiotherapy will reduce the tumor.

Treatment of patients with cardiovascular syphilis concerns itself first with management of the complications such as congestive heart failure, angina pectoris, and pulmonary infection secondary to bronchial compression. It is wise to withhold specific spirocheticidal agents until these complications are reasonably well controlled.

It is generally agreed that antisyphilitic drugs administered in the early stages of syphilis will effectively prevent crippling cardiovascular manifestations later in life. There is no unanimity of opinion concerning their use once cardiovascular disease has become established, particularly when prolonged and potentially toxic forms of therapy have had to be employed. The discovery of penicillin as a nontoxic agent effective against tertiary syphilis has influenced the decision in favor of specific treatment of all patients with cardiovascular syphilis. Unfavorable reactions attributable to specific antisyphilitic treatment are fortunately very uncommon in cardiovascular syphilis. They are particularly dangerous in persons with syphilitic ostial stenosis. Their appearance may be minimized by cautious initial treatment with mild treponemicidal drugs. The regimen employed by the author consists of preliminary preparation with four to eight injections of bismuth subsalicylate, 0.2 Gm. each. The longer preparatory period is employed in individuals suspected of having involvement of the coronary ostiums. This is followed by penicillin, beginning with

doses of 5000 units every three hours, doubling the dose every three days up to 50,000 units every three hours, for a total dosage of 6 to 10 million units. The optimum plan of treatment is uncertain and may not be established for many years. With further experience it is possible that the treatment period may have to be prolonged. The slowly absorbed, long-acting penicillin preparations have certain advantages from the point of view of ease of administration and maintenance of sustained therapeutic levels in the tissues. They as well as the newer orally effective antibiotic agents will undoubtedly gain wider use in the management of late syphilis as the medications are perfected and the time-dose relationships are defined.

Antisyphilitic treatment can be expected to kill spirochetes and relieve active inflammation. It may relieve some of the symptoms and may retard progression of the disease and prolong life. No amount of specific treatment will restore elastic tissue which has been lost. An aneurysm, once formed, will persist, and may progress because of local hemodynamic changes incidental to abrupt widening in the size of the stream bed. Attempts have been made to reinforce the wall of an aneurysm by wiring and electrocoagulation within the sac, or by wrapping the outside with "Polythene Cellophane." These procedures have had limited application and doubtful success. The advances of the past few years in vascular surgery make it seem possible that short-circuiting operations may soon be feasible in appropriate cases.

ARTERIOSCLEROSIS OF THE AORTA

Arteriosclerosis is the most common affection of the aorta. The factors which are believed to contribute to its development are increased intravascular tension, disturbances in circulating lipoids, affections of the nutrient vessels, and the ill-defined changes associated with aging. It is not a single entity but consists of varying combinations of proliferative and degenerative processes. Dilatation, elongation, and tortuosity of the aorta result from loss of elastic fibers and replacement of the muscle coat with collagenous tissue. Aneurysm is uncommon and is more likely to affect the descending aorta. Intimal changes range from microscopic deposition of lipoid material to pronounced thickening and formation of large atheromatous nodules or plaques. Secondary

changes may develop in the form of necrosis, small hematomas, calcification, and ulceration.

Arteriosclerosis of the aorta is generally symptomless. The major clinical manifestation arises from rigidity of the wall. The loss of elasticity results in an increase in pulse pressure, manifested by a rise in systolic pressure, the diastolic remaining unchanged or declining slightly.

Thrombosis may develop in the aorta secondary to trauma or to retroperitoneal inflammation, or without apparent cause. It occurs more often at the site of an aneurysm, an ulcerated atherosclerotic plaque, or of an embolus which has lodged at the bifurcation. The symptoms depend upon the extent of the lesion and the rapidity with which it develops. Gangrene of the legs occurs mainly in the embolic or rapidly progressive thrombotic disease. The slowly progressive type develops insidiously, often over a period of years, and is manifested by weakness or intermittent claudication in the legs and thighs, diminished or absent femoral pulses, muscular atrophy, and failure of penile erection. Terminally, the process may extend to the mesenteric and renal vessels, resulting in visceral infarction and uremia.

An arteriosclerotic aneurysm frequently may be identified roentgenologically by the presence of calcific densities which outline the dilated walls. Changes in lumen in the lower abdominal aorta can be visualized by special angiographic techniques which involve intraaortic or intraarterial injection of "Diodrast." The thrombosed lower abdominal aorta has been resected successfully in a few cases.

DISSECTING ANEURYSM

Dissecting aneurysm of the aorta has been recorded on the average of once in about 380 necropsies. It has been observed frequently as a complication in coarctation of the aorta, rarely in arteriosclerosis, and almost never in syphilitic aortitis. In most cases the disease is associated with a change in the media described first by Erdheim as cystic medionecrosis. The defect in the principal supporting structure in the aortic wall provides a weak point which may rupture under conditions of increased intravascular tension, the tear involving the overlying less elastic intimal lining. This occurs usually in the root, less often at the sharp turns or elsewhere in the aorta. The tear may heal with formation of a local scar in the aortic wall. The pulsating blood

stream penetrates the wall at the site of the tear and dissects along cleavage planes on either side of the media. The dissection may extend centrally into the sinuses of Valsalva, or peripherally along the entire length of the aorta, eventually perforating through the adventitia.

The etiology is unknown. Hypertension is present in most cases. The condition has been reported in a few instances following thyroidectomy in persons with severe hypertension. There is evidence that the primary disturbance may at times be occlusive or inflammatory disease in the vasa vasorum. The pathologic picture has been reproduced experimentally by destroying a segment of the adventitia rich in nutrient vessels.

Dissecting aneurysm occurs predominantly in middle-aged and elderly persons, and affects males more often than females. The symptoms, signs, and differential diagnosis have been discussed in detail in Chapter 3. The diagnosis can be established on clinical grounds. The three main features are the character of the pain, the evidence of interference with arterial flow in various aortic tributaries, and the evidence of terminal perforation. The chief characteristics of the pain are attainment of peak severity at the onset, its persistence, and wide radiation.

The blood flow may be impaired in any of the branches of the aorta from the root to the bifurcation. The chief manifestations may be reduced or absent arterial pulsations in the neck or legs, syncope, renal or mesenteric infarction, and bizarre myelopathy. Electrocardiographic changes of myocardial infarction are not present except in the rare instances when the dissection involves the coronary ostiums.

Distortion of the aortic valves gives rise to systolic and diastolic murmurs at the base. Low-grade fever, leukocytosis, and elevated sedimentation rate appear as indications of tissue necrosis if the patient survives long enough. Perforation of the adventitia may occur anywhere along the

course of the aorta, resulting in hemorrhage into neighboring structures, symptoms of shock, and death. Perforation of the aorta near the root usually results in hemopericardium and cardiac tamponade. The ensuing clinical picture resembles closely that of myocardial infarction with shock, distended neck veins, and widened area of cardiac dullness. Of aid in differential diagnosis is the absence of the characteristic electrocardiographic pattern of myocardial infarction. The diagnosis may be confirmed when rapid widening of the aortic shadow can be detected on successive x-ray films. Angiocardiogram in some instances may reveal the distortion in the aortic lumen and corresponding thickening in the wall. The patient is usually too ill to permit much manipulation, and x-ray films taken at the bedside are not often helpful.

Most patients die several hours or days after the onset of pain. Prolonged survival, in some cases for years, has been reported in individuals in whom the dissecting process is directed along a plane close to the intima and terminates in one or more perforations back into the lumen of the aorta, forming a multichanneled vessel. Treatment is entirely symptomatic.

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Peripheral Vascular Disease

Eugene A. Stead, Jr.

Symptoms and Signs Pointing to Peripheral Vascular Disease
Points in History and Physical Examination
Disturbances in Arterial Function
Special Points in History and Physical Examination
Organic Obstruction
Spasm of Arteries and Arterioles
Disturbances in Small Vessels from Changes in Blood
Prognosis in Disease of Arteries
Treatment of Arterial Insufficiency
Disturbance in Venous Function
Varicose Veins
Thrombophlebitis
Pulmonary Embolus and Infarction
Disorders of Peripheral Lymphatic Vessels
Acute Lymphangitis
Chronic Lymphatic Obstruction
Leg Ulcers in Patients Without Peripheral Vascular Disease
Use of Special Diagnostic Tests

SYMPTOMS AND SIGNS POINTING TO PERIPHERAL VASCULAR DISEASE

POINTS IN HISTORY AND PHYSICAL EXAMINATION

One should suspect peripheral vascular disease in a patient with the following symptoms and signs:

1. Pain in an extremity which is induced by exercise and relieved by rest. Pain which is influenced by posture, is localized to one digit, is unilateral, or is paroxysmal.
 2. Impaired pulsations of peripheral arteries.
 3. Abnormal color of the skin, particularly when affected by raising or lowering of the part.
 4. Gangrene, ulceration, impaired nail growth, scleroderma, excessive calluses, or paronychial infections.
 5. Abnormal pulsations, enlarged veins, or edema.
 6. Unusual warmth or coldness.
 7. Swelling, atrophy, or difference in length of extremities.
 8. Auscultatory evidence of arteriovenous fistula.
 9. Cyanosis of digits when immersed in cold water.
 10. Peripheral neuritis.
- If the above signs and symptoms are ab-

sent, peripheral vascular disease need not be considered.

The arteries, capillaries, veins, and lymph vessels may be involved separately or in varying combinations. The disturbances may be from organic disease of the vessels or from abnormal constriction or dilatation caused by dysfunction of the autonomic nervous system.

DISTURBANCES IN ARTERIAL FUNCTION

SPECIAL POINTS IN HISTORY AND PHYSICAL EXAMINATION

Arterial insufficiency causes disturbances in nutrition to the part. The following points in the history and examination are to be noted:

1. History of Sensitivity to Cold with Blanching or Cyanosis of Digits. On examination, the part with arterial insufficiency may be colder than the corresponding part of the opposite extremity.

2. Symptoms of Muscle and Nerve Ischemia. Pain which develops in the muscles of the foot or calf on walking and disappears on rest is called intermittent claudication. If exercise is continued after pain is present, the muscles may become tender. In more severe ischemia of the leg, pain may occur at rest and be relieved by dependency. The pain of ischemic neuritis is severe and diffuse, with severe exacerbations. Sharp shooting pains may dart through the entire extremity. The acute paroxysms are apt to occur at night.

3. State of Peripheral Vessels. Presence or absence of femoral, popliteal, dorsalis pedis, and posterior tibial pulses is noted. Gangrene of the digits may occur without disturbances in these pulses. In the absence of a palpable pulse, the skin may show no evidence of malnutrition.

4. Blanching on Elevation, and Redness and Cyanosis on Dependency. On elevation to a 90-degree angle, the part becomes pale and at times white. The extent of the pallor indicates the extent of the arterial insufficiency. If only the toes

or a part of a toe are involved, the pallor is limited to the ischemic area. The color returns slowly on lowering the part to heart level. The pallor occurs on elevation because the blood in the capillaries and venules drains out of the part by gravity, and because the effective arterial pressure is lowered by having to overcome the hydrostatic force of a column of blood extending from the heart level to the elevated part. Some pallor on elevation will occur in a normal foot, but the pallor of arterial insufficiency is much more marked.

When the part hangs down, the blood flow is increased temporarily over the horizontal position because the hydrostatic pressure is added to the pressure created by the heart. The increase in arterial pressure is effective until the veins fill. Then it is opposed by an equal column of blood on the venous side, and the pressure differential between artery and vein returns approximately to the differential present in the horizontal position. The minute vessels of the part, being in a state of chronic injury because of an inadequate circulation, are dilated. When these vessels first fill, they are red. Varying degrees of cyanosis gradually develop because of the slow blood flow.

5. Atrophic Changes in Skin and Edema. The skin becomes thin and atrophic. Slight edema with loss of normal wrinkles is common. If the patient keeps the foot dependent day and night to relieve pain, pitting edema may develop from the combination of a high capillary pressure from dependency and the damaged state of the capillaries caused by ischemia.

6. Gangrene.

7. Infection. Devitalized tissue offers a good place for infection to spread. When peripheral neuritis is present, infection may be more prominent than ischemia. Osteomyelitis may occur.

8. Neurologic Examination. Peripheral neuritis is a common complication of diabetes. Buerger's disease, periarteritis nodosa, and arteriosclerosis may cause neuritis because of the interference with the blood supply to the nerves. In periarteritis, motor paralysis, as well as sensory loss and pain, is common.

9. Occupation. There may be a history of unusual exposure to cold and dampness. Use of the pneumatic hammer has been said to cause Raynaud's phenomenon.

10. Determination of Cause of Arterial Circulatory Insufficiency. If the findings are those of

arterial circulatory insufficiency, it must be determined whether the insufficiency results (a) from occlusive disease entirely, (b) from overactivity of the sympathetic nervous system, (c) from abnormal reaction of the blood vessels to cold, (d) from the effect of cold agglutinins or cryoglobulins on the physical state of the blood, or (e) from a combination of mechanisms. The constrictor effect of the autonomic nervous system may be removed by paravertebral block of the appropriate sympathetic ganglion with cocaine or by release of vasoconstrictor tone by body heating. In either method, the subject, with body exposed, is placed in a cool room (temperature 18° to 20° C.). The body temperature may be raised by enclosing the trunk in a heating cabinet or by immersing two uninvolved limbs in water baths at 43° C. for 40 minutes. When vasodilatation is produced in the upper extremities by body warming or by blocking of the sympathetic ganglion, the temperature of the digits rises rapidly to between 30.5° and 33° C. If the temperature rises to between 27° and 29° C., there is moderate organic vascular disease. If no rise occurs or if the temperature falls, advanced local arterial disease is present. Body warming is the simplest and most effective method of relieving vasoconstrictor tone in the upper extremities. It fails occasionally in the lower extremities. Therefore, if full vasodilatation does not occur, paravertebral block is indicated in the lower extremities.

ORGANIC OBSTRUCTION

Peripheral Arteriosclerosis. The etiology and pathology of peripheral arteriosclerosis have been discussed in Chapter 240. The history and physical findings are those of arterial insufficiency. The diagnosis is based on the following factors:

1. Age of the patient. It usually occurs after 50.
2. Sex. Males are more commonly affected than females.
3. Diabetes. The incidence of arteriosclerosis is increased in patients with diabetes.
4. Evidence of arteriosclerosis is usually present bilaterally, although the symptoms may be unilateral.
5. There are no symptoms of arterial disease in the upper extremities.
6. The arteries, as seen by x-ray, are frequently calcified.

7. In patients with diabetes, the small vessels may be occluded, while the larger vessels are only moderately diseased. Local gangrene of the skin of the toes may occur, even though the rest of the foot is warm.

8. In patients with diabetes, neuropathy is common.

Thromboangiitis Obliterans. This condition was described fully by Buerger in 1908. It is an obliterative vascular disease affecting chiefly the peripheral arteries and veins of males in early adult life. The etiology is unknown. It is more common in Jews. The disease involves primarily the blood vessels of the extremities. Involvement of other vessels occurs only after extensive lesions have developed in the extremities. Usually the process begins in medium- and small-sized arteries, and affects large arteries, such as the femoral and brachial, only in the late stages and in severe progressive disease. Veins are involved less commonly. The lesion is a nonsuppurative panarteritis or panphlebitis and is segmental, leaving normal vessels between diseased segments. Thrombus formation follows, in which recanalization may occur. The lesions come in crops, producing complete and usually permanent obstruction, followed by the development of extensive collateral circulation. The history and physical findings are those of arterial insufficiency or superficial phlebitis. The diagnosis is based on these considerations:

1. Age. Onset is usually between 20 and 45 years of age.

2. Sex. Males predominate in a ratio of 75 to 1.

3. Race. One half of patients is Jewish.

4. Migratory phlebitis preceding or accompanying arterial disease.

5. Severe pain at rest from ulceration or from ischemic neuritis.

6. Absence of calcification as seen by x-ray.

7. Small vessels of the hands may be involved. Thrombosis of mesenteric, coronary, cerebral, or renal arteries is not uncommon.

Thrombosis. Thrombosis of the larger arteries of the lower extremities is common in the natural course of arteriosclerosis and thromboangiitis obliterans. Whether or not dramatic symptoms of acute arterial insufficiency appear will depend on the degree of collateral circulation which has developed. Gradual narrowing of a major vessel may progress unnoticed to complete occlusion, because the symptoms of arterial insufficiency

may not develop until the collateral channels begin to thrombose.

Embolus. Emboli are usually fragments from more centrally placed thrombi. The occurrence of sudden arterial insufficiency without physical findings of marked peripheral vascular disease generally indicates an embolus. The common sources are:

1. Mural thrombus from the left atrium in a heart with chronic auricular fibrillation.

2. Mural thrombus from the left atrium in a heart with mitral stenosis, and commonly, but not necessarily, with auricular fibrillation.

3. Mural thrombus from myocardial infarction of the left ventricle or, more rarely, from acute or subacute myocarditis.

4. Thrombi on valves from subacute or acute bacterial endocarditis.

5. Thrombi in the aorta or its large branches.

6. Venous thrombosis in patients with a right-left shunt from congenital heart disease.

Emboli are likely to lodge at the bifurcation of large vessels. A saddle embolus riding on the bifurcation of the aorta may cause circulatory insufficiency in both lower extremities. The signs of circulatory insufficiency are usually considerably distal to the embolus because of the effectiveness of collateral circulation. The degree of circulatory impairment caused by arterial obstruction and that caused by secondary arterial spasm cannot be determined on inspection. The effects of paravertebral block must decide this question. The local examination reveals the symptoms and signs of arterial insufficiency. Loss of motion and of sensation may occur rapidly. Pain has been discussed on page 76. At first there is no pain at the site of the embolus, but tenderness may develop after a few hours, as the embolus sets up a local inflammatory reaction in the vessel.

Exposure to Cold; Trench Foot. Extremities with normal blood vessels are injured by prolonged exposure to cold. Dependency and wetness combined with cold cause tissue damage even though actual freezing of the tissues does not occur. On warming, the injury results in extreme vasodilatation with swelling of the part because the capillaries have been damaged. Later, true capillary flow in the skin may cease because of capillary stasis and thrombosis while flow continues through A. V. communications. This gives the clinical picture of superficial gangrene in a

warm part. Whether complete recovery or gangrene occurs depends upon the extent of the injury. Persistent tenderness because of fibrosis and ischemic neuritis may develop.

Obstruction of Main Arterial Trunk by External Pressure, or by Syphilitic or Dissecting Aneurysms. Broad insertion of the scalenus anticus muscle with or without cervical rib is a rare cause of Raynaud's phenomenon or organic arterial occlusion. The vascular disturbances may be reflex from compression of a portion of the brachial plexus. At times, trauma from compression of the artery causes thrombus formation with or without embolic phenomena distal to the area of injury.

Persons who sleep with their arms hyperabducted above the head or whose occupation causes them to work with their arms hyperabducted may develop numbness and tingling from occlusion of the subclavian-axillary vessels. Usually discomfort causes the arms to be moved to a different position, but gangrene of the fingers has been reported in some cases.

Syphilitic aneurysm or dissecting aneurysm may cause obstruction to the main artery supplying the limb.

SPASM OF ARTERIES AND ARTERIOLES

Raynaud's Disease and Raynaud's Phenomenon.

Raynaud's disease is idiopathic bilateral paroxysmal contraction of the arteries and arterioles of the digits, usually without local gangrene. The primary fault seems to be a local sensitivity of the digital vessels to cold. The attacks are precipitated by cold or emotion, and are relieved by warming. Raynaud's phenomenon consists of paroxysmal attacks of ischemia of the digits occurring in the course of other diseases, such as scleroderma, thromboangiitis obliterans, cervical rib, arteriosclerosis, crutch paralysis, and pneumatic hammer disease. Diagnosis of Raynaud's disease from the history and examination is made from the following points:

1. Sex. Females are affected much more often than males.

2. Age. It is less common before puberty and after 40, though it may occur at any age.

3. Bilateral and symmetric involvement of digits. It is more common in hands than in feet.

4. Attacks of cyanosis can be reproduced by immersion of hands in cold water. The digital ar-

teries and arterioles contract. The finger becomes blue if the minute vessels remain dilated, pale if they contract. On rewarming, reactive hyperemia occurs.

5. If the disease is of many years' duration, small superficial areas of gangrene may occasionally be present.

Diagnosis of Raynaud's phenomenon is made if the above findings are noted in conjunction with organic arterial disease, scleroderma, cervical rib, or history of the use of a pneumatic hammer. In the beginning, it is frequently impossible to differentiate between benign Raynaud's disease and progressive scleroderma with Raynaud's phenomenon.

Scleroderma. This is a diffuse disease of the collagenous system with skin and visceral manifestations. The etiology is unknown. Raynaud's phenomenon is frequently seen before the characteristic skin changes occur. In many instances the skin changes are localized to the distal portions of the extremities (acroscleroderma). The skin becomes boardlike, and is bound down to the underlying tissues. Decreased sweating, increased pigmentation, and calcification of the skin occur. Gangrene of the digits, with marked shortening of the phalanges, is not uncommon (sclerodactylia). Involvement of the esophagus, heart, and lungs may occur early or late in the disease.

Ergotism. Spasm of the arterioles with thrombosis and gangrene is produced by ergot poisoning. In past times, it was seen in epidemic form as the result of the contamination of rye with ergot fungus (*Claviceps purpurea*). It is occasionally seen after the repeated use of ergot to induce abortion or after the use of ergotamine tartrate for pruritus.

Reflex Spasm. Any painful area in the extremities may cause symptoms and signs of ischemia from stimulation of the autonomic nervous system. The ischemia of embolus or thrombus is intensified by reflex activity. Ischemia from organic disease of the vessels, from arteriosclerosis, or from thromboangiitis obliterans may be intensified by active vasoconstriction mediated through the autonomic nerves.

DISTURBANCES IN SMALL VESSELS FROM CHANGES IN BLOOD

Changes in the physical state of the blood may cause small-vessel obstruction. Patients with

sickle-cell anemia are prone to multiple thromboses. The leg ulcers seen in this disease are probably an example of small-vessel thrombosis on the basis of mechanical obstruction caused by the sickled cells. When the titer of cold agglutinins is high, exposure to cold may cause Raynaud's phenomenon. The development of globulins which precipitate in the cold (cryoglobulins) in patients with leukemia or myeloma may also cause Raynaud's phenomenon.

PROGNOSIS IN DISEASE OF ARTERIES

The prognosis will depend upon the age of the patient, the rate of progression of the primary disease, and the degree of the development of the collateral circulation. In *arteriosclerosis*, the patients are elderly, the coronary and cerebral vessels are apt to be affected by the disease, and all of the vessels of the extremities are usually diseased. Once gangrene develops, the chances of saving the extremity are not good.

In *thromboangiitis obliterans*, the prognosis for life is usually good. If symptoms are present which indicate that visceral vessels are involved, the prognosis becomes more guarded. The chances of losing a limb are more difficult to estimate. Fingers are occasionally lost; the hand almost never. One or both lower limbs are more frequently lost. The clinical course is very variable. In some patients, there is no further progression after one or two episodes of arterial occlusion. In others, the disease is moderately progressive with long periods of relative quiescence between periods of arterial occlusion. The progression of the disease exceeds the formation of collateral circulation, and eventually damage to the vascular tree is moderate to severe. In time, new lesions may cease to develop. In certain patients, occlusion of large arteries occurs with severe, persistent arterial insufficiency or gangrene. In a few, the disease is rapidly progressive and gangrene develops in two or more extremities.

In *arterial obstruction* from an embolus or thrombus, the prognosis is greatly influenced by age and the general condition of the patient. The embolus would appear to have the best prognosis because the peripheral arterial tree might be undamaged. However, this assumption is modified by the fact that the embolus frequently comes from a mural thrombus caused by congestive failure or myocardial infarction, and the mor-

tality and development of gangrene in embolus and thrombosis are approximately the same.

In *Raynaud's disease*, as defined in this discussion, the prognosis is good by definition. Complications are rare and the digits are not lost. In *Raynaud's phenomenon* accompanying other disease, the prognosis is that of the primary disease. Thus, in scleroderma associated with Raynaud's phenomenon, the outlook depends on the extent and rate of progression of the scleroderma. This is true whether the sclerodermatous changes are generalized or are still localized to the extremities.

TREATMENT OF ARTERIAL INSUFFICIENCY

Chronic Arterial Insufficiency. Since the etiology of arteriosclerosis and thromboangiitis is not known, treatment directed toward prevention or removal of the primary factors is not possible.

GENERAL CARE. Three points in general care should be stressed.

1. LOW-CHOLESTEROL DIET IN ARTERIOSCLEROSIS. Many patients with arteriosclerosis have high serum cholesterol values. There is evidence that the cholesterol levels can be lowered in many instances by a low-cholesterol diet if it is followed over long periods. This offers the only direct approach to treatment of the arteriosclerotic process itself.

2. DIABETES. In any patient over 40 with peripheral vascular disease, the possibility of diabetes mellitus should always be remembered, and a fasting blood sugar level determined even if there is no glycosuria.

3. COMPLETE ABSTINENCE FROM TOBACCO. The course of thromboangiitis is modified if smoking is stopped completely. Many physicians are unwilling to assume responsibility for the care of a patient with thromboangiitis unless the patient consents to give up smoking entirely. Many observers advise against smoking in arteriosclerosis, although the adverse effects of smoking seem less certain here than in thromboangiitis.

CARE OF LOCAL AREAS. The care of the local area with circulatory impairment from arteriosclerosis, thromboangiitis, or damage from exposure to cold is similar. The greatest danger is gangrene in the toes. This is usually precipitated by *trauma, infection, or burns*, all of which can ordinarily be prevented by good foot care. Care of the feet means careful washing in tepid water.

at night; keeping the skin pliable with lanolin; use of a bland dusting powder to absorb perspiration; use of warm, finely-woven woolen socks in winter; careful cutting of the nails, with the end of the nail cut straight across to avoid ingrowing nails. ~~X~~ Epidermophytosis must be treated when present, but strong ointments or solutions are to be avoided. Twice daily soaking in 1:8000 potassium permanganate solution is satisfactory. Dry heat is contraindicated. Remember that sensation may be impaired because of peripheral nerve involvement. Heat above the temperature of the blood raises the temperature of a part with impaired blood supply much more rapidly than that of a normal part. In this situation the blood acts as a cooling system to lower the temperature of the tissues, and if this cooling system does not function efficiently, burns occur. Heating the part by reflex vasodilatation is safe, local heat may raise the metabolism without a corresponding increase in blood supply, and precipitate gangrene. The shoes should fit perfectly and should be broken in gradually. If any break in the skin or blister occurs from any cause, the patient should go to bed and call his physician. Reflex vasoconstriction is to be minimized. In the winter, there is need not only for adequate protection for the part itself, but also for attention to preserving the warmth of the body. No local protection will keep the extremities warm if the trunk is cool and the body is attempting to preserve heat.

Reflex vasoconstriction may accompany organic occlusive vascular disease. If body warming or paravertebral block demonstrates release of reflex tone, improvement of the circulation to the extremity by sympathectomy is indicated. Some observers have reported improvement after sympathectomy even though paravertebral block caused no rise in temperature. Sympathectomy is occasionally harmful in advanced disease, because it may divert the greatly limited supply of blood from the severely ischemic tissues to the more normal tissues of the part.

~~X~~ Buerger's exercises are useful. They have the disadvantage of being too tiresome to continue for a long period of time. They help because, when the foot is dependent, the effective arterial pressure is increased until the pressure from gravity is counteracted by an equal column of blood in the veins. The foot is emptied by raising it just far enough above heart level to produce collapse of the veins and slight pallor. It is then returned

to the dependent position. The ideal conditions are (1) maximum lowering of the foot below heart level, leaving it there until the veins are full, and (2) the least elevation for the shortest period of time which will suffice to empty the foot. When the valves of the veins of the legs are competent, walking slowly is an effective form of Buerger's exercises. The contraction of the muscles forces blood up the deep veins, the venous pressure falls sharply as the muscles relax, and the high arterial pressure produced by gravity is effective until the veins fill.

Pyogenic infections of the feet and toes are common in patients with impaired blood supply. This is particularly true if peripheral neuritis is present. If an apparently gangrenous part is warm, infection is playing an important role, and intensive penicillin therapy may greatly change the picture. Each time the doctor must ask himself: Is infection or ischemia the primary cause of the acute episode?

Acute Arterial Insufficiency. In the acute circulatory insufficiency caused by thrombosis or embolus, immediate and repetitive release of sympathetic tone by paravertebral blocks of the sympathetic chain is essential. Tetraethylammonium bromide or "Priscol" may be tried if the necessary equipment for the paravertebral block is not at hand. The coagulability of the blood is lowered by the immediate intravenous injection of heparin, and, after determining the prothrombin time, administration of dicumarol is started by mouth. Heparin is continued at four-hour intervals until the dicumarol has lowered the prothrombin concentration to effective anticoagulant levels. If the arterial insufficiency is the result of an embolus, effective anticoagulant therapy must continue for approximately three weeks until there has been time for the site of the embolus to be covered with endothelium.

Operative removal of an embolus may be considered if surgery is available in the first 8 to 10 hours. In most instances, the complicating heart disease or generalized vascular disease makes surgery inadvisable.

The part should not be elevated. The body should be heated, but local heat should not be applied to the involved extremity. Some authorities advise active cooling or even refrigeration of the part during the interval between the occlusion of the artery and the consideration of surgery.

Raynaud's Disease. The body should be dressed warmly so that the vessels in the hands and feet will dilate to help dispose of body heat. The hands and feet should be protected with warm socks and gloves. Minor episodes of "dead fingers" should not occasion alarm. If these measures are not adequate, "Priscol" given orally in doses of 25 to 75 mg. every three or four hours is frequently helpful.

Raynaud's Phenomenon. Adequate heat to the body and protection of the extremities from cold and trauma are important. The response of the underlying disease to therapy is more important than the treatment of the vasospasm. When associated with scleroderma, the prognosis is guarded. "Priscol" has been reported to be effective in controlling the vasospasm. Sympathectomy may be tried, but the effect is usually temporary. Testosterone has been reported to have a favorable effect in scleroderma when given for several months.

Amputation. The indications for amputation are: (1) gangrene, (2) uncontrollable infection, (3) intractable pain, and (4) such complete loss of function from deformity or contracture that the limb is a burden. Amputation is a last resort, and conservative therapy has saved many limbs. The site of amputation must be at a level where tissue nutrition is good. In the last analysis, the amount of bleeding at operation and the appearance of the tissues after incision determine whether the stump will be viable. Usually, clinical observation determines the level of the trial incision, but special tests such as the appearance time of intravenous fluorescein and the effect of intradermal histamine may be helpful.

DISTURBANCE IN VENOUS FUNCTION

VARICOSE VEINS

Dilatation and tortuosity of the superficial veins of the lower extremities result from constitutionally defective valves affected by postural strain, or from the enlargement of the superficial circulation to compensate for obstruction of the deep circulation. The obstruction of the deep circulation usually results from deep thrombophlebitis. Increased blood flow from an acquired or congenital arteriovenous fistula is a rare cause of varicosities.

In a normal subject who stands motionless for a short time, the hydrostatic pressure in the leg

veins is equal to the height of a column of blood extending from the fourth rib to the level of the vein. In a man 6 feet in height, the pressure at the ankle is about 105 mm. Hg. Blood from the foot is returned by the force of the heart beat and all of the valves are open. These pressure relations are the same, therefore, in valved and nonvalved veins. On contracting the muscles of the leg and thigh, blood is forced up the extremity by the high intramuscular tension. With normal valves, it cannot be forced downward or outward into the superficial circulation through the communicating veins. The blood in the superficial veins of the leg is not forced upward by the contraction because the skin tension does not exceed the hydrostatic pressure. When the extremity is relaxed, blood does not flow downward into the muscles because the valves control it. Blood enters the veins in the muscles from the arteries and from the superficial veins by way of the communicating veins. Back flow from the cava is prevented by valves, and the runoff through the communicating veins lowers the pressure in the superficial veins effectively. The fall in hydrostatic pressure in the venous system lowers capillary pressure effectively and prevents edema. When the valves of the veins are destroyed, the venous and capillary pressures are not lowered by exercise. Chronic edema, petechial hemorrhage, poor drainage, and infection frequently result.

Varicose veins fall into the following groups: (1) Simple dilatation of the veins with competent valves. The lowering of capillary pressure by exercise is maintained and edema does not result. Superficial venous thrombosis in the dilated, tortuous vessels may be troublesome. (2) Varicose veins with incompetent valves in the superficial veins, but competent perforating and deep valves. On walking, the venous pressure is not lowered unless the superficial veins are prevented from filling from above by local pressure. When the superficial veins are correctly obstructed by a tourniquet, exercise effectively lowers the venous pressure. (3) Varicose veins with incompetent valves in the superficial and communicating systems. In many of these patients the varicosities have resulted from thrombophlebitis of the deep veins, and the valves of the deep veins are destroyed. Exercise has no effect in lowering the venous pressure when walking. Brawny edema may mask the superficial varicosities, and their extent is rarely realized until the venous tree is

visualized by the use of "Diodrast." Intractable chronic ulcers are common. (4) Rarely, the deep veins are completely obstructed, and the superficial veins are needed to return blood from the limb.

Treatment of the first two groups by the combination of high ligation and injection of sclerosing solutions, or removal by vein stripping, is satisfactory. The treatment of the last two groups is less satisfactory, and prevention by more intensive treatment of the deep-vein thrombophlebitis is the most satisfactory answer. Destruction of the superficial varicose veins may be helpful even if the valves of the deep veins are destroyed, because the varicose superficial veins are rarely necessary to return blood from the leg. Once the condition is present, it is beneficial to prevent edema formation by application of external force to counteract the effect of gravity. Bed rest with elevation of the part allows healing. The application of pressure bandages or of a jelly boot prevents the breakdown of the healed lesion when the patient is up. One should remember the magnitude of the hydrostatic force one must counteract when the patient stands. "Ace" bandages are rarely adequate; a pure rubber roller bandage 3 inches wide and 15 feet long is much more effective.

THROMBOPHLEBITIS

Thrombus formation in veins is common. Dilated, tortuous, superficial varicose veins frequently become tender and hard, with redness of the overlying skin. The inflammatory reaction usually subsides uneventfully, and embolic complications are unusual. Recurrent superficial venous thrombosis is a common occurrence in the natural history of thromboangiitis obliterans. Local trauma from the administration of various solutions and medications is a not uncommon cause of superficial thrombophlebitis. Again, embolic phenomena are rare.

Thrombus formation in veins occurs at times in all acute and chronic infections, after operations, and after childbirth. It is common in patients with chronic debilitation, heart failure, or carcinomatosis, and occasionally occurs in apparently normal persons. Venous thrombosis is apt to occur contiguous to areas of local infection or trauma. It is seen in the pelvis in puerperal infection and in the prostatic veins after prostatectomy. In the majority of instances, the thrombus

begins in the deep veins of the calf and extends proximally. The process may cause very little reaction in the vein wall (phlebothrombosis) and, if this is the case, the thrombus is particularly prone to break loose and lodge in the pulmonary tree. On the other hand, the reaction may involve the veins of the entire extremity, with the inflammatory reactions extending into surrounding lymph channels (thrombophlebitis). With an extensive reaction, the clot adheres tightly to the vein wall, and then embolic phenomena are less common.

The precise etiology of phlebothrombosis and thrombophlebitis is unknown. Slowing of the blood stream seems to be an important factor in thrombus formation. Acceleration of the clotting time probably plays a part. The role of changes in the vein walls has not been determined. In spite of the severe systemic reaction and the evidence of the reaction of inflammation in the extremity in the more fulminating cases, no infectious agent has been found.

Local symptoms may be absent. A rise in pulse rate or an unexplained slight fever in a patient in bed may be the only sign of phlebothrombosis, and the condition may not be recognized until an embolus has lodged in the pulmonary artery. Several days later, tenderness in one or both calves may occur. Tenderness in the calf and pain in the calf on dorsiflexion of the foot may be the only sign. If the foot is dependent, slight edema and cyanosis may be observed.

At the other extreme is the painful, swollen, cyanotic leg of acute thrombophlebitis. In this condition, the arteries are not involved directly, but intense reflex vasoconstriction may occur and at times the arterial pulse is felt with difficulty. Fever and leukocytosis are present.

Treatment is divided into three parts:

1. Prevention of clot formation in the leg veins by early ambulation or by bandaging of lower extremities when the patient is confined to bed, and by the use of heparin and dicumarol.

2. Prevention of pulmonary emboli after leg veins are involved. Anticoagulant therapy is usually successful. Pulmonary emboli continue in an occasional patient, and ligation of both common femoral veins or the vena cava becomes necessary. As pulmonary emboli present a medical and surgical emergency in which correct therapy is frequently lifesaving, a separate section will be devoted to this topic.

3. Prevention of destruction of lymphatic vessels and veins which leads to persistent edema and chronic ulcers. Pain is relieved and edema clears more quickly when the sympathetic tone is released by repeated paravertebral blocks. Anticoagulant therapy may reduce the number of vessels permanently thrombosed. Elevation and proper bandaging will minimize the edema. Particular attention to bandaging should be given when the patient is allowed to be up.

PULMONARY EMBOLUS AND INFARCTION

Diagnosis. The diagnosis of pulmonary emboli and infarcts will be made in direct proportion to the index of suspicion of the attending doctor. The following facts are important to remember:

1. Origin of emboli. In the majority of instances, pulmonary emboli arise from clots occurring in the deep veins of the calf. The fewer the symptoms of phlebitis, the more likely the presence of emboli. Emolic phenomena in the lungs may be the first sign of venous thrombosis in the legs. In pelvic operations, after childbirth, and in pelvic infections, the emboli may arise from the pelvic veins. At times when heart disease is present, they come from auricular or ventricular thrombi, but even in patients with heart disease the peripheral veins are the more common site of origin.

2. Emoli frequently come from the calf veins in the absence of local symptoms and signs. If there are no physical signs of phlebitis in the legs, there is an approximately equal chance that the embolus comes from the right or the left leg. If there are signs of involvement of the right calf, this does not prove that the embolus originated from the veins of the clinically diseased calf. As the conditions favorable to venous thrombosis usually exist bilaterally, the veins of both calves are apt to be involved, and the embolus may well have come from the apparently normal leg.

3. Pulmonary embolus and pulmonary infarction are not synonymous terms. A distinction must be made between pulmonary embolus and pulmonary infarction. We are all aware that the terms coronary occlusion and myocardial infarction have different meanings. The former indicates the obstruction of a coronary vessel by a thrombus; the latter, death of cardiac muscle. Similarly, a pulmonary embolus may cause obstruction of a branch of the pulmonary artery

without death of lung tissue. If the tissue dies, the embolus has produced a pulmonary infarct.

4. The symptoms and signs of pulmonary emboli are extremely variable. The symptoms and signs of pulmonary embolism range from transient dyspnea and apprehension to profound dyspnea, circulatory failure, and death. Pain is absent unless the circulation is almost completely blocked. It is possible that the substernal pain occurring in this condition is caused by myocardial ischemia from coronary insufficiency, secondary to a high right ventricular pressure and a falling systemic arterial pressure. On examination the lungs are clear. The pulmonary second sound may be accentuated. X-ray examination shows no abnormal densities. Close examination may show that the vascular shadows are decreased in a portion of the lung. The electrocardiogram may show a characteristic pattern. When the emboli are small, progressive dyspnea and the development of cor pulmonale may dominate the picture.

5. The symptoms and signs of pulmonary infarction are extremely variable. The symptoms and ~~signs~~ of pulmonary infarction are those of pleurisy, consolidation, raising of clotted blood from the lungs, fever, and leukocytosis. Shock frequently develops. If the heart is abnormal, profound and intractable congestive failure may develop. The infarcts may be small in size and, even though blood is present in the sputum, the x-ray of the chest may appear normal. Many emboli may lodge before one small infarct develops. Small platelike areas of atelectasis at the bases are the most common x-ray findings, though at times the areas of infarction are very extensive. It is not uncommon to have infarcts occur without chest pain, without x-ray findings of atelectasis or consolidation, and without bloody sputum. The appearance of shock, intractable congestive failure, or unexplained fever in a patient with heart disease may be the only indication.

Treatment. The use of anticoagulants and venous ligation have both been vigorously recommended by their proponents. Either method is reasonably satisfactory once the diagnosis of pulmonary embolus is made. Early diagnosis is most important. Failure to realize that a patient may have a pulmonary embolus without detectable signs of infarction has frequently caused unnecessary delay in therapy. In other instances the presence of fever and signs of consolidation have led to a wrong diagnosis of pneumonia.

If anticoagulant therapy is used, the following facts must be remembered: (1) The patient is liable to sudden death at any time, and immediate reduction of clotting by the use of heparin is necessary. Dicumarol must be used in effective doses with the realization that the danger of bleeding from overdosage is much less serious than the danger from more emboli. (2) The effectiveness of heparin administration is determined by measuring the clotting time; that of dicumarol administration, by measuring the prothrombin time. These determinations are not interchangeable, and fatal hemorrhage may result if one uses the clotting time to control the administration of dicumarol. (3) One or more emboli are apt to occur after effective anticoagulant therapy has been started, because this therapy will not dissolve clots already formed, and will not prevent clots floating in the veins from dislodging. (4) Therapy at effective levels must be continued from 14 to 28 days, until the clots within the deep veins are organized and covered with endothelium. (5) In many debilitated patients the prothrombin concentration will be below the normal level before dicumarol therapy is started, and only small amounts of dicumarol will be needed to lower the prothrombin concentration to effective levels. The prothrombin concentration must be determined before the initial dose of dicumarol is given.

~~X~~ If venous ligation is used, the following points must be remembered: (1) The source of the embolus is unknown and, therefore, both femoral veins or the vena cava must be ligated. (2) An occasional immediate mortality is unavoidable if caval ligation is done; the ligation of both femoral veins under local anesthesia is a safer procedure in most severely ill patients. (3) In certain patients ligation is best followed by the use of anticoagulant therapy. (4) The amount of edema of the legs after ligation appears to depend to a large degree on the extent of the thrombophlebitis. In most instances the collateral circulation is adequate to prevent edema if the thrombophlebitis has not been extensive. The late effects of the extensive enlargement of the ovarian and vertebral venous plexus which may occur after caval ligation are not yet known.

In summary, both anticoagulant therapy and venous ligation are effective means of preventing further pulmonary emboli from leg and pelvic veins. The anticoagulant therapy has the ad-

vantage of being easy to start if the diagnosis of pulmonary embolus is not certain. It is effective regardless of the site from which the emboli are arising. It not only prevents pulmonary emboli, but it may also protect the leg veins against further damage from clotting. It has the disadvantage that occasionally it does not stop the emboli, and then venous ligation may be lifesaving.

Venous ligation has the advantage of certainty that no further clots will come from those particular veins distal to the ligation. It is more reassuring to the attending physician if he has had little experience with the use of anticoagulant therapy. It is safer than poorly controlled anticoagulant therapy. It should be remembered that one type of treatment does not exclude the other. It is possible that anticoagulant therapy should be used more commonly after ligation.

DISORDERS OF PERIPHERAL LYMPHATIC VESSELS

Water and electrolytes which leave the capillaries can reenter the capillaries without difficulty. Protein and various forms of particulate matter pass into the lymphatic capillaries. If the lymphatic drainage to a part is blocked, the extracellular fluid will gradually assume a high protein content. The capillary filtrate may contain very small amounts of protein, but, as the water can be reabsorbed by the blood capillaries and the protein cannot, an effective concentrating mechanism is present. When the lymph vessels are normal, lymph flow depends on muscular contraction, respiratory movements, transmitted movements from arterial pulsations, and, to a certain extent, on gravity. Complete immobilization of the lower extremity in a patient sitting in a chair leads to physiologic lymphatic obstruction.

ACUTE LYMPHANGITIS

When bacterial infection in an extremity is not localized, the inflammatory products pass proximally along the lymphatic channels. The material carried in the lymph channels causes dilatation of the small blood vessels about the lymph vessels, and their courses are outlined by one or more red streaks. Before chemotherapy was available, lymphangitis always carried a serious prognosis because it is a sign of uncontrolled, spreading infection. Immobilization of the part greatly reduces the rate of spread of the infection by reducing the rate of lymph flow.

With chemotherapy, fear of lymphangitis and the surgery necessary with lymphangitis has largely disappeared.

CHRONIC LYMPHATIC OBSTRUCTION

Widespread obstruction of the lymph vessels may result from congenital or familial disorders of the lymph vessels. The lymphedema of the familial type is called Milroy's disease. Acquired chronic lymphedema results from obstruction of the lymph channels by neoplasm, scar, operative removal of lymph nodes, and fibrosis caused by x-ray therapy. It may follow low-grade lymphangitis from filariasis, from lymphogranuloma venereum, and from repeated streptococcal infections. It may be a complicating factor in certain instances of severe edema following thrombophlebitis.

In its early stages, lymphedema cannot be distinguished physically from any other form of soft pitting edema. On laboratory examination, the high protein concentration separates it from cardiac and nephritic edema, but not from the fluid of myxedema. Lymphedema causes fibrosis in the tissues, and in time the tissue becomes hard and brawny. The skin may be thick and folded with indolent ulcerations.

Treatment of Chronic Lymphedema. Early and persistent therapy is important. If marked edema is prevented by postural drainage, by effective bandaging, and by limiting upright activity to periods short of edema formation, much of the fibrosis and recurrent infection will be prevented. This program calls for persistence on the part of both doctor and patient. Acute attacks of lymphangitis can be controlled by appropriate chemotherapy.

LEG ULCERS IN PATIENTS WITHOUT PERIPHERAL VASCULAR DISEASE

In a normal subject an injury to the skin of the foot or ankle is much more serious than one to the hand or wrist. In the ambulatory patient, lesions on the lower leg and foot may heal slowly. If healing does not occur promptly, the patient should be put to bed and the part elevated. If the lesion is allowed to become chronic, low-grade local phlebitis, lymphangitis, and arteritis develop. Even if the main vessels to the part are unaffected, these local changes cause poor tissue

drainage and tendency to recurrent infection and ulceration. A nonhealing, undramatic ulcer of the lower leg is an emergency and requires bed rest until healing occurs.

USE OF SPECIAL DIAGNOSTIC TESTS

The history and physical examination will establish the presence or absence of arterial insufficiency. When the circulation is normal, no instruments are necessary to demonstrate the fact.

~~X~~ The skin shows no trophic changes and does not blanch abnormally on elevation. ~~If the arterial pulses~~ are palpable. If the main artery is occluded by pressure for several minutes, release of pressure will cause bright red reactive hyperemia. Heating of the body causes the extremities to warm, and immersion of the part in hot water brings out the capillary pulse. Histamine pricked into the skin produces a typical wheal and erythema. When there is obvious arterial insufficiency, these findings are changed as outlined under Special Points in History and Physical Examination, page 1348. As noted elsewhere, when other signs of arterial insufficiency are present it is not safe to attempt to demonstrate the capillary pulse by placing the involved extremity in hot water.

Special tests have been of value in understanding the normal physiology of the peripheral circulation. They have been of use in quantitating the degree of damage caused by pathologic processes and have aided our understanding of the development of collateral circulation. They have been of use in determining, in at least a semi-quantitative way, the effects of therapy in occlusive vascular disease. They have not contributed greatly to the care of the individual patient because simpler methods of examination have given adequate information.

The following tests are useful at times:

1. Measurement of skin temperatures in a cool room (18° to 20° C.) before and after release of sympathetic tone. When the blood supply is decreased by occlusive arterial disease or by reflex vasoconstriction, or by both, the extremities cool. ~~X~~ Release of sympathetic tone is accomplished by paravertebral block, by spinal anesthesia, or by raising the rectal temperature by body warming. If the skin temperature does not rise, the decrease in blood flow is the result of occlusive vascular disease. A rapid rise to 30.5° to 33° C.

indicates normal blood supply. An intermediate rise indicates both reflex sympathetic constriction and occlusive vascular disease. This test has the virtue of simplicity and has proved to be of clinical use.

2. Arteriography and venography. The arterial tree may be visualized by x-ray after the intraarterial injection of 35 per cent "Diodrast." The exact point of arterial obstruction and the pattern of the collateral circulation can be determined. While direct visualization has greatly increased our knowledge of pathologic physiology, it is rarely needed clinically. Visualization of the veins by the injection of "Diodrast" is occasionally useful.

3. Circulation time to the extremities. Several methods are available. The fluorescein test is the most objective. Three ml. of a 20 per cent aqueous solution of fluorescein are injected quickly into the antecubital vein, and the time of appearance of a greenish yellow glow in various parts of the body is observed. When arterial insufficiency is present, the appearance time of the fluorescein is

prolonged. In severe ischemia no fluorescein may appear.

4. Oscillometer. This is a volume recorder which magnifies the changes in volume which normally occur with each cardiac systole. The ordinary blood pressure recording apparatus may be used as a crude oscillometer. Refinements of the oscillometer have not increased its clinical usefulness.

5. Histamine wheal test. If the arterial circulation is inadequate, histamine pricked into the skin gives a subnormal or absent reaction.

6. Measurement of blood flow by plethysmographic technics has advanced our knowledge of the circulation, but the method is not suitable for routine clinical use.

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Section 3—The Kidneys

The modern concept of renal disease began to develop as the result of the classic descriptions of clinical features by Richard Bright. Among numerous others who made lasting contributions, the names of Magnus-Levy (disordered excretion of salt), Friedrich von Müller (concept of nephrosis), Volhard and Fahr (correlation of clinical and pathologic findings), Thomas Addis and Donald Van Slyke (natural history of the renal disorders), and Homer Smith (develop-

ment of methods of testing the various renal functions) are especially noteworthy.

The reader will be aided in the interpretation of the discussion to follow by reviewing Chapter 19, which deals with principles of renal function, and with the important manifestations of renal disorders. Before discussing the specific diseases of the kidneys, an attempt will be made to clarify certain topics which are frequent causes of confusion.

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Some General Aspects of Renal Disorders

Gladys J. Fashena and T. R. Harrison

The End-Stage Kidney
Relationship Between Renal Disease and Hypertension
Hypertensive Encephalopathy
Concept of Nephrosis
Renal Impairment and Renal Failure
Classifications of Renal Disease

The End-Stage Kidney. Much of the confusion which arises concerning the subject of renal disease, and many of the mistakes in diagnosis, arise from one fact. This is that the several common types of bilateral renal disease eventually tend to produce a single terminal clinical picture which is characterized especially by excretory failure, with uremia, and usually also by hypertension, cardiac enlargement, and vascular retinopathy. If the patient is seen only at this stage it is often difficult and sometimes impossible to decide whether the initial process represents glomerular nephritis, benign nephrosclerosis, malignant nephrosclerosis, or pyelonephritis. In some instances this decision may be difficult, even after gross and microscopic examination of the contracted and scarred kidneys.

From a practical standpoint the important decision which must be made in the uremic patient is not that of the etiologic nature of the primary process, but that of its possible responsiveness to therapy. Once one knows that the excretory failure is due to scar tissue in the kidney, treatment can at best be palliative. When, however, there is a possibility that obstruction, infection, congestion, or acute renal injury is

responsible for the excretory failure, the application of the proper treatment may prolong life sufficiently for the injured kidneys to have time to begin to recover. In a uremic patient it is, therefore, necessary to know whether the excretory failure is prerenal or renal (Chapter 19), whether there is an element of congestive heart failure superimposed on acute or chronic renal disease, whether an obstructive disorder of the urinary tract is present, and whether the renal process is acute or chronic. It is to the chronic process, with extensive scarring, that the term "end-stage kidney" should be applied.

Relationship Between Renal Disease and Hypertension. This is another frequent source of confusion. Although certain differences of opinion still exist concerning this question, the more prevalent point of view may be summarized as follows: It is clear that disease of the kidneys may induce hypertension. This is exceptional when the renal disease is unilateral, but common when the kidneys are diseased bilaterally. However, the majority of cases of hypertension appear to be due primarily, not to renal diseases, but to extrarenal disorders (Chapter 13). When the kidneys are not responsible, the etiologic factor is frequently unknown, and the term "essential" hypertension is often applied to such instances. Regardless of its cause, hypertension tends to induce disease in the small

vessels in certain areas of the body, and the renal arterioles and small arteries are particularly susceptible to damage as the result of increased pressure. It may be stated, therefore, that a large proportion of cases of advanced renal disease, particularly in persons over the age of 40, are the result of hypertension, but that most cases of hypertension are not due to primary renal disease. Once the hypertension has caused renal disease, the latter may aggravate the hypertension, which may in turn lead to further renal damage, etc. When this vicious cycle proceeds slowly, the term "benign hypertension," or "benign nephrosclerosis" is employed, provided one can be sure that the hypertension is primary and the renal disease secondary. When, on the other hand, the vicious cycle proceeds rapidly, the condition is called malignant hypertension or malignant nephrosclerosis. These terms refer to the rate of progression and not to the underlying cause. Hence, either an individual with primary renal disease and secondary hypertension, or an individual with primary hypertension and secondary renal disease, may develop malignant nephrosclerosis and malignant hypertension. Some believe that the benign and malignant forms of hypertension represent fundamentally different diseases, but the more prevalent view holds that they differ only in rate of progression.

Hypertensive Encephalopathy. Many patients with renal disease suffer from acute episodes characterized by rise in blood pressure above the previous level, and by disorders of the nervous system which last for minutes, hours, or days, and then disappear without clinical evidence of lasting damage. Spasm of cerebral arteries is generally thought to be the cause of these attacks, although in some instances there is evidence that increase in intracellular water in the brain may be responsible. The clinical syndrome appears in two forms, depending upon whether the disturbances in the nervous system are chiefly of generalized or focal nature.

The general form usually appears in individuals without previous long-standing hypertension, and without preexisting cerebral vascular disease. It is seen in women with eclampsia, and in children and young adults with acute nephritis. Aside from a rising blood pressure, the attacks are characterized by headache, visual disturbances which may progress to blindness,

vomiting, papilledema, stupor, coma, stertorous breathing, and convulsions. When the condition is induced by excessive administration of water to a person whose kidneys have relatively diminished capacity to excrete water, there may, in addition, be evidence of excretion of water by extrarenal channels, and lacrimation, salivation, diarrhea, and sweating may be the outstanding features.

The focal type of hypertensive encephalopathy may appear in any individual with chronic hypertension, but is especially frequent in persons with the malignant type. This disorder is characterized by a rise in blood pressure above the usual level, and by focal disturbances of the nervous system. Loss of consciousness is common at the onset, and localized or generalized convulsions may occur. There likewise may be disturbances of speech, vision, or hearing. Paralysis, involving one half of the body or one extremity only, is especially common, and sensory disturbances may occur. This type of hypertensive encephalopathy is thought to result when generalized vasospasm affects an individual who already has cerebral vascular disease, and it is believed that the focal nature of the disorder can be accounted for by the greater local anoxia occurring in areas supplied by vessels previously diseased. However, other competent investigators believe that this focal type of hypertensive encephalopathy is always attended by lesions in the nervous system, and that even though the symptoms may clear up entirely, small anatomic changes persist. The clinical picture may, in the beginning, resemble exactly that of a cerebral vascular accident due to hemorrhage, thrombosis, or embolism, and the differentiation may be impossible unless the patient is observed for a number of hours, or even for several days.

Concept of Nephrosis. This term was introduced in order to emphasize the difference between those types of renal disease which are primarily inflammatory, and those which are fundamentally "degenerative" in nature. Some confusion has arisen from the fact that the most common cause of the clinical picture of "nephrosis" is a phase of glomerulonephritis which is primarily an inflammatory disease. Further confusion stems from the use by some writers of the term "nephrosis" to designate not a pathologic process, but a clinical picture. This picture is

characterized by massive proteinuria, marked hypoproteinemia, and intractable edema. As employed in this chapter, the term "nephrotic syndrome" will be used to designate this clinical picture, while the term "nephrosis" will be employed to describe renal disease which is not primarily of inflammatory or vascular origin, but which is basically "degenerative" in nature.

Renal Impairment and Renal Failure. These have been discussed previously (Chapter 19), but a few of the more salient points may be summarized.

Diminished excretory capacity of the kidney (renal impairment) is characterized in its earlier stages by reduced ability of the kidney to respond to an unusual load (excretory impairment without failure). In the later stages there is diminished ability to respond to the usual load. The earlier type of impairment is recognized by diminished renal performance (excretion of dyes, maximal concentrating power, clearance of urea) under conditions of stress, but the level of nitrogenous substances remains normal in the plasma. The term "renal failure" should be reserved for advanced renal impairment, with elevation of the blood urea and creatinine.

The relative importance of renal and nonrenal factors in the production of renal excretory failure, and the significance of functional alterations in the conservatory as well as the excretory capacity of the kidneys, have already been considered (Chapter 19).

Classifications of Renal Disease. Disorders of the kidney may be classified logically from a number of different standpoints. *Etiologic* classification would involve subdividing renal disease into types due to bacterial infection, immunologic disturbances, chemical injury, etc. The difficulty with such a classification is that in many instances the primary etiologic process is not well understood. The *pathologic* classification would divide renal disease into those types which are primarily inflammatory, degenerative, and ischemic. Such a classification has many advantages, but suffers from the disadvantage that the various groups overlap, and that one type may lead to another, secondarily. The *morphologic* classification, according to whether the glomeruli, tubules, or blood vessels are primarily involved, suffers from the same disadvantages

and in even greater degree. The *functional* classification, according to whether renal blood flow, glomerular filtration, tubular excretion, or tubular reabsorption is primarily involved, has the advantage of centering interest on the functional disturbances, which are what the physician treats, but has a disadvantage in that the various impairments tend to occur together in most types of renal disease. The *chronologic* classification into acute or chronic is of important practical value, in that acute renal diseases are much more responsive to treatment than are chronic disorders, but is incomplete, and must be supplemented if it is adopted. The *clinical* classification divides renal disease on the basis of the natural history of the various types, with particular emphasis on the chronicity. This classification is a combination of the various others, and will be adopted here. It should be realized, however, that any classification employed will necessarily suffer from certain disadvantages. In order that the reader may be oriented for the discussion to follow, the classification to be adopted is briefly summarized at this point.

- I. The Acute Inflammatory Disorders:
 - A. Acute glomerular nephritis
 - B. Acute pyelitis and pyelonephritis
 - C. Rarer forms of acute nephritis:
 1. Embolic
 2. Focal
 3. Interstitial
 4. Papillitis
- II. The Nephroses:
 - A. The common types of acute nephrosis
 - B. The nephrotic stage of glomerular nephritis
 - C. Intercapillary glomerulosclerosis
 - D. Rarer nephrotic states:
 1. Renal amyloidosis
 2. Syphilitic nephrosis
- III. The Common Chronic Renal Disorders:
 - A. Chronic glomerular nephritis
 - B. Nephrosclerosis:
 1. Benign
 2. Malignant
 - C. Pyelonephritis
- IV. Miscellaneous Disorders of the Kidneys

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See p. 1390.

The Pathogenesis and Natural History of Renal Disorders

Gladys J. Fashena and T. R. Harrison

Acute Inflammatory Disorders
Acute Glomerular Nephritis
Acute Pyelitis and Pyelonephritis
Rarer Forms of Acute Nephritis
Nephrotic States and Allied Disorders
Common Types of Acute Nephrosis
Nephrotic Stage of Glomerular Nephritis
Intercapillary Glomerulosclerosis (Kimmelstiel-Wilson Disease)
Rarer Nephrotic States
Common Chronic Renal Disorders
Chronic Glomerular Nephritis
Nephrosclerosis
Chronic Pyelonephritis
Miscellaneous Disorders of the Kidneys

ACUTE INFLAMMATORY DISORDERS

ACUTE GLOMERULAR NEPHRITIS

Acute diffuse glomerulonephritis is the most common form of clinically important renal disease in childhood, and is less common in the adult. The true incidence of the disease is not known, since milder cases often escape detection. The disease is most prevalent between the third and seventh year of life, and occurs more commonly in males than in females. There appears to be little tendency to family susceptibility, and climate apparently plays no important role, as the incidence is approximately the same in the northern and southern parts of the United States.

Etiology. The most important etiologic factor appears to be extrarenal infection, particularly of the upper respiratory tract. The usual infecting organism is the beta-hemolytic streptococcus. Scarlet fever, although an important streptococcal disease predisposing to acute glomerulonephritis, is less commonly the cause than are other types of streptococcal infections. The pneumococcus apparently may be occasionally responsible for the antecedent infection, in which case the nephritis which develops has a tendency to show nephrotic elements, in that the patient develops massive proteinuria and considerable edema during the course of the disease. In some instances glomerulonephritis follows staphylococcal infections of the skin or other sites. During World Wars I and II, the disease occurred with considerable frequency among men exposed to

prolonged cold and exhaustion, but it is generally thought that these factors played only an accessory role, though an important one, in predisposing to infection.

The exact mechanism of the production of diffuse glomerular lesions in man is not known with certainty. There is no direct bacterial invasion of the kidney. The bulk of accumulated evidence suggests that the inflammatory process is a manifestation of allergy or hypersensitivity to a bacterial product, or to a complex antigen formed by the union of bacterial products with kidney tissues. Antistreptococcal antibodies can be demonstrated in high titer in the blood of individuals who develop nephritis following a streptococcal infection. Furthermore, the explosive onset of the renal symptoms several weeks after the onset of the bacterial infection suggests that time is needed for antibody formation. The shorter latent period with acute exacerbation is in keeping with this concept. In experimental animals lesions which closely resemble the human disease have been produced by nephrotoxic serums from heterologous species, and more recently identical lesions have been produced by the inoculation of homologous kidney extracts combined with killed streptococci.

Pathology. Grossly, the kidneys are normal-sized or slightly swollen. Occasionally, the swelling may be marked. The surface is usually pale, and small hemorrhages may be seen (on the cortical surface). The early microscopic lesion is an inflammation in the capillary tufts of the glomeruli characterized by swollen, proliferated, capillary endothelial cells which often obstruct the blood flow, proliferation of the epithelial cells of the capsule, and infiltration of the entire glomerulus with polymorphonuclear cells and monocytes. Albuminous fluid, red corpuscles, and white cells may be seen in the capsular spaces and in the tubules. The tubule cells are swollen and granular, and may contain hyaline or fatty deposits. The interstitial tissues tend to be edematous and congested, with a minimal amount of

inflammatory cellular reaction. When acute glomerulonephritis heals, there may be no residual microscopic evidence of the disease. Where the disease goes on to a chronic state, fibrotic changes become more marked and glomerular destruction ensues. There is very little anatomic evidence of generalized capillary damage in acute glomerulonephritis. One occasionally sees small petechial hemorrhages in organs other than the kidney, including the skin.

Cardiac involvement, as demonstrated by the electrocardiogram, by cardiac enlargement, or by frank congestive failure, occurs in a large number of these patients, but the nature of the cardiac change is poorly understood. Cardiac failure has been reported in the absence of any demonstrable microscopic changes in the heart, while others have described varying degrees of cloudy swelling and granular changes within the muscle fibers. Occasionally one encounters inflammatory infiltration of the interstitial tissues of the heart, in which instance a true myocarditis may be postulated.

Cerebral edema is present in some of the cases. There is no good microscopic clue as to its genesis.

Pathologic Physiology. Newer clearance techniques indicate that the fundamental functional defect in acute glomerulonephritis is a marked reduction in the amount of glomerular filtrate formed from the blood passing through the kidney (filtration fraction). The renal blood flow has been reported as being normal or slightly reduced. The possible explanations for these findings are: (1) That the permeability of the glomerular filter is reduced; (2) that the blood flow through the kidney is shunted, so that it fails to perfuse the glomeruli; and (3) that there is an alteration in the relative tone of the afferent and efferent arterioles, such that glomerular capillary pressure is lowered while blood flow is maintained at a nearly normal figure. Against the first hypothesis, it may be said that the constant presence of both albumin and red corpuscles in the urine of acute nephritis is difficult to reconcile with the idea of diminished glomerular permeability. As far as the presence of a shunt is concerned, although such a mechanism has been demonstrated with certainty in the rabbit, it is uncertain how much shunting of blood occurs in the human kidney. If a shunt mechanism were operating, one would have to postulate not only a diminished glomerular blood flow, but also a normal tubular blood

flow, in order to account for the relatively high "Diodrast" clearances observed. Whether a shunt mechanism is capable of by-passing the glomeruli and yet giving adequate tubular perfusion is not certain, but this seems unlikely. With regard to the third hypothesis, a low filtration rate would necessarily depend on a reduction of the effective filtration pressure inside the glomerular loop. The only type of alteration which could produce this would be a constriction of the afferent arterioles out of proportion to whatever tone may be present in the efferent arterioles. It has been affirmed that renin is present in the systemic blood in human cases of acute glomerulonephritis with hypertension, and it is tempting to suppose that the renin mechanism accounts not only for hypertension, but also for decreases in the filtration fraction on the basis of arteriolar constriction. However, the general picture of the renal hemodynamics in acute nephritis does not give support to this view, because the renal action of renin and hypertensin (angiotonin), like that of epinephrine, is mainly on the efferent arterioles, and results in a fall in renal blood flow and a rise in the filtration fraction. Whatever the mechanisms involved, there is general agreement that the amount of glomerular filtrate formed is markedly reduced. According to one point of view, this reduced volume of filtrate is brought in contact with relatively healthy tubular tissue which continues to operate blindly on the small volume offered, concentrating it and reabsorbing solutes; thus urea diffuses back into the blood in large amounts, and sodium chloride and water are, likewise, retained because the tubule cells have an improved opportunity for reabsorption from the retarded stream of tubular urine. This state of affairs has been referred to as glomerular-tubular imbalance, and in turn leads to edema and increased plasma volume. Another point of view holds that retention of electrolytes and water is related, not to diminished filtration, but to increased tubular reabsorption as the result of some unknown mechanism. In any case, the hypervolemia thus produced places an increased load upon the heart, and may also result in increased venous pressure, even in the absence of clinically detectable heart failure. Direct measurements of the blood volume in acute nephritis have been variously reported as normal or increased, so that one cannot, in every instance, postulate hypervolemia as the explanation for the

rather regularly observed increase in venous pressure. Possibly, peripheral capillary and venous constriction serves as a mechanism for increased venous pressure in some instances.

The exact cause for the cerebral edema which occurs in some cases is not clear. In some instances its presence is correlated with an elevated spinal fluid pressure, occurring in conjunction with high venous pressure. Although cerebral edema may occur, it does not appear to be the whole or even the usual explanation for hypertensive encephalopathy. In the majority of these cases the spinal fluid pressure is within normal limits, and there is no papilledema. Furthermore, measures designed to produce dehydration, such as the use of diuretics, often fail to control the symptoms in the average case. It is thought by some that the cerebral symptoms which appear, following an acute rise in blood pressure, are in greatest probability due to cerebral ischemia resulting from the generalized vasoconstriction which is also the cause of the hypertension. Others hold that the generalized vasoconstriction leads to passive dilatation of cerebral arterioles, and that the resulting local rise in capillary pressure induces cerebral edema. There appears to be little correlation between episodes of hypertensive encephalopathy and the degree of renal impairment or of water retention. Furthermore, when the blood pressure is reduced by relaxation of the vasoconstriction, the cerebral symptoms disappear, unaccompanied in many instances by diuresis.

Symptoms. There is great variability in the clinical pattern of glomerulonephritis. As a rule the child with this disease is not severely prostrated, but the adult is more likely to be. The most frequent presenting manifestation is hematuria antedated by or coincident with mild periorbital edema. In about half the cases the urine is grossly bloody for the first few days, shading off into a smoky, dirty, grimy hue. Usually there is a decrease in the total urinary output, and mild generalized edema is present. Marked edema usually is not seen in acute glomerulonephritis except where fluids have been forced in the presence of oliguria and during cardiac failure. Rarely, edema may be a much more striking symptom, and may simulate nephrotic edema. Such patients often exhibit a lowered total plasma protein and an elevated blood cholesterol. Body temperature is usually moderately elevated for the first five or six days

of the illness, then gradually falls to about 100° F., fluctuating at this level for a variable period. At times, gastrointestinal symptoms such as loss of appetite, vomiting, and constipation may occur. Less often diarrhea is present. Some patients, particularly those who have outspoken hypertension, complain of headache. Occasionally, the presenting symptom is dyspnea or some other evidence of acute cardiac decompensation, and the urinary manifestations are so mild that they may be overlooked if a careful examination is not made.

On physical examination, little is usually found, aside from evidences of a residual upper respiratory infection and slight generalized edema. In approximately half of the cases the heart will be somewhat enlarged, but this is often difficult to detect by clinical examination; in about 20 per cent of the cases, there is evidence of frank congestive failure. The degree of cardiac damage appears to be related directly to the intensity and persistence of the hypertension. In 60 to 70 per cent of the cases, varying degrees of hypertension (usually slight to moderate) will be present. In those with an elevated blood pressure and good cardiac reserve, the rate does not accelerate; when congestive failure is present or imminent, tachycardia and gallop rhythm are usually present.

A better understanding of the variable clinical picture can be gained by considering in detail some of the cardinal features.

Urinary Findings. A definite diagnosis of acute glomerulonephritis cannot be made in the absence of hematuria, yet the amount of blood in the urine is extremely variable; and, occasionally, in the first day or two of the disease when hypertension is already present, very few or no red blood corpuscles may be detected by routine urinalysis. Soon, however, hematuria appears and makes the diagnosis evident, although in some cases the amount of blood in the urine is never very great. Gross hematuria occurs in about one half of the cases. It is important to examine freshly voided urine specimens for red corpuscles and casts, since both of these elements may disappear when alkaline or dilute urine is allowed to stand.

The amount of protein also varies greatly, and is not correlated with the severity of the disease. The amount usually decreases as the process heals, but protein is the last abnormal element to

disappear from the urine. In those cases which progress to the chronic stage of the disease, proteinuria usually persists, and is demonstrated best by examination of concentrated 12-hour specimens. It is important to rule out orthostatic proteinuria as a cause for persistence of this finding. Patients exhibiting proteinuria and irregularly occurring hematuria for more than a year may be considered to have entered the chronic stage of glomerulonephritis, in which the prognosis is grave.

The specific gravity of the urine during the acute phase is usually high, even when corrected for the presence of protein. In some cases, however, the ability of the kidney to excrete a concentrated urine is lost. The volume of urine is usually reduced considerably, but may be normal throughout the illness. In approximately 5 per cent of the cases, there is marked oliguria approximating anuria. Sudden diuresis may occur at any time, resulting in the excretion of retained fluid. There does not appear to be significant correlation between arterial hypertension and volume of urine.

Cerebral Symptoms. Hypertensive encephalopathy may appear following an acute rise in blood pressure, and is probably related to alterations in cerebral blood flow, resulting from the generalized vasospasm which is also the cause of the hypertension. The part played by cerebral edema in the genesis of the symptoms is not clear. The symptoms persist during the hypertension, and consist chiefly of headache, drowsiness, vomiting, and convulsions. Restlessness, dimness of vision, and diplopia may be present. When the blood pressure is reduced, the cerebral symptoms disappear quite promptly. There does not appear to be correlation between these episodes and the degree of renal impairment or of water retention. Episodes of hypertensive encephalopathy usually last only a day or two and spontaneously regress with a fall in blood pressure, although death may occur during the cerebral attack. Recovery under appropriate treatment is usually rapid and complete, but some residual damage may result occasionally.

Cardiac Symptoms. The heart is affected to some degree in from 75 to 80 per cent of the cases, and heart failure accounts for about one third of the deaths in patients with acute glomerulonephritis. In the usual case, evidence of cardiac disorder is limited to electrocardiographic changes

which include flattening or inversion of the T waves in one or more leads, with occasional transient increased amplitude of the T waves. Inversion of the T wave occurs late in the cycle, and is not infrequently preceded (especially in leads I and II) by a slightly depressed upward-bowed segment. Transient inversion of the T waves occurs as frequently in lead III as in lead I, but the incidence of heart failure is greater in association with inversion of the T waves in lead I. Many other abnormalities in the tracings occur during acute glomerulonephritis, but are less frequent. Seventy-two per cent of the total group of patients studied in a large series showed some electrocardiographic abnormality. There was a higher incidence of electrocardiographic changes in the patients with hypertension.

Severe myocardial impairment may be manifested by cardiac enlargement, rapid pulse, gallop rhythm, systolic apical murmur, large liver, passive pulmonary congestion, dyspnea, orthopnea, increased venous distention, and finally by generalized edema. Frank cardiac failure almost never occurs in the absence of hypertension. Acute glomerulonephritis is secondary only to rheumatic fever as a cause of acute cardiac failure in children, and the presence of marked hypertension is strong evidence in favor of a nephritic origin of cardiac failure. Cardiac signs usually subside rapidly with a fall in blood pressure. The cardiac enlargement usually disappears rather slowly, requiring about six to eight weeks. The heart failure appears to result from the double strain of increased peripheral resistance and increased inflow load (Chapter 14).

Renal Function. Renal excretory function, as measured by the usual laboratory tests, is within normal limits in about one half of the cases. In the majority of the remainder, an elevation of the blood urea nitrogen and other excretory products is the only evidence of impaired function. A mild acidosis may occur as the result of retention of phosphates, sulfates, and other waste products. There is no constant correlation between the degree of hematuria and the retention of nonprotein nitrogen. In about half of the cases phenolsulfonphthalein excretion is delayed. Oliguria of extrarenal origin may lower the excretion of this dye. Reduction in the rate of urea clearance also occurs in approximately half of the patients, particularly in those with greatly diminished urinary output. It returns to normal early in the con-

valescent phase of the disease. When an acute case progresses to chronic nephritis, the clearance rate for urea remains at a low level.

Clinical Course. The clinical pattern varies according to whether the patient has an initial or a secondary attack. In the latter instance the latent period after the inciting infection tends to be shorter, the duration of symptoms is longer, and the prognosis is more grave. When one is dealing with an initial attack, as is usually the case in a child, improvement, as manifested by abatement of the constitutional symptoms, usually begins within one to two weeks after the onset of the disease, and gross blood disappears from the urine about this time. As a rule, the blood pressure becomes normal after a week or two, and the blood chemical findings during the second week. Diuresis usually commences after three or four days during the second week, and the patient may lose as much as 10 per cent of body weight, even though no clinical evidence of edema is present. The urine slowly becomes more nearly normal during a period of several weeks, the last abnormal element to disappear being albumin. Several urinalyses must be performed to establish cessation of the disease, as erythrocytes may be absent one day and appear again subsequently. When a more delicate procedure such as the Addis count is employed, increased numbers of red blood corpuscles will be found in the urine for about three to four months, in the average case. Thus, while the average patient is usually well, clinically, within about two weeks, he still has diseased kidneys for several months, and possibly even longer. In rare instances complete clearing of the urine may take a year or more. The blood sedimentation rate is a useful measure of the progress of the disease. It remains rapid in the average case for about three months. Recurrent attacks of acute glomerulonephritis and acute exacerbations of the chronic phase differ from the pattern which has been described in that the attacks are usually longer in duration, and that the likelihood of recovery is much less.

Prognosis. The prognosis in an individual with an initial attack of acute glomerulonephritis is generally good, but it is unpredictable in any given case. There is a positive correlation between the severity of the onset and the mortality during the acute stage, but there appears to be none between the severity of the acute stage and the development of chronic nephritis. In child-

hood, over 90 per cent of the cases recover completely, somewhere between 5 and 8 per cent of the patients develop chronic nephritis, and somewhat less than 2 per cent of the patients die during the acute stage of the illness. The causes of death during the acute stage are cardiac failure, hypertensive encephalopathy, or anuria, with cardiac failure much the most common of the three. In adults, the acute attack is often superimposed on a kidney damaged by a previous acute attack, a smaller proportion of the patients recover completely, and in many the disease passes into the chronic state. It is not uncommon to see a recrudescence of the disease before complete healing has occurred, in association with a fresh respiratory infection, or following the removal of infected tonsils or teeth. Unfavorable signs pointing to the development of chronic nephritis are persistence of hematuria, persistently elevated arterial pressure or sedimentation rate, persistence of proteinuria, and continued low urea clearances.

Treatment. The most important considerations involve the management of excretory failure, congestive failure, and hypertensive encephalopathy when these conditions occur. These problems will be considered later, but the general management may now be discussed. It is generally agreed that patients should be kept at strict bed rest during the acute course of a renal disorder. The fact that renal blood flow is increased in the recumbent position may furnish physiologic basis for this custom. The exact length of time for maintaining bed rest is a matter of some dispute. Some argue that the patient with acute nephritis should be kept in bed until the urine is entirely normal and the erythrocyte sedimentation rate is within normal limits. However, since the latter may remain elevated for many months, in the absence of other clinical and laboratory evidences of activity, there are those who believe that such drastic restriction of activity is unnecessary. There is general agreement that bed rest should be enforced as long as there is any progressive change in any of the significant laboratory findings, and as long as the patient presents clinical evidence of disease. Return to activity should be gradual and on a trial basis, the urine being examined frequently and the findings used as a guide to the amount of exertion permitted.

During the first few febrile days of acute glo-

merular nephritis, a liquid diet is best tolerated. Diets should be very low in sodium, potassium, and protein. Sodium favors edema formation, dietary potassium in the presence of oliguria may lead to serious intoxication, and protein increases the renal osmotic work and the degree of proteinuria and acidosis. A diet satisfactory for this purpose is one consisting of 25 to 30 Gm. of protein, with less than 1 Gm. of sodium chloride and with a high caloric content of carbohydrate foods low in potassium. Sufficient sparing of body protein can best be achieved by assuring a total caloric intake of 30 or more calories per day per kilogram. Infants and younger children should receive a correspondingly higher number of calories with 1.5 Gm. of protein per kilogram per day.

Throat cultures should be made at intervals in all patients with acute nephritis, and a urine culture at the onset is desirable.

Since most patients present evidence of persistent infection, respiratory or otherwise, penicillin is almost always indicated. Whether this drug has any effect on the ultimate course is not yet clear.

Surgical procedures should not be undertaken during the acute stage of nephritis unless they are absolutely essential. Tonsillectomy should be postponed until two or three months after the onset of the disease. If, however, the tonsils are infected and the disease persists for more than three months, tonsillectomy may be considered. Usually, no improvement results. On the other hand, one occasionally sees exacerbations of the disease following tonsillectomy. Penicillin should be administered for 24 to 48 hours before and after operation.

ACUTE PYELITIS AND PYELONEPHRITIS

Acute infections of the urinary tract are much more common than is generally appreciated. Such infections are rarely limited to a single portion of the urinary tract, and for this reason the terms pyelitis and cystitis, so commonly used, are scarcely accurate. Infections of the renal pelvis usually involve the renal parenchyma as well, producing pyelonephritis, and there is commonly some associated inflammation of the ureters and bladder. The clinical symptoms may or may not point to the urinary tract as the source of infection, and the diagnosis is established only by the demonstration of pus cells and bacteria in the

catheterized urine. Very rarely during ureteral obstruction, there may be neither pus cells nor bacteria, and in other instances one or the other of them may be absent. Repeated examinations of appropriate specimens, however, will usually demonstrate both of these elements. Normal urine obtained by catheter is sterile but contains a small number of white blood cells, ordinarily not more than one or two per low-power microscopic field in a fresh uncentrifuged specimen. Clumps of white cells are not present normally.

Etiology and Pathogenesis. The observations that the colon bacillus is an unusual blood stream invader and yet a common cause of pyuria, that the incidence of pyelonephritis is highest in the diaper age, that it is six times as common in females as in males, all lend support to the belief that infection of the urinary tract most commonly occurs by the direct ascending route rather than by the hematogenous one. Stasis of urine is the usual prerequisite for infection of the urinary tract. In children, congenital malformation of the urinary tract is the commonest cause of stasis and hence of chronic urinary tract infections, being present in about 75 per cent of the cases. The tract may be obstructed by a calculus, foreign body, neoplasm, or inflammatory swelling. The presence of a "neurologic bladder" may impede the flow of urine, and occasionally pyuria results from the rupture of an abscess into the urinary tract or the proximity of an inflamed appendix. The common causes of pyelonephritis in adults will be mentioned later.

Many different organisms are responsible for urinary tract infection, but the colon bacillus accounts for about 80 per cent of all cases in children. Less frequently encountered are the staphylococcus, hemolytic streptococcus, *Streptococcus faecalis*, and, still less commonly, other organisms such as those of the *Salmonella* and dysentery groups. Multiple bacterial infection is not uncommon, particularly in chronic cases.

Urinary tract infections due to the tubercle bacillus are discussed in the chapter dealing with tuberculosis.

Pathology. The infection may be unilateral, but is more commonly bilateral. In mild cases the changes are limited to hyperemia, edema, and leukocytic infiltration. In pyelonephritis the interstitial spaces and tubules of the kidney contain collections of small round cells and polymorphonuclear cells. In some acute forms miliary

abscesses occur throughout the parenchyma of the kidney. This is particularly true in hematogenous infection. The infection may produce some dilatation of the pelvis and ureter, and occasionally one sees inflammatory thickening of the ureter which may be responsible for urinary obstruction, with proximal dilatation of the ureter and pelvis, and in some instances with the development of ureteritis and pyelitis cystica.

Symptoms. The symptomatology varies greatly, depending upon the severity of infection, the type of invading organism, and the extent of the pathologic process. In children the onset is usually abrupt, with fever which may be low grade or high grade, and which is characteristically "spiking" in character. There may be no localizing signs pointing to the urinary tract, or the patient may complain of frequency of urination, urgency, and dysuria. Occasionally there is pain, sharp or dull, over the kidney region in the costovertebral angle, with muscular spasm and tenderness to palpation. Infants and young children are likely to be irritable, and disturbances of the central nervous system, such as convulsions, as well as gastrointestinal disorders, such as vomiting, are prone to occur. It is important to emphasize that in some instances no subjective symptoms of urinary tract infection are present. The duration of the disease is variable, lasting from one to four weeks, as a rule. The great majority of cases subside after this period, and the fatality rate is extremely low. Since urinary tract obstruction is such an important predisposing factor in the genesis of this condition, and since structural anomalies constitute an important cause of urinary tract obstruction, the incidence of recurrences is high.

The diagnosis is based on the demonstration of pus cells and bacteria in the urine. These must be repeatedly searched for, since in the early acute obstructive stage of the disease, when the patient may be most ill, the urine may be normal. In the more severe cases involving the renal parenchyma, granular and hyaline casts are also present. One may occasionally see red blood corpuscles, although these do not ordinarily occur in the early stages of the disease. It is important to emphasize that one must be certain of the origin of the pus, since the commonest source of pus in voided urine specimens is from vaginal secretion and not from the urinary tract. Many patients have been erroneously treated for months or

years for pyelitis, when the origin of pus cells was in the vagina. It is, therefore, desirable to examine catheterized specimens in the case of females, and clean voided specimens in the case of males, which are obtained following thorough bathing of the genitals with soap and water. Only specimens obtained by catheter are suitable for bacterial culture in the female.

Management. Many mild cases of urinary tract infection will subside spontaneously without specific therapy. Prior to the use of sulfonamide drugs the usual treatment consisted of bed rest, fluids, administration of alkali, and other types of symptomatic treatment, and this was often sufficient to control an acute case. Since the advent of the sulfonamide drugs, however, these have been used extensively and with excellent effect in the control of urinary tract infection. Sulfadiazine and sulfamerazine administered jointly in divided doses, totaling 0.75 Gm. each daily, will control infections caused by most strains of colon bacilli, and by many other urinary pathogens. For a given total dosage, crystallization of these compounds in the urine is less apt to occur if both, rather than either, are employed. From the standpoint of sensitivity reactions, it is better to employ these two drugs which have similar haptogenic properties (Chapter 35) rather than one of them plus some other sulfonamide compound.

When organisms other than the colon bacillus are responsible, bacteriostatic drugs other than sulfonamides may be of value (table 106). Therapy should be continued for at least one week after the urine has become sterile. When streptomycin (or penicillin) is employed in a person with disturbed fluid balance, the combination of the sodium and potassium salts may be preferable to either alone (Chapter 28). If an obstructive anomaly is present, infection tends to recur after the therapeutic regimen is stopped, and under these circumstances a thorough investigation of the urinary tract is urgently indicated.

RARER FORMS OF ACUTE NEPHRITIS

Embolic (Thrombotic) Nephritis. This type of glomerulonephritis is characterized by the presence of focal lesions involving only a part of the glomerulus. Usually the percentage of glomeruli showing lesions is small and, since only a part of the capillary bed of each glomerulus is destroyed,

Table 106

CHEMOTHERAPY OF COMMON TYPES OF URINARY TRACT INFECTION

Organism	Aureo-mycin	Chlor-amphenicol	Peni-cillin	Sulfa-diazine	Strepto-mycin	Mandelic Acid	Remarks
<i>Escherichia coli</i>	2	1	0	3	4	5	
<i>Aerobacter aerogenes</i>	2	1	0	3	4	5	
<i>Proteus</i>	1*	1*	0	1*	1*	0	
<i>Pseudomonas aeruginosa</i> (<i>B. pyocyanus</i>)	1*	1*	0	1*	1*	5†	
<i>Staphylococcus aureus</i>	2	0	1	3	0	4	
<i>Streptococcus faecalis</i> (enterococcus)	1	0	2	0	4†	3	† May enhance effectiveness of penicillin. Not of value alone.

Numerals indicate approximate order of preference.

Streptomycin is more effective when urine is alkaline.

Mandelic acid is only effective when the pH of urine is brought below 5.5; it is contraindicated in patients with renal failure.

renal insufficiency seldom develops. Embolic glomerulonephritis is usually seen in association with subacute bacterial endocarditis (Chapter 239), but may also occur in conjunction with acute bacterial and acute rheumatic endocarditis, and in septicemias without endocarditis.

The usual clinical manifestation of embolic glomerulonephritis is hematuria with or without accompanying proteinuria. Since only a part of the capillary bed is destroyed, renal insufficiency seldom develops. In occasional instances, the lesions may be so large and numerous as to produce renal insufficiency.

Focal Nephritis. This term is used to indicate a disorder of the kidney occurring in the course of an acute infection, and is characterized chiefly by hematuria without hypertension, edema, or renal excretory impairment. The absence of these features, the fact that the disorder sets in during rather than after the acute phase of the infection, and the rapid clearing of the hematuria, distinguish it from glomerular nephritis. Sections of the kidneys reveal small scattered glomerular areas of inflammation, limited to glomerular tufts.

Acute Interstitial Nephritis. This disorder is occasionally seen during severe acute infections, such as diphtheria, pneumonia, typhoid fever, etc. The kidneys become somewhat swollen and the interstitial tissues are infiltrated with leukocytes or lymphocytes. There is usually pronounced cloudy swelling of the tubules; glomerular changes are minimal or absent. This condition should be suspected when an individual with a

severe acute infection develops renal excretory failure, without hypertension, edema, or hematuria. The management is that of the primary disease process, plus the management of renal excretory failure. This type of nephropathy is particularly common in dogs.

Acute Papillitis. This disorder, which probably represents a fulminating form of pyelonephritis, has been recognized only in recent years. It usually occurs in persons with diabetes, and consists of marked inflammation with necrosis or suppuration of the kidneys, the process beginning in the region of the collecting tubules in the papillae, and extending outward toward the cortex. Aside from the management of the diabetic state, the treatment is that of acute renal failure (as discussed later), plus attempts to demonstrate the infective agent and to apply appropriate bactericidal therapy.

NEPHROTIC STATES AND ALLIED DISORDERS

COMMON TYPES OF ACUTE NEPHROSIS

Degenerative Type: MILD FORM. Proteinuria usually of slight degree and sometimes accompanied by increase in white blood cells and cylindruria, may occur in the course of febrile diseases, in disturbances of fluid balance, and in certain hepatic diseases. The anatomic basis for these changes appears to be parenchymatous or hydropic degeneration of the convoluted tubules,

and occasionally hyaline droplet degeneration, fatty degeneration, or bile pigment deposition in the epithelial cells of the kidney. Renal function is unimpaired and the manifestations of renal injury are usually transient, subsiding when the underlying cause is corrected.

SEVERE FORM (LOWER NEPHRON NEPHROSIS). A variety of precipitating factors may result in acute renal insufficiency which develops according to a characteristic pattern, and which results in essentially the same pathologic picture in the kidney. The renal injury appears to be secondary either to direct toxic action upon the parenchyma, or to profound circulatory changes involving renal blood flow. Among the conditions leading to the development of this picture are hemolytic transfusion reactions, severe trauma to muscle, nontraumatic muscular ischemia, burns, heatstroke, blackwater fever, prolonged peripheral circulatory failure, toxemia of pregnancy, uteroplacental damage, alkalosis, sulfonamide intoxication, and poisoning with certain vegetable and chemical agents, the most common of which is mercury. Most of these conditions have in common the destruction of tissue or blood and the development of early shock. In all, the renal lesion is characterized by degeneration and often necrosis most marked in the distal segments of the tubules, frequently accompanied by deposition of some heme compound in the lower nephron and the collecting tubules. The term hemoglobinuric nephrosis has been used widely, but since all instances are not characterized by the deposition of heme compound, the term lower nephron nephrosis is probably preferable.

Pathology. Grossly, the kidneys are usually somewhat swollen and the weight is often increased. The organ is soft, the capsule is easily stripped, and the outer surface is smooth and pale. The cut surfaces ooze clear or slightly bloody fluid. The cortex is distinctly widened and bulges. It is moist and pale in contrast to the dusky medulla, the striations of which are often accentuated. In the inner zone of the cortex and sometimes elsewhere as well, a distinctly whitish strip is sometimes seen. The histopathology has four distinctive features: (1) Degeneration or actual necrosis which involves, mainly, focal portions of the lower segments of the nephron—i.e., the thin loop of Henle and the distal convoluted tubule. (2) Edema and cellular reaction which develops in the stroma around the more severely

damaged portions of the tubules. There are commonly associated thromboses of the adjacent veins. (3) In instances where blood or tissue destruction has taken place, casts of a heme compound which lie within the lumen of certain of the lower segments of the nephron and of the collecting tubule. (4) Relatively slight or no structural changes in the upper part of the nephron. The damage to the tubule cells varies from slight degeneration to complete necrosis. The lesions are characteristically focal in distribution, affecting small areas rather than whole segments. When the survival period exceeds three or four days, regeneration of tubule cells is evident. The healing process proceeds rapidly, and usually within 10 days most damaged tubules are completely relined. Two kinds of casts are common within the tubular lumens, the most conspicuous type being pigmented masses of a heme compound. The second type of cast is nonpigmented, hyaline in texture, stains faintly with eosin, and resembles a dense coagulum of protein. It is much less common than the heme cast.

When hemoglobin or myoglobin are liberated in the vascular system, these compounds are excreted by the kidney as threshold substances, appearing in the urine when the blood concentration reaches the neighborhood of 150 mg. %. Both pigments may exert a specific transient vasoconstrictor action upon renal arterioles, when the concentration in plasma exceeds a certain level. When either pigment is present in plasma in high concentration, a portion is reabsorbed by the proximal tubule, but the remainder stays in solution until the increasing acidity and sodium chloride concentration of the intratubular fluid cause heme-pigment precipitation in the lower portion of the nephron. The relationship between these pigment deposits and renal injury is conjectural. Hemoglobin and myoglobin in pure solution are not toxic for animal kidneys, but acid hematin appears to cause intense renal vasoconstriction and tubular injury. Heme breakdown products, proteolytic enzymes, and adenosine triphosphate have all been suspected of causing tubular damage either by direct toxic action or by bringing about renal vasoconstriction with resulting anoxia.

There is a growing belief that renal ischemia resulting from shock is of fundamental importance in the pathogenesis of this syndrome.

It is known that inadequate circulation brings

about renal vascular constriction as a compensatory mechanism, and also that the circulation in the kidney can vary independently of the general circulation. For example, when in shock, the total circulating volume decreases to approximately one-half the normal value; the flow through the kidneys decreases to $\frac{1}{10}$, $\frac{1}{20}$, and even less. The immediate effect of this is marked depression of urinary output, and the eventual result is reversible and finally irreversible damage to the nephron.

The "ischemic" and "toxic" theories of the mechanism of lower nephron nephrosis can be combined into a single general concept, if it be assumed that both factors are important, and that they may be interrelated. Thus it may be that the toxicity of a given substance may depend not only on the concentration in the blood, but also on the renal blood flow, an amount of a given compound which would be tolerated readily by a kidney with normal blood flow being capable of exerting deleterious effects in the presence of reduced blood flow.

Several hypotheses have been advanced to account for the diminution in urinary output characteristic of lower nephron nephrosis. These include (1) shutdown in renal circulation; (2) mechanical obstruction of tubules by debris and casts, with resulting inability of the glomerular filtrate to pass into the pelvis of the kidney; (3) unselective reabsorption of glomerular filtrate by damaged tubules, allowing some or all of the glomerular filtrate to diffuse back into the blood of the peritubular capillaries; (4) back-diffusion of glomerular filtrate into the peritubular capillaries, as a result of the increased intrarenal pressure produced by the renal swelling within a tight capsule; and (5) the shunting of blood from the renal artery directly to the medulla. The latter mechanism is thought to be under neurologic control, to be brought into play as a result of remote injury and shock, and to the result in cortical ischemia with marked reduction in the amount of glomerular filtrate formed.

Symptoms. The salient feature of the disease is marked oliguria or anuria, with rapidly progressing renal insufficiency. Two commonly associated findings are shock and vomiting. Many cases show no clear-cut clinical manifestations of shock, but appropriate tests may reveal hemococentration as an indication of loss of plasma, and of a deficit in the volume of the circulating

blood. In sulfonamide intoxication and some of the other chemical poisonings, shock cannot be demonstrated by clinical criteria. Therefore, it does not appear to be invariably present. When it does exist, it usually responds to the usual therapeutic measures. Another important symptom is excessive vomiting which may set in soon after the onset, or may not occur for a day or two.

Diminution in urinary output occurs invariably, and reduction is noted within the first 24 hours of the renal insult. Despite intake of large volumes of fluids and other measures to restore elimination, oliguria persists and becomes more marked. The daily amount of urine passed is reduced to less than 500 ml., and frequently progresses into anuria. The urine, as it is passed, is usually highly acid and the specific gravity tends to become fixed at approximately 1.010. In many instances the urine may be frankly bloody or smoky for the first day or two, and, regardless of color, it often gives a positive benzidine reaction. Proteinuria of varying degree occurs early and persists throughout the illness. Microscopically, the urine contains granular casts, often pigmented casts, and sometimes red corpuscles or pigmented spherules of heme compound.

The changes in the chemical composition of the blood reflect the renal shutdown. The non-protein nitrogen rises rapidly, and by the third day it may be above 150 mg. %. A rise of urea nitrogen at a rate faster than 30 mg. % per day indicates the probability that accelerated protein breakdown, as well as defective excretion, is present. There is a concomitant increase in potassium and phosphate, and often a decrease in the alkali reserve. There may also be a lowering of the concentration of blood chloride. Early but moderate rise in blood pressure is one of the cardinal signs of the lower nephron syndrome. A common sequence consists in a fall in the blood pressure to shock levels on the first day, restoration to normal on the second day, and a moderate hypertension on the third day, with a maintenance of this level thereafter, or a further increase. The occurrence of edema is variable. It is usually slight or moderate, but sometimes it is generalized. More often it is confined to the lower extremities or to the lungs. Uremia develops in all cases in which death may be attributed primarily to renal failure and not to the precipitating condition. Typical manifestations of uremia usually appear during the last two or three days of life.

Prognosis. The mortality rate in lower nephron nephrosis is generally considered very high. The course of the disease is relatively brief, the survival period usually being from 3 to 10 days. There are those who believe that the high fatality rates reported in the past were due as much to faulty management as to the disease itself. Until recently it has been customary to force large volumes of fluid in the belief that this would stimulate diuresis, and it is probable that many of the deaths attributed to renal failure were the results of water intoxication (Chapter 28). Accumulation of potassium in blood plasma and extracellular fluid has serious toxic effects, and it is consequently important to restrict potassium intake in anuric patients. The prognosis in patients with lower nephron nephrosis depends largely on treatment employed, since the underlying renal lesion usually will proceed to complete healing.

The treatment of lower nephron nephrosis is essentially the treatment of acute renal failure, as discussed later.

NEPHROTIC STAGE OF GLOMERULAR NEPHRITIS

The nephrotic syndrome is characterized by massive proteinuria, marked hypoproteinemia, intractable edema, and lipidemia, and is one of the most striking phenomena of renal disease. This clinical picture frequently appears during the course of chronic diffuse glomerulonephritis, and may also be seen in renal amyloidosis, syphilis, intercapillary glomerulosclerosis, and renal vein thrombosis. In children and in young adults the syndrome occasionally develops in the absence of evidence of chronic renal disease, as so-called "pure" or lipoid nephrosis. A prolonged debate has taken place regarding the existence of this entity. It is claimed by some that the disorder is renal in origin, either a disease entity of itself or the result of an unrecognized glomerulonephritis, and by others that it is primarily extrarenal, perhaps on the basis of some obscure derangement of protein metabolism. Conflicting opinions regarding the pathogenesis of various manifestations likewise exist; but whatever the etiology and pathogenesis of the picture, the nephrotic syndrome presents certain uniform and consistent features.

The nephrotic syndrome presents somewhat different problems according to whether it occurs before or after puberty. The discussion to follow will deal primarily with the disease in children, in whom it is more commonly encountered.

Etiology. The cause of the nephrotic syndrome is unknown. In those patients in whom it develops in the course of chronic glomerulonephritis, it may be presumed that the manifestations are related in some way to extrarenal infection with the streptococcus or some other organism. On the other hand, in many cases, particularly in children, evidence of preceding infection is entirely lacking. Exacerbations in the clinical manifestations frequently occur following respiratory infections of varied etiology, but occasionally one observes spontaneous diuresis and an elevation in the plasma protein level following intercurrent infection. At best, one can state only that the relationship to infection is obscure.

The symptom complex is primarily one of children and young adults, and it frequently makes its appearance in the second or third year of life. In young children, the evidences of chronic nephritis are less frequently encountered than in adults, and many juvenile patients may proceed to complete recovery after a variable period of disability. In adults, the progression to terminal nephritis almost invariably occurs.

Pathology. The pathologic changes encountered in the kidney are not uniform. In most instances changes can be seen in the glomeruli which consist either of diffuse thickening of the basement membrane, or actual proliferation of varying degree. A few cases have been reported in which no change whatever could be detected in the glomeruli. In spite of this fact, it is to be presumed that there is an alteration in glomerular permeability to protein, since coagulated protein material can be seen in such instances within Bowman's capsule. Although it has been reported that biopsy of the kidney in a patient who has recently developed the nephrotic syndrome may show no histologic deviation from the normal structure of the tubular epithelium, tubular changes are usually striking after the disorder is well established. These consist of massive accumulations of fatty and colloid droplets in the cells of the convoluted tubules. In focal areas one may see pyknotic tubular nuclei, and there may even be focal necrosis with desquamation of tubular cells. In the lumens of the collecting tubules, casts are frequently encountered. The fatty drop-

lets consist of lipids of various sorts, particularly cholesterol esters, and there is evidence to indicate that the refractile colloid droplets which are also present may represent deposition of protein in the tubule cells. When the syndrome occurs in conjunction with amyloid disease, one finds a deposit of complex protein in the pericapillary spaces between the basement membrane and the capillary endothelium. This process may progress to complete glomerular destruction.

PATHOLOGIC PHYSIOLOGY

Proteinuria. Massive proteinuria is one of the most impressive and characteristic features of the nephrotic syndrome. The 24-hour protein output usually is between 5 and 10 Gm., but may vary from a few to 40 Gm., depending on the disease process and the protein intake. Albumin is the predominating urinary protein, and the electrophoretic pattern of the urinary protein often bears a startling resemblance to the plasma of normal individuals. In some cases globulin is prominent in the urine as well. It appears that the protein is derived from plasma protein, probably by filtration through glomeruli with altered permeability. The fact that one can see precipitated protein material in the glomerular space on microscopic sections supports this view. There is nothing to suggest that protein is excreted through the tubules. It is highly probable that diminished reabsorption of protein by tubule cells may be an important factor contributing to the proteinuria. It has been suggested that the massive protein excretion is due to the fact that the protein itself is abnormal, and is, therefore, disposed of as a foreign substance. However, the studies which have supported this view have not been done with homogeneous fractions, and there is no clear-cut evidence that an abnormal protein occurs either in the plasma or in the urine of such patients. Indeed, the massive proteinuria which ensues following the intravenous administration of normal serum albumin suggests very strongly that defective glomerular and tubular activity, and not abnormal protein, plays the dominant role. Proteinuria in any given patient will tend to vary considerably in relation to the protein intake.

Hypoproteinemia. Electrophoretic studies of plasma proteins in the nephrotic syndrome have shown that these are greatly altered. There is a marked reduction of albumin, usually an increase in the alpha-globulin, beta-globulin, and

fibrinogen fractions, and almost always a reduction in gamma-globulin. No reliable evidence exists that the proteins are qualitatively altered. The older chemical method of separating the protein fraction by precipitation with various concentrations of ammonium sulfate, frequently yields falsely high albumin values because this fraction is contaminated with alpha-globulin. The contaminating substances have a molecular weight many times that of albumin, and therefore the osmotic pressure of the plasma protein may be much lower than such chemical determinations of the albumin content would indicate.

Albuminuria is probably the most important factor leading to the production of hypoalbuminemia. This is borne out by the repeated observation that reduction in proteinuria usually results in a tendency for the plasma proteins to approach normal levels. However, there are reasons to believe that other factors are important as well. Protein loss in the urine may not exceed 4 or 5 Gm. a day, and in some patients who have a reduction in urinary output, it may be as little as 1 to 2 Gm. a day. According to various estimates of human plasma regenerative ability, such a loss is much below normal replacement capacity. When nephrotic patients are kept in positive nitrogen balance for long periods of time by means of high-protein diets, the plasma protein level does not necessarily rise. In juvenile patients, it is extremely difficult to maintain positive nitrogen balance. The optimal intake appears to be in the region of 3 Gm. per kg. of body weight, and much in excess of this amount may eventuate in reduced rather than increased protein assimilation. Another line of evidence pointing toward disturbed nitrogen metabolism is the presence of chronic reduction in plasma amino acid levels ("Ninhydrin" method), which is accentuated before and during a "nephrotic crisis." Since the principal site of albumin formation is the liver, a number of workers have sought evidence of disturbed liver function, but no unequivocal evidence of such a disturbance exists. The evidence suggests, then, that there is a fundamental defect in protein synthesis which varies quantitatively from patient to patient, but unequivocal proof of this assumption is lacking.

Edema. This symptom constitutes the most disabling feature of the nephrotic syndrome. The distribution of edema fluid appears to be governed by the factors of gravity and tissue tension.

The pathogenesis of nephrotic edema is not definitely settled. The principal factors involved are the plasma protein concentrations in relation to the osmotic pressure acting across capillary membranes throughout the body, as a determinant of the volume of interstitial fluid, and renal activity in relation to the retention or excretion of water and electrolytes. These factors are obviously interrelated, and must be considered together. There is little doubt that decreased plasma protein concentration, with resulting decreased oncotic pressure, results in increased filtration of water and diffusible solutes into the interstitial tissue, with the eventual development of edema. In the nephrotic syndrome the oncotic pressure drops even more sharply than chemical determinations of total protein might indicate, because the proteins of greatest osmotic activity are specifically withdrawn from the blood, and there is a concomitant increase of lipoprotein molecules of great molecular weight and correspondingly low osmotic activity. Under conditions of gradually developing lowered osmotic pressure, we may presume that an expansion of extracellular extravascular fluid volume occurs, until the increment in tissue tension balances the deficit in oncotic pressure. Such a theory postulates that the increment in extracellular fluid occurs at the expense of the plasma volume. The published figures for plasma volume are conflicting, but in most cases it appears to be somewhat reduced. When anemia is a complicating factor, the reduction is less marked. With diuresis, the plasma volume rises above normal and returns to normal when the body weight is stabilized. Doubt has been cast on the validity of this hypothesis by observations that diuresis and loss of edema may occur in the absence of any detectable change in the plasma protein concentration, and even in the presence of a fall in plasma osmotic pressure. However, in most instances, these observations were made without reference to changes in volume of the extracellular and plasma compartments. It is entirely possible that under conditions where the plasma osmotic and mean filtration pressures are almost balanced, a small increase in osmotic pressure of the plasma is enough to shift water immediately out of the interstitial compartment into the vascular compartment, resulting in an increase in plasma volume, but no detectable change in the plasma osmotic pressure. An alternative suggestion has

been that increased capillary permeability is a factor responsible for edema formation. Evidence that this occurs is lacking, since the edema fluid and transudate in the nephrotic syndrome usually contain very little protein, almost always less than 0.5 Gm. per hundred ml.

A quite different concept of the genesis of nephrotic edema is offered by those who believe that renal dysfunction in the disposal of water and electrolytes is primarily concerned, and that accumulation at the periphery is a secondary phenomenon. Certainly, retention of water and electrolytes by the kidney does occur, but the nephrotic patient appears to handle these substances in a manner that differs quantitatively rather than qualitatively from the normal. There is no reliable evidence, therefore, that such a defect constitutes the primary mechanism.

The possibility that increased formation of antidiuretic hormone by the posterior pituitary is responsible in part for the water retention has been suggested by the appearance of antidiuretic substances in the urine. There is no evidence, however, that either posterior pituitary or adrenal cortical dysfunction have primacy in determining increased tubular reabsorption of sodium in this disease.

Spontaneous diuresis has frequently been observed during various infectious diseases, and particularly during measles. The relationship to measles is so remarkable that the disease has been used as a method of treatment. Diuresis has also been described in response to pyrogenic reactions following administration of typhoid vaccine. It is known that fever gives rise to striking changes in the renal and peripheral circulation. The cardiac output rises and blood flow through the kidneys and skin increases, apparently as the result of vasodilatation. It is also known that diuresis may be produced by the intravenous administration of concentrated human albumin, when the plasma volume and the renal blood flow are increased by such therapy. How these changes are related to the withdrawal of tissue fluids is unknown, but they suggest that hemodynamic factors play an important role.

Lipidemia. One of the striking manifestations of the nephrotic syndrome, as of other hypoalbuminemic states, is the disturbance of lipid metabolism which gives rise to hypercholesterolemia and hyperlipemia. Plasma cholesterol is always elevated in this condition, levels as high as 2000

mg. % having been observed. Cholesterol esters appear to rise in most cases to the same extent as free cholesterol. The other lipid fractions are almost always increased as well, frequently enough to render the plasma opaque and milky in appearance. The nephrotic patient can apparently burn fats as efficiently as normal persons.

The causes of lipidemia in this condition may be partially elucidated by experimental studies of hypoalbuminemia induced by plasmophoresis. This has been found to be accompanied by lipidemia. It is possible that thyroid hormone deficiency may be concerned, although thyroid therapy has usually been disappointing.

Renal Function. On the whole, renal excretory function is surprisingly well preserved in the nephrotic syndrome. Studies of glomerular filtration rate and urea clearance have shown that these functions may not only be normal, but also may actually be supernormal to a considerable degree. Renal blood flow has variously been reported as elevated, normal, or slightly reduced. Tubular function, as measured by maximum tubular excretion of various substances, is usually unaffected.

Symptoms. The onset is insidious and the presenting symptom is usually edema. In children, a previous history of an upper respiratory infection or disturbance of the urinary tract is usually completely lacking. It is presumed that the edema is preceded by massive proteinuria for a variable period. The development of edema may be gradual or sudden, but eventually generalized anasarca of extreme degree develops, usually accompanied by ascites. Pallor becomes marked even in the absence of significant anemia. The appetite fails, lassitude and irritability develop, and severe malnutrition eventually occurs, but is masked by the massive edema and does not become apparent until diuresis supervenes. The phase of severe edema persists for weeks or months, and ascites may become so extreme as seriously to hamper respiratory excursions. Bilateral hydrothorax may also develop during this phase. Marked shifts in fluid characteristically occur with changes in posture, and in time there may be sudden massive movements of fluid from the peripheral tissues to the abdominal cavity, and vice versa. Gastrointestinal disturbances such as diarrhea and vomiting are not uncommon, and may be caused by generalized edema of the intestinal wall.

The urinary output is scanty and varies inversely with the degree of edema. The specific gravity is usually high and proteinuria is marked, usually between 0.5 and 2 per cent. Hyaline, granular, and cellular casts are present in large numbers, and white blood cells are usually increased in number. At the onset of the disease an increase in red corpuscles is usually not present, but microscopic hematuria eventually appears sporadically in almost every case, and even gross hematuria may occur. The development of persistent gross hematuria during the nephrotic syndrome is usually a serious prognostic sign, and indicates extensive involvement of the glomeruli and the probable existence of chronic glomerulonephritis.

Characteristic blood chemical changes are marked reduction in total protein primarily at the expense of the albumin fraction. Blood lipids are increased, particularly the cholesterol fraction, and the urea nitrogen is usually within normal limits. Occasionally, one observes mild increases in urea nitrogen which may be dependent upon increased reabsorption rather than upon reduction in glomerular filtration.

Anemia of variable degree may be present, particularly when clear-cut glomerulonephritis coexists. The erythrocyte sedimentation rate is usually markedly elevated. The serum calcium is frequently reduced, but ionized calcium is presumably normal, since the reduction apparently involves only the protein-bound fraction.

Ascitic fluid and edema fluid are usually opalescent and contain very little protein, the amount varying from 0.15 to 0.5 Gm. per hundred ml.

A lowered basal metabolic rate has been reported frequently in conjunction with the nephrotic syndrome, but is open to question on the basis of the difficulty in computing the true metabolic rate in the presence of massive weight distortion due to edema. Some patients apparently do have a truly depressed metabolic rate which may be explained in some instances on the basis of generalized severe malnutrition. Thyroid therapy has little effect on the course of the disease.

Sudden hypertensive episodes, with or without an accompanying encephalopathic symptom, may occur during the course of the illness. It is claimed by those who believe in the entity of pure or lipoid nephrosis that the appearance of

hypertension, hematuria, or azotemia rules out this diagnosis and indicates the existence of chronic glomerulonephritis. However, careful study of patients with the nephrotic syndrome over long periods of time will usually reveal one or more of these findings, even though the patient may later go on to what appears to be complete recovery.

The clinical pattern in adults resembles that described in children except for the closer relationship to demonstrable acute glomerulonephritis, the greater frequency of hypertension, the lesser likelihood of recovery, and the greater tendency to progress to renal excretory failure.

Complications. Patients with the nephrotic syndrome are unusually susceptible to infections of all types. Acute and chronic upper respiratory infections predominate, and septicemia is a not infrequent complication. The pneumococcus is a common invading organism, but the streptococcus and other pathogens may be the etiologic agent. Acute peritonitis is another frequent complication, and before the era of sulfonamides and penicillin was a common cause of death in these patients. The pneumococcus is the most frequent invader of the peritoneal cavity, but infections due to other organisms, including *E. coli* and the tubercle bacillus, are not rare, and hence it is desirable to identify the organism. Erysipelas-like infection, consisting of red, tender patches over various portions of the body, chiefly the abdomen, occur not infrequently. They resemble erysipelas except that the margins are not elevated and the erythema is splotchy rather than homogeneous. These skin lesions are accompanied by fever and other signs of acute infection, such as headache and vomiting. Often the edema increases suddenly during such an episode with concomitant decrease in urinary volume. The term "nephrotic crisis" has been used to describe these episodes as well as acute febrile episodes accompanied by a generalized increase in edema without overt signs pointing to the site of infection. Sudden diuresis may follow any of the infective complications seen with this syndrome. Why this should occur in some instances, whereas only exacerbation of the disease occurs in others, is poorly understood.

Prognosis. The course of the nephrotic syndrome is variable. A large number of juvenile patients who appear to have the signs of "pure" lipoid nephrosis at the onset of their illness

develop, after a period of months, unmistakable signs of chronic glomerulonephritis, and these patients, like most adult patients, eventually progress to the clinical state associated with the end-stage kidney. Other patients have recurrent bouts of edema which may persist over a period of years, in spite of which eventual complete recovery may occur. It is unusual for a recovery to occur if the edema lasts more than a year, however. Before the era of sulfonamides and penicillin, many of these patients succumbed to intercurrent infections such as pneumonia or peritonitis, before evidences of renal insufficiency developed. At the present time, however, it is usually possible to carry patients through these acute complications with the aid of these therapeutic agents, and the present causes of death are chiefly renal failure, occasionally cardiac failure, and hypertensive encephalopathy. Reports of the incidence of complete recovery of young children from the nephrotic syndrome vary from 25 to 50 per cent. In adults the disease almost always progresses eventually to the end-stage kidney with uremia, unless terminated earlier by intercurrent disorders. The rare instances of recovery in adults appear to occur in patients without hypertension.

The treatment of the nephrotic state will be discussed later.

INTERCAPILLARY GLOMERULOSCLEROSIS (KIMMELSTIEL-WILSON DISEASE)

This disorder usually occurs in individuals with long-standing diabetes (Kimmelstiel-Wilson disease), and may appear even though the diabetic state is mild. It may also occur in the absence of diabetes. The morbid anatomy is that of a noninflammatory focal fibrosis of the glomerular tufts. The chief clinical features are moderate to massive proteinuria, hypoproteinemia, edema, and hypertension. The condition, therefore, bears a close resemblance to the subacute or nephrotic stage of chronic glomerular nephritis, and cannot be differentiated from it except by the fact that in the absence of diabetes, the latter condition is the likely cause of such a clinical picture, while in the presence of diabetes, intercapillary glomerulosclerosis is the likely cause. The therapeutic problems are those of the management of the diabetes (Chapter 59), the treatment of hyper-

tension, and the management of renal edema and of uremia, as considered below.

RARER NEPHROTIC STATES

Renal Amyloidosis. This condition should be suspected in any individual presenting enlargement of the liver and/or spleen, plus moderate to massive proteinuria, edema, and hypoproteinemia. Hypertension may occur but is exceptional. The disorder may be confused with cirrhosis of the liver or congestive heart failure (Chapter 14). Many of the individuals will have evidence of tuberculosis, syphilis, multiple myeloma, or some chronic pyogenic infection such as osteomyelitis, bronchiectasis, or lung abscess. However, the absence of a chronic infection does not exclude amyloidosis, as some of the instances occur without any known predisposing factor. The therapeutic problems are those of the management of uremia. The diagnosis is essentially dependent upon the demonstration of an abnormally rapid disappearance of Congo red from the blood stream into the tissues, as amyloid tissue has a high affinity for this dye. In order to avoid a false positive interpretation of the test it is essential that urinary elimination be taken into account. Unfortunately, this is not a completely reliable test, but in the absence of a positive Congo red test, the diagnosis cannot be made with certainty.

Syphilitic Nephrosis. This is a very rare disease but is important because, unlike most of the nephroses, it is amenable to specific therapy. The usual clinical picture is that of edema and proteinuria, without hypertension or hematuria, in an individual with the history of syphilitic infection (usually recent) and a positive Wassermann reaction. Antisyphilitic therapy (Chapter 143) will usually result in dramatic relief of symptoms. Although one of the less common causes of chronic nephrosis, this condition should be borne in mind because of its curability.

Still rarer causes of the nephrotic state include the arteritic and collagen disorders (Chapter 38), multiple myeloma, and other hemopoietic disorders (Section 1 of Part VII).

COMMON CHRONIC RENAL DISORDERS

CHRONIC GLOMERULAR NEPHRITIS

The patient with acute glomerular nephritis may recover completely; may develop a nephrotic state, and from this pass into the terminal stage; may pass into a latent stage; or may have an insidious progression, with or without acute exacerbations, into the final phase (fig. 212).

When the disorder becomes latent, the only manifestation may be persistent proteinuria.

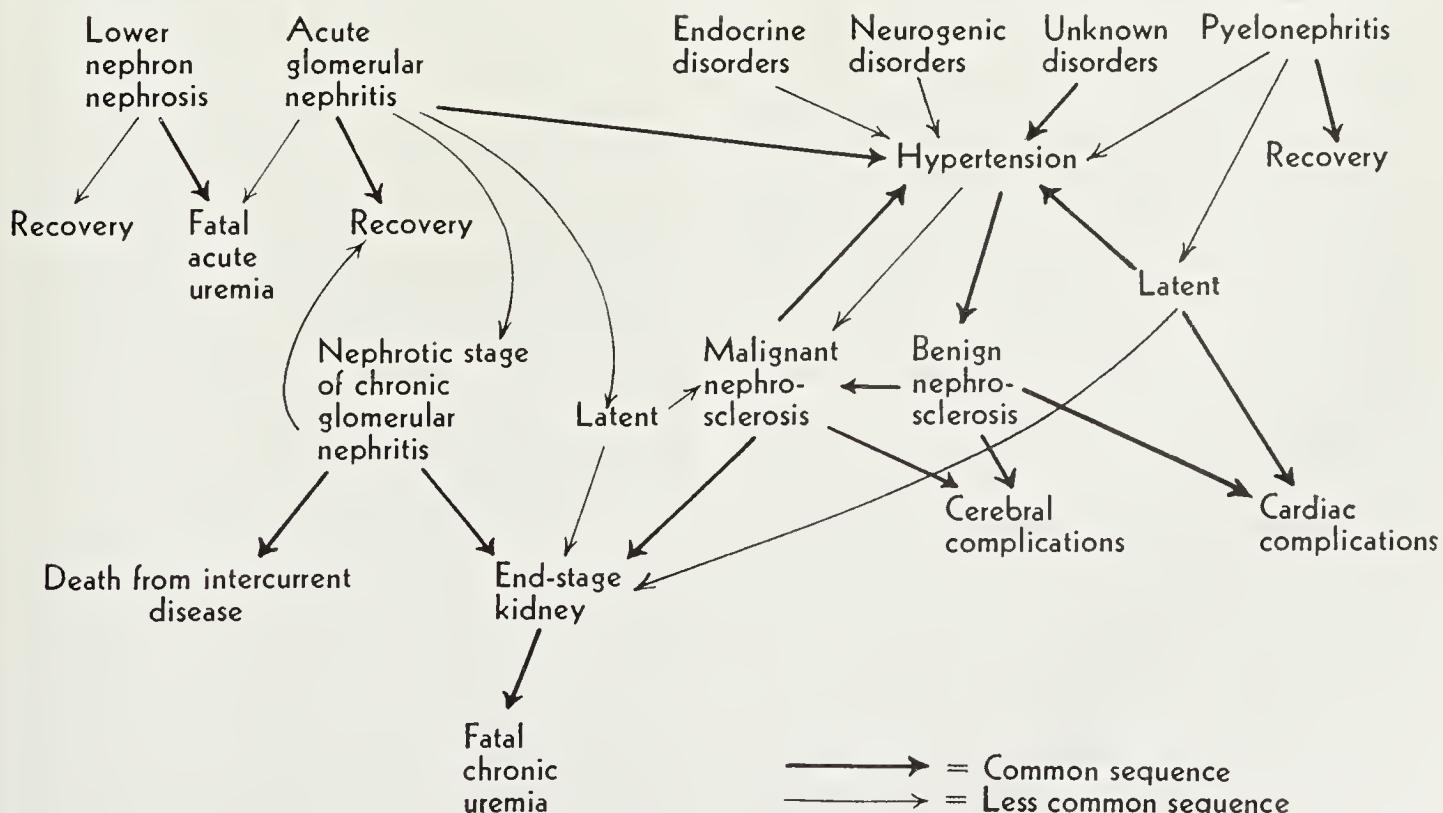


FIG. 212. Clinical course of important types of bilateral renal disease.

Episodes of hematuria may occur. Rarely such a state may persist throughout life but, more commonly, the patient eventually develops hypertension, and finally uremia supervenes.

The cardinal features of the end stage of glomerular nephritis are hypertension (with or without the complications of congestive heart failure and cerebral vascular disease) and uremia. The hypertensive state may endure for a few months or for many years. In the latter instance the patient may have a clinical picture which bears a close resemblance to that of benign (essential) hypertension, with the difference that proteinuria of some degree is constantly present, that anemia is commonly found, and that the various tests of renal function (Chapter 19) will reveal impairment.

In the majority of patients in the terminal stage of chronic glomerular nephritis, hypertension is of moderate degree. The usual levels of blood pressure encountered in adults are 180 to 220 systolic, and 110 to 140 diastolic. The extreme elevations commonly observed in the terminal stage of the malignant phase of essential hypertension are exceptional in patients with glomerular nephritis. Vascular retinopathy is usually encountered, with arteriovenous nicking, variations in the caliber of the vessels, spots of hemorrhage and exudate and, less frequently, papilledema. The retinal changes are similar to those seen in the terminal stages of primary nephrosclerosis, but are likely to be less extreme. Cardiac enlargement, with prominence of the sharply localized forceful impulse indicative of left ventricular hypertrophy, is the rule, and occasionally congestive heart failure occurs either in the form of acute pulmonary edema or as the more chronic type.

When, as is frequently the case, the terminal phase of glomerulonephritis develops after the nephrotic stage, a dramatic change in the clinical picture may occur. As uremia progresses and acidic substances accumulate, the acidosis is at first compensated for by the excretion of an acid urine, and by formation of ammonia, as well as by an increased excretion of carbon dioxide through the lungs. When these compensatory mechanisms fail, fixed base is excreted as a final means of ridding the body of acid. As sodium is excreted, water likewise passes into the urine, and the patient who may have suffered from intractable edema for many months tends

to lose edema and to develop a stage of extracellular fluid deficit. This is often aggravated by the vomiting, which is one of the earliest and most distressing manifestations of uremia.

Study of the kidneys of patients dying of chronic glomerular nephritis serves to explain many of the features of the clinical state. The kidneys are markedly and symmetrically reduced in size. The capsule strips with difficulty, leaving a pitted, granular surface. The cut section reveals narrowing of the cortices and obliteration of the normal renal architecture. Microscopically, one sees that most of the glomeruli have become hyalinized, while others reveal partial obliteration. An occasional glomerulus will display the last evidence of activity of the disease in the form of a still recognizable crescent in Bowman's capsule. Many of the tubules will have disappeared, with collapse of the fibrous stroma, while other tubules display varying degrees of dilatation. The blood vessels reveal thickening of the walls, and hyperplasia of the intima is common. Occasionally, when the blood pressure has been unusually high, changes indicative of malignant nephrosclerosis—i.e., necrotizing alterations in the arterial wall—will be found, in addition to the changes of glomerular nephritis.

The clinical picture of uremia has already been described in some detail, and the mechanism of some of the more important of the protean manifestations of the uremic state have been discussed (Chapter 19). It should be pointed out here that uremia develops insidiously in patients with glomerular nephritis, and may endure for many months. In this respect the disorder resembles pyelonephritis and the obstructive renal diseases, and is unlike malignant nephrosclerosis, in which death usually occurs within a few weeks after the onset of the manifestations of uremia.

The treatment of the end stage of glomerular nephritis will be discussed later.

NEPHROSCLEROSIS

There are two varieties of this disorder, and although they tend to overlap, they should be considered separately for the sake of clarity.

The term "benign nephrosclerosis" is used to indicate slowly progressive vascular changes in the kidneys, occurring as the result of long-standing hypertension. The large renal vessels may or may not show atheromatous changes.

The small and medium-sized arteries display thickening of the muscular layer, hyperplasia of the intima, and narrowing of the lumen. Hyalinization and narrowing of afferent glomerular arterioles is common, but only a minority of them are extensively involved. An occasional glomerulus may be obliterated with atrophy of the corresponding tubules. Such areas of ischemic atrophy of the kidney may alternate with hyperplastic areas in which the glomeruli are somewhat enlarged and the tubules dilated. This alternation gives rise to a granular kidney which, in the fully developed disease, may be somewhat contracted but does not reach the extremely small size commonly observed in individuals dying of chronic glomerular nephritis. The process resembles glomerulonephritis, however, in that the two kidneys are symmetrically involved, and differs in this respect from pyelonephritis, in which asymmetric involvement is the usual finding.

The clinical picture of patients with benign nephrosclerosis is dominated by hypertension and its sequelae. These include cardiac enlargement, congestive heart failure, angina pectoris, myocardial infarction, and cerebral vascular disorders (Chapter 269). Episodes of hypertensive encephalopathy are frequent in the more severe cases, but less so than when the disorder is of the malignant type. In a few instances the fundamental cause of the hypertension may be discernible, and may be related to disorders of the endocrine glands or of the nervous system. However, in the majority of instances the mechanism of hypertension remains unknown, and to these the unsatisfactory term "essential hypertension" is applied. It should be emphasized that the pathologic term "benign nephrosclerosis" and the clinical term "benign hypertension" are applied to instances in which the primary process is extrarenal, the changes in the kidneys are relatively slight and are clearly secondary to the hypertension, the urine remains normal or displays only slight change, and the clinical progression is slow. Although such patients regularly display slight to moderate changes in the retinal vessels, the striking evidences of vascular retinopathy, such as papilledema, extensive hemorrhages, and numerous patches of exudate, are absent. Benign nephrosclerosis is commonly attended by many years of useful living, and eventually the patient succumbs to senile dis-

orders, to intercurrent disease, or to one of the common complications, congestive heart failure, coronary arteriosclerosis, or cerebral vascular disease. Patients with benign hypertension in its pure type do not die of uremia. The problem, therefore, as seen clinically, is not the problem of renal disease, but that of hypertension, which has been discussed previously (Chapter 13).

Malignant Nephrosclerosis. This term, which is used to designate the pathologic alterations observed in patients presenting a clinical picture of malignant hypertension, covers two allied but somewhat different states. In the first of these the malignant changes, which consist of arteriolar necrosis, are superimposed on the pre-existing benign hypertension of long duration. This is a common event in those individuals who are between the ages of 35 and 55, and who, having had mild hypertension for a number of years, develop a rapidly progressive rise in blood pressure, and the clinical picture to be described.

The other, and much rarer, type of malignant nephrosclerosis is the type which progresses very rapidly, and terminates fatally in uremia within a year or two after the onset of hypertension. This is usually seen in younger patients, and is rare beyond the age of 45. Patients presenting this acute type of malignant hypertension are found at post-mortem examination to have normal-sized or slightly enlarged kidneys, with hemorrhages on the surface ("flea-bitten" kidneys), the dominant microscopic changes being necrosis of the afferent arterioles, with ischemic alterations of the glomeruli and tubules. It should be emphasized that malignant nephrosclerosis in this acute form, and malignant nephrosclerosis superimposed on benign hypertension, are not separate diseases. They represent different degrees of acuteness—i.e., different rates of progress of the vicious cycle whereby hypertension leads to renal vascular change, which leads to further hypertension, etc. However, it should be pointed out that while benign nephrosclerosis is, by definition, a state in which the hypertension is primarily extrarenal, malignant nephrosclerosis may be superimposed on any condition which causes hypertension, whether this primary disorder be renal (such as glomerulonephritis or pyelonephritis), or extrarenal, such as "essential" hypertension (i.e., hypertension of unknown cause).

Except for the patient's age and for the dura-

tion of the hypertension, the clinical pictures of the acute type of malignant nephrosclerosis, and of the chronic type which is superimposed on preexisting hypertension (regardless of the cause of the hypertension) tend to be similar. The outstanding features are the manifestations of uremia plus extreme elevations of blood pressure (especially of the diastolic level), and striking alterations in the retinal vessels. Marked narrowing of the arteries, with the so-called "silver-wire" appearance, marked arteriovenous compression, obliteration of the vessels, extensive hemorrhage, and exudate are the rule. Papilledema is common, and is likely to be most marked when the malignant nephrosclerosis is of the acute type. Hypertensive encephalopathy is common, and more particularly so in the older group of patients who are likely to have focal seizures superimposed on the preexisting vascular disease. Such cerebral vascular episodes, with pronounced focal symptoms, are frequently the forerunners of cerebral vascular accidents, with enduring manifestations. The cerebral complications are occasionally fatal, and rarely such patients die of congestive heart failure. However, the vast majority of individuals with malignant nephrosclerosis succumb to renal excretory failure, with the clinical picture of uremia (Chapter 19).

The differentiation of these several varieties of nephrosclerosis from each other, and from other conditions leading to the end-stage kidney, may present great difficulty. Benign nephrosclerosis may be diagnosed with confidence in any individual known to have had well-marked hypertension for a number of years, and in whom the diastolic pressure persistently remains below 120 mm. Hg, the retinal changes are limited to arteriovenous nicking without hemorrhage or exudate, renal function remains relatively good, and proteinuria is either absent or minimal. Malignant nephrosclerosis superimposed on benign nephrosclerosis may be diagnosed when an individual known to have presented the clinical picture of benign hypertension for a considerable number of years, begins to display the rapidly progressing pattern described below. The acute type of malignant nephrosclerosis may be diagnosed when a young person known to have had recently a normal blood pressure and a normal urine, begins to develop a rapidly rising blood

pressure, with outspoken evidence of vascular retinopathy and progressive renal excretory impairment soon leading to uremia. The urinary findings may be of aid, in that these tend to be progressive with the acute type of malignant nephrosclerosis, the amount of albumin increasing and the amount of blood in the urine increasing with the passage of time. Hematuria of marked degree does not occur in benign hypertension, and is rare when malignant hypertension becomes superimposed on benign hypertension. The differentiation of malignant hypertension from benign hypertension rarely presents difficulties, but the decision as to whether one is dealing with the acute or chronic type of malignant hypertension is often difficult. As a rule these types of malignant hypertension can be differentiated from the end stage of glomerular nephritis, or of pyelonephritis, by the higher blood pressure and the more marked eye ground changes, the rapid progression, the tendency of the urinary picture to become steadily worse, and the relatively short duration of life after the onset of uremia. However, the final stage of these various diseases may in the end be indistinguishable from each other, because any of these several disorders may terminate in malignant nephrosclerosis, and the differentiation can then be made with certainty only when one has had a chance to follow the patient during the earlier stages.

The treatment of malignant nephrosclerosis is essentially the treatment of hypertension and the treatment of uremia. These problems will be considered later.

CHRONIC PYELONEPHRITIS

Chronic pyelonephritis differs somewhat from the other major kidney diseases previously discussed in that there is usually a much more obvious and straightforward etiologic background. It seems definite that pyelonephritis is an infectious disease in which common microorganisms are implicated. In most examples of pyelonephritis there is some urinary tract disease or anomaly quite apart from any changes which may occur in the parenchyma of the kidneys themselves. Apparently, the basic defect which most commonly results in the infection of the kidney and subsequent changes of pyelonephritis is obstruction. The obstruction may be of any type and at almost any point in the urinary

tract. Even "physiologic" obstructions such as the "cord bladder" with secondary urinary tract infection may be the background upon which pyelonephritis may develop.

It does not seem pertinent to this discussion to enter into the debate as to whether or not the parenchyma of the kidneys is infected by the blood stream from above or by ascending infection from the lower urinary tract. The fact is that both routes of infection of kidney parenchyma can be accomplished experimentally, and it appears that the one common denominator which appears to be necessary for the successful experimental production of pyelonephritis is obstruction at some point in the urinary tract. It should be pointed out that although in most clinical instances an obstructive lesion can be demonstrated, a few cases will be encountered in which definite, well-marked obstruction cannot be located.

Characteristically, there is asymmetry in the lesions of pyelonephritis, there being great differences in size and degree of change between the two kidneys. Not infrequently the disease is bilateral, but seldom are the changes of equal severity on the two sides and frequently there are congenital abnormalities which produce asymmetry. This difference in size and degree of involvement of the two kidneys is the most important point of differentiation from the types of renal disease already discussed, because the microscopic differentiation between this disease and glomerulonephritis in the end stage is not easy, and, in fact, may be impossible.

In some instances pyelonephritis is bilateral, but in other instances the primary process is confined to one kidney, and the changes occurring in the opposite kidney are the result of nephrosclerosis consequent to hypertension. In the earlier stages, evidence of urinary tract infection—i.e., the presence of numerous leukocytes and bacteria in the urine—may be outspoken, but in the later stages the originally infected kidney is contracted and scarred, and under such circumstances the usual methods of examination may fail to reveal anything other than the findings commonly observed in nephrosclerosis.

The disorder is more common in women than in men, and chronic pyelonephritis is probably the most common cause of hypertension in women under the age of 35. The process fre-

quently begins during pregnancy, but in females it is not rare during childhood. There is considerable evidence which suggests that in the female the initial infectious process may be in the periurethral glands. It is likewise possible that pregnancy as well as various pelvic tumors tend to compress the ureters, interfering with drainage, and thereby to favor infection in the renal pelvis. Outspoken obstruction in the urinary tract is the usual cause in males, in whom prostatic enlargement and urethral stricture constitute frequent initiating factors. A considerable proportion of the patients with chronic pyelonephritis will be found, on careful study of the urinary tract, to have congenital anomalies of the kidneys (horseshoe kidney), compression of the ureters by fibrous bands, or by anomalous arteries, etc. Renal stone constitutes another common cause of chronic pyelonephritis, and, as has been mentioned, infection in the renal pelvis predisposes to stone formation, so that a vicious cycle may be created. Pyelonephritis is common in persons with diabetes and is especially frequent in individuals with disease of the spinal cord.

The clinical course of pyelonephritis is very variable. In many instances, and especially when only one kidney is involved and well-marked hypertension does not occur, the disease may remain essentially silent and be recognized at autopsy as only an incidental finding which produced few or no symptoms during life. In other instances the process may produce a clinical picture closely mimicking that of benign nephrosclerosis ("essential" hypertension). In some patients the renal disorder may produce rapidly progressive hypertension, which leads to injury of the renal arterioles, this in turn causing further hypertension, with further arteriolar injury and the typical picture of malignant nephrosclerosis. Under these circumstances it may be impossible to differentiate the process from primary nephrosclerosis.

The diagnosis of chronic pyelonephritis presents few difficulties if the patient is seen in the early stage, and if the urine is carefully studied for evidences of infection, such as numerous leukocytes and bacteria. When the patient is seen in a later stage, in which the presenting manifestation is hypertension of either the slowly progressive or the rapidly progressive type, the following points should lead to a sus-

picion that pyelonephritis may be the underlying cause: (1) a story of acute pyelitis or of unexplained chills and fever associated with unilateral pain in the flank; (2) a story of renal colic, of hematuria, or of frequency or dysuria in the past; (3) the presence of numerous leukocytes and bacteria in the catheterized specimen of urine; (4) a persistently positive urine culture when this procedure is carried out under conditions which tend to exclude contamination; (5) radiologic studies of the kidneys. In certain instances intravenous pyelograms will yield important information, but in many suspected cases ureteral catheterization, with study of the urine obtained from each kidney, and retrograde pyelograms are necessary.

In the treatment of chronic pyelonephritis, the first problem is that of eradicating any active infection which may be present. This depends on the recognition of the infecting organism, and for this purpose repeated cultures of urine specimens obtained by catheter, with all precautions against bacterial contaminants, is necessary. Once the infecting agent has been identified, attempts are made to keep the pH of the urine at a level which is unfavorable for the particular organism, and to utilize bactericidal agents which are particularly effective against this organism (table 106).

Operative procedures may be of value in many patients with pyelonephritis. In certain instances urethral or ureteral dilatation will be desirable. In others, drainage of the renal pelvis will be indicated. When the disease is entirely unilateral, and when the differential renal functional tests indicate that the diseased kidney has completely lost its excretory function, nephrectomy may be indicated, provided the opposite kidney has normal or supernormal function. Under such circumstances hypertension will occasionally be relieved by unilateral nephrectomy. When, however, both kidneys are involved, or when a kidney which has a considerable degree of excretory function is removed, the hypertensive process is rarely alleviated, and may even be aggravated.

The remaining problems in the management of pyelonephritis are essentially those of the treatment of hypertension and treatment of uremia, as discussed in other portions of this chapter, and also as discussed in Chapters 13 and 19.

The clinical course of the common types of renal disease, their relationship to each other, to hypertension and to uremia, are illustrated in figure 212.

MISCELLANEOUS DISORDERS OF THE KIDNEYS

Polycystic Disease. The convoluted tubules are derived from the metanephrogenous mesoderm; the straight collecting tubules develop from the metanephric diverticulum. Normally, these structures unite to form the complete tubule. When, as the result of developmental defect, such a union fails to take place in numerous nephron units, the filtrate passing down the convoluted tubules cannot escape through the normal collecting channels, and remains to form multiple cysts. (This explanation still seems valid for the infantile type but has been called into question in the adult type.) These increase slowly in size and eventually cause pressure atrophy of the intervening functional units.

The clinical picture is that of slowly progressive excretory impairment, usually accompanied by a moderate degree of hypertension. The disorder may produce symptoms and even death during infancy, but more commonly the characteristic specific diagnostic feature, *bilateral, symmetric nodular palpable masses in the flanks*, first becomes apparent in the young adult, and slowly progressive uremia occurs. The diagnosis depends on the presence of the masses and on characteristic deformity of the pyelogram. Surgical treatment with exposure of the kidneys, and puncture of available cysts, may produce temporary benefit. Otherwise, the management is that of hypertension and of uremia.

Congenital Excretory Dysfunction. There exist a number of rare congenital primary tubular functional changes which may or may not show coincident anatomic changes. Presumably, these are dependent upon specific dysfunctions of certain energetic systems in the tubule cell, upon which depend selective absorption or excretion of one or more plasma components. One of the best known of these is the de Toni-Fanconi syndrome, a disease of young children characterized by hypochloremia, glycosuria, hypocalcemia, hypophosphatemia, elevation of the organic acids of the blood, and ketonuria. The clinical symptoms include growth and developmental deficiency, marked anorexia, polyuria, and a high incidence of respiratory and

urinary tract infections. Roentgenologic examination of the long bones reveals rachitic changes.

A second variety of congenital tubular dysfunction, supposedly involving the loop of Henle and the distal convoluted tubule, is characterized by diabetes insipidus which is resistant to "Pitressin" therapy.

Inability to absorb specific ions such as sodium and chloride has also been described.

Hydronephrosis. This condition is usually due to obstructive lesions (often of congenital origin), but may appear when no obstruction is demonstrable. In most instances it is associated with infection, and the problems presented are those of pyelonephritis, as already discussed, or of surgical intervention. The reader is referred to standard works on urologic surgery.

Nephrolithiasis. Certain general principles in relation to stone formation in the urinary tract have already been considered (Chapter 19). The condition should be suspected when attacks of renal colic occur, with violent cramping pains in

the flank, abdomen, groin, or genitalia, and especially when such attacks are accompanied by hematuria. Since the calculi are usually radiopaque, the x-ray is of great diagnostic value. The problems of treatment are essentially surgical and are outside the scope of this book.

Tuberculosis of the Kidney. The reader is referred to Chapter 128.

Tumors of the Kidney. These should be suspected in all instances when patients present unexplained hematuria or evidence (by x-ray) of metastatic lesions in the lungs or the bones. In children the common renal neoplasm (Wilms's tumor) is readily palpable, but in adults the types of tumors commonly encountered cannot usually be felt. Intravenous and retrograde pyelograms are of greatest value in diagnosis. Since the problems of diagnosis and management involve the specialized techniques of urologic surgery, the reader is referred to books on this subject.

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See p. 1390.

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General Principles of Diagnosis and Therapy of Renal Disease

Gladys J. Fashena and T. R. Harrison

Principles of Diagnosis

Principles of Therapy

Treatment of Acute Excretory Failure

Treatment of Intractable Renal Edema

Treatment of Hypertensive Encephalopathy

Treatment of Congestive Failure

General Management of Patients with Chronic Renal Disorders

PRINCIPLES OF DIAGNOSIS

The *recognition of renal disease* depends primarily upon examination of the urine, and especially upon the detection of protein. Although inflammatory or neoplastic disease of the lower urinary tract may be accompanied by proteinuria, the decision as to whether the kidneys are responsible can usually be made readily in accordance with the following considerations:

(1) When the lower urinary tract is at fault the patient will usually complain of frequency, hesi-

tancy, urgency, or dysuria, while such symptoms are absent or minimal in most instances of renal disease. (2) Proteinuria, associated with lower urinary tract disease, is commonly accompanied by mucous shreds, and by disproportionate pyuria or hematuria; such findings are minimal or absent in chronic renal disease, and proportionally less marked in acute renal disease. (3) The presence of casts indicates that at least part of the protein is coming from the kidney. (4) The presence of renal functional impairment, as shown by decreased concentrating power, indicates a renal disorder; other renal functional tests (impaired excretion of phenolsulfonphthalein, elevation of blood urea, etc.) have similar significance if the general state of the patient is such as to exclude disorders of fluid balance or of the circulatory system as possible causes. (5) The co-

existence of hypertension, vascular retinopathy, or edema makes it probable that proteinuria is of renal origin. (6) When, on the basis of these considerations, it has become clear that the kidneys are responsible for proteinuria, only four important general causes need be considered: (1) febrile disorders; (2) circulatory disturbances; (3) orthostatic proteinuria; and (4) primary renal disease. The first two having been excluded by the general examination, the third can be eliminated by obtaining urine excreted during prolonged recumbency.

The decision having been made that disease of the kidneys exists, the *determination as to the type of renal disease* is made on the basis of the entire clinical picture, plus the urinary findings (tables 15 and 16, Chapter 19). Aside from some of the surgical disorders of the kidney, which will not be discussed here, the only common source of difficulty is the patient who is seen in the terminal phase of renal failure with hypertension and uremia. This problem has already been discussed in some detail, and it has been pointed out that, in the absence of knowledge of the clinical and urinary findings during the earlier phases of the process, it may be impossible to decide whether nephrosclerosis, glomerulonephritis, or pyelonephritis represents the initiating disorder. The important points in differential diagnosis between the several forms of acute nephritis, and between the several different disorders leading to the nephrotic state, will be obvious from the preceding discussions.

PRINCIPLES OF THERAPY

TREATMENT OF ACUTE EXCRETORY FAILURE

Aside from the conditions which cause prerenal azotemia (Chapter 19), acute excretory failure is most commonly seen in connection with lower nephron nephrosis and, less frequently, in the course of acute glomerular nephritis. Acute excretory failure is characterized by severe oliguria or anuria and by retention of excretory products. The basic principle of management of excretory failure is to preserve as far as possible the normal volume and composition of the body fluids. To achieve this aim the following program is suggested: (1) the electrolyte structure of the body should be defined initially by measurements of the serum concentration of chloride and bicarbonate, as well as of sodium when possible. Any marked deviation from normal should be

corrected by appropriate salt or bicarbonate therapy (Chapter 28). (2) A daily fluid intake should be allowed which is just sufficient to keep the body weight constant. This can be roughly estimated by calculating insensible loss and adding to this the urinary output of the previous day (Chapter 28). In hot weather, allowance should be made for sweating as well. It is now recognized that the forcing of water upon an anuric or oliguric patient whose anuria is due to a primary renal disturbance will not result in diuresis, but will merely result in the retention of water, dilution of body electrolytes, and the eventual development of symptoms of water intoxication. Likewise, the administration of sodium chloride in large amounts is hazardous and may lead to fatal pulmonary edema. (3) Frequent repetition of relevant laboratory determinations should be made as a guide to therapy, and proper amounts of sodium chloride and bicarbonate or lactate solution should be administered to restore the serum concentrations to satisfactory values (Chapter 29). (4) From 30 (adults) to 75 (infants) calories per kg. of body weight should be furnished each day by the administration of lactose orally, when this is tolerated. Since most anuric patients vomit frequently, intravenous glucose is usually necessary. Here, the objective of furnishing maximum calories without too much water, and without likelihood of venous thrombosis, can often be achieved by the administration of about 1.5 liters of 15 per cent glucose. The importance of an adequate caloric intake, in avoiding excessive protein catabolism, is often forgotten. (5) The unregulated intake of substances ordinarily excreted in the urine, especially potassium, should be avoided.

Using these principles of therapy, it is frequently possible to tide the patient over the period of acute anuria, with minimal disturbances in the composition and volume of the body fluid. When urinary output is again reestablished, the kidney is frequently incapable of concentrating urine for a period of several days or even weeks, and it is then necessary to change drastically the mode of therapy and to administer large volumes of fluid and electrolytes to cover the urinary loss. It is not uncommon for such a patient to excrete 5 or 6 liters of water per 24-hour period, which must be replaced along with appropriate electrolytes if dehydration is to be avoided.

When anuria is prolonged, nitrogenous and phenolic waste products, and metabolites and doubtless other toxic metabolic products as well, accumulate in the blood stream, and in all probability contribute to the patient's death. To rid the body of these products a number of means have been devised which have yielded varying degrees of success. Continuous gastric lavage will rid the body of considerable amounts of urea and, presumably, of other waste products as well, and has been advocated as a treatment for acute uremia. Recent clinical experience with the use of an artificial kidney based on the principle of dialysis indicates its therapeutic usefulness in patients with anuria or oliguria associated with excessive nitrogen retention and disorders in electrolyte balance. Although the procedure is complicated, its use may be life-saving in patients with the lower nephron syndrome since the ultimate outlook for complete healing of the renal lesion is so good.

The management of chronic excretory failure is similar to that just discussed for acute excretory failure, but a successful outcome is far less likely.

TREATMENT OF INTRACTABLE RENAL EDEMA

There is no specific therapy for the control of nephrotic edema. The treatment of patients with this symptom is largely supportive, and aimed at the prevention and control of infection, the maintenance of reasonably good nutrition, and the removal of excessive quantities of accumulated fluids by a variety of methods, none of which is satisfactory. Such patients should be given a liberal protein intake made up largely of those animal proteins such as milk, liver, and beef, which are known to form plasma albumin readily. In children the protein intake should be at a level of 3 Gm. per kg. of body weight. In adults, the daily intake should approximate 100 to 150 Gm. Protein supplements, such as casein and lactalbumin, are useful in maintaining patients in positive nitrogen balance, particularly during the periods of diarrhea. When the high-protein diet produces no response after adequate trial, it should be abandoned and a diet moderate in protein (80 to 100 Gm. for an adult of average size) and adequate in total calories should be used.

Although the use of a low-sodium intake has not been shown to be very effective in reducing

nephrotic edema, it is well recognized that a high-sodium intake tends to aggravate the edema, and therefore should be avoided.

Diuretic drugs are usually disappointing in this condition. Urea, when administered in large doses, may induce diuresis, but is contraindicated if there is any indication toward elevation of urea nitrogen. It is usually useless and possibly harmful. The combination of a xanthine diuretic with a mercurial diuretic is occasionally effective, but is often disappointing and cannot be used too often because of the toxic effect of mercury upon the tubule cells. Renal failure may be precipitated by mercurial diuretics. The administration of small amounts of typhoid vaccine, intravenously, has been suggested, and is occasionally followed by high fever and diuresis, but on the whole its use has been disappointing. Thyroid therapy also appears to be of little benefit.

A number of different osmotically active materials of high molecular weight have been used intravenously, in an attempt to increase the oncotic pressure and thus to induce diuresis. One of the earliest of these, acacia, produced favorable results in a number of instances, but has been abandoned largely because of its toxic effect upon the liver. Blood transfusions and the intravenous infusion of concentrated human plasma have been used extensively without any dramatic or long-lasting results, in the usual case. Concentrated salt-poor albumin, when given in large quantities, will produce a satisfactory though temporary diuresis in 50 per cent or more of the patients. The diuresis is only temporary, however, in spite of continued albumin therapy, and soon excessive albuminuria balances almost all of the albumin administered. Since the amount of albumin needed to obtain a temporary weight loss of 10 to 20 kg. of water represents a large number of plasma donations, this represents a highly uneconomic form of therapy.

In patients with large collections of ascitic fluid, peritoneal drainage is an effective way of relieving respiratory and cardiac distress, and disturbances from pressure upon the gastrointestinal tract. Following aspiration the fluid may continue to leak from the opening for several days, and often all of the ascitic fluid is lost through this fistulous tract.

It has been demonstrated many times that measles is often followed by a spontaneous diuresis, and it is suggested by several different groups of workers that the deliberate exposure of a non-

immune patient to measles might be indicated in this condition. The mechanism of a measles-induced remission is not completely understood, but the evidence indicates that the diuresis is preceded by a decrease in albuminuria and hence, presumably, by a rise in plasma osmotic pressure.

TREATMENT OF HYPERTENSIVE ENCEPHALOPATHY

Although the elevation of systolic blood pressure in patients with acute nephritis may be related to increased cardiac output as the result of hypervolemia, it seems certain that the diastolic elevation is due largely to generalized vasospasm. The hypertension may result both in hypertensive encephalopathy and in cardiac failure. Therefore, attempts should be made to lower the blood pressure whenever diastolic elevation becomes definite. This can be done quite effectively in children, and in a small percentage of young adults, by the intramuscular injection of a 50 per cent solution of magnesium sulfate in doses of 0.2 ml. per kg. of body weight. This usually has to be administered several times at four-hour intervals, to keep the pressure at a satisfactory level, following which the blood pressure can usually be controlled satisfactorily by the oral administration of from 15 to 30 ml. of 50 per cent magnesium sulfate two or three times daily. (It is remarkable that in the nephritic patient this amount of the drug rarely produces catharsis.) If the patient is voiding large amounts of urine, larger doses of the drug may be needed to produce the desired effect. Occasionally, intramuscular and oral administration of magnesium salts is ineffective, and it is necessary to resort to the intravenous injection of 100 to 200 ml. of a 1 per cent solution of the salts. This must be done very slowly, with simultaneous recording of the blood pressure at intervals of two or three minutes. A 10 per cent solution of calcium gluconate should be on hand for immediate intravenous injection, should respiratory depression occur. The intravenous administration of 5 to 10 ml. of a 10 per cent solution of calcium gluconate, or a 5 per cent solution of calcium chloride, is effective in counteracting the severe respiratory depression and drowsiness which may result from magnesium sulfate therapy. The beneficial effects of magnesium salts appears to depend on their ability to relax arteriolar spasm. If signs of associated cerebral edema are present, lumbar puncture may be effective in controlling the manifestations of

encephalopathy. Oxygen therapy may also produce beneficial results.

In patients with chronic renal disease, episodes of hypertensive encephalopathy may be treated by similar means, although the value of magnesium sulfate is dubious. Sedative drugs, and measures designed to reduce emotional stress, are of especial importance, while venesection and spinal tap may be useful in selected cases.

TREATMENT OF CONGESTIVE FAILURE

Treatment of this complication is not essentially different from the treatment of cardiac failure in general. Strict bed rest should be enforced, with barbiturate or morphine sedation as indicated, provided it is realized that persons with renal disease often tolerate morphine and other drugs poorly. It should be remembered that children are particularly susceptible to the action of opiates, and should be given morphine in small doses, not over 1 mg. per 5 kg. of body weight. Oxygen therapy is useful. Digitalization should be carried out in the usual manner. The response to digitalis is usually dramatic in persons with heart failure due to acute nephritis, in contrast to the response seen in active rheumatic myocarditis with cardiac failure. Since cardiac insufficiency is associated with hypertension in almost every instance, and the symptoms tend to disappear rapidly when the blood pressure is reduced, magnesium sulfate therapy is indicated, as outlined previously. If the urinary volume is small, it is often advisable to limit the fluid intake to an amount equal to the insensible water loss, plus urinary output, in order that increasing edema or enlarging blood volume may not further hamper cardiac action. Sodium intake should be drastically reduced in this, as in all other types of cardiac failure. When cardiac failure and renal excretory failure coexist, the restriction of sodium intake tends to benefit the former and aggravate the latter, while the administration of sodium salts has the reverse effect.

GENERAL MANAGEMENT OF PATIENTS WITH CHRONIC RENAL DISORDERS

The management of the chronic renal disorders may be divided into several main problems:

1. *The treatment of primary or secondary causative factors: Obstruction and infection in the urinary tract should be sought for, and especially*

when there is a story of dysuria, frequency, and hesitancy or fever. The general physician should have a high index of suspicion toward such disorders; their final detection and their management will often call for the special skills of the urologic surgeon. The treatment of urinary tract infection has already been discussed. *Congestive heart failure* is a common and frequently remediable complication of renal disease, and often aggravates the renal status. It is especially important to look for evidence (such as hematuria or cellular casts) of *acute renal injury* which may be reversible (Chapter 19).

2. *Physical activity*, which does not produce dyspnea or undue fatigue, may be allowed. The concomitant hypertension is much more likely to be aggravated by *emotional stress* than by moderate physical activity. A flare-up in the acuteness of the process, as shown by increased degree of proteinuria or by gross hematuria, calls for a period of complete rest. The advantages of rest periods in the middle of the day, and of frequent vacations, are obvious.

3. *The dietary management* of chronic renal disease is still controversial, some holding that protein should be restricted, others that this is unnecessary. In the absence of complete information, it appears wise to reserve drastic protein restriction for patients with nitrogen retention, and to allow adults in the less advanced stages a protein intake of 60 to 80 Gm. per day. The presence or imminence of congestive heart failure calls for drastic restriction of sodium. The hypertensive state will likewise be aided in certain patients (although not in the majority) by rigid restriction of sodium to a daily intake of less than 200

mg. (500 mg. of sodium chloride). Once excretory failure develops, restriction of sodium may cause more harm than benefit. In the terminal phase, renal acidosis or vomiting may lead to rapid excretion of sodium with consequent extracellular fluid deficit, and under such circumstances sodium salts should be administered. Since hypertension predisposes to atheroma, cholesterol and animal fats should be restricted in patients with significant elevation of blood pressure, except in the terminal and hopeless phase, in which the patient should be allowed to eat whatever is desired.

4. Of especial importance are *attempts to prevent infections*, especially those of the respiratory tract. Public gathering places should be avoided during the winter months. Members of the family who have "colds" should keep away from the patient. It is probable that patients with chronic renal disease, and especially those with glomerular nephritis, will be benefited by taking penicillin orally (about 200,000 units twice daily when economic circumstances permit) during the late autumn, winter, and spring. This seems more logical than to administer sulfonamides, which may be nephrotoxic, and recent evidence suggests that it is no less effective in preventing streptococcal infections.

5. The remaining problems in the management of chronic renal disease consist essentially in the treatment of congestive heart failure (Chapter 238), of hypertension (Chapter 13), of hypertensive encephalopathy (as discussed above), and of uremia (Chapter 19).

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See p. 1390.

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Cystitis

Gladys J. Fashena and T. R. Harrison

Symptoms
Diagnosis
Treatment

Almost invariably, infection of the bladder wall is the result of extension either (1) from an infec-

tion in the upper urinary tract (pelvis and parenchyma of kidney) or (2) from an infection localized in the lower genitourinary tract (urethra, prostate, etc., in males; urethra and uterine cervix in females). The rare exceptions are those

instances of cystitis presumably secondary to distant focal infections (interstitial cystitis, sometimes called Hunner or elusive ulcer), and those cases of cystitis due to extension of an infection present in the neighboring pelvic organs (for example, a low-lying acutely inflamed appendix resting on the bladder, or a pelvic peritonitis due to a ruptured intestine in typhoid fever). Even in the presence of pathogenic bacteria, persistent or significant infection rarely takes place unless stasis or trauma is present. Hence, in all cases of cystitis, it is important to determine whether the infection is originating above or below the bladder, and whether conditions favorable for the development of the infection are present (for example, trauma due to calculus or repeated catheterizations, or stasis due to prostatic enlargement, contracture of the vesical orifice, urethral stricture, cystocele).

The bacteria most commonly responsible are the bacilli of the colon group; less frequently the causative agents are members of the staphylococcus and streptococcus groups; still more uncommon are the proteus and pyocyaneus organisms, gonococcus, Friedländer's bacillus, and the tubercle bacillus.

Symptoms. The symptoms of cystitis are pain on urination, frequency, and pyuria demonstrated in a properly collected specimen of urine. Fever over 100° to 101° F., and the constitutional symptoms associated with a high fever, are rarely due to cystitis per se. When such symptoms exist, they usually indicate the presence of an acute infection in the kidney pelvis or parenchyma, in which case pain and tenderness common to renal involvement may be elicited; or an acute infection in the lower genitourinary tract, as in acute prostatitis, which is manifested by the characteristic tenderness and distribution of pain. In the majority of instances of cystitis associated with high fever, acute pyelonephritis or pyonephrosis is present.

Diagnosis. Pyuria, established on the sediment of a properly collected specimen of urine, means that cystitis is likely. This means a catheterized specimen in the female, and the second glass of a two-glass specimen in the male. When this is associated with evidences of kidney involvement, the procedure for further investigation is that which has already been described for infections

of the kidney: urine culture, flat plate of kidneys to determine presence of calculi or of perinephric abscess, excretory and retrograde pyelograms to determine presence of anomalies or other causes of stasis. When there is little or no fever, investigation of the lower genitourinary tract is carried out to discover a possible source of infection or cause of stasis. If this latter study reveals no logical basis for the cystitis, attention is then directed to the upper urinary tract, which may be harboring a low-grade and relatively asymptomatic infection, which may be revealed only by careful urologic study. In most cases, the primary cause can be readily disclosed if a thorough and systematic urologic investigation is carried out. In some cases, the exact nature of the disorder may not be immediately apparent. Pyuria, without bacteria being demonstrable in the urinary sediment, should arouse the suspicion of tuberculous infection, and appropriate special stains, cultures, and guinea-pig inoculations should be carried out. Symptoms of intense bladder irritation with relatively few red and white blood corpuscles in the urine, and with no organisms appearing in the stained sediment, is highly suggestive of interstitial cystitis.

Treatment depends on the nature of the primary lesion and on the organism responsible for the infection. The details have been discussed in the appropriate sections.

THE KIDNEYS

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Section 4—The Respiratory Tract

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Introduction

John S. Chapman

Physiology
History
Physical Examination
Additional Diagnostic Procedures

Physiology. The activity of the respiratory system consists of two principal components: the first, the mechanical displacement of gases, or ventilation; the second, the diffusion of these gases through the alveolocapillary membrane, or alveolar respiration. Clinically, ventilatory insufficiency is manifest as the subjective symptom of dyspnea, while alveolar respiratory failure is marked by hypoxia.

As pointed out in Chapter 9, ventilation results from muscular work during inspiration and from elastic recoil of the lungs during expiration, but for this work and recoil to be effective in displacement of gases, the airways must be patent. Thus among the major respiratory causes of dyspnea are any kind of obstruction of the air passages, any disease or injury which impairs the medullary center or its effector neurons, damage to the chest wall and muscles of respiration, and large collections of fluid or gas which markedly alter effective intrapleural pressure. Of all causes, however, pain sufficient to limit respiratory motion is the most common.

Of the measurements of ventilatory function, the simplest is the vital capacity determination. Although this test is useful in patients in whom there is no expiratory obstruction and hence finds its greatest value in the study of patients with cardiac disorders, most respiratory diseases are associated with some degree of bronchial obstruction. In such patients vital capacity measurement, which takes no account of time, is less valuable than the maximum breathing capacity (M.B.C.) test which plots, against time, the volume of gas ventilated. A healthy young male, for example, can ventilate at the rate of 150 liters per minute, though his vital capacity may be only 4500 ml. On the other hand, it is not unusual

to find patients with severe obstructive emphysema who can force a vital capacity breath of 3500 ml., though their maximum breathing capacity may be no more than 50 liters per minute. If one wishes, he may then calculate the breathing reserve by determining the basal breathing requirement, which in the healthy young male may be about 6 liters per minute. Using the formula

$$\frac{\text{Maximum breathing capacity} - \text{Basal requirement}}{\text{Maximum breathing capacity}} \times 100 = \text{Breathing reserve}$$

one will establish the breathing reserve of the healthy individual as 96 per cent, while that of the emphysematous patient will be (since he will have a larger basal requirement) $\frac{50 - 8}{50} = 84$ per cent.

Hypoxia is the result of alveolorespiratory insufficiency, but can be recognized clinically only when it is of such degree as to produce cyanosis. Unfortunately, since cyanosis is usually evident only when as much as 5 Gm. of hemoglobin is in a reduced state, rather severe grades of hypoxia may exist before the physician becomes aware of them. The obvious means of study, of course, is the chemical determination of the oxygen content and saturation of arterial blood, a technic not often available. The newly devised oximeter only partially fulfills the requirement of a simpler and easier test. Until some accurate and simple measure of reduced hemoglobin is available, the physician can only suspect hypoxia from such signs as mental disturbances.

Hypoxia and ventilatory failure have been discussed above as separate conditions, but one often sees the two conditions combined in the patient. Obviously, if ventilation falls below a certain point, hypoxia is certain to result. Similarly, the hypoxic individual is usually also

dyspneic. The problem in any patient, however, is to attempt to understand the mechanisms producing the total picture. That means that factors giving rise to dyspnea must be treated mechanically—by aspiration of secretions, by withdrawal of pleural fluid or air, or by relief of bronchiolar spasm—while hypoxia calls for oxygen. The usual error is to try to use oxygen for relief of both parts of respiratory inadequacy.

History. In dealing with diseases of the respiratory system, one finds the history falling naturally into two divisions. The first relates to such general constitutional symptoms as malaise, loss of weight, fever, etc. The other relates particularly to the respiratory tract, and may afford excellent clues to the nature of the disease.

Cough (see Chapter 10) is an almost universal complaint, and the condition of onset, frequency, episodes of aggravation, and periodicity during 24 hours may be most helpful in assisting one to arrive at an opinion. The patient with bronchiectasis frequently states that his cough is worst when he lies down; the patient with bronchitis, that sudden changes in temperature are prone to induce paroxysms of nonproductive coughing; and the patient with carcinoma of the bronchus, that the cough pattern has changed and become more frequent.

Chest pain has to be evaluated in relation to respiratory motion, as opposed to twisting and bending of the trunk. A sharp localization and considerable superficial tenderness should lead one to search for chest wall rather than pleural disease, while retrosternal discomfort bespeaks tracheal and bronchial disorder. Persistent and increasing pain in the same region, pain unrelieved by change in position or voluntary restriction of ventilation, is often due to carcinoma.

The character of the sputum is a source of much important information. One should question the patient about the total daily quantity, the color, consistency, odor, and taste. A foul or unpleasant-tasting purulent sputum calls to mind at once carcinoma, bronchiectasis, and abscess; while a frothy, sticky, tenacious, and colorless sputum is frequently described by patients with emphysema or chronic bronchitis, though a somewhat similar type may result from carcinomas in certain areas of the lung.

Blood spitting varies from the slightly streaked sputum of patients with carcinoma, emphysema, or chronic bronchitis, to profuse pulmonary

hemorrhage which is more characteristic of tuberculosis, bronchiectasis, and bronchial adenoma.

Though patients do not often offer wheezing as one of their major complaints, the importance of this symptom is so great that no respiratory history is adequate which does not specifically mention wheezing. If there is a sharp localization, the examiner should think immediately of carcinoma, tuberculous bronchial stenosis, or adenoma. If, however, wheezing is described as generalized but variable in intensity, the history points more strongly toward asthma, bronchitis, or emphysema.

Physical Examination. Aside from the standard procedures, certain additional maneuvers often prove useful. Pain which is well localized calls for careful palpation of the thoracic wall, to detect the grating of a broken rib or the presence of a palpable tumor or chest wall defect. If the patient has mentioned a wheeze, or even though he has denied it but other elements in history are suggestive, the examiner should listen at the patient's open mouth for a rasping sound during forced expiration. In the same way, a story of wheeze or a strong suspicion of a bronchial obstruction should lead one to auscultate carefully for persistent rhoncus near the sternum or beside the spine.

The association of groups of physical findings is common, and the recognition of this association most useful in making a physical diagnosis. The combination of flatness, absent breath sounds, a few rales, and a persistent expiratory rhoncus points strongly toward carcinoma, while the same findings without the rhoncus point strongly toward abscess. In contrast with these signs, one more usually discovers bronchovesicular or bronchial breath sounds over areas of tuberculosis.

The distribution of physical findings is also of considerable diagnostic value. Lesions found in the upper lobes posteriorly, particularly if the signs are bilateral, are almost always tuberculous in origin. The signs of abscess commonly are unilateral, and very frequently localize in the dorsal segment of the lower lobe or in the axillary segment of the upper. Bilateral lower lobe disease suggests bronchiectasis.

Finally, one should bear in mind that all these statements in regard to symptoms and signs are not absolute, but represent only the more frequent associations, and that these statements

relate only to the chronic diseases of the respiratory system.

Additional Diagnostic Procedures. When one is confronted with a patient presenting chronic pulmonary disease, his most difficult task is to eliminate tuberculosis. The sputum must be searched repeatedly for acid-fast organisms. If one or two direct smears are negative for *Mycobacterium tuberculosis*, 24-, 48-, or 72-hour pooled specimens should be concentrated and searched. If the sputum is very abundant and purulent, the patient may be given penicillin for three or four days and subsequent sputums studied, since often a profuse secondary infection produces so much pus that dilution of tubercle organisms below the point of discovery may occur. Finally, sputum or gastric washings should be subjected to culture and/or guinea pig inoculation. Wet mounts of sputum mixed with sodium hydroxide are often of value in demonstrating fungi and yeasts, but, when mycotic disease is suspected, cultures on Sabouraud's medium also should be done.

Pleural fluid should be subjected to complete chemical, cytologic, and bacteriologic examination.

Thoracoscopy may reveal information in obscure diseases of the pleura, and sometimes furnishes material for histologic examination. Bronchoscopy is of the greatest value in every condition in which any type of bronchial disease is suspected. Aside from the information derived from direct inspection, information that may locate more accurately a roentgenographic lesion or afford presumptive evidence of tuberculosis or carcinoma, the instrument is most useful

in obtaining secretions for culture or cytologic examination. Bronchography, in addition to revealing the degree and distribution of bronchiectasis, sometimes may furnish significant information about lesions which lie beyond the range of the bronchoscope. Diagnostic pneumothorax, except as it may sometimes be required to indicate the extrapulmonary position of a tumor, is of little use, while lung puncture to obtain a biopsy should be performed only when all other methods have failed, and only when one is certain that his needle will not traverse the free pleural space.

The Papanicolaou technic for the study of small clusters of cells, either from pleural fluid or sputum, affords an excellent additional means of diagnosis of malignant tumors. But, except in the hands of pathologists of considerable experience, it may be misleading. While those who have extensively used this method in the study of carcinoma of the bronchus are enthusiastic, other pathologists prefer fixed sections of centrifuged secretions.

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Disorders of Chest Wall and Mediastinum

John S. Chapman

Anomalies and Disorders Involving Chest Wall

Diseases of Mediastinum

Mediastinitis

Pneumomediastinum

Tumors of Mediastinum

ANOMALIES AND DISORDERS INVOLVING CHEST WALL

The commonest anomalies of the chest wall are developmental abnormalities of the ribs, which include bifidism, and agenesis of the first ribs, cervical ribs, and lumbar ribs. Clinically, these conditions are usually of little or no significance except as cervical ribs occasionally give rise to brachial plexus pain or obstruction of the subclavian vessels. To the thoracic surgeon they may assume considerable importance in the planning of thoracoplasty.

Severe *scoliosis* or *kypheoscoliosis* is frequently associated with bronchiectasis on the compressed side, while, functionally, the derangement of the thorax is a common source of dyspnea.

Pigeon chest, marked by a tremendous antero-posterior diameter of the thorax and a prominent, prowlike sternum, seems not to impair ventilatory or alveolorespiratory function, and is clinically of importance chiefly in differentiation from the barrel chest of emphysema.

Funnel chest is much more important from the standpoint of functional disorder. On occasion, the sternum may be so markedly depressed as to displace the heart into the left axilla, while the rib motion is so much impaired that respiration becomes almost exclusively diaphragmatic. This disorder, which is apparently familial, is readily recognized in early life, and is amenable to various surgical procedures. Results are most satisfactory if operation can be achieved in childhood.

Injuries of the thorax which are associated with multiple rib fractures, or separation of the sternum from the ribs, are of as much concern to the internist as to the surgeon. The patient usually presents the picture of severe shock associated with marked embarrassment of respiration, cyanosis, and great pain. One observes that

the unsupported chest wall moves in a paradoxical manner, the sternum or affected side being drawn inward during inspiration. Numerous rhonchi are audible. In addition, traumatic pneumothorax, with subcutaneous and mediastinal emphysema, frequently is seen as a result of laceration of the lung. Hemoptysis and bleeding into the pleural cavity are by no means rare.

The patient's condition requires immediate and well-considered measures. Shock and hemorrhage call for transfusion of whole blood. Tension pneumothorax, if present, demands immediate decompression, even with the use of continuous suction if the escape of air is rapid. The presence of blood and secretions in the airways necessitates bronchial aspiration at frequent intervals. Although one or two injections of morphine are necessary during the acute emergency, this drug should be discontinued as soon as possible, since its depressant action on the cough reflex and the respiratory center tends to perpetuate and aggravate both bronchial obstruction and hypoxia. Intercostal nerve block, successfully performed, is far more efficient in relieving pain, and has none of the disadvantages of the use of narcotics. As the patient emerges somewhat from severest danger, the problem of the immobilization of the flailing chest wall arises. Heavy adhesive strapping markedly limits the motion of the chest wall but is a potent cause of retained secretions. Sandbags offer quite as good immobilization without such great danger of atelectasis and pneumonia.

Infections of the chest wall are rarely of much moment, but on occasion severe phlegmons may develop along the tract of an aspirating needle. Tuberculous and actinomycotic pleurocutaneous fistulas may result either from repeated aspiration or, rarely, spontaneously.

Tumors of the chest wall commonly arise either from intercostal nerves or from ribs. Fibromas, sometimes persisting in benign form only to undergo sarcomatous degeneration later, have been described.

If the diaphragm may be considered a part of the chest wall, its commonest disorder is *hiatus hernia* (see Chapters 3, 257). Traumatic hernias occur chiefly on the left side, and give rise to a confusing picture characterized by the manifestations of an acute surgical abdominal disorder as well as by those of acute respiratory embarrassment. The involved side of the chest is motionless and breath sounds are absent, but one may hear peristaltic sounds sometimes as high as the clavicle. The roentgenogram of the chest commonly reveals marked shift of the heart and mediastinum into the normal side of the chest, while on the otherwise dense side small radiolucent areas, sometimes with fluid levels, indicate the presence of bowel above the diaphragm. A glass of barium suspension followed fluoroscopically will serve to remove any doubt.

Eventration of the diaphragm, a congenital anomaly usually involving the posterior leaf of the left half of the diaphragm, may be mistaken on physical examination for pleural effusion or diaphragmatic elevation following phrenic paralysis. Roentgenographically, before the lateral view clearly reveals the nature of the lesion, the suspicion is of hernia or phrenic paralysis.

DISEASES OF MEDIASTINUM

The mediastinum is bounded above by the thoracic inlet, below by the nonpleuralized part of the diaphragm, and laterally by the medial surfaces of the parietal pleura. In this compartment, which separates the two pleural cavities, are the trachea and first parts of the bronchi with their associated lymph nodes, the esophagus and its related nodes, the heart and great vessels, the thoracic duct, the vagus, phrenic, and left recurrent laryngeal nerves, various branches of the thoracolumbar outflow, and the remnant of the thymus. Among these structures the only tissue which can be considered truly mediastinal is the loose areolar tissue and the collections of fat which lie among and around the structures mentioned above. Infection commonly results in rather rapid distention of the mediastinum, since firm supporting tissue is lacking, and in spreading inflammation, since fascial planes do not exist. In health the mediastinal structures are so elastic that ready displacement can occur from minor changes in pressure in a pleural cavity. Mediastinal shift is, therefore, a very common finding in diseases of the lungs or pleura.

MEDIASTINITIS

Primary syphilitic mediastinitis and tuberculous mediastinitis have been described, and other primary infection may occur. A type of mediastinitis associated with viral invasion of the tracheobronchial tree is recognized infrequently but, in fact, may be quite common. The organism probably reaches the tracheobronchial nodes, where it sets up a lymphadenitis that results in fever, a sense of retrosternal oppression, and poorly localized pain in the center and upper portion of the chest. Since the enlargement of the lymph nodes is so slight, the condition is not evident in roentgenograms, and one can only suspect its existence. It is fairly well substantiated by autopsy that mediastinal lymphadenitis, whatever the infecting agent, may well be the precipitating factor in the development of pericarditis.

The more dramatic type of mediastinitis, a spreading, pyogenic inflammation or acute abscess, is the result either of severe derangement of the organs which lie within the mediastinum or of descending infection from acute retropharyngeal or cervical abscess. The disease is marked by high fever, marked retrosternal pain which may be referred to the back, difficulty in breathing, a cough of a pressure type, and dysphagia. At times films at various angles fail to demonstrate clearly the inflammatory process, in which case diagnosis is most difficult, while in other cases roentgenograms may reveal considerable widening of a portion of the mediastinum and even the fluid level of abscess. In every patient with cervical or retropharyngeal abscess, the physician should keep in mind the possibility of mediastinitis, and should be on the alert for symptoms.

Although diseases (notably cancer) of the bronchus may rarely perforate and lead to mediastinitis, the most common cause by far is disease of the esophagus. Perforation may result from missiles, from rough instrumentation, from attempted dilatation of strictures, and, even when the greatest care is used, from passage of the esophagoscope into pouches or diverticula. Spontaneous perforation may follow neurosurgical procedures, and spontaneous rupture may occur during retching and vomiting. Ulceration is seen in association with peptic esophagitis, with severe burns involving a large area of the

body surface (Curling's ulcer), and above all, with carcinoma of the esophagus.

In all of these situations the patient presents the picture of severe, acute illness, superimposed on cachexia if carcinoma is the cause, or associated with shock in the event of acute perforation. Gases at once enter the mediastinum, along with infected secretion, and may produce Hamman's sign. If the volume of gas is large it may dissect its way into the neck where subcutaneous emphysema will be demonstrable. Pain is frequently intense and may radiate to the back or upward into the neck.

X-ray recognition depends upon the demonstration of streaky or patchy translucent areas overlying the mediastinal structures. In patients who survive long enough, widening of the mediastinum and fluid level may be present.

Surgical exploration and drainage is urgently indicated, with repair of the defect if its nature permits. Penicillin in doses of 1 million to 10 million units daily is necessary.

PNEUMOMEDIASTINUM

This condition may be either traumatic or spontaneous. The escape of gases into the mediastinum is also frequent in perforation of the herniated stomach or of the esophagus. Traumatic pneumomediastinum is usually associated with chest wall injury of considerable magnitude. In patients who have suffered trauma, the escape of gas is rapid and dissection through the mediastinum into the neck occurs within a short time. Hamman's sign, a to-and-fro crunching, clicking, or tapping (as variously described), is audible over the precordium. The cardiac dullness is reduced in area and the heart sounds commonly are distant. Crepitus of the subcutaneous tissue is readily palpable in the neck, and sometimes over considerable areas of the body. The x-ray reveals considerable widening of the mediastinum, with large streaks of gas separating the major structures.

Neither the pneumomediastinum nor the subcutaneous emphysema constitutes a very serious threat to the patient, though disfigurement may be severe at the time. Only rarely is it necessary to make incisions about the base of the neck to permit the escape of gases. Rather, the attention should be directed to the chest wall and pulmonary injury. Infection seems to be quite rare.

Spontaneous pneumomediastinum is said to

occur predominantly in young males who previously have been in excellent health. The pathogenesis, as described by Macklin, is the escape of air from the alveoli into the perivascular tissue of the lung, from which the gas makes its way into the mediastinum. The onset is sudden, usually with severe pain retrosternally, and often with radiation into the neck, shoulders or arms, so that coronary occlusion stands high in the differential diagnosis.

The direct diagnosis depends upon the discovery of the crunch, which is said to be audible in some patients only when they are placed in certain positions. In a fairly high proportion of patients, left-sided pneumothorax may be demonstrable also.

The radiographic signs of small pneumomediastinum are said to be unusual prominence of the aortic knob, a very clear outline of the pulmonary arterial segment, or a band of radiolucency lying along the border of the heart. Most competent radiologists insist upon more definite signs than these—i.e., the demonstration of streaks or patches of gas in the mediastinum. The usual projection is inadequate, and oblique and lateral films at full expiration often prove more informative. Since small left pneumothoraces alone may produce a crunch indistinguishable from Hamman's sign, conclusive proof of pneumomediastinum depends upon the elicitation of the crunch in the absence of a pneumothorax or upon the absolute demonstration of mediastinal gas by roentgenogram.

TUMORS OF MEDIASTINUM

The differential diagnosis of tumors of the mediastinum is by no means easy, and one should bear constantly in mind that in most areas aortic aneurysm is by far the most likely possibility. Its exclusion may be most difficult if expansile pulsation is not evident on fluoroscopy or kymography, and if the usual signs of aneurysm (see Chapter 241) are wanting.

The most common primary malignant tumors are the lymphomas. The nodes of the mediastinum enlarge massively, often producing pressure on such adjacent structures as the trachea, bronchi, and esophagus. Physical signs may consist only of a positive D'Espine sign, once thought to occur only in tuberculous mediastinal adenitis; or occasionally one may detect dullness to either side of the trachea or spine. If no

peripheral nodes are available for biopsy, and if sternal puncture fails to suggest a definite etiology, the patients should be given a short test dose of deep x-ray irradiation. If marked reduction in the mass is not apparent at once, alternative diagnoses of benign tumors and cysts, bronchogenic carcinoma, and sarcoidosis have to be considered.

The only other important primary malignant tumor of the mediastinum is the thymoma, which may or may not be associated with leukemia or myasthenia gravis. These tumors also are often markedly radiosensitive.

The most frequent benign tumor of the mediastinum is the dermoid, which commonly occupies the anterior superior mediastinum, and which may attain considerable size. Symptoms are such as may be expected from tracheal compression, cough, stridor, wheeze, and moderate dyspnea. Percussion frequently reveals dullness lying to one side of the sternum. Roentgenographically, the tumor is usually smooth in outline, sharply delineated both laterally and posteriorly, and sometimes 10 cm. or more in diameter. A few such dermoid cysts possess calcific changes in the capsule, which, if found, are quite diagnostic.

Another tumor of the superior mediastinum which occurs frequently is a thoracic extension of nodular goiter. Symptoms due to tracheal compression, esophageal obstruction, and recurrent laryngeal paralysis may occur. The tumor is recognized by the presence in the neck of a bulky mass, the lower border of which cannot be outlined. On x-ray it is seen that the mass extends above the clavicle into the neck, while downward its growth may extend as far as the arch of the aorta. The growth may be either unilateral or bilaterally symmetric. Fluoroscopically, it may be seen to move upon swallowing, and to be nonpulsatile.

Fibromas, chondromas, myomas, and neurofibromas may arise from the thoracic wall, the mediastinum, or, rarely, from the lung itself, and may attain very large bulk.

Cysts with walls showing gastric or enteric

mucosa usually lie as solid, round shadows in the lower and posterior mediastinum, while those of bronchogenic origin are similarly seen as solid, round shadows in close relation to the hilum. Occasionally, these cysts, which represent the blind pouch of a rudimentary bronchus, may discharge their contents and be discovered only as air-containing, thin-walled cavities.

Pericardial coelomic cysts, "spring-water cysts" of the mediastinum, are found in near relation to the pericardium and are often of considerable size. It is frequently necessary to exclude pericardial effusion or myocardial enlargement. Such cysts develop in the embryonic coelomic cavity, come to be lined by a membrane resembling ordinary serous mesothelium, and are filled with clear, serous fluid.

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Diseases of the Pleura

John S. Chapman

Inflammation of the Pleura

Hydrothorax

Treatment of Pleural Effusion

Pneumothorax and Hemopneumothorax

Upon being confronted by a complaint of chest pain, one's first consideration must be to determine if that pain arises as a result of pleural disease. In the differential diagnosis one must exclude disease of the heart and great vessels, the esophagus, the chest wall, the spine, the spinal cord, the intercostal nerves, and the abdominal viscera, while at the same time one must be familiar enough with reference of pain (see Chapter 3) to appreciate that pleural pain may be referred to the abdomen, or that it may radiate to the neck (diaphragmatic pleurisy). In addition to eliciting a careful description of the pain, one must be diligent in examination of the chest wall, its muscles, and bones. Quite frequently the pain of fractured rib, particularly if it occurs as a result of hard and chronic cough, is indistinguishable from pleurisy unless one exerts a springing pressure upon the sternum, which results in instant, severe, sharply localized pain. Similar maneuvers will elicit the pain that results from separation of the costal cartilage from rib, a condition in which radiography is of no advantage. Careful palpation elicits a point localization, and may reveal offset or fusiform swelling at the costochondral junction.

INFLAMMATION OF THE PLEURA

Pleuritis is rarely a primary disease, but results from extension of infection from contiguous areas. The most direct source obviously is the lung, and inflammation of the pleura is common in such diseases as the various bacterial pneumonias, abscess, tuberculosis, and actinomycosis. Extension of infection through the diaphragm, either by way of lymphatics or through direct erosion, may produce pleurisy. Commonly involving the right pleura particularly are amebic and bacterial abscess of the liver; a subphrenic collection of pus resulting from a perforated

viscus, and perinephric abscesses may be associated with pleural inflammation.

Pleural reaction is also common in infarcts of the lungs, the zone of reactive hyperemia reaching the pleural surface and commonly producing fluid in the pleural sac.

Neoplasms of the lung, either by metastasis or direct extension, commonly reach the pleural surface and excite reaction, while metastases from distant organs may seed the pleura directly or, as in the case of carcinoma of the breast, extend through the chest wall to produce disease of the parietal pleura.

Finally, disseminated systemic diseases of unknown etiology are frequently associated with pleurisy, along with involvement of other serous cavities. Typical of this group is disseminated lupus erythematosus, but pleural disease may also be a phase of periarteritis and, rarely, of sarcoidosis. Pleurisy due to rheumatic fever is nearly always associated with severe heart disease.

Pathologically, the first expression of pleurisy is redness, edema, dulling of the surface, and the appearance of fibrin deposits on the visceral pleura. Clinically, this phase corresponds to acute dry pleurisy. In such instances auscultation reveals a coarse, to-and-fro grating over the affected area. This stage is not demonstrable radiographically.

As the disease progresses, the acutely inflamed pleura begins to throw out an exudate which is at first usually serofibrinous. Arrest of the process may take place either at the dry stage or at this stage, but in the case of suppurative infections the fluid rapidly takes on the aspect of pus, as greater numbers of neutrophils and large quantities of fibrin make their appearance. In either the serofibrinous or purulent phase, there is usually generalized chest pain, frequently most severe in the lower thorax. Dyspnea not only expresses voluntary and involuntary splinting of the chest, but may be a result of considerable quantities of fluid. Characteristic physical signs include

a shift of the heart and mediastinum to the opposite side, flatness, and usually greatly diminished or absent breath and voice sounds. The indications are for thoracentesis.

The final or healed phase of any of these pleural reactions, whether wet or dry, serofibrinous, purulent, or bloody, is the organization of pleural fibrin. The degree and extent of the resultant fibrous or adhesive pleurisy depend upon the amount of fibrin in the thorax and its distribution. A small area of acute dry pleurisy may have as its residue only a thin, filmy adhesion or, as in the case of a tuberculous nodule, a short, thick cord. Pleurisy that has produced great quantities of fibrinopurulent exudate, or that has been associated with a considerable amount of bloody fluid, may, on the other hand, give rise to marked pleural thickening with contraction of the entire hemothorax, marked retraction of the heart and mediastinum into the affected side, and a marked elevation and fixation of the diaphragm. The function of the underlying lung is completely abolished by the rigidity of the chest wall.

Serofibrinous fluid belongs to the exudative type and is characterized by specific gravity above 1.016, relatively high protein content, and fairly numerous to innumerable cells. A fluid of this character may be encountered at some time in any of the inflammatory, embolic, or neoplastic diseases of the pleura. Further differentiation is possible on the basis of cell counts. In typical cases (and one should always remember that there are plenty of atypical cases) the more frequent exudates may be analyzed according to the cellular findings shown in table 107. It should be understood that these figures are only rough approximations: tuberculous fluid may contain considerable numbers of red corpuscles, or, if the

inflammation is intense, may show innumerable neutrophils with hardly any lymphocytes. Any of the effusions developing from abscess may present fewer neutrophils at first appearance and may contain red corpuscles on occasion, while fluid that results from infarct or metastasis may occasionally be almost pure blood.

HYDROTHORAX

In this condition, which is not associated with any significant pleural reaction, there is the accumulation in one or both pleural sacs of a thin, yellow fluid which is distinguished by a specific gravity of 1.014 or less, low protein content, and very rare cells. This fluid is the time-honored transudate, and is most commonly encountered in congestive heart failure, nephrosis, and other hypalbuminemic states. The development of such fluid is associated with no pain, while dyspnea is an expression of the cardiac status, the anemia, or the acidosis, rather than of ventilatory insufficiency. The physical signs do not differ from those encountered in inflammatory fluids.

Chylothorax, a condition encountered very rarely, is usually associated with neoplastic erosion of the thoracic duct. The fluid aspirated is characteristically milky in appearance, and shows microscopically great numbers of fat droplets.

TREATMENT OF PLEURAL EFFUSION

The withdrawal of pleural fluid is indicated whenever there is evidence of such fluid. The three main objectives are: (1) mechanical relief of dyspnea; (2) re-expansion of lung and obliteration of pleural space in all inflammatory pleurisy; (3) the acquisition of information from the fluid and from complete visualization of the lung. All three purposes demand complete emptying of the

Table 107

Disease	Red Corpuscles	Polymorphonuclear Leukocytes %	Lymphocytes %	Eosinophils %	W.B.C.
Tuberculosis.....	0	10-20	80-90	0	1,000 or less
Bacterial pneumonia.....	0	85-95	5-15	0	10,000 or more
Pulmonary abscess.....	0	95	5	0	10,000 or more
Metastases.....	Very numerous	15-25	75-85	0	1-900
Periarteritis, etc.....	Variable but present	20-40	40	10-30	1-900
Infarct.....	Numerous	10-20	80-90	0	1-500
Subphrenic abscess.....	Few	60-90	10-40	0	10,000 or more

pleural sac. Repeated taps are perfectly justifiable so long as they serve any one of the above purposes. So long as one follows a careful technic with regard to asepsis, is generous with local anesthetic agent, and keeps his aspirating system closed to the atmosphere, he need have little fear of accidents. Lung laceration and the production of pneumothorax may be avoided by the use of an anchoring clamp on the needle, advancement of which should be stopped the instant the pleura is traversed.

In order that no vital information may be lost, one should have sterile tubes at hand, some of which should contain an anticoagulant, since clotting may set in very rapidly and completely ruin the specimen for detailed study.

The minimum examination of pleural fluid should include one's own gross observations as to color, odor, viscosity and turbidity, specific gravity, a total and differential cell count, and protein determination. In addition, various cultures for tubercle bacilli, fungi, or anaerobic organisms, guinea pig inoculation, and Papanicolaou or other cytologic study may be necessary.

The treatment of pleurisy is the treatment of the fundamental disease, for which, unfortunately, in many instances there is no specific therapy. In such cases the problem resolves into one of relieving the patient's dyspnea by repeated taps. When the etiologic agent is bacterial, however, the effusion is commonly treated by aspiration of the pleural contents and injection of antibiotics (e.g., 100,000 to 200,000 units of penicillin every other day). This method is extremely successful in the very early stage of serofibrinous pleurisy, when but two or three such treatments may be necessary for complete cure. There are, however, definite conditions under which the treatment should not be followed: (1) marked loculation of fluid; (2) the presence of large collections of fibrin; (3) steadily increasing cellular content of the fluid; (4) failure to secure good response within 7 to 10 days; (5) bronchopleural fistula. Persistence in medical treatment in the face of these conditions usually results in the formation of severe fibrothorax, with great chest wall deformity and marked loss of lung function. The consequent morbidity is incomparably greater than that of open surgical drainage. Should fibrinolytic agents become available some of these problems of the medical management of empyema will be solved.

PNEUMOTHORAX AND HEMOPNEUMOTHORAX

Pneumothorax. Spontaneous pneumothorax may be either primary or secondary to some evident disease of the lung. When obvious cause is apparent on physical, roentgenographic, or laboratory examination, it is usually either tuberculosis, abscess, or carcinoma; but, occasionally, generalized bullous emphysema is the causative disease. In all of these instances, the problem is much graver than in that of primary spontaneous pneumothorax, not only on account of the gravity of the underlying disease but also by reason of the strong probability that the opening through the pleura may be persistent, that escape of air into the pleura continues, that infection is almost certain to occur, and that as a result of all these facts the lung can be re-expanded only with the greatest difficulty. The signs and symptoms are the same as those given below for uncomplicated primary spontaneous pneumothorax. Treatment also is essentially the same as that given for the primary condition, except that in these instances the instillation of penicillin into the pleura and parenteral administration of large doses of the drug are strongly indicated. For consideration of tuberculous spontaneous pneumothorax with empyema and persistent bronchopleural fistula, see Chapter 128. Particularly in the case of putrid abscess with associated large empyema and patent bronchopleural fistula, there is urgent need of open surgical drainage to manage both the abscess and the empyema, as well as to prevent spill-over into healthy lung tissue.

Primary spontaneous pneumothorax is a condition the cause of which is not known. For a long time all cases of spontaneous pneumothorax were ascribed to nonapparent tuberculosis, but tuberculosis is considered to be the etiologic factor only (1) when a considerable amount of exudate, associated with fairly high (100° F., or more) temperature, occurs; or (2) when numerous apicodorsal adhesions are demonstrated. The most generally accepted theory at this time seems to be that the pneumothorax is the result of the rupture of pulmonary bullae or subpleural blebs. Neither the cause of the bullae nor the immediate mechanism of rupture is satisfactorily explained.

The escape of gas into the pleural cavity usu-

ally is associated with marked pain which may be felt in any part of the chest on the affected side, or referred to the neck or abdomen. Such pain is aggravated by any physical exertion, and mildly by respiration, but the pain may increase rather steadily in the absence of physical activity. As a rule, when the patient is put to bed, pain subsides within 24 to 48 hours after the onset. Dyspnea develops early as a result of pain, but becomes more intense later if the accumulation of pleural gas develops positive pressure (tension pneumothorax).

On examination, the affected side appears full and motionless, and it is especially noteworthy that expiratory motion is absent. The trachea and heart will be shifted only in case of considerable pneumothorax. Fluoroscopy and x-ray reveal various degrees of pulmonary compression.

The immediate treatment is bed rest plus relief of pain, which frequently may require morphine (15 mg.), though codeine (30 to 60 mg.) or "Demerol Hydrochloride" (100 mg.) may be sufficient. Some authorities start oxygen at once, but this would not appear to be necessary unless cyanosis is present. The reabsorption of nitrogen from the pleural cavity, which results from inhalation of 100 per cent O₂, does not seem a sufficient justification for its use in the absence of cyanosis. On occasion, if the patient is in considerable distress and the pneumothorax is large and under positive pressure, aspiration of air is indicated. While one may relieve a patient merely by syringe removal of gas, the pneumothorax machine with its manometer is a more precise method. It is preferable to remove only 200 to 300 ml. of gas on each occasion, and to remove it frequently, rather than to attempt very extensive decompression, since the rapid withdrawal of gas tends to reopen and perpetuate the pulmonary-pleural communication. In some few cases accumulation of gas is so rapid and distress so great that more heroic treatment is indicated. In such cases a sterile 18 French urethral catheter may be inserted through the second anterior interspace and connected to a water trap. Even in very severe cases, this measure is usually followed by rapid re-expansion. In some few patients the recurrence of pneumothorax is so frequent and disabling as to call for surgical intervention, which usually consists of the removal of the bulla-bearing area, if one is present, and careful pouddrage of the pleural surface. Recur-

rences following such procedures have not been reported.

Hemopneumothorax. In about one out of eight patients with spontaneous pneumothorax, the onset of the collapse is associated with rather free hemorrhage into the pleural cavity. In these instances of spontaneous hemopneumothorax, which supposedly occur on the same basis as simple pneumothorax, the bleeding is assumed to result either from the avulsion of an adhesion from the substance of the rapidly collapsing lung, or from accidental involvement of a pleural vessel in the rupture. To the usual picture of spontaneous pneumothorax there is added, under these conditions, signs and symptoms suggesting acute blood loss. In perhaps 10 per cent of hemopneumothoraces bleeding may be extreme (hence almost all the pathologic material available on spontaneous pneumothorax is derived from autopsies of individuals who bled to death).

The physical findings include pallor, sweating, and shock, in addition to the expected signs of pneumothorax plus basal dullness. X-ray studies usually reveal rather extensive collapse with a fluid level on the affected side.

The treatment indicated is that for spontaneous pneumothorax in general, with additional management for shock and hemorrhage when indicated. In the usual case, bleeding decreases as the lung collapses farther down, but sometimes it continues very actively, necessitating transfusions. As a rule, blood and pleural fluid should be withdrawn within a day or two to prevent formation of clot or extensive deposition of fibrin on the visceral pleura. In the more severely bleeding cases, aspirations may be required every four or five hours to relieve dyspnea. The medical management of such patients should be continued only long enough to prepare for open thoracotomy with direct control of bleeding.

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Diseases Primarily of Circulatory Origin

John S. Chapman

Embolism and Infarction
Hemosiderosis
Ayerza's Disease

Active hyperemia is the result of almost any kind of infection, while passive hyperemia is the result of congestive heart failure (see Chapters 14, 238). Congenital anomalies of the heart and great vessels rarely, if ever, produce direct effects upon the pulmonary parenchyma, although aneurysm of the aorta frequently may produce bronchial obstruction with consequent diffuse infiltration and suppuration (see below). In extensive roentgenographic surveys, aneurysm of the pulmonary artery is encountered occasionally: the condition is of interest chiefly from the fact that it must be differentiated from aortic aneurysm, carcinoma of the bronchus, and hilar adenopathies.

EMBOLISM AND INFARCTION

These conditions, the pulmonary phase of thromboembolic disease (see Chapter 242), have only fairly recently been sufficiently recognized clinically. Pulmonary embolism without infarction is a frequent cause of sudden death in patients recovering from surgery, severe injury, coronary occlusion, and severe infectious disease. Such emboli are usually of considerable size and are nearly or completely occlusive of the pulmonary arteries. The clinical picture is one of sudden collapse associated with sudden, excruciating substernal pain which may refer to the upper extremities, so that differentiation from coronary obstruction may be most difficult. Death may occur within a few seconds or the patient may

survive, exhibiting pallor, cyanosis, sweating, peripheral vascular collapse, and partial loss of consciousness. Within a period of some minutes to hours, the embolus breaks up, the circulatory status improves, and the shock picture is replaced by one of multiple pulmonary infarcts.

Pulmonary infarction is the result of the occlusion of a pulmonary artery by foreign material such as clot or marrow fat (following severe fractures). The infarcted area early presents grossly the appearance of red infarction, and microscopically the appearance of liquefaction necrosis. Later, the gross appearance is that of the so-called white infarct, while still later it is possible that the most careful search of the lung will fail to show any residual damage, as the complete dissection of the pulmonary arterial tree may show no evidence of clot or of recanalization.

The infarction may succeed a clinical picture of embolism, as described above, or may (and more usually does) manifest itself as the sudden onset of severe pleuritic pain, followed immediately by cough, cyanosis, and dyspnea and, a little later, by blood spitting. On occasion, there is a repetition of the attack, with pain in some other area of the same or the opposite side.

Pleural pain is very common and usually very severe. If the pain has been at all striking or persistent, the patient should be observed closely for evidence of pleural fluid. In doubtful cases the aspiration of sterile, bloody fluid of fairly high specific gravity (1.014 to 1.018), with a relative paucity of white cells, affords good confirmation of one's suspicion.

Hemoptysis varies in amount but is usually not over perhaps 100 ml. on any occasion. Frequently it is much less, and when it is characteristic the expectorated blood is quite dark and semiliquid in consistency. The duration of blood spitting may be as long as three or four days, depending upon the size and number of infarcts which have occurred.

The temperature rises within a matter of hours after the infarction, and it is of some clinical significance that the fever is not ushered in by a chill. The level of pyrexia frequently is not very high, rarely passing 101.5° F., and often not exceeding 100° F. The duration, regardless of treatment with penicillin or sulfonamides, usually is four to five days with defervescence by lysis, unless there is complicating pleural effusion or repeated infarction, or unless the emboli are mycotic and part of a picture of severe generalized infection.

Physical findings on examination of the chest of patients with pulmonary infarction are variable. In the case of quite large infarcts, one encounters dullness, bronchial breath sounds, increased whispered voice sounds, and numerous medium moist rales. In other cases, particularly where there are numerous small infarcts, there may be suppression of the voice and breath sounds with rales or, occasionally, large rhonchi. In still others, if the infarcts are small and not numerous, discovery upon physical examination is unlikely. If effusion into the pleural cavity occurs, the signs are those of any pleurisy with effusion: flatness, absence of the breath and voice sounds, and diminished fremitus.

In all patients in whom the possibility of pulmonary infarction exists, a most careful examination of the lower extremities is necessary. The signs and methods of examination have been described in Chapter 242, but it should be pointed out that infarction may occur well in advance of any evidence of phlebothrombosis, no matter how careful and detailed the examination. However, in the absence of Homans' sign, or any calf or plantar tenderness, one should be alert to slight differences of temperature in the two legs, to any difference in the size of the visible veins, and to measurable differences in the circumferences of the calves.

Leukocytosis as a rule is not high, the leukocyte count rarely passing 12,000 to 14,000, and left shift is only moderate. Icterus may be present

if hepatic function is impaired, but in other cases one can find confirmation of the suspected infarction in elevated urine urobilinogen. The electrocardiographic finding of "acute cor pulmonale" with typical S1-Q3 configuration is rather unusual, and among cardiac patients may be entirely concealed by other abnormalities.

The x-ray findings in infarction of the lung are by no means so simple as the classic description of a wedge-shaped shadow with the base at the periphery. An infarct may have almost any shape, and rarely presents a triangular shadow in the normal posteroanterior projection. The base of the infarct may be against any surface of the pleura, including the diaphragmatic and the interlobular septums, so that, in essence, the normal chest film reveals any shape that may result from the passage of a plane through a cone. If infarcts are multiple, one may gain from the film a clue in the predilection of infarcts for the left lower lobe—a result of the comparatively straight course of the pulmonary artery to that portion of the lung. Such multiple infarcts may well be mistaken radiographically for bronchopneumonia, but if one has serial films he will note an unusually rapid clearing, and will find that infarct shadows within four to five days are replaced by horizontal linear shadows, the so-called "plate atelectases." These two roentgenologic findings are strongly confirmatory in questionable cases.

While the persistence of small shadows is usually of brief duration, large infarcts may remain visible for as long as three or four months and may give rise to repeated bloody effusions, so that they may well be mistaken for neoplasms. Single infarcts of some size have to be distinguished from lobar pneumonia, a differentiation often difficult to make if leg signs are absent.

Infarcts resulting from fat emboli differ in no respect from those derived from clot. The diagnosis should be suspected if the patient has recently suffered extensive fracture, particularly of the femur or pelvis. The suspicion may be confirmed by the discovery of free and phagocytized fat droplets in the sputum (best seen in wet mounts or with Sudan III stain), provided there has been no recent ingestion of fat or possible cause for lipid pneumonia, and provided urine collected in an ether-washed container also reveals fat droplets.

The treatment of pulmonary infarction is the

treatment of the phlebothrombosis or thrombo-phlebitis which produces it (see Chapter 242). In spite of the fact that penicillin is frequently prescribed on the basis that it may prevent infection in the previously damaged lung, there is at hand no real evidence that the antibiotic is of value. Whether the administration of anticoagulants has direct effect upon the infarct itself is moot: the duration of x-ray shadows of infarction is so variable that demonstration of such an effect would be most difficult. Hemoptysis is not of sufficient moment to call for any special treatment other than reassurance. Pleural effusions, if present, should be aspirated, since they may be of diagnostic value, but particularly since they contribute to dyspnea.

In severe cases of blood stream infection, mycotic emboli may give rise to multiple abscesses of the lung. External drainage of such abscesses cannot be contemplated, and the entire treatment has to be directed against the pulmonary abscesses and their source (frequently a post-partum uterus following abortion). Usually the blood culture will be positive and the choice of antibiotic or other drug will depend upon the organism involved. If penicillin is the drug of choice, dosage should begin at 3,000,000 units daily.

HEMOSIDEROSIS

On occasion, in cases of mitral stenosis with long-standing congestive heart failure, the chest

film may reveal well-defined miliary nodulation which has been shown pathologically to be deposits of hemosiderin with associated pulmonary fibrosis. Whether lung function is significantly impaired by these changes is not known, since the cardiac phase of the disease is of greater importance.

AYERZA'S DISEASE

The clinical features of Ayerza's disease are those of pulmonary emphysema and fibrosis with severe and long-standing right heart failure, with deep cyanosis, marked clubbing of the fingers, and secondary polycythemia. The condition, also called *cardiacos negros*, was attributed originally to a syphilitic pulmonary endarteritis. In North America the general consensus is that most such cases are simply marked pulmonary fibrosis and emphysema with cor pulmonale and severe congestive failure of the right side of the heart. The rare primary pulmonary atheromatosis, likewise, may give rise to such a picture.

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251

Diseases of the Bronchi and Pulmonary Parenchyma

John S. Chapman

Acute Bronchitis
Chronic Bronchitis
Pulmonary Fibrosis and Emphysema
Bronchiectasis
Abscess of the Lung

Certain of the more important specific infections of the lungs, such as tuberculosis and the pneumonias, have been discussed in preceding chapters. For the sake of convenience, the vari-

Bronchial Obstruction ("Atelectasis")
Chronic Organizing Pneumonia (Chronic Fibroid or Interstitial Pneumonia)
Cystic Disease of the Lung
Adenomatosis

ous neoplastic disorders of the respiratory system are considered in Chapter 252. The discussion to follow will be concerned with the remaining disorders of the lungs and bronchi.

ACUTE BRONCHITIS

Bronchitis may occur as a primary disease, may develop in the course of other specific infectious diseases, or may occur as a result of primary pulmonary involvement. Commonly the distribution is diffuse, but occasionally it is localized.

Among the specific infectious diseases in which bronchitis is a prominent phenomenon are pertussis, influenza, typhoid fever, and the exanthemas, but bronchial irritation has also been reported in malaria, some of the rickettsial diseases, and in those worm infestations marked by a pulmonary phase. In addition, a localized and chronic inflammatory bronchitis is very common in the draining bronchus from a tuberculous cavity.

In many individuals almost every invasion by the common cold results in a descending infection which eventually produces an acute inflammation of the trachea and bronchi. The disease is usually mild and tends to run its course within one or two weeks.

Such gases as were used in World War I produced intense bronchial irritation which, in severe cases, went on to pneumonia or pulmonary edema. Under industrial conditions, exposure to these gases may develop on occasion; from this standpoint the most important are ammonia, chlorine, sulfur dioxide, hydrogen sulfide, and, under special conditions, phosgene. It is conceivable that severe exposure may result occasionally in emphysema.

In *acute bronchitis* the complaints are those of cough, expectoration at first of scanty mucus, later of more abundant mucopurulent material, and very commonly a sense of rawness located behind the sternum and extending somewhat to either side. The patient states that cough is associated with tearing pain located in the same areas. The temperature is variably elevated, more commonly only mildly, but occasionally to as much as 103° F. Profuse sweating may occur and there are variable degrees of prostration.

Physical examination reveals mild to severe acute illness in a patient with racking, dry cough. In the usual case there is injection and edema of the nasal and pharyngeal mucous membranes. Unless the bronchitis is superimposed on some chronic disease, the examination of the chest is noteworthy only for variable large rhonchi and occasional inspiratory fine wheezes.

X-ray of the lungs reveals no evidence of disease, and laboratory studies commonly present the positive findings of moderately elevated white blood count with some increase in polymorphonuclears and a mild left shift. Sputum usually contains a variety of common inhabitants of the respiratory tract, with Gram-positive cocci in the great majority. Other laboratory studies are of no value except for the exclusion of bronchitides associated with typhoid fever and the other specific infectious diseases.

Treatment should consist primarily of bed rest. Cough syrups containing codeine offer some degree of symptomatic relief, and aspirin may be used to control fever as well as the generalized discomfort. Only in patients with associated serious disease does there seem justification for resorting to penicillin or the sulfonamides.

CHRONIC BRONCHITIS

In a certain percentage of patients cough and expectoration persist sometimes for many months. In the early mornings the cough is usually productive, but it frequently occurs during the night in paroxysmal form with little or no sputum. Sometimes frank hemoptysis may occur, but more usually the patient complains only of blood-streaked sputum. Pain is not a prominent feature in such illness, and there is no fever, weight loss, or decline in strength or vigor. Of this group a large number have additional complaints referable to the nose or paranasal sinuses, and postnasal drip is very common. A personal or familial history of allergy is usually lacking, while the history of smoking is almost always present.

Examination usually reveals a somewhat hyperemic but frequently crusted and dry nasal mucosa. The pharynx either is of a "granular" or lymphoid character or presents the appearance of unusual, dry redness. The physical examination of the lungs presents nothing more than occasional rhonchi or a rare inspiratory wheeze. No changes in the circulatory status are evident and there is no clubbing of the fingers.

The chest film is normal in appearance and the blood count not remarkable. Sputum as a rule is rather scanty and is composed of tenacious mucus in which there are relatively few cells or organisms. Films of the sinuses frequently present no evidence of disease.

The differential diagnosis in such individuals

is of considerable importance, since neither the negative chest film nor physical examination can be considered sufficient to exclude more serious disease. In a certain number of cases tuberculosis first manifests itself in such fashion, so that the sputum must be carefully searched and cultured to exclude that disease. Carcinoma of the bronchus and bronchiectasis constitute other possibilities that need to be absolutely excluded; therefore, these patients may often require bronchoscopy and bronchography before one can conscientiously reassure them completely.

At bronchoscopy the mucosa of the trachea and bronchi appears unusually red and somewhat redundant, and has a tendency to stick to the instrument. Coughing is usually marked during bronchoscopy of such patients, and it may be observed that the walls of the trachea and bronchi almost collapse shut during cough. Secretions are usually very scanty. Rarely is it possible to find ulceration or definite granulation. Biopsy, if taken, reveals only chronic inflammation.

~~X~~ Bronchograms commonly reveal a loss of finer branches, with much beading (due to droplets of mucus) along the larger branches. Mild degrees of cylindric bronchiectasis sometimes are observed.

The first step in treatment consists of the exclusion of any possible irritants. Tobacco is interdicted. If the patient's occupation brings him into contact with dust, fumes, gases, or paint, in many cases he will never get rid of his cough until his environment has been changed. He should avoid public gatherings and should attempt to maintain both his house and his place of work as thermostable as is possible. Usually some degree of humidification of the air, particularly in winter, is required. Moderate exercise in the open has seemed of some value, as has much out-of-door activity in the sun during the summer.

For immediate symptoms a codeine-containing cough syrup and a steam kettle afford about as much relief as can be obtained. Particularly when sputum is scanty and tenacious, the addition of potassium iodide or ammonium chloride may be of some benefit. In certain patients the antihistamine drugs may offer additional relief. These things failing, one may try a large number of expedients, usually with little success. Occasionally, a patient recovers entirely following

diagnostic bronchoscopy. Not infrequently one may have to prescribe residence in a climate warm, sunny, and dry throughout the year.

PULMONARY FIBROSIS AND EMPHYSEMA

Pathologically, the lungs are greatly increased in size and are noncollapsible. Bullae are frequent along the lung margins and may be present throughout. Histologically, one sees interstitial fibrosis or chronic inflammation, marked distention of the alveoli with flattening or rupture of the alveolar septums, and partial obliteration of the capillaries. Changes, either chronic inflammatory or fibrous in character, have been found in the bronchiolar mucous membrane, suggesting that bronchiolar obstruction may be the fundamental factor in the pathogenesis of the disease. Correlative findings usually consist of some degree of enlargement of the chamber and thickening of the wall of the right ventricle, with dilatation of the pulmonary artery.

The patient's chief complaint is usually shortness of breath which develops on exertion and is unassociated with pain. The other main complaints are chronic cough and expectoration. The dyspnea differs from that of the cardiac patient in that it is usually less conspicuous at night and is frequently entirely relieved by recumbency. It is not paroxysmal in nature nor is it associated with any particularly notable wheezing. If the disease is advanced, loss of weight is a frequent complaint, a symptom that arises from the fact that the act of deglutition with inhibition of the respiration interferes severely with the patient's breathing.

Physical examination reveals an individual in obvious respiratory difficulty, sometimes with frequent cough. The face frequently is suffused and is dusky red if not cyanotic. The neck veins may appear somewhat distended when the patient is upright: The chest is very large and is so raised that the neck appears shortened, an effect increased by the associated kyphosis usually present. Ordinarily, the anteroposterior diameter of the chest is increased, but if pleural symphysis has occurred prior to the emphysema this finding may be lacking. Upon first inspection it may appear that the chest wall moves rather well, but further study will reveal that the motion consists of an upward and forward thrust of the sternum with no evident rotation of the ribs. Close obser-

Reduced Reserve Air
n Complemental Air

Chap. 251

THE RESPIRATORY TRACT

alveolar CO₂ + O₂ - also in sputum 1407
vation reveals that inspiration is short in duration as compared with expiration. On percussion, hyperresonance is encountered throughout, and it is easy to perceive that the level of the diaphragm is extremely low, while its movements are greatly diminished. The breath sounds are characteristically almost inaudible, but now and then when sounds are heard they have a bronchovesicular quality due to the very long duration of expiration. Rales are present rarely, though an occasional inspiratory wheeze may be encountered.

The heart border cannot be located by percussion nor apical impulse by palpation. Heart sounds are characteristically extremely distant and may be entirely inaudible due to the interposition of the voluminous lung. Usually, when sounds can be heard at all, they are loudest at the xiphisternal junction or in the pulmonic area, where the second sound is frequently much louder than the aortic second. Visible pulsation in the epigastrium can be confirmed by palpation of a downward thrust with each systole.

The liver commonly may be felt about 3 to 4 cm. below the costal margin, but this probably represents displacement rather than enlargement. Signs of passive hyperemia and congestive heart failure are by no means common. Clubbing of the fingers is not striking in pure emphysema, though mild cyanosis of nail beds may be seen. In rare individuals who are extremely dyspneic the pulse pressure may be quite small and one may discover paradoxic pulse.

The diagnosis is best made on history, physical examination, and fluoroscopy. In the latter study observation is directed mainly to the diaphragm, which in characteristic emphysema moves not over 2 to 4 cm. from maximum inspiration to maximum expiration, and performs this motion quite slowly. Vital capacity is a misleading determination since an emphysematous patient, given plenty of time for long expiration, may furnish rather good figures in this test. Maximum breathing capacity, which takes into account the factor of time, is greatly reduced even though vital capacity may appear nearly normal.

Röntgenograms of the chest reveal unusually lucent lungs with but few markings. Sometimes the diaphragms appear scalloped as a result of the presence of large bullae, while the heart may present very striking prominence of the pulmonary arterial segment (fig. 213).

Reduced residual air
Vital capacity
Max. B. C. reduced
Expiration phase prolonged

The sputum, which is mucoid and scanty, offers little information. Secondary polycythemia has been described, but is evidently not a common associated phenomenon. Electrocardiograms may also be disappointing in that right axis deviation may be found in perhaps not over half the cases. CO₂ combining power + chlorides —

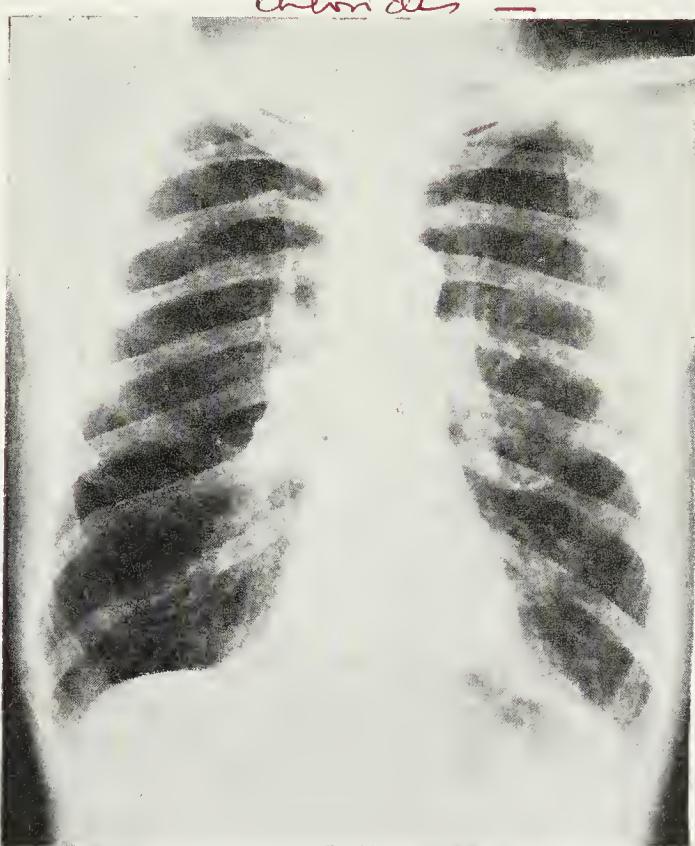


FIG. 213. Severe pulmonary fibrosis and emphysema. Note the very low, flattened diaphragm and the loss of lung markings, particularly in the right upper lobe.

More detailed study of the respiration of patients with emphysema reveals a large residual air with a small tidal air volume, together with reduction of reserve air and complemental air. The alveolar gases are high in carbon dioxide and relatively low in oxygen, a condition reflected in the gas contents of the arterial blood. On account of the high carbon-dioxide content of the blood, the body attempts to compensate by a retention of alkali, so that the carbon dioxide-combining power is greatly increased and the chlorides decreased. Decompensation of the gaseous acidosis does not occur until the pH changes downward.

The differential diagnosis is rarely difficult, though perennial asthma may offer some trouble, particularly when one recalls that the emphysematous patient may occasionally present a good many expiratory wheezes, while one may encounter an asthmatic patient who exhibits no

wheezing. Usually the history, the age at onset, the presence of eosinophilia, and continued observation will suffice to differentiate the two. Emphysema, on account of the complaint of dyspnea, is frequently mistaken for cardiac disease, but real attention to the details of the physical examination should be sufficient for differentiation. It is worth noting, however, that in the age level of emphysema, 40 to 60 or older, significant hypertensive or arteriosclerotic heart disease may be a complicating factor, but that if heart failure is apparent it will more likely be on the basis of one of these etiologic agents than purely on the basis of *cirr* pulmonale.

Not rarely there arises the question of associated bronchiectasis in patients with emphysema. If persistent moist rales are heard over the lower lobe areas one may be reasonably sure of the coexistence of the two diseases. Beyond this point it is undesirable to go, since the introduction of oil into the bronchi of emphysematous individuals may produce a rather severe acute dyspnea, and since in any case such persons may not be considered for surgical treatment of bronchiectasis. When iodized oil is introduced, the characteristic pattern is that of loss of all the finer branch bronchi associated with some irregularity of contour, and possibly slight dilatation of the large branches.

The treatment of obstructive emphysema falls under two main headings: the first, the general measures which have already been described as useful in chronic bronchitis; the second, the free use of bronchodilating drugs. Of this group one of the most generally successful is aminophylline, commonly prescribed as 0.5 Gm. rectal suppository. Almost equally good are nebulized epinephrine and certain of its synthetic derivatives, while oral ephedrine is a fairly efficient symptomatic drug in less severe cases. Nebulized antibiotics may be used if the sputum contains much pus, but one should bear in mind that the disease tends to be progressive and that the best results are far from satisfactory.

BRONCHIECTASIS

The pathogenesis of bronchiectasis, as demonstrated by experiment and supported by clinical observations, seems to be the development of a necrotizing bronchitis behind a bronchial obstruction. Neither infection nor obstruction alone would seem to be adequate. No specific or-

ganisms are involved, although they are usually anaerobes, nor is any specific type of obstruction necessary. The dilating force as applied to the diseased bronchial wall is chiefly an external pull due to the negative intrapleural pressure. Cough is apparently a result rather than a cause of dilatation.

A special type of bronchiectasis, that seen in infants with cystic fibrosis of the pancreas, is thought to be due to a disorder of mucous glands such that the mucus secreted is extremely tenacious and thick. Upper respiratory infections are common among such marasmic infants, so that both the obstructive and infective elements are present. Since most such infants die in early life, the combination of pancreatic fibrosis and bronchiectasis is of interest primarily to pediatricians.

Pathologically, the diseased lung reveals markedly dilated bronchi between which there is fibrosis and chronic inflammation. The cartilages are missing in many cases, and oftentimes no residue of the original bronchial wall can be found. In certain areas the walls may be composed of abundantly vascular granulation on a fibrous tissue base, while numerous angiomatous capillaries may be seen in other sections. Immediately surrounding the saecules a polymorphonuclear infiltration is visible, while at some distance slides reveal round-cell infiltration and young fibroblasts, as well as much old, hyalinized fibrous tissue.

Rather characteristically, the disorder begins early in life, often following bronchopneumonia associated with measles or pertussis, but occasionally it may date from some definite later episode such as "postoperative pneumonia." There is commonly a history of repeated pulmonary episodes, frequent colds, general decline in health and strength, intermittent low-grade fever with sweating, and, above all, persistent cough with expectoration. One common feature of the history, almost diagnostic in itself, is the statement that cough develops upon lying down. The sputum is described as abundant, yellowish, sometimes chunky and hard, but by no means universally as foul. Hemoptysis is quite frequent and at times may be severe. Pleuritic chest pain frequently develops with each fresh infection, but is usually rather transitory and rarely very severe.

Physical examination often reveals a patient

who appears chronically ill. In characteristic cases, over the area of disease the examiner encounters mild lag, dullness, diminished breath and voice sounds, and considerable numbers of variable-sized moist rales. In the rare instances of disease of the upper lobe only, the sole physical sign may consist of moderate impairment of the percussion note. In bronchiectasis limited to the middle lobe, if much shrinkage of the diseased lobe has occurred, there may be no physical signs at all. The distribution of physical signs is usually lobar or segmental in character, and some of the common areas of involvement are: a lower lobe only; right lower and right middle lobes; left lower and lingular segments; bilateral lower lobes with middle and lingular disease; right middle and lower lobe with lesser disease in the left lingular segment and its reverse. Clubbing of the fingers is usually pronounced.

Roentgenogram of the chest sometimes appears entirely normal, either because there is very little fibrosis or pneumonia, or occasionally—and this is particularly true on the left—because the bronchiectatic lobe is so completely contracted as not to be visible in the routine projection. In more characteristic instances, heavy linear stranding is to be seen radiating downward and laterally from the hilum, while in a few cases the affected lobes may appear almost solid (fig. 214).

Laboratory work is of little diagnostic advantage other than in the exclusion of tuberculosis as a possible cause or associated disease. The sputum, characteristically purulent, does not often settle out in the classic three-layered form. On slide and culture no significant organisms are found.

The bronchoscope may reveal somewhat dilated and displaced orifices of the lower lobe, with evidence of chronic inflammation and with abundant purulent secretion. Bronchograms, which should be used only for diagnosis and mapping, should show complete outlining of the major branches of both lower lobes, the middle lobe, the lingular segment of the left upper, and some of the branches of the right upper. Several views are necessary for complete study, including posteroanterior and lateral upon filling the first side, and both oblique views. The amount of oil used in filling both sides should not exceed 15 to 20 ml., but it is preferable to study only one side at a time.

The basic treatment is surgical extirpation of the diseased areas, a procedure that can now be carried out with a mortality of not over 2 per cent. Unfortunately, either because of the extent or distribution of the disease or because of associated emphysema, extrapulmonary disease,

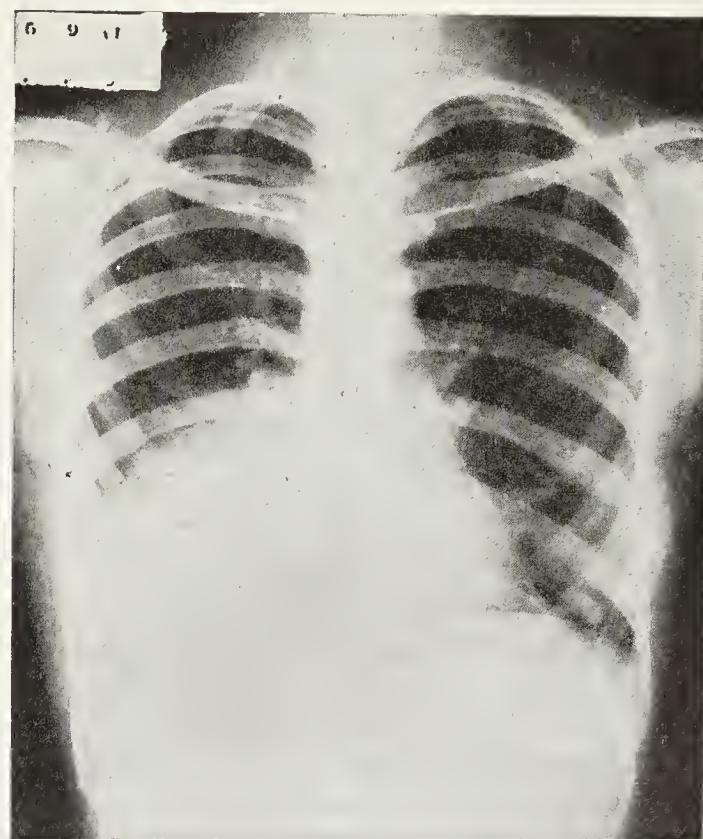


FIG. 214. A severe bilateral lower-lobe bronchiectasis. There is associated overdistention of the upper lobes to compensate for the contraction of the lower lobes.

or age, a certain group of patients has to be classified as inoperable and treated medically. For these patients the most that can be accomplished is amelioration of symptoms and prolongation of life.

Postural drainage is the most important single measure in the management of inoperable bronchiectasis. Four or five times daily, and for 10 to 15 minutes at a time, the patient should adopt the position in which experience shows he will have most profuse drainage, and make persistent coughing and chest-squeezing efforts. Oftentimes the patient, in attempting to avoid this somewhat unpleasant part of his daily routine, will state that he does not cough at all during the time he is in drainage position, but does produce sputum after assuming a more natural one. This argument should not deter the physician from insisting upon continuation of postural drainage. Persistent, regular use of the measure

may often reduce sputum production by as much as 75 to 80 per cent, and commonly changes a putrid pus to an odorless one.

Other than these measures, those general rules set out for patients with chronic bronchitis are indicated. In addition, if the bronchiectatic patient is at all depleted, he should be ordered to take an after-lunch rest period of an hour, and to secure 9 or 10 hours of rest at night. Practically all patients should receive penicillin, parenterally, at the first sign of fresh infection. Some patients who have abundant and foul sputum derive considerable relief from the inhalation of penicillin solution or dust, but there is the disadvantage that a certain proportion may become sensitized to the drug. Aureomycin may be of use in patients who are so sensitized or who have organisms resistant to penicillin. Much the same effect may be obtained by residence in a warm, dry climate, supplemented by rigorous postural drainage.

ABSCESS OF THE LUNG

Although pulmonary abscess may develop as a result of almost any kind of pneumonia, in association with carcinoma of the bronchus, and with many varieties of bronchial obstruction, and though sometimes multiple abscesses may result from septic embolism or aspiration of stomach contents, the term connotes the acute, putrid variety that results from anaerobic infection. These typical abscesses are thought to result primarily from the aspirated organisms of gingivitis, but the organisms recovered on culture are much more frequently anaerobic streptococci than Vincent's organisms.

Pathologically, the first step in the process is a severe, necrotizing pneumonia usually associated with inflammatory obstruction of the segmental or lobar bronchus involved. Within a short time central liquefaction occurs and bronchial drainage begins. The cavity that results, however, is not entirely the result of destruction, but in large part derives from a valvelike action in the draining bronchus which steadily inflates the original small hiatus. Definite cavitation is usually demonstrable within five days, and fluid level in the cavity may become apparent very shortly afterward.

The antecedent history will often elicit as a predisposing cause some type of loss of consciousness, so that chronic alcoholism is one of the most

closely associated diseases. However, in a patient with impaired gag reflex or very foul mouth, epilepsy, head injury, general anesthesia, or sometimes merely extreme fatigue and very deep sleep may be the precipitating factor.

The onset is usually abrupt, sometimes with a chill, and is manifested by rapidly rising temperature to as high as 105° F. Pleuritic pain is usually marked and well localized over the affected segment. Cyanosis and dyspnea are present, and clubbing develops within a period of as little as two weeks. Cough, often severe, at first is productive of only a scanty mucus, but as necrosis progresses the sputum may become dark green or dark red, with intolerable odor. Sometimes, when the disease follows its natural course, bronchial drainage is marked by a sudden gush of a considerable quantity of malodorous pus and blood. If this occurs, the temperature frequently drops quickly to a subnormal level, and the patient displays sweating and prostration.

Physical examination of the chest in most cases reveals a lag due to pleuritic pain, marked dullness which can often be established as definitely segmental in location, impaired breath and voice sounds, and only a few rales. The favorite topographic sites for abscess are the dorsal segments of the lower lobes and the axillary segments of the upper lobes, although any portion of the lung may be involved. The typical segments are represented by areas lying between the sixth and eighth ribs posteriorly, and, in the upper lobes, by changes high in the axillas.

The chest film commonly reveals at first a dense patch of pneumonia, frequently lying over the eighth posterior rib or just above the fissure line against the lateral chest wall. Cavitation is at first slight and the wall appears thick and irregular; but, as the disease grows older, the cavity enlarges, the surrounding pneumonia is replaced by atelectasis and fibrosis, and the cavity wall appears thinner. Fluid level is frequent, but is not necessary for roentgenologic diagnosis. Lateral films will assist in the exact localization.

During the acute stage of the disease, there is marked elevation of the total white count with a neutrophilic leukocytosis and a left shift. Other studies in the acute abscess are of little value.

At the time penicillin and the less toxic sulfonamides became available, the treatment of acute, putrid abscess had become well standard-

ized, and consisted of a one-stage drainage procedure which was indicated not only on the basis of draining out pus but also on the ground of admitting oxygen freely into the site of anaerobic infection. But these drugs, as well as streptomycin and aureomycin, have so changed the clinical

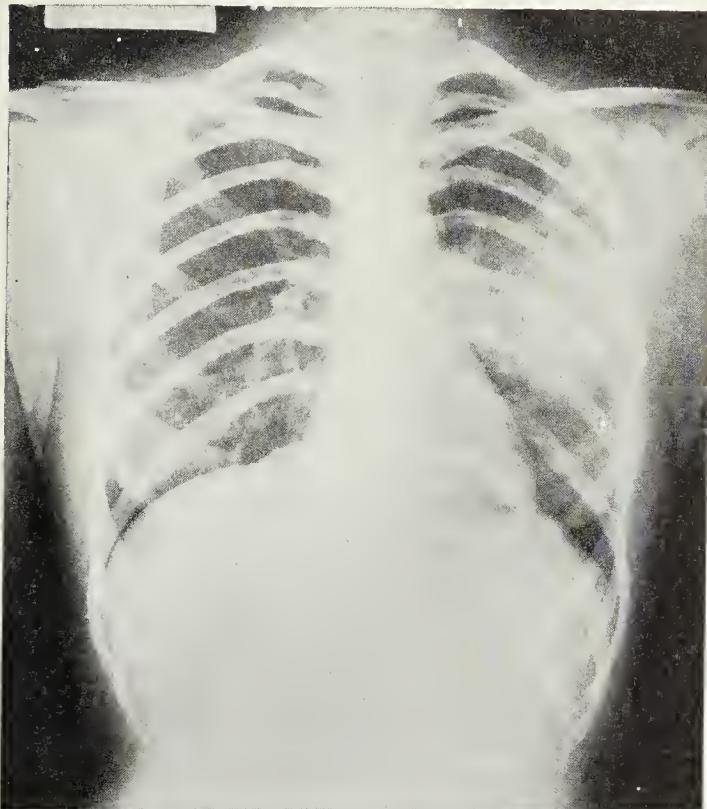


FIG. 215. Acute abscess of lung with rarefaction underlying the third anterior rib.

behavior of acute abscess that considerable difference of opinion now exists. The facts are simple: About 20 per cent of abscesses formerly healed satisfactorily on medical treatment alone; the acute abscess which was drained properly healed with little residue; the subacute or chronic abscess responded very badly to surgical drainage, and most often required lobectomy. With penicillin (in dosage up to 1 million units per day), supplemented in some cases by aureomycin, streptomycin, or sulfadiazine, one can probably secure results comparable to those of early surgical drainage in perhaps 80 to 90 per cent of abscesses. The remaining patients, however, no longer present indications for drainage but, with very rare exceptions, require resection. Best results, as well as one can judge at this time, seem to call for antibiotic treatment during the acute phase. Films of the chest should be made at five-day intervals and medical treatment continued as long as definite clearing and decrease in cavity size are demonstrable. If, at any point in the

course of the disease, satisfactory progress is not evident, surgical consultation is indicated. In most instances the recommendation is likely to be resection.

In instances in which the chest film suggests the possibility of a chronic abscess of the lung, one must be on the alert to exclude tuberculosis and—in elderly patients, particularly—to make certain that the abscess is not a result of carcinoma of the bronchus. Sputum must be examined carefully and repeatedly for acid-fast bacilli, and bronchoscopy is strongly indicated. Once the diagnosis is established, the treatment, if there are no contraindications to surgery of such magnitude, is resection. In those patients who cannot undergo resection, the treatment is essentially the same as that for bronchiectasis.

BRONCHIAL OBSTRUCTION ("ATELECTASIS")

This particular terminology is used not only because the obstruction of the bronchus is the primary and important phenomenon and the change in the lung secondary, but also because the lobe or segment beyond the bronchial block is not merely airless but is filled with secretions and bacteria. Of much more import than the identification of bacteria beyond the block are the nature and duration of the obstruction itself. The cause of the block may be within the bronchus, when it may be a foreign body, an inflammatory stricture, an acute swelling, a tumor, or merely a mucous plug; or extrinsic, as in the case of aneurysm, mediastinal adenopathy, or extrinsic carcinoma. Only that atelectasis which arises as a result of compression of the lung from without, as by fluid or pneumothorax, is relatively benign in character, since only in that type is free bronchial drainage available. In this instance the remedy, of course, is the removal of the material producing compression of the lung, which upon re-expansion suffers no fibrosis or loss of function, except as the pleura may stiffen or adhere.

Bronchial obstruction may be recognized by the presence of a lag upon inspiration, a decrease in the size of the hemithorax, a shift of the mediastinum and trachea to the affected side, and elevation of the diaphragm of that side. In the acute and earliest stages, such as immediately postoperatively, there has not been time for solidification of the obstructed segment, and

dullness is not encountered. Breath sounds in such instances, however, will be diminished, and large, bubbling sounds may be heard over the hilum. This, of course, is the optimum instant for intervention, since most surely no serious damage will have taken place in the lung parenchyma.

The x-ray examination of the chest in which bronchial obstruction has existed more than a few hours reveals a shift of the trachea and mediastinum, a narrowing of the intercostal spaces, an elevation of the diaphragm on the affected side, and a dense, homogeneous shadow which occupies less than the normal volume of the segment or lobe involved. Except when obstruction is on the basis of tuberculous bronchitis, when the sputum will contain acid-fast organisms, laboratory studies are of little value.

The immediate problem is to determine the nature of the block, and for that purpose bronchoscopy alone will suffice. There is no justification for delay or elaborate preliminary studies, since the longer a lobe remains obstructed the more certain will be its destruction either through suppuration or fibrosis. In some instances bronchoscopy may relieve the obstruction; in others, where the bronchial orifice is the site of unyielding fibrous stricture or of tumor, only lobectomy or pneumonectomy is adequate for cure.

CHRONIC ORGANIZING PNEUMONIA (CHRONIC FIBROID OR INTERSTITIAL PNEUMONIA)

This condition, in which a primary exudative reaction fails to resorb and is replaced by lymphocytic reaction and eventual fibrous change, is not a primary condition, but is a part of the pathologic picture in areas adjacent to chronic suppuration of the lung. It is regularly present surrounding areas of incompletely resolved pneumonia and in the vicinity of carcinoma and of bronchiectasis. One of its most potent causes is bronchial obstruction. The treatment is extirpation when possible; otherwise, the patient should be managed as described in the discussion of the medical treatment of the bronchiectasis.

CYSTIC DISEASE OF THE LUNG

Although some authorities regard all cysts as congenital in origin, the consensus is that in most instances they are acquired. In the newborn, one occasionally encounters very large, single cysts which rapidly replace an entire lung.

In adults one may see occasionally single cysts which from time to time vary in size, and which may eventually become infected when abscess-like symptoms appear. Hemoptysis likewise may be a presenting complaint. For those without symptoms, observation is sufficient, but sooner or later nearly all cysts become infected and prove annoying enough to require surgical intervention, usually in the form of lobectomy.

Multiple cysts of the lung are usually distributed bilaterally, and give rise to a history closely resembling that of bronchiectasis. On physical examination the chest is usually over-distended, with most of the findings characteristic of emphysema in the areas affected except that many moist rales may be encountered in some patients. Numerous wheezes also may sometimes be heard.

The x-ray reveals thin, ring shadows, varying in diameter from 1 to 10 cm., and scattered about both lungs. In some of these there may be fluid levels, but in spite of infection the walls remain quite thin. Studies other than bronchography are unrevealing. The iodized oil in such cases reveals irregular, beaded dilatations of the smaller bronchi and bronchioles, and in some cases the oil may be seen to outline small cysts along its course, and to pass through them into the continuation of the bronchiole. Hence the alternate name, cystic bronchiectasis. Since the situation is irreparable if bilateral, the treatment is palliative and does not differ from that of nonsurgical bronchiectasis.

ADENOMATOSIS

The exact nature of this disease is obscure, but it is rather commonly believed to be viral, since a similar disease is found in sheep and has proved to be transmissible. The patient is acutely and severely ill, with an irregular and protracted temperature elevation. Physical examination presents evidence of consolidation involving one or more lobes, and the x-ray is confirmatory. Characteristic of the disease is the expectoration of large amounts of clear mucus, in which cytologic studies will reveal the characteristic cells. These cells resemble those found post mortem lining the alveoli, and are of such character as to lead some authorities to regard the disease as an alveolar cell carcinoma of multicentric origin. No treatment is of any avail and the outcome, so far as is known, is uniformly fatal.

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Neoplastic Diseases

John S. Chapman

Carcinoma of the Bronchus
Bronchial Adenoma
Metastatic Tumors of the Lung

New growths of the lungs, mediastinum, and chest wall are divided properly into primary and metastatic, benign and malignant. Esophageal tumors have been presented under a separate discussion (see p. 257), and will not be considered further except as they arise in the differential diagnosis of other tumors. Of all new growths which lie within the thorax it should be said that, quite aside from the histology of the tumor, its effect may be serious as a result of pressure against or erosion of certain of the contents of the thorax. On the other hand, many quite large tumors remain essentially asymptomatic and are discovered only upon routine chest roentgenography.

CARCINOMA OF THE BRONCHUS

Cancer arising from epithelium of the bronchus is by far the most frequent and most important tumor of the thorax. Histologically, these cancers are divided according to cell type into squamous, undifferentiated, and adenocarcinoma. Since they may arise wherever bronchial epithelium exists, the tumor may develop in any portion of the lung, although the squamous type is more often found arising in the major bronchi, while

adenocarcinoma and undifferentiated cell types arise more peripherally. All grades of malignancy are encountered, but it is more common for the squamous type to follow a rather slow evolution, and for the other types to pursue a more malignant course.

Carcinomas of the bronchus are eight times as common in men as in women, and many authorities are inclined to attach great importance to prolonged and heavy smoking of tobacco as a possible etiologic factor. Such cancers may be encountered at almost any age, but are commonest after 40. There is no demonstrable relationship to race, occupation, or previous pulmonary diseases.

As in the case of other malignant tumors, dissemination may be by local extension, blood stream, or lymph channels. In the case of the centrally growing tumor, however, there is not only the question of the tumor itself, but also the fact that it rapidly produces bronchial obstruction with suppuration of the segment of lung distal to it. Since tumors in these areas more commonly metastasize to regional lymph nodes, there is early widening of the mediastinum and frequent invasion of various of its contents.

The more peripheral tumor is apt to metastasize first to the pleura and chest wall, and later to spread, via the blood stream, to such favorite

and frequent sites as bone, adrenal cortex, brain, liver, and subcutaneous tissue.

Symptoms are most commonly cough, expectoration, wheeze (well localized by the patient sometimes), and hemoptysis, which may vary from slightly streaked sputum to very considerable bleeding. The sputum is frequently mucoid in character, until infection develops beyond the tumor or within it, when the material is frankly purulent and sometimes quite foul. Shortness of breath will be an important complaint if a large segment of lung is obstructed, or if there is massive mediastinal metastasis. Pain depends almost entirely upon whether or not pleural or osseous (often costal) metastases have occurred. However, a fair number of patients without these complications not infrequently complain of a dull pain parasternally or in the interscapular area, a pain which may arise from the bronchus itself. As the disease progresses there are the usual complaints relating to any malignant disease—loss of weight and strength, poor appetite, fever, and malaise.

One particular bronchogenic carcinoma sometimes identified by the special name of *superior sulcus* or *Pancoast tumor*, which grows over the apex of the lung and quickly extends into the adjacent structures, deserves remark on account of the nearly complete absence of respiratory symptoms. This tumor makes its presence known through invasion of the brachial plexus and the subclavian vessels. Pain in the hand and arm is usually extreme, there are various patches of anesthesia and atrophy, and there is frequently obstruction of the vein or artery with ischemia or, much more commonly, marked swelling.

Examination of the chest usually reveals an area of flatness with absent breath and voice sounds. There may be a few medium moist rales adjacent, but the most important physical sign is the presence of an expiratory rhonchus or wheeze heard persistently over the area of tumor. Sometimes evidence of bronchial obstruction is obtained best by listening with the naked ear before the patient's open mouth, as he makes a prolonged, forced expiration. Clubbing of the fingers is common, and joints may be painfully swollen (pulmonary osteoarthropathy).

X-ray commonly reveals the picture of "atelectasis," with a dense, homogeneous shadow radiating outward from the hilum and with shift of the mediastinum toward the affected side, as

well as elevation of the diaphragm and narrowed intercostal spaces. In a few instances no shadow of segmental or lobar obstruction is seen, but instead a marked obstructive emphysema of the affected side with a thinning of lung markings, depression of the diaphragms, widening of the

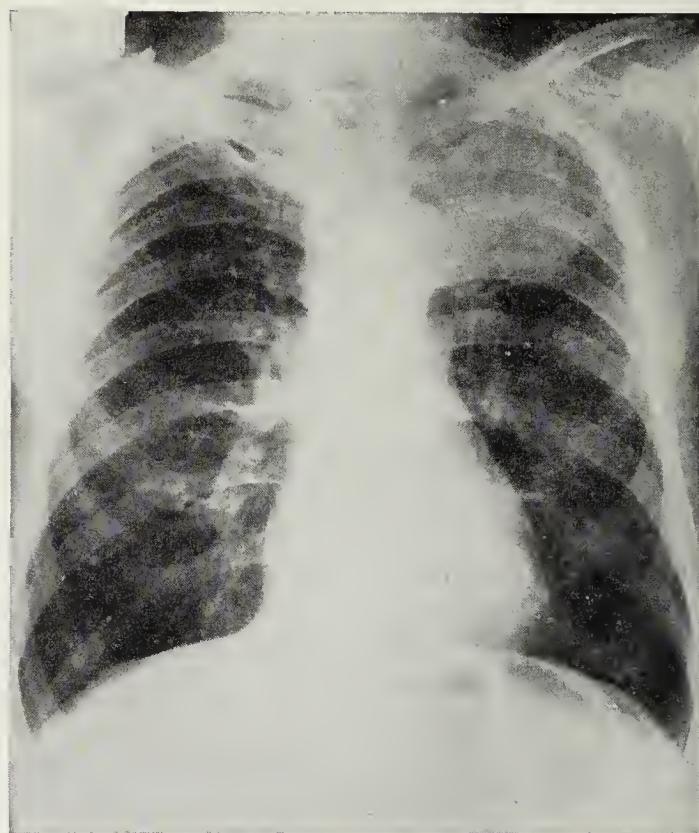


FIG. 216. Carcinoma of the bronchus.

intercostal spaces, and shift of the mediastinum away from the lesion. The peripherally growing tumor usually may be seen as a solid, rounded shadow lying subpleurally and not distinguishable roentgenographically from tuberculoma. (See figure 221.)

Bronchoscopy is of great value in those tumors which in the posteroanterior and lateral projections are seen to arise near the hilum, although in some of the more distant tumors some degree of suggestive information may be obtained, and secretions may be sucked out for cytologic study, for which some prefer the Papanicolaou stain. (See Plate I, facing p. 288.) If accessible nodes are involved these may be removed for examination.

In a final group of cases no definite diagnosis will be possible, and exploratory thoracotomy will have to be performed. Since this procedure is an almost completely innocuous one when performed by well-trained thoracic surgeons, it should be called for with increasing frequency, as surgery offers the only present curative pro-

cedure for bronchial cancer, and as successful extirpation may well demand exploration of the chest before a positive diagnosis is obtainable.

Contraindications to exploration of the chest are related to the signs and symptoms produced by metastases. Obviously, a pleural effusion, whether it contains carcinoma cells or not, means spread to the pleura and inoperability. Horner's syndrome; evidence of involvement of the central nervous system; nodes in the neck or axilla; enlarged, nodular liver; roentgen evidence of bone destruction or persistent, boring bone pain before such evidence is available; hoarseness with paralysis of a vocal cord; obvious widening of the mediastinal shadow—all these are additional points to search for, any of which, upon discovery, would contraindicate operation. There is some question as to whether or not diaphragmatic paralysis from invasion of the phrenic nerve is an absolute contraindication, but most surgeons are now willing to proceed with exploration in spite of this sign.

Of patients presenting themselves for study, only about 25 per cent prove finally to have resectable tumors, and only 25 per cent of this group survive as long as five years, so that at the end of such a period only 6 per cent of the entire group remain alive. As poor as this showing is, it compares fairly favorably with resection for such carcinomas as those of the stomach.

Not infrequently in the inoperable group will be found patients, chiefly elderly men, who have been under fairly close observation for some months during which "an unresolved pneumonia" or "an abscess" has waxed and waned roentgenologically as courses of penicillin have been administered. Carcinoma of the bronchus, then, should be strongly suspected in any instance of a patient who presents the history and findings of an abscess in which the onset has been insidious and the resolution slow. In the same age group every case of pneumonia, especially those in any way atypical, should be followed to complete clearing of x-ray and physical signs. Above all, it is important to be on the alert in such individuals for persistent localized chest pain or for expiratory wheeze.

Palliative treatment consists of the free use of narcotics to relieve pain, the employment of antibiotics and sulfonamides to keep infection at a low level, and the aspiration of pleural effusion for the relief of dyspnea. If infection is minimal

deep x-ray irradiation may be attended by considerable improvement and, though rarely, by a long remission. Although the use of nitrogen mustard as a palliative measure has been suggested, the writer has so far seen no significant benefit from this drug. In patients whose pain is uncontrollable by narcotics—a group that particularly includes the superior sulcus type—medullary tractotomy is most helpful.

BRONCHIAL ADENOMA

This rather remarkable neoplasm commonly arises in a large bronchus, and grows both centrally and peripherally. In most instances it is seen within the lumen of a main bronchus as a cauliflower-like tumor which is highly vascular and which bleeds (sometimes dangerously) upon the slightest touch. In other instances the visible portion is small, while the bulk of the tumor grows in a branch bronchus and gives rise to a large, bulky shadow near the hilum. This mass, however, does not represent invasion but is actually encapsulated by the tremendously distended and thinned-out wall of the branch bronchus. Histologically, these adenomas present a structure which varies in different portions so that at times a pathologic diagnosis of adenocarcinoma is made.

A point of differential diagnosis is that these tumors are commonly encountered in young people and in females. In many instances the history is of long duration and usually relates to mild mucoid expectoration with occasional massive hemoptyses in the midst of what the patient has regarded as a normal state of health. For some reason there is, as a rule, little or no suppuration beyond the obstruction.

Physical examination may reveal a wheeze audible at the open mouth. Usually there is obstruction of a lobar bronchus with corresponding absence of breath and voice sounds, and dullness. In other instances, the obstruction having been present for so long a time, the shrunken and obstructed lobe occupies so small a space as not to be discoverable upon physical examination, the other lobe having distended sufficiently to fill the hemithorax. In such case the only sign will be that of reduced breath sounds upon the side of the overdistended lobe, with perhaps very slight shift of the mediastinum and elevation of the diaphragm.

The diagnosis finally has to be made by bron-

choscopy and biopsy. In some instances removal through the bronchoscope can be accomplished satisfactorily, but in many removal is incomplete and local recurrence takes place. The majority of patients require exploration and lobectomy, for



FIG. 217. Hematogenous metastasis from sarcoma of the ileum, clinically marked by intense dyspnea and cyanosis. (Courtesy, Dr. C. L. Martin.)

much of the importance of adenoma lies in the difficult differential diagnosis from carcinoma.

METASTATIC TUMORS OF THE LUNG

Metastasis to the lung may take place by direct extension or by way of the blood stream. Representative of the first type of extension is the hepatoma, which may erode through the diaphragm and extensively invade the lower lobe, even to the point of appearing within the lumen of the bronchus. Blood-borne metastases are, of course, far more frequent, and are classifiable roentgenographically in three main divisions: large, coalescing growth usually found bilaterally in the lower lobes; miliary disseminations; and the so-called cannonball type, which may be either single or multiple. Obviously, the pattern of the metastases can give no reliable clue as to the primary site, but it is a fairly dependable general statement that the miliary and

conglomerate groups are usually carcinomatous, while the large nodular metastases usually result from hypernephroma, testicular tumors, sarcomas, and melanomas.

Unlike the primary carcinoma of the bronchus, metastatic tumors rarely give rise to cough, expectoration, or hemoptysis. Pleuritic pain on occasion may be very severe, but the most characteristic symptom is usually dyspnea, and this is particularly true of miliary metastases. Physical findings not infrequently are quite unimpressive, although, when there is considerable coalescence in the lower lobes, one may discover dullness, diminished breath sounds, and a few rales.

The only possible treatment is symptomatic and palliative. Hormonal therapy is worth trying in the case of tumors of gonadal origin, radioactive iodine for some thyroid carcinomas, and x-ray irradiation for highly sensitive sarcomas. If pleural fluid is present, aspiration is indicated

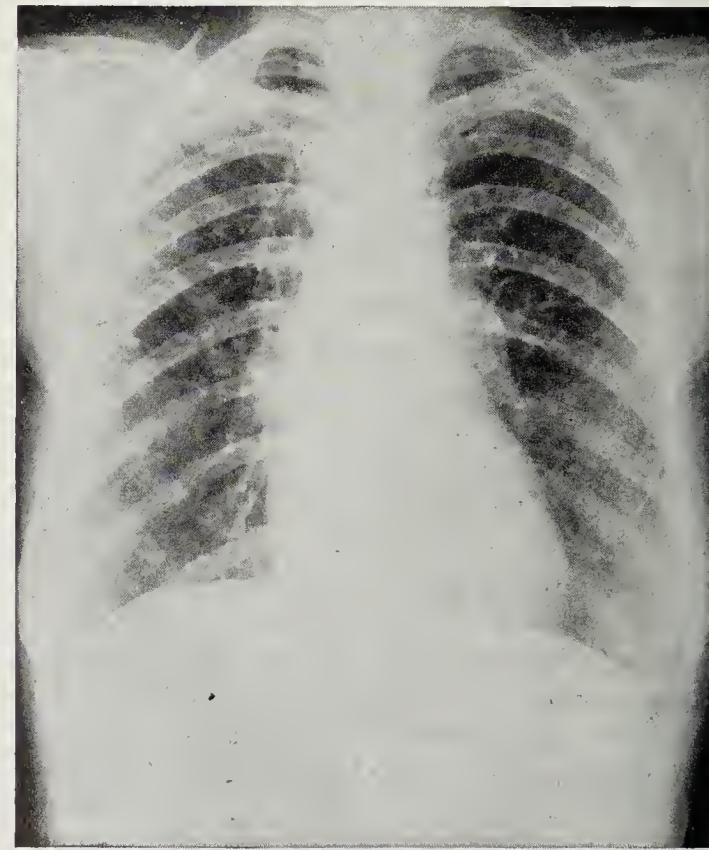


FIG. 218. So-called lymphangitic carcinomatosis metastatic from a carcinoma of the cervix. (Courtesy, Dr. C. L. Martin.)

for the relief of dyspnea. Rarely, dyspnea resulting from bronchial edema may be relieved somewhat by atropine, aminophylline, or epinephrine. If dyspnea and cyanosis are marked, morphine should be used with care, since marked depres-

sion of the respiration may result from quite moderate doses.

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Miscellaneous Disorders Due to Aspirated Foreign Bodies

John S. Chapman

Lipid Pneumonia

Aspirational (Enzymatic) Pneumonia

The aspiration of large foreign bodies, which is encountered most commonly in children, is marked by the sudden onset of strangling, choking, coughing, and cyanosis. If the object is small enough to pass down to a lobar or branch bronchus, the acute picture subsides for a few days, and then the syndrome presented is that of bronchial obstruction with suppuration beyond, particularly when the offending substance is vegetable. In other cases, if the body is non-absorbable, after coming to rest in one branch bronchus with a subsidence of symptoms, it may after a few days become dislodged and again repeat the original episode as it is shuttled about in the trachea and major bronchi. There is only one treatment—bronchoscopy with removal.

Characterized by very similar symptoms, except for the additional one of hemoptysis, is the condition called broncholithiasis, in which from time to time pieces of calcium erode through the bronchial wall and are expectorated. Since the calcium particles derive from lymph nodes in the hilar area, this condition is encountered more frequently among older people. The treatment is bronchoscopy if the patient should have any prolonged period of obstruction.

LIPID PNEUMONIA

This condition results from the aspiration of oily material, and occurs most commonly in

patients who have ingested large quantities of mineral oil over a prolonged period or in infants or adults who have been subjected to the use of oily nose drops. In a limited area and to a minor extent, a lipid pneumonia probably takes place following every injection of iodized oil. The histologic picture is that of foreign-body giant-cell reaction with lymphocytes and mononuclear leukocytes. In chest films one usually finds a bilateral lower lobe distribution which is patchy and irregular, but occasionally the infiltration may be found involving other areas and even single segments. The earliest phase is said to be indicated only by the increased basilar markings. The sputum examined fresh under the cover glass reveals numerous free fat droplets, as well as phagocytes filled with oil droplets which take up Sudan III.

ASPIRATIONAL (ENZYMATIC) PNEUMONIA

Occasionally, one encounters a bilateral lower lobe pneumonia characterized by the rapid formation of multiple small abscesses and by a very severe course. There is usually a history of unconsciousness associated with vomiting, as, for example, in severe alcoholism or in rough and unsatisfactory general anesthesia. Pathologically, the abscesses are found to be very acute, with little fibrous reaction, and their lining walls are marked by a slimy membrane. In some cases it is possible to demonstrate stomach contents lying

within these abscesses. The peculiar character of the abscesses and pneumonia is considered the result of the activity of the ferments and hydrochloric acid of gastric juice as well as of the presence of foreign protein.

A variation of the above condition is encountered in patients who have suffered tracheoesophageal or bronchoesophageal fistula as a result of neoplasms, or in infants with congenital tracheoesophageal fistula, although in both of these instances the evidence of enzymatic digestion of the lung is usually much less marked. The treatment for all of these conditions is repeated bronchoscopic aspiration, the use of large doses of penicillin, and, in the fistula cases,

efforts to correct the condition. In the case of the adult whose carcinoma of the esophagus (see Chapter 257) has invaded the bronchus or trachea, there is, of course, the possibility of gastrostomy as a partially palliative measure. The outlook in such instances is so bad and the usual duration of life so short after perforation that there is little chance for intervention, and even less that the intervention will be successful.

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Unusual Roentgenographic Findings

John S. Chapman

Miliary-like Infiltrations
The Solitary, Round Nodule

MILIARY-LIKE INFILTRATIONS

Upon discovering widely disseminated, small-sized infiltrations throughout the lung fields, one's first impression is of miliary tuberculosis (see Chapter 128). Similar infiltrations, however, are occasionally encountered in other diseases.

~~X~~In sarcoidosis the lesions are slightly larger than those of miliary tuberculosis and are nearly always somewhat more coalescent. As a rule the hilar lymph nodes appear radiographically enlarged. Other evidence in favor of sarcoidosis will be the relative good health of the patient, lack of significant fever, maintenance of weight and strength, and absence of dyspnea. Other signs of value will be enlargement of peripheral nodes (perhaps 75 per cent), bone lesions (about 25 per cent), skin lesions (25 to 50 per cent), and disease of the eye and its adnexa (about 25 per cent). The tuberculin skin test will be negative in all strengths in from 60 to 90 per cent (depending on the locality) of all patients, and the great majority will be found to have true hyperglobulinemia and either high normal or truly

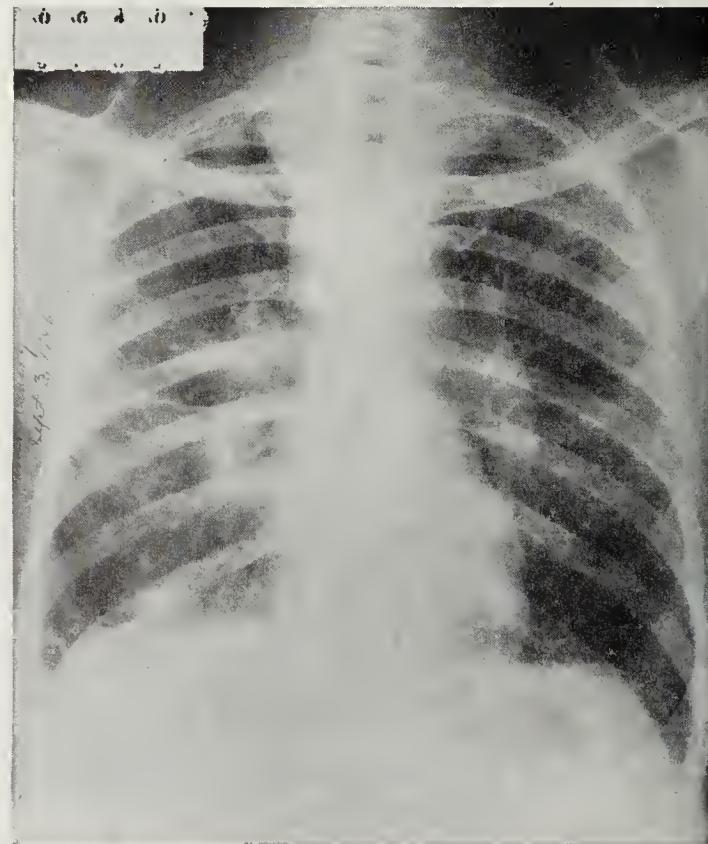


FIG. 219. Sarcoidosis of the lungs. Note particularly the massive hilar adenopathy and marked widening of the superior mediastinum. The original fine nodulation is overshadowed by coalescence and fibrosis.

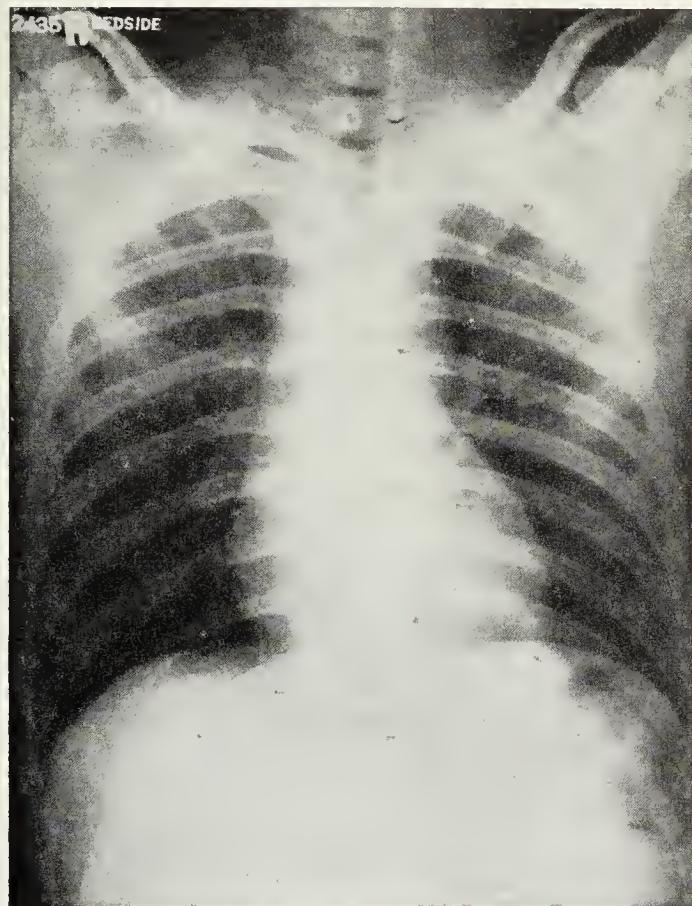


FIG. 220. Miliary tuberculosis. The nodules are so small that they can be perceived only in the upper portions of the lung fields. (Courtesy, McKinney Veterans Administration Hospital, and Dr. Francis Reichsman, Chief of Tuberculosis Service.)

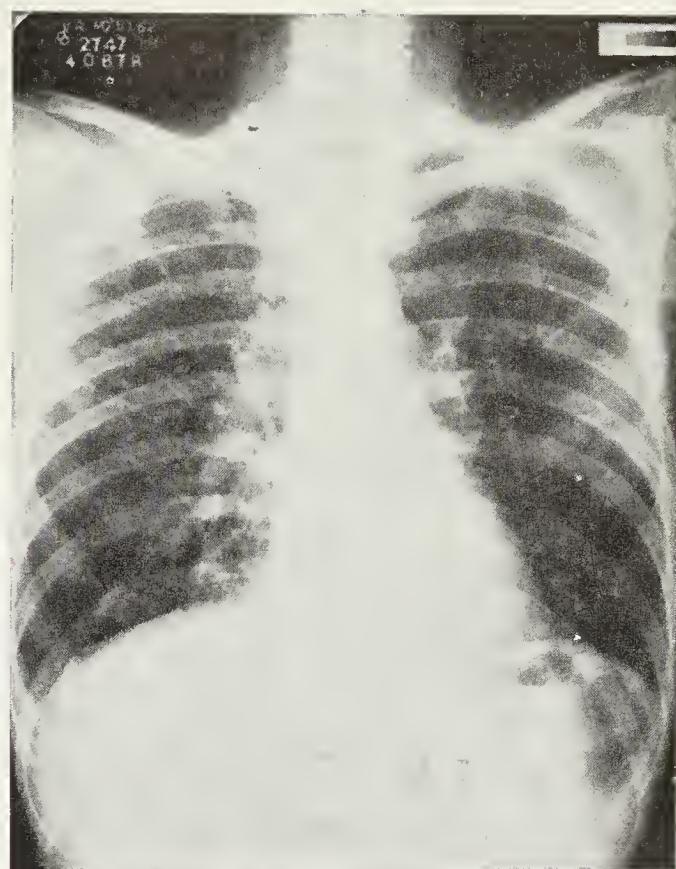


FIG. 222. Periarteritis nodosa. (Courtesy, McKinney Veterans Administration Hospital, and Dr. Francis Reichsman, Chief of Tuberculosis Service.)

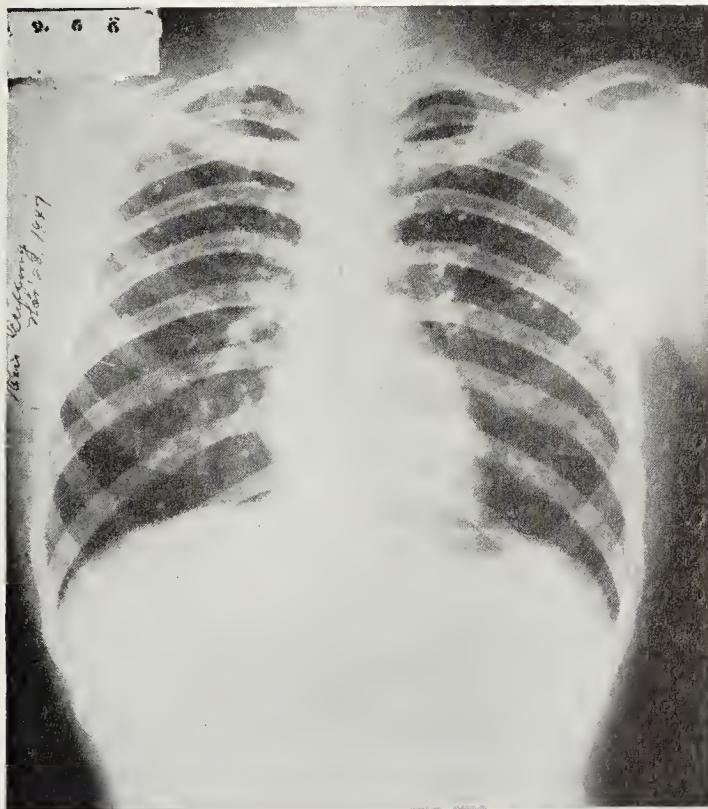


FIG. 221. Numerous pulmonary calcifications with positive histoplasmin skin test and negative tuberculin and coccidioidin tests.

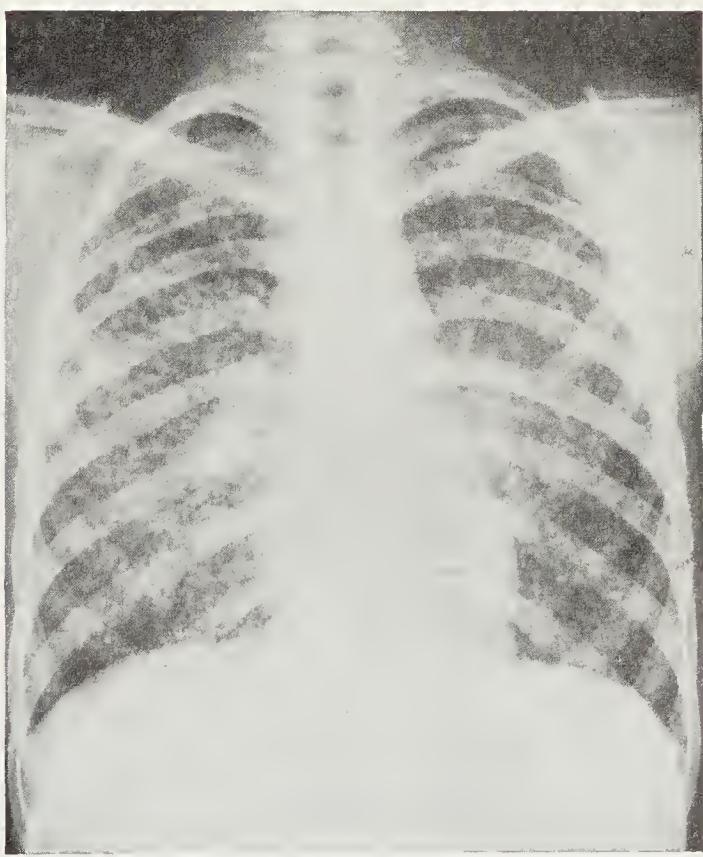


FIG. 223. So-called cave disease. There was gradual clearing over a period of eight months.

elevated blood calcium. One writer reports significant eosinophilia in the majority of his series. ~~X~~ Hemosiderosis will also usually be differentiable on the film alone, chiefly by reason of cardiac enlargement with characteristic configuration resulting from mitral stenosis. A history of rheumatic fever and the discovery of valvular lesions on physical examination will be of further aid, as well as the fact that miliary tuberculosis is practically never associated with severe rheumatic heart disease.

~~X~~ Lymphangitic carcinomatosis frequently produces a roentgenographic lesion very similar to that of miliary tuberculosis. Clinically, such patients are usually extremely dyspneic but, unlike the tuberculous patient, commonly have little elevation of the temperature. A very careful search may be necessary to find the primary site of cancer, and in a certain number of instances the search fails altogether. One of the commonest sites of origin is the bronchus itself, where the primary growth may be so small as almost to be overlooked at autopsy. Other primary sites are the thyroid, the breasts, the colon, the pancreas, and the kidney.

~~X~~ First or early second stage silicosis may at times simulate miliary tuberculosis rather closely, but as a rule the infiltrations are larger, there is an associated reticular fibrosis, and the hilar shadows are exaggerated. Fever is not present, and at these stages the patient may have very little dyspnea. A history of an occupational exposure is conclusive.

~~X~~ Bronchiolitis, a rare disease most frequently seen in infants or occasionally in adults who have been exposed to extremely irritating gases, may produce innumerable small infiltrations throughout both lungs. Such patients are extremely ill, the temperature is very high, and the dyspnea is progressive. The duration of such an illness is said not to exceed five or six days.

~~X~~ Histoplasmosis may produce an acute, widespread, miliary seeding of the lung which can be differentiated from miliary tuberculosis only by the discovery of the causative organism. In a healed phase this disease may result in innumerable small, rounded, well-defined nodules of calcific density. Such a phase, if it is, in fact, the result of histoplasmosis, as the histoplasmin skin test suggests, is completely asymptomatic. There is no evidence that reactivation may occur or that there may be associated sufficient fibrosis to

give rise to dyspnea in the patient's later years.

Coccidioidomycosis, both roentgenographically and clinically, may manifest itself as a miliary disease of the lungs which is indistinguishable from miliary tuberculosis except upon the basis of history of residence in one of the endemic areas, the occasional association of rash, and the discovery of the organism.

~~X~~ Periarteritis nodosa sometimes results in a diffuse, patchy infiltration of the lungs, but the lesions are commonly much larger than those seen in miliary tuberculosis. The involvement of many different systems, which is also characteristic of tuberculosis, is not a differential point in itself, but the predilection of periarteritis for muscles and peripheral nerves is a distinguishing feature. Eosinophilia in the peripheral blood, if present, is a reliable point of differentiation.

~~X~~ Acute diffuse interstitial fibrosis of the lung may, upon first glance, seem roentgenographically to resemble miliary tuberculosis, but upon closer inspection will be found to possess a more stranded and nodular character. The patient is acutely ill, and has high fever, much cough, and relatively slight expectoration. The disease seems to be extremely rare and, so far as is known, it is uniformly fatal within a matter of weeks.

So-called ~~X~~ "cave disease" seems to be an infectious disease of unknown etiology, characterized by an average incubation period of 10 days, a rather abrupt onset with epistaxis, headache, high fever, and squeezing chest pain, but only moderate prostration and slight acceleration of the pulse. This disorder received its name because it was observed in persons who had spent some hours in a cave. The possible roles of infection by fungi, sensitivity, and irritation by dust remain uncertain. At its height the disease is said to be recognized in chest films by a miliary or slightly larger infiltration with some tendency to coalescence, and with moderate enlargement of the hilar lymph nodes. In the case of a single patient the differential diagnosis might be very difficult for a time, but at the time when the patient with miliary tuberculosis would reasonably be expected to be moribund, the patient with "cave disease" would frequently show improvement in all respects.

THE SOLITARY, ROUND NODULE

Occasionally, a roentgenogram of the chest may reveal a dense, homogeneous nodule, which

is fairly sharply circumscribed from adjacent pulmonary tissue. Such nodules may vary in size from 1 to as many as 8 cm. in diameter, and frequently may be asymptomatic, although the patient should be very carefully questioned about chest pain and streaked sputum. Of a fairly large collection of material removed at operation, perhaps 65 per cent of such lesions are carcinomas of the bronchus, about 30 per cent are tuberculomas, 3 per cent are healed coccidioidal granulomas, and the remainder are benign lung tumors or solitary metastases from hypernephroma, testicular tumor, or sarcoma. These

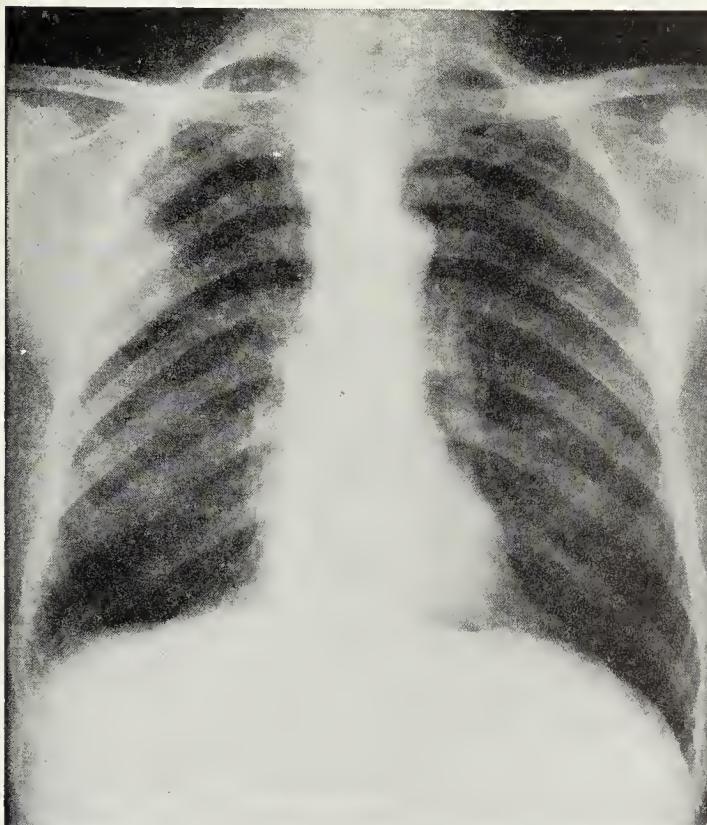


FIG. 224. Characteristic peripheral bronchogenic carcinoma. (Courtesy, Dr. D. L. Paulson.)

figures, however, are colored by the fact that they are derived from surgical exploration. If figures were available for all such nodules it would be reasonable to suspect that the incidence of carcinoma would be lower, and that of tuberculoma and solitary metastasis higher. The incidence of the coccidioidal nodule, of course, will vary geographically, being much higher in California, Arizona, New Mexico, and some parts of Texas than along the East Coast or in the Middle West.

Clinically, upon being confronted with such a problem, one has usually little or no history

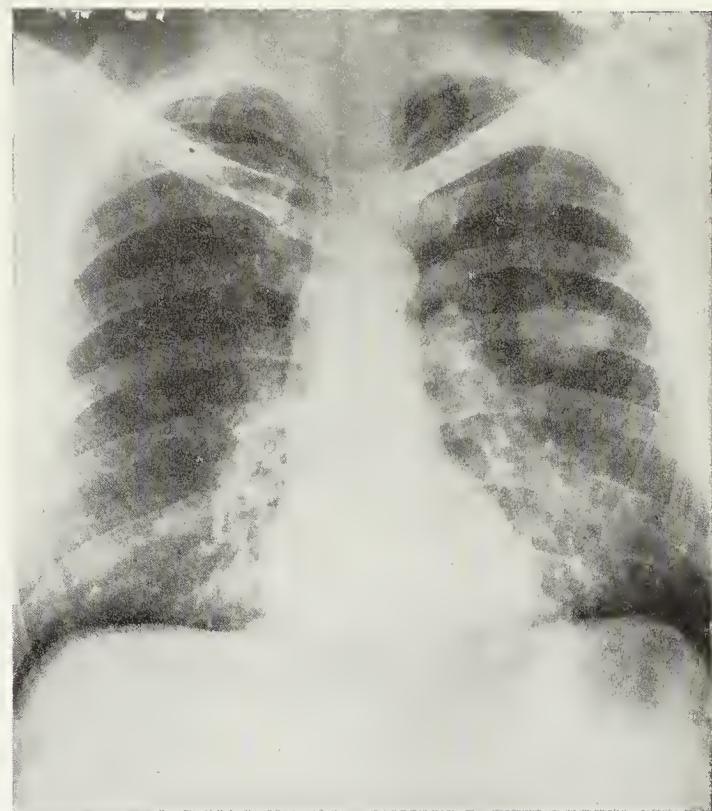


FIG. 225. The solid filled-in cyst of primary coccidioidomycosis. (Courtesy, Dr. Robert R. Shaw.)

upon which to proceed. Pain and blood-streaked sputum strongly indicate carcinoma, but occasionally may be encountered in the other conditions. Secretions usually are totally absent, but

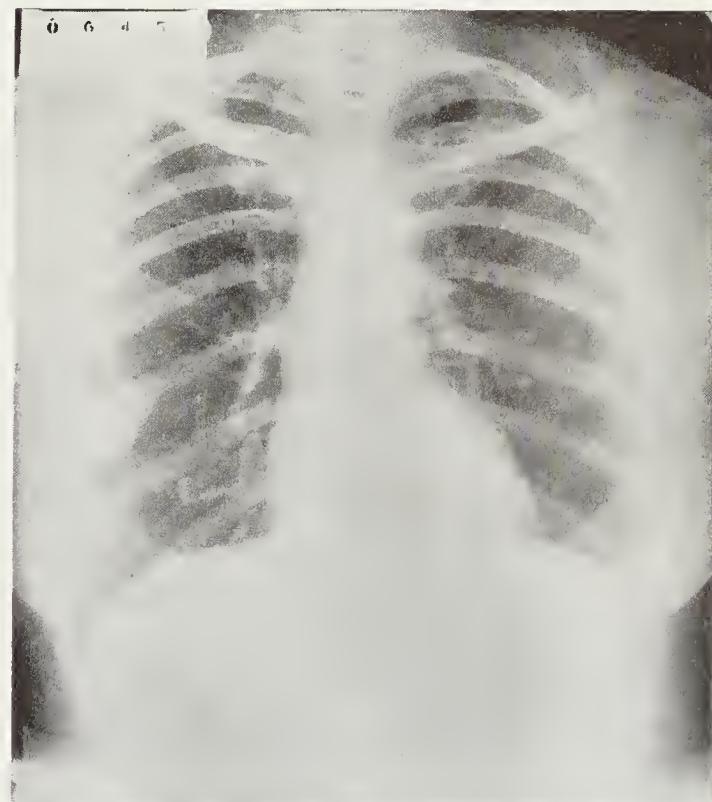


FIG. 226. Tuberculoma. Note close resemblance to peripheral carcinoma.

if any can be obtained by bronchoscopy or gastric washings they should be subjected to complete study, including inoculation on Sabouraud's medium and into guinea pigs. Any material obtained from bronchoscopy, of course, should have thorough cytologic examination. Skin tests both with tuberculin and with coccidioidin may afford at least suggestive information. The only safe procedure, when one is in any doubt, is surgical exploration.

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Section 5—The Alimentary Tract

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Introduction

Thomas E. Machella

Functional Disorders of the Gastrointestinal Tract

Roentgenology of the Gastrointestinal Tract

Survey Film

Barium Meal

Small-Intestinal Enema

Intestinal Intubation

Barium Enema

Barium-Air Double Contrast Enema

Endoscopic Methods of Gastroenterology

The more important manifestations of disorders of the alimentary tract have already been discussed. These include dysphagia (Chapter 15), indigestion (Chapter 15), constipation (Chapter 16), diarrhea (Chapter 16), and ileus (Chapter 4). The section to follow will deal with the alimentary disorders from the standpoint of specific diseases, rather than symptoms. Before discussing these specific diseases, certain general principles will be considered.

FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT

No attempt will be made to discuss functional disorders of the gastrointestinal tract in detail. It must be pointed out, however, that such disorders exist, and that they are not infrequently responsible for gastrointestinal complaints. It is not possible to arrive at their relative incidence on the basis of available statistics because of the selective nature of the reported clinical data. Admitting such limitations, however, some rough estimate of their frequency may be obtained by an analysis of the case histories of patients referred to a hospital out-patient clinic specifically for their gastrointestinal complaints. In 30 per cent of a group of 6492 such patients, no organic basis for gastrointestinal symptoms could be demonstrated, and the symptoms were ascribed to emotional disturbances. Though a temporary functional gastrointestinal disturbance may occur in a healthy person under the influence of an emotional upheaval, more prolonged and severe changes in gastrointestinal

functions on an emotional basis may lead to actual morphologic changes in the gastrointestinal tract. Examples of the latter include peptic ulcer, some forms of gastritis, duodenitis, chronic ulcerative colitis, regional enteritis, and, in some instances, megaesophagus on the basis of cardiospasm. These diseases occur in those who are high-strung and hypersusceptible reactors to stimuli, when they have been subjected to a variety of emotional and physical frustrations and insults. The successful medical management of such patients calls for a sincere, understanding, helpful, and sympathetic attitude on the part of the physician, combined with an ability to instill confidence and hope. Induction of remissions and reduction in the incidence of relapses depend on the discovery and successful handling of the emotional problems concerned. Usually, a good doctor can handle such problems satisfactorily, but occasionally special psychiatric aid may be required.

It is also important to recognize functional disturbances of the gastrointestinal tract which are nonpsychogenic in origin but are secondary to primary disorders of other organs and systems such as diseases of the gallbladder, liver, pancreas, heart, kidneys, pelvic organs, endocrine glands, and the nervous system. In addition, metabolic and deficiency diseases, allergic states, and infectious and toxic conditions may give rise to functional gastrointestinal disorders.

ROENTGENOLOGY OF THE GASTROINTESTINAL TRACT

Roentgen examination is the most important laboratory aid in the diagnosis of disorders of the gastrointestinal tract. It should be performed not only in every patient in whom an organic lesion of the alimentary tract is suspected, but also in those in whom functional disorders are to be detected. The various roentgen techniques in-

clude a survey film, barium meal occasionally supplemented by the insufflation of air into the stomach, small-intestinal enema, special intubation technics, and the barium-water enema and barium-air contrast examinations of the colon.

Survey Film. A preliminary or survey film of the abdomen may sometimes furnish useful information in a variety of conditions which give rise to gastrointestinal symptoms. It may aid in the localization of calcific deposits in the pancreas, gallbladder, kidneys, mesenteric lymph nodes, and other abdominal and pelvic structures. It is useful in confirming the presence of free fluid when physical signs are not clear, and in localizing masses involving retroperitoneal structures which interfere with the clarity of the shadows of the iliopsoas muscles. When intestinal obstruction is suspected, preliminary films of the abdomen should be made in both the recumbent and upright positions, and examined promptly for evidence of air or air-fluid levels in the intestinal loops. Thus, information not only as to the diagnosis but also as to the location of the distended loops and the site of obstruction is obtained. A survey film of the abdomen should also be made when perforation of a viscus is suspected. In such cases, a collection of air may be found in the uppermost portion of the abdomen, depending on the position of the body when examined with the beam of roentgen rays horizontal, or at the site of the perforation if the latter is walled off by exudate or adhesions. The survey film is of no value in identifying or localizing nonobstructing lesions which involve the mucosa of the gastrointestinal tract. For this purpose, a contrast medium is essential.

Barium Meal. In the absence of evidence of intestinal obstruction or of a perforated viscus, and unless the patient is vomiting, one can proceed in most instances with the administration of a barium meal by mouth for the purpose of examining the esophagus, stomach, duodenum, and small intestine, and obtaining certain types of information concerning the colon. The behavior of the barium meal should be observed fluoroscopically, because the final solution of diagnostic problems often depends on a careful fluoroscopic examination. Much information can be obtained about the functional behavior of alimentary structures which is not possible from roentgenograms. It is important to realize, however, that fluoroscopic examinations vary in their

reliability, depending on the expertness of the observer. The exposure of a film offers the advantage of a permanent visual record of the lesion at any one time. The use of spot and pressure film devices is of value in the many instances when information concerning mucosal relief is desired.

If the clinical manifestations point to an obstructing or ulcerating lesion in the esophagus or stomach, roentgen examination should precede passage of a tube or endoscopy, as the risk of the former examination is less. It should also initiate the diagnostic survey of all patients who have recently recovered from a gastric or duodenal hemorrhage. The roentgen examination of the esophagus, using capsules filled with barium and thick and thin liquid barium mixtures, is useful in the demonstration of cardiospasm, esophageal tumors, diverticulum or ulcer, hiatus hernia, esophageal varices or stricture, and nonopaque foreign bodies, and to outline extrinsic mediastinal masses.

In the stomach, study of the barium meal may reveal ulcer, cancer, polyps, hypertrophic gastritis, syphilis (hourglass stomach), tumors of adjacent regions, gastrojejunal ulcer, and foreign bodies. It is also useful in detecting functional disturbances of the stomach in that it supplies information on the characteristics of peristalsis and tonus as well as on the emptying time. Patients with gastric ulcer under medical management should be re-examined at the end of three weeks. Persistent ulcerative lesions necessitate surgical intervention to rule out the possibility of gastric carcinoma. Lesions of the fundus of the stomach are more apt to be overlooked than those elsewhere in the stomach, because of the inaccessibility of this area to palpation. The barium meal is of little value in the diagnosis of many forms of gastritis, but may reveal well-developed hypertrophic gastritis. Such studies require careful evaluation of the character of the mucosal relief.

Air, introduced by means of a tube, is sometimes used for a contrast in the examination of the stomach. A double contrast picture may be obtained by administering a small amount of barium. This type of examination is especially useful in demonstrating polypoid tumors as well as pressure defects produced by extragastric lesions.

Fluoroscopic and roentgenographic studies of

the behavior of a barium meal are of value in the diagnosis of lesions of the small intestine, in the demonstration of disease in neighboring structures causing persistent displacement of a loop or loops of intestine, and in revealing abnormalities in the mucosal pattern and motility. The examination of the small intestine, however, presents difficulties because of the overlapping loops. The duodenum and the terminal ileum are the only two segments which can be examined satisfactorily. The rapid transit of the barium meal necessitates frequent roentgen examinations. The barium should enter the cecum in about three hours; any delay should arouse suspicion. The normal mucosal pattern varies, but it is affected by many conditions such as emotional disturbances, drugs, deficiency disease, inflammation, adhesions, constipation, obstructions, and neoplasms.

The study of the colon on the second day after a barium meal is not an essential in the investigation of a patient suspected of having colonic disease, as it is impossible to fill the colon completely and, therefore, many colonic lesions cannot be demonstrated satisfactorily. The procedure, however, can furnish information concerning the position and functional state of the colon which may not be so satisfactorily obtained by barium enema alone. It is of special value in the diagnosis of "spastic" colon. When used for this purpose, antispasmodics should be withheld.

Small-Intestinal Enema. Examination of the small intestine following intubation of the duodenum and the continuous gravity introduction of 500 to 1000 ml. of a thin barium mixture offers many advantages in the study of the small intestine and in the diagnosis of obscure lesions. The procedure permits an orderly filling of the loops from above downward and a demonstration of the entire small intestine. The barium reaches the cecum in about 15 minutes.

Intestinal Intubation. The roentgen examination, using the Miller-Abbott tube, can supply valuable information concerning small-intestinal lesions and disorders. Normally, about three hours are required for the balloon to pass through the intestine into the cecum. When the balloon fails to advance in three to four hours, a lesion may be suspected, providing sufficient slack of the gastric portion of the tube has been allowed. If the sufflated balloon enters the cecum, an

obstructing lesion of the small intestine is usually eliminated. In paralytic ileus, the rate of passage of the balloon is much slower than in mechanical ileus. After deflation of the balloon, the injection of 30 to 40 ml. of a thin barium mixture at the site of its arrest may demonstrate clearly the site and the nature of the lesion causing the obstruction. The barium should be withdrawn promptly after the examination is completed. If surgery is decided on, the tube is left in place as a guide to the point of obstruction, as well as for the purpose of deflating the bowel during the post-operative period.

Barium Enema. The introduction of an opaque medium into the colon through the rectum is necessary in the diagnosis of organic disease of the colon. For this purpose a mixture of water and barium is most commonly used. The procedure is useful in demonstrating colonic tumors, granulomas, diverticulosis, ulcerative colitis, megacolon, and extracolonic intraabdominal masses. It is also of value in studying the terminal ileum. The examination should not be relied upon to exclude lesions of the colon distal to the lower sigmoid and lesions of the rectum. Diseases of these areas are best detected by proctosigmoidoscopy. Small lesions involving the flexures of the colon, unless carefully searched for, may be readily overlooked. Conditions which may contraindicate the performance of a barium enema include a painful anal fissure, a tight rectal stricture in the absence of a colostomy, suspected appendicitis, and any acute illness in which the preparation for and the performance of the enema would prove exhausting to the patient.

Barium-Air Double Contrast Enema. The diagnostic value of the roentgen examination of the colon may be enhanced by the introduction of air after evacuation of most of the barium. The contrast furnished by the air and the barium adhering to the lumen of the bowel reveals the character of the mucosal relief. Small polyps and carcinomas not seen on the usual barium enema films may be demonstrated by this method. Great care and, at times, repeated examinations are necessary in interpreting films, as retained fecal masses may be very confusing and may simulate the appearance of polyps.

Roentgenology of the gastrointestinal tract is not an infallible procedure. Lesions may be missed even by those with great skill and much

experience. Consequently, when the clinical evidence indicates the possibility of serious disease and the roentgen study is negative, the examination should be repeated. The need for multiple or repeat examinations, to discover an early carcinoma of the stomach or a polyp of the colon, is not generally appreciated.

ENDOSCOPIC METHODS OF GASTROENTEROLOGY

The endoscopic procedures of value in diagnosis and sometimes in treatment of gastrointestinal diseases are esophagoscopy, gastroscopy, and

proctosigmoidoscopy. These will be discussed in greater detail later.

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Diseases of the Mouth

Thomas E. Machella

Disturbances of Fluid Balance
Hemopoietic Disorders
Nutritional Disorders
Endocrine and Metabolic Disorders
Metallic Poisoning
Infectious Diseases

Careful inspection of the mouth often yields important information. Aside from the signs of various local diseases of the oral structures, which will not be discussed in this book, significant evidence of systemic disturbances is often encountered. Of the disorders which frequently produce abnormalities in the mouth, the following are especially important:

Disturbances of Fluid Balance. These have been discussed in some detail in Chapter 28. Dryness of the mucous membrane, longitudinal wrinkling of the tongue, and salivation are likely to be indications of water deficit, extracellular fluid deficit, and water excess, respectively.

Hemopoietic Disorders. Pallor of the mucous membranes is a better index of anemia than is pallor of the skin. Atrophy of the papillae of the tongue, with loss of the characteristic dorsal granularity, is observed in most patients with pernicious anemia, and in occasional instances of chronic hypochromic anemia. A bright red, sore

tongue may be seen in pernicious anemia. A deep maroon color, instead of the normal reddish pink of the oral surfaces, is typical of polycythemic disorders. Hemorrhagic spots on the palate and cheeks are common in the more severe thrombocytopenic purpuras, both primary and secondary. Hypertrophy of the gums may be produced by leukemia.

Nutritional Disorders. The tongue is characteristically deep red ("beefy") in patients with pellagra and in many patients with sprue, even when suggestive of riboflavin deficiency, but may be due to other causes such as improperly fitted dentures. "Spongy," swollen, and sometimes bleeding gums are observed in the advanced stages of scurvy.

Endocrine and Metabolic Disorders. Bronze-colored spots of pigmentation on the buccal mucous membrane of the cheeks and palate are suggestive of Addison's disease, although somewhat similar areas may be seen in patients with hemochromatosis. The tongue is likely to be large and pale in persons with myxedema. Macroglossia may also be observed in acromegaly and in primary systemic amyloidosis. Soreness and burning of the tongue, without obvious

change in appearance, may be a manifestation of diabetes.

Metallic Poisoning. Granular black pigmentation of the gums at the points of insertion of the teeth, and diffuse reddening of the oral mucous membranes with profuse salivation are suggestive of intoxication with lead and mercury, respectively.

Infectious Diseases. Numerous alterations of the oral cavity may occur. Among the more characteristic are the "strawberry tongue" of scarlet fever, the Koplik spots of measles, the palatal petechial hemorrhages of bacterial endocarditis, and the heavily coated tremulous tongue of typhoid fever.

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Diseases of the Esophagus

Thomas E. Machella

Esophagoscopy
Tumors of the Esophagus
Benign Stricture of the Esophagus
Cardiospasm
Peptic Ulcer of the Esophagus
Inflammation and Infections of the Esophagus
Diverticulum of the Esophagus
Congenital Short Esophagus with Thoracic Stomach and Esophageal Hiatus Hernias
Miscellaneous Conditions
Diagnosis and Differential Diagnosis of Esophageal Lesions

The esophagus is subject to a large variety of diseases, some of which, if permitted to advance, lead to starvation. The most characteristic symptom of esophageal disease is dysphagia. Another important symptom is pain, often characteristic but at times so variable in its location that the unwary physician fails to think of an esophageal lesion as responsible, does not find its cause in other organs, and labels the patient a psychoneurotic. In general, the area of predilection of esophageal pain overlies the site of the lesion. Lesions of the lower esophagus, however, because of the proximity to the diaphragm and other structures innervated by the sympathetic and parasympathetic nervous systems, may give rise to a more diversified reference of pain. In addition to dysphagia and pain, esophageal lesions may give rise to heartburn, vomiting, hemorrhage, anemia, and manifestations of secondary pulmonary and mediastinal infection.

The suspicion of esophageal disease is aroused by the patient's history. Physical examination is of no aid in the diagnosis, which is established by

the use of roentgenologic and esophagoscopic procedures. Improved methods of surgical technique, developed during recent years, provide a more hopeful prognosis for some of the lesions previously considered inaccessible to surgical treatment.

ESOPHAGOSCOPY

The great value of esophagoscopy lies in the fact that all parts of the esophagus down to the stomach can be seen with the naked eye. Not only does this method of direct visual inspection assist greatly in diagnosis, but also it permits the removal of biopsy specimens and, by the use of special lenses, the photographing of pathologic lesions. It is also of material aid in treatment, as in the use of special forceps for the removal of foreign bodies, the application of special drugs to ulcerated surfaces, and the injection of sclerosing solutions into esophageal varices. However, extreme care and a thorough knowledge of the anatomy and pathology of the tracts with which the esophagoscope must come in contact are necessary, as the danger of perforation is a real one.

Indications for esophagoscopy include any persistent abnormal sensation referable to the esophagus, or any disturbance of its function. The examination should always be preceded by an inspection of the pharynx with a tongue depressor, and of the larynx and pyriform sinuses

with a mirror in order to avoid overlooking pharyngeal or laryngeal disease which may be responsible for the symptoms. It should also be preceded by a fluoroscopic study of swallowing function, lateral films of the cervical and thoracic spine for evidence of spurs or vertebral disease, and a roentgenologic examination of the thoracic organs. Contraindications to esophagoscopy include aneurysm, extensive esophageal varices, spurs on, or active disease of, the cervical vertebrae, and acute necrotic or corrosive esophagitis. In such instances, esophagoscopy should not be performed except for urgent reasons, such as the removal of a foreign body when delay might be detrimental. In acute esophagitis caused by caustics, examination should be deferred until sloughing has ceased and healing of the weakened places has occurred.

TUMORS OF THE ESOPHAGUS

CARCINOMA

Incidence. Carcinoma of the esophagus is the most common cause of dysphagia in older persons, and is primarily a disease of later midlife. It occurs more frequently in males.

Pathology. The most common sites at which the lesion occurs are at the points of anatomic narrowing. Grossly, there are three types: ulcerative, polypoid, and diffuse infiltrative or scirrhous. The most common variety, the ulcerative, rarely causes obstruction until late. The polypoid type produces obstruction early and may undergo necrosis. The diffuse infiltrative variety converts the involved section of the esophagus into a firm, constricted tube, is primarily obstructive, and has less tendency to ulcerate. In all three types extension to the mediastinal structures, pleura, and pericardium may occur. As obstruction develops, the portion of the esophagus above the lesion dilates. Histologically, squamous cell types, which occur more frequently than adenocarcinoma, may be found anywhere in the esophagus, and are frequently poorly differentiated. The adenocarcinomatous type occurs more frequently in the lower third of the esophagus, and at such times presents difficulty in determining whether the tumor is of esophageal or gastric origin.

Metastases from all three gross types of carcinoma occur, usually to the regional lymph nodes. Secondary involvement, by metastasis or

extension, has been found in the nodes and various structures in the chest, mediastinum, neck, and abdomen, and in the spine. The more frequent ulcerative variety tends to metastasize earlier.

Symptoms. Carcinoma of the esophagus brings about clinical symptoms and signs because of obstruction, ulceration, infection, and metastasis. A common first symptom is a vague, often indescribable sensation referable to the neck, throat, or esophagus, which has been present for a variable length of time before troublesome dysphagia occurs. The dysphagia progresses in the average case for a period of six to eight months before medical advice is sought. During that time the dietary has changed from one containing solid foods to one consisting entirely of liquids. Pain is not a common onset symptom. Other less frequent onset manifestations include melena, an enlargement of the cervical or axillary lymph nodes, or the lodgment of a foreign body in the esophagus.

Late symptoms and complications include regurgitation of food and belching as a result of obstruction; hoarseness due to involvement of the larynx or recurrent laryngeal nerve, or to a laryngotracheitis secondary to overflow of material into the larynx; cough due to reflex irritation from the growth, to overflow of esophageal contents into the larynx, or to an esophageal-bronchial fistula; signs of pulmonary suppuration as a result of perforation into the respiratory passages or lung tissue; hematemesis as a result of erosion of an esophageal vessel or perforation into major blood vessels or into the pericardium; and pain as a consequence of infiltration and ulceration of the walls. The pain is frequently mild and burning in type, but may become so severe as to require opiates. It is usually experienced in the midline underlying the site of the carcinoma, and may be referred to the back, face, neck, or abdomen. The average loss of weight at the time medical aid is sought is approximately 25 pounds. Secondary and nutritional anemia occurs, the degree being masked by dehydration. Hiccup is a frequent complaint in patients with lesions of the lower third. Fever may occur as a result of infection. One must be continuously on the alert for cases in which the local symptoms are slight and the dominating picture is caused by metastasis or extension. Metastases from a small ulcerating lesion,

missed during roentgenologic examination of the esophagus, have on occasion been responsible for a large nodular liver.

Treatment. ACTIVE. Surgical removal of the early lesion affords the only chance of cure. In skilled hands any segment of the esophagus can be removed successfully, and in an increasingly high percentage of cases a direct anastomosis can be made between the stomach and the esophagus. Bronchoscopy should be performed in all cases in which surgery is contemplated in order to see if the lesion has extended into the trachea or left main bronchus, in which case the lesion is very likely inoperable. In pedunculated polypoid tumors, surgical diathermy may be employed successfully.

PALLIATIVE. Dilatation of the constricted area may make the patient more comfortable and is worthy of trial when the lesion is located near the cardia. Intubation of the area with a stiff rubber or metal tube inserted through an esophagoscope may be applicable to a small number of patients. Gastrostomy may also, at times, be avoided by bouginage over a string guide and subsistence on liquids and strained foods. Strikingly favorable responses may sometimes be obtained following roentgen therapy alone, or combined with implantation of radon seeds. The results in general, however, have been disappointing. Opiates and other pain-relieving drugs should not be spared in cases proved inoperable.

Prognosis. The prognosis for cure is hopeless except when an early lesion is diagnosed and complete removal is possible. The duration of life after the diagnosis has been established averages six months. Death results from cachexia, secondary infection, hemorrhage, or the effects of metastasis or extension.

SARCOMA

Primary sarcoma, usually a lymphosarcoma or round-cell sarcoma, of the esophagus is rare. Though the lesion is found more frequently in younger individuals, not only the average age incidence but also the sex distribution, sites of occurrence, symptoms, and roentgenologic and endoscopic appearance are quite similar to those of carcinoma. A positive diagnosis is made by microscopic examination of tissue obtained through an esophagoscope. There is less tendency to metastasize than in carcinoma, but the lesions

grow more rapidly. The clinical course in lymphosarcoma may be prolonged by deep x-ray therapy.

BENIGN TUMORS

These are rare and may attain considerable size without producing symptoms, although the pedunculated tumors may cause obstruction when relatively small. Bleeding may occur. The diagnosis may be suspected when roentgenologic study reveals a filling defect, especially in the upper part of the esophagus in a young person. Biopsy and microscopic examination are necessary for proof of the diagnosis. Since the tumors may undergo malignant change, they should be removed when this is technically feasible.

BENIGN STRICTURE OF THE ESOPHAGUS

Etiology. The most common cause of benign stricture of the esophagus is the swallowing of caustic or corrosive agents. Other causes include scarring associated with the healing of peptic ulcer, injury to the esophagus following swallowing of a foreign body, and esophagitis complicating certain infectious diseases. The most common sites of strictures are at the points of anatomic narrowing.

Symptoms. The main symptom is dysphagia, the severity of which depends upon the extent of the injury to the esophagus and the completeness of the obstruction. The symptoms, present during the acute stage of inflammation and ulceration, may subside within a week or two, but recur in 6 to 10 weeks and become progressively worse with contraction of the scar. As the obstruction becomes more complete, difficulty is encountered in swallowing fluids and even saliva, and at such times evidences of malnutrition and dehydration appear. Pain is seldom present after the initial trauma due to the irritant has healed.

Treatment. The immediate treatment in many instances should be directed toward improvement of the nutritional status of the patient and the correction of dehydration and acid-base imbalance. Fluid, electrolytes, proteins, amino acids, dextrose, vitamins, and blood can be administered parenterally.

Active treatment of the stenotic lesion consists of gradual dilatation by peroral esophagoscopic bouginage or by retrograde bouginage over a string after a preliminary gastrostomy.

When bouginage is not feasible, some form of surgery will be necessary.

CARDIOSPASM

The term *cardiospasm* has become attached to a syndrome, the main symptom of which is dysphagia, and the basis, a functional constriction at the lower end of the esophagus with dilatation above. Synonyms include achalasia of the cardia, phrenospasm, functional hiatal stenosis, spasm of the esophagus, preventriculosis, and megaesophagus. The incidence is about equally divided between the sexes, and is greater in individuals of the asthenic habitus. The most frequent age of onset of symptoms is in the fourth decade.

Etiology. The exact mechanism by which cardiospasm occurs has not been established to the satisfaction of all. There would appear to be a functional derangement in tonus of the involved segment secondary to an imbalance of the sympathetic-parasympathetic innervation. Predisposing factors include emotional disturbances, organic disease of the vagus, irritation of the esophagus by adhesions or kinking, organic disease of the stomach near the cardia, and involvement of Auerbach's plexus by inflammation or degeneration.

Pathology. The esophagus is an elongated and enormously dilated smooth sac above a point of constriction through which a finger may be thrust with surprisingly little effort. The esophageal dilatation terminates at a point where the lumen normally narrows, but at this point there is no sign of a hypertrophied sphincter. In some instances, when the esophagus is greatly dilated, the lower portion of the sac is spread out over the diaphragm so that a part of it sometimes falls below the level of the opening into the stomach (fig. 227). Such a sacculation tends to close the opening by the pressure of its contents, and at times makes mechanical dilatation of the cardia difficult or impossible. The walls of the dilated esophagus are in a state of chronic inflammation as a result of stasis, fermentation of food, and infection.

Serial sections of the cardia removed from patients who have died of cardiospasm may reveal a more or less complete absence of ganglion cells between muscular coats, but this finding is not encountered in all cases.

Symptoms. The earliest onset symptom is usually a subjective feeling of impediment to the free passage of food down the esophagus. As a rule there is more difficulty with solids than with liquids, but this is not true in all cases. The dysphagia may be associated with a slight pain

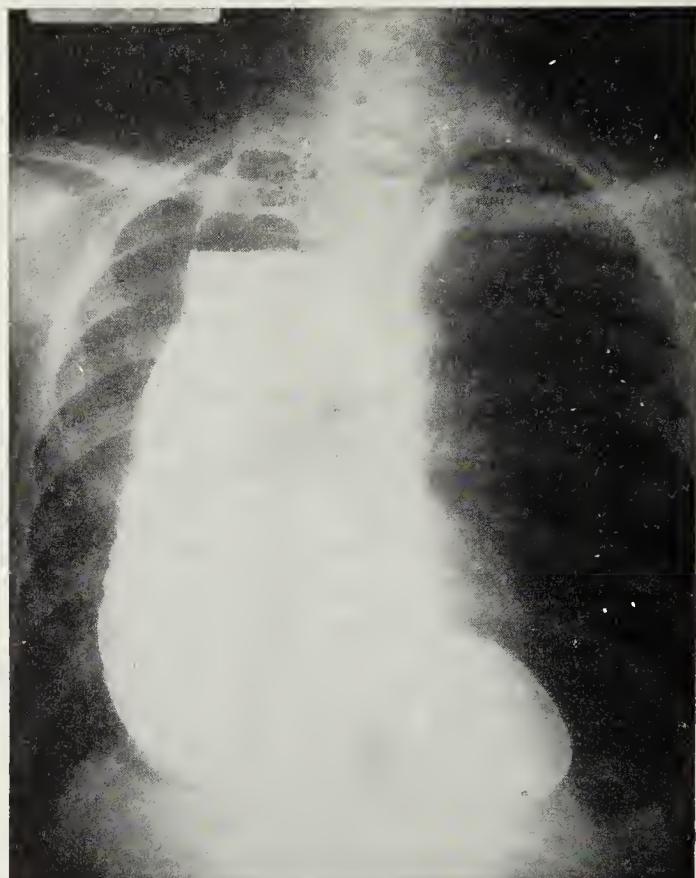


FIG. 227. Roentgenologic appearance of megaesophagus due to cardiospasm. The lower portion of the elongated esophagus lies on the diaphragm. The esophagus contains 2700 ml. of barium suspension.

or sensation of burning or pressure at or near the episternal notch; in some cases considerable pain is experienced. It may radiate to the back, neck, ears, or lower jaw. An episode of substernal pain and dysphagia may be precipitated by the ingestion of a large quantity of food or cold liquid, or by an emotional upset.

At first, attacks of dysphagia and pain may occur only occasionally. Subsequently, the attacks recur more frequently and become more severe. Finally, substernal fullness or discomfort is constantly experienced. At such a time foul odors, resulting from fermentation and decomposition of food in the dilated esophagus, are noted. In the recumbent position, esophageal content may spill over into the respiratory passages. The pressure of the dilated esophagus on the trachea and respiratory passages may cause cough and dyspnea.

When the esophagus has become enormously dilated and retentive, the patient manifests evidences of malnutrition, such as weight loss, anemia, and the stigmas of vitamin deficiency.

Complications. Complications of cardiospasm include esophagitis, which is usually present in cases with long-standing stasis; ulceration; erosions; diverticulum in association with megaesophagus; mediastinitis; aspiration pneumonia; lung abscess; spontaneous pneumothorax; and esophageal bronchial fistula. The wall of a dilated esophagus may be so thin that it is ruptured readily or pierced by instruments and is capable, upon very moderate trauma, of transmitting infection into the mediastinum.

Treatment. Psychotherapy should be employed in those patients whose symptoms are precipitated by emotional disturbances. If psychotherapeutic measures fail and there is no marked esophageal dilatation and stasis, a satisfactory response will usually follow one or more peroral dilatations of the constricted segment. Antispasmodic drugs of the atropine group have been, as a rule, ineffective.

In more advanced cases the nutritional status of the patient very frequently requires improvement before any active specific therapeutic measures can be undertaken. This may be accomplished by parenteral means or by the introduction of a rubber tube guided over a previously passed string. In such cases, if all peroral attempts at dilatation fail after nutrition has been improved and existing deficiencies corrected, a preliminary gastrotomy with retrograde dilatation of the constriction may be performed. If the esophagus is tremendously dilated and elongated so that dilatation is not possible (fig. 227), the constricted segment may be excised and the lower end of the esophagus anastomosed to the stomach.

PEPTIC ULCER OF THE ESOPHAGUS

For a discussion of peptic ulcer of the esophagus, see Chapter 259.

INFLAMMATION AND INFECTIONS OF THE ESOPHAGUS

Acute Esophagitis. Acute esophagitis may be produced by the swallowing of irritating or corrosive agents, by frequent vomiting, and by reflux of acid gastric juice in the supine position

in individuals who have a relaxed cardia. The chief symptoms are pain, hematemesis, and dysphagia.

Chronic Esophagitis. Chronic esophagitis may be caused by lesions in or outside the esophagus which produce stasis of food and secretions within its lumen, and by residual damage from repeated episodes of acute esophagitis. The symptoms are similar to those of acute esophagitis. Roentgenologic examination, as in acute esophagitis, may reveal intermittent diffuse spasm of the involved portion. If the inflammation has been present for a prolonged period of time, a diffuse fibrous stricture and a dilated proximal esophagus may be demonstrated.

Specific Infections of the Esophagus. Tuberculosis, syphilis, and fungous infections of the esophagus are rare. The diagnosis is established by bacteriologic and/or microscopic examination of material or tissue recovered through an esophagoscope.

Treatment. Treatment of the above conditions consists of special dietary measures aimed at providing esophageal rest. Stricture may require dilatation, while complete obstruction may require gastrostomy. When the lesion is caused by a specific agent, treatment consists of general and specific measures employed in the therapy of such infection elsewhere in the body.

DIVERTICULUM OF THE ESOPHAGUS

There are two main types of esophageal diverticula—pulsion and traction. The pulsion type occurs on the weakly supported posterior aspect of the hypopharynx, which is continuously subjected to pressure from food and esophageal intraluminal pressure. The traction type, a true diverticulum, develops as a result of traction exerted by the healing of inflamed lymph nodes adherent to the esophagus or by disease of the vertebrae. It is the most common type and occurs at the level of the bifurcation of the trachea or near the left main bronchus. Occasionally, when an obstructing lesion is located distal to such a diverticulum, the increased intraesophageal pressure may cause its enlargement; such a diverticulum is referred to as a pulsion-traction type.

The pulsion type of diverticulum more commonly causes symptoms. They are directly related to the size of the sac and referable to the act of swallowing. The most common early com-

plaint is a sensation of irritation in the throat. Eating and swallowing are frequently associated with gurgling noises. Regurgitation of food becomes disturbing and the patient loses weight from malnutrition. Pain is seldom produced. The breath may have a foul odor. Occasionally, a soft tissue mass may be detected in the left side of the neck. In advanced cases the enlarging sac may descend into the mediastinum, angulate the esophagus, and give rise to obstructive symptoms. Traction diverticulum usually is asymptomatic, but may give rise to substernal distress, dysphagia, or hemorrhage. In rare instances it may perforate into surrounding structures.

The treatment of the pulsion type of diverticulum requires surgery. The traction type rarely requires treatment.

CONGENITAL SHORT ESOPHAGUS WITH THORACIC STOMACH AND ESOPHAGEAL HIATUS HERNIAS

One of the commonest conditions overlooked in patients admitted to a clinic specifically for gastrointestinal complaints is herniation of a portion of the stomach through the esophageal hiatus. One of the main reasons for this is that the presenting symptoms may be so diversified and may so resemble those due to diseases of other organs and systems that the unwary physician fails to think of a hiatus hernia as responsible.

Three types of hiatus hernia are differentiated anatomically. They are: (1) congenital short esophagus with a portion or all of the stomach in the thorax; (2) paraesophageal hiatus hernia in which a portion of the stomach herniates through the hiatus but the esophagus is of normal length and occupies a normal position; and (3) esophagogastric hiatus hernia in which the esophagus is shortened and its lower end, plus a portion of the stomach, herniates through the hiatus. In general, the three types may cause similar clinical manifestations which arise as a result of (1) incarceration of the herniated portion; (2) congestion and erosion of esophageal or gastric mucosa in the constricted portion; or (3) obstruction to passage of material into the stomach. Predisposing factors in the development of the noncongenital varieties are conditions which lead to an increase in intra-abdominal pressure such as severe physical

strain or trauma, pregnancy, chronic constipation, and prolonged coughing or vomiting.

Symptoms. The symptoms caused by hiatus hernia may be so varied that they are best grouped into various categories or syndromes, depending on the nature of the presenting complaints.

GROUP 1. PAIN. The most common symptom caused by a symptomatic hiatus hernia is pain. When due to constriction or incarceration of the herniated portion, it may vary in character from a sensation of discomfort and fullness to a sharp colic, and is experienced in the substernal area, epigastrium, right upper quadrant, or precordium, or it may be referred to either shoulder and arm. More characteristic than the site of the pain is its association with certain definite activities such as eating, assuming the recumbent position, or engaging in activities which increase intra-abdominal pressure, such as bending over, straining at stool, or lifting heavy objects. Pain due to reflux of acid gastric content onto a congested or ulcerated gastric or esophageal mucosa may be sharp, but is usually burning or gnawing in type and is relieved by milk or antacids or by assuming the prone or erect positions which prevent reflux into the esophagus. The variation in the sites to which the pain may be referred is responsible for suspecting disease of other organs such as the heart, stomach, gallbladder, or pancreas.

GROUP 2. DYSPHAGIA. A certain proportion of hiatus hernia patients present themselves primarily because of dysphagia for solid foods.

GROUP 3. GROSS GASTROINTESTINAL HEMORRHAGE. Hematemesis and melena may occur as a result of bleeding from a congested or ulcerated esophageal or gastric mucosa. Failure to look for and detect a hiatus hernia after bleeding has ceased accounts for a certain percentage of cases which comprise the group "gastrointestinal hemorrhage of undetermined origin."

GROUP 4. UNEXPLAINED ANEMIA. Not infrequently the presenting symptoms of hiatus hernia may be those of an anemia as a result of chronic, low-grade blood loss from a congested or ulcerated mucosa of the esophagus or stomach.

GROUP 5. CORONARY ARTERY DISEASE SYNDROME. The pain of hiatus hernia may be referred to the same dermatomes as coronary artery pain, and may be associated with palpitation and tachycardia. The identifying characteristics

of hiatus hernia pain have been discussed in Group 1.

It should be kept in mind that hiatus hernia and coronary artery disease may coexist, and at times great difficulty is experienced in ascribing the symptoms properly.

GROUP 6. PULMONARY SYNDROME. Productive cough, cyanosis, and dyspnea, especially after meals, may be the presenting symptom when most or all of the stomach lies in the thorax.

GROUP 7. MIXED SYMPTOMS. Some patients with hiatus hernia complain of symptoms referable to the gastrointestinal tract, such as pain, belching, nausea, vomiting, and heartburn, along with symptoms due to anemia or referable to the cardiorespiratory system.

GROUP 8. ASYMPTOMATIC GROUP. In a certain proportion of patients the hiatus hernia is asymptomatic and is discovered as an incidental finding during roentgen examination for other purposes.

Treatment. Most patients with a hiatus hernia will be benefited by conservative management. The regimen should include a dietary of bland foods frequently administered and free of gas-forming items, reduction in weight, the avoidance of factors which lead to an increase in intraabdominal pressure, and sleeping in a semi-Fowler position. If esophagitis or ulceration is present, a peptic ulcer regimen should be instituted. A strictured esophagogastric junction may require dilatation. Surgery should not be contemplated until conservative measures have been tried and have failed. The exact type of hernia must be clearly established preoperatively, as the congenital short esophagus with thoracic stomach may not be amenable to surgery.

MISCELLANEOUS CONDITIONS

FOREIGN BODIES IN THE ESOPHAGUS

The lodgment of a foreign body usually produces discomfort or obstruction to the passage of solid food. Perforation may give rise to manifestations of mediastinitis or to subcutaneous emphysema of the neck.

FISTULA OF THE ESOPHAGUS

Fistula of the esophagus may lead into the trachea or one of the large bronchi, the lung, the pleural or pericardial cavity, or the mediastinum.

The lesion is rare and usually represents a complication of some other esophageal lesion, especially that of an ulcerating carcinoma. The possibility of a fistula should be entertained when esophageal symptoms are followed by cough and expectoration of food. Treatment—conservative or surgical—depends upon its size, the underlying etiologic process, and the symptoms produced.

ESOPHAGEAL VARICES

Dilatation of the submucosal veins in the lower end of the esophagus occurs in association with portal hypertension secondary to intrahepatic or extrahepatic portal vein obstruction. The most frequent associated conditions are portal cirrhosis, Banti's syndrome, and portal vein thrombosis. Symptoms ascribable to the varicosities are due to loss of blood, and they depend on the amount of and the acuteness of the bleeding. They vary from anemia and occult blood in the stools in low-grade leaks, to massive hematemesis, melena, and collapse as a result of shock due to blood loss.

Treatment includes injection of the dilated veins with sclerosing solutions, splenectomy, ligation of the coronary veins, establishment of a fistula between the portal vein and the inferior vena cava, or anastomosis of the splenic to the renal vein. One of the latter two procedures is preferable in patients with portal hypertension. Active bleeding from esophageal varices may be controlled temporarily by air insufflation of a balloon attached to one lumen of a double-lumen Miller-Abbott tube. The other lumen can be used for introduction of fluids and nutriments into the stomach while intraesophageal tamponade is being exerted.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF ESOPHAGEAL LESIONS

In this section only the commonest clinical picture characteristic of certain esophageal diseases will be described. Variations from the characteristic clinical picture do occur, and are described in the sections dealing with individual diseases. It should be appreciated that a final diagnosis depends on roentgenologic and esophagoscopy measures.

Carcinoma. A history of progressive dysphagia for solids in an elderly individual, more often a male, justifies a tentative diagnosis of carcinoma.

Roentgen examination, particularly fluoroscopy, will usually reveal an irregular subtraction defect associated with narrowing of the lumen at the site and slight dilatation proximally. The most conclusive diagnostic procedure is esophagoscopy with removal of a specimen of tissue for microscopic examination. By such means, sarcoma and benign tumors may also be differentiated. One should not be satisfied with one or two negative biopsies. Repeated attempts may be necessary before satisfactory tissue is obtained. When esophagoscopy is not feasible, examination of suitably stained sediment of washings may reveal the presence of malignant cells, especially when the carcinoma is of the ulcerative or polypoid variety.

Cardiospasm. A history of episodes of dysphagia and substernal discomfort precipitated by the ingestion of a large amount of food or of cold liquids, or by an emotional disturbance, at first occurring only occasionally but subsequently more frequently and with increasing severity in middle-aged, ptotic individuals, suggests cardiospasm as the most likely diagnosis. The roentgenologic demonstration of a smooth, regular, spindle-shaped constriction at the cardia with considerable uniform dilatation of the proximal esophagus should establish the diagnosis. Occasionally, esophagoscopy is required to rule out other conditions such as benign stricture, carcinoma, and involvement by scleroderma.

Stricture. The development of dysphagia for solids six to eight weeks after the subsidence of symptoms of acute esophagitis should suggest the diagnosis of stricture. The roentgenologic appearance varies with the degree of contraction and narrowing. Usually there is a central narrowing of the lumen with dilatation above. Stricture in the lower third may produce a defect resembling a carcinoma, especially if food particles are retained. There may be more than one narrowed area if a corrosive agent has been swallowed. Esophagoscopy is essential for a definite diagnosis.

Foreign Body. The sudden onset of discomfort beneath the sternum and of dysphagia for solids, usually with a history of having swallowed a specific object, suggests the lodgment of a foreign body in the esophagus. Roentgenologic examination should demonstrate a radiopaque foreign body, while nonopaque objects may be revealed by the use of opaque mediums.

Congenital Short Esophagus with Thoracic Stomach. This anomaly may be encountered at all ages, and rarely gives rise to symptoms directly referable to the esophagus unless esophagitis or peptic ulceration at the esophagogastric junction are present. At such time, pain beneath the sternum while the patient is in the recumbent position and which is relieved by lying prone or by assuming an erect or semi-Fowler position is characteristic. Hemorrhage may also occur as a result of congestion or ulceration in the constricted segment. Roentgenologic examination with the patient in supine or Trendelenburg position reveals a nontortuous, normally situated esophagus which fails to reach the diaphragm and opens into the cardia of the stomach which is also located in the thorax. The characteristic longitudinal gastric rugal markings are seen above the level of the diaphragm, at which point the stomach is constricted. Esophagoscopy reveals supradiaphragmatic gastric mucosa.

Paraesophageal Hiatus Hernias. The occurrence of pain in the epigastrum or lower sternal region in a middle-aged, overweight person, during or soon after eating, when the recumbent position is assumed or when activities are performed which increase intraabdominal pressure, suggest the presence of a sliding or intermittent type of hiatal hernia. Fluoroscopic examination in the Trendelenburg position, with the patient straining, will reveal barium in the herniated portion of the stomach above the diaphragm. Cessation of the act of straining is followed by a descent of the herniated portion into the abdomen. When the hernia is fixed above the diaphragm, there is usually difficulty in getting the barium to enter it and, commonly, the abdominal portion of the esophagus cannot be identified in either the erect or the recumbent position. Esophagoscopy should be performed in all patients in whom roentgenologic evidence is inconclusive. It may reveal congestion or ulceration of the esophageal mucosa as well as supradia-phragmatic gastric mucosa.

Esophageal Diverticulum. The occurrence of gurgling noises in association with eating and swallowing, fetor oris, regurgitation of undigested food, cough, and the absence of pain suggest a diagnosis of the pulsion type of esophageal diverticulum. Roentgenologic examination usually reveals a large, symmetric, smooth sac with a fluid level. A thin barium meal, after filling the

pouch, overflows into the esophagus. In some instances evacuation of food and retained secretion may be necessary before a satisfactory roentgenologic study can be made. Traction diverticula rarely cause symptoms and usually are discovered during roentgenologic examination for other purposes. They appear as sharply defined, regular outpouchings which fill and empty readily. The opening from the esophagus can be localized by esophagoscopy.

Fistula. The complaints of cough and expectoration of food, following the onset of dysphagia, characterize a fistula between the esophagus and respiratory passages. Fluoroscopic examination will reveal the stream of barium flowing into the trachea or bronchus.

Esophageal Varices. Esophageal varices are usually asymptomatic unless an esophagitis co-exists or unless they bleed. Their presence should always be searched for in diseases associated with portal hypertension. Roentgenologic demonstra-

tion of esophageal varices is best made with the patient straining in the recumbent position, using thin and thick barium mixtures. The characteristic appearance is a moth-eaten, beaded, or wormy irregularity of the mucosa that is caused by barium retained in the crevices between the varices. A negative roentgenologic examination does not exclude their presence.

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Diseases of the Stomach

Thomas E. Machella

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INTRODUCTION

In order to explain the cause of symptoms ascribed to the stomach, one not only must conduct a complete systemic symptom review and a thorough physical examination but also must have access to roentgenologic, gastroscopic, and other laboratory procedures. This is so because symptoms referable to the stomach may be produced by diseases of other organs as well as by motor and secretory disturbances due to emotional and psychogenic influences. Physical ex-

amination is of only limited value in diagnosis because a large part of the stomach lies beneath the costal margin (while the patient is in the supine position) and, consequently, is inaccessible to palpation. The proximity of the pancreas, liver, colon, and other structures to the stomach is not infrequently responsible for incorrectly ascribing a mass or tenderness to a gastric origin. Consequently, the diagnosis of gastric disease depends largely on roentgenologic examination supplemented, when necessary, by gastroscopy. At times, however, even these and other laboratory procedures are of no help and laparotomy must be performed to establish a precise diagnosis.

Most physicians appreciate the fact that the full stomach occupies a lower position in the abdomen than the empty one and that the stomach,

empty or full, occupies a lower position in the abdomen in the erect than in the supine position. What is generally not appreciated is that in the supine position the most dependent portion of the stomach is not the greater curvature but the posterior wall of the fundus and the body. This means that in this position, a common one assumed by sick patients, ingested materials will pool in the fundus which occupies the concavity to the left of the vertebral column, and that such material will not leave the stomach unless the individual turns on his right side or on his abdomen, or assumes a semi-Fowler position. The failure to take this fact into consideration in debilitated patients may result in anorexia, nausea, gastric fullness, regurgitation into the esophagus, and a failure to obtain the expected effect of orally administered drugs.

GASTROSCOPY

Direct visual inspection of the interior of the stomach by means of a gastroscope furnishes an indispensable aid in the diagnosis of gastric disease. The examination is essential for the diagnosis of various types of chronic gastritis wherein even the best x-ray relief technics may be of no aid. Other indications for gastroscopy include the differentiation of benign from malignant ulcers, unexplained gastrointestinal bleeding, the detection of small polyps in pernicious anemia, the identification of the nature of nonopaque foreign bodies, and the detection of gastrojejunal ulcer not visualized roentgenologically. In such cases the procedure is also of value in following the response to therapy. Contraindications to gastroscopy include dysphagia, extensive esophageal varices, severe pulmonary or mediastinal disease, peptic ulcer of the esophagus, aortic aneurysm, suspected corrosive and phlegmonous gastritis, perforating peptic ulcer, intraabdominal inflammatory disease, and marked scoliosis and kyphosis. Relative contraindications, in which it is necessary to balance the severity of the condition against the indication for gastroscopy, include angina pectoris, cardiac decompensation, various psychoses, and the presence of spurs on the anterior surface of the cervical spine. Gastroscopy should always be preceded by roentgenologic examination of the chest, esophagus, and stomach.

It should be realized that gastroscopy has its

limitations. The interpretation of the gastroscopic appearance is dependent largely on the skill and experience of the endoscopist. Furthermore, there are certain areas of the stomach which cannot be seen through the gastroscope. The "blind" areas include: a small strip of the posterior wall in contact with the instrument during the whole of the examination; the lower pole of the stomach, whether it is formed by the greater curvature or by the posterior wall; the part of the cardia immediately adjacent to the objective, especially at the side of the lesser curvature; and the portion of the lesser curvature of the antrum beyond the angulus.

CARCINOMA OF THE STOMACH

Carcinoma of the stomach ranks high among the common causes of death. It occurs at any age, but is primarily a disease of adult life. The disease is encountered among all races, in all parts of the world, and is more common in males.

Etiology. The cause of gastric cancer is unknown. Its incidence is unrelated to position in life, occupation, and eating, drinking, and smoking habits or abdominal trauma. It is very doubtful that heredity is a factor, although susceptibility to malignancy would appear to be inherited in a few families.

The role of alleged precancerous lesions of the stomach is not universally agreed upon. Of these, gastric ulcer, atrophic gastritis, and benign polyp are regarded by some as premalignant lesions. The relationship of benign chronic ulcer to carcinoma, if any, is difficult to prove; a few isolated cases have been suggestive. The role of chronic atrophic gastritis as a premalignant lesion also is not settled. In some cases the transition of small areas of hyperplasia associated with gastritis to papilloma and to carcinoma has been strongly suspected. The question as to whether there is a higher incidence of gastric carcinoma in patients with pernicious anemia than in patients of the same age group without pernicious anemia has not been answered to the satisfaction of all. A certain proportion of benign gastric polyps undoubtedly undergo malignant degeneration. Malignant change has also been demonstrated in association with diffuse polyposis of the stomach.

Pathology. The most common sites of gastric cancer are the antrum and pyloric canal, where approximately 50 per cent of all gastric neoplasms originate. The next most commonly in-

volved site is the lesser curvature (25 per cent). The greater curvature and the cardiac end are each involved in approximately 8 per cent of gastric cancers, with the remainder occurring upon the anterior and posterior walls of the body. Four macroscopic types occur, according to Bormann's classification.

TYPE I. (Less than 5 per cent.) A polypoid, sharply circumscribed, slowly growing tumor protruding into the gastric lumen.

TYPE II. (15 to 20 per cent.) An ulcer surrounded by a raised border. Infiltration is uncommon and metastasis late.

TYPE III. (About 15 per cent.) An ulcer with a definite border on one side only. The wall of the stomach is infiltrated and metastases occur early.

TYPE IV. (About 60 per cent.) A thickened, indurated, diffuse, infiltrating lesion of the wall of the stomach often without grossly detectable borders. This type includes the scirrhous carcinoma and the spheroid cell carcinoma. The scirrhous carcinoma may transform the entire stomach into a thick-walled, inflexible structure, the lumen of which may be contracted. This appearance has been called "leather-bottle" stomach and "linitis plastica." The prognosis of type IV after resection is poor. Metastases tend to occur early.

Symptoms. The onset symptoms are vague and indefinable. The disease progresses so stealthily that its presence is neither suspected nor recognized until it is well advanced. In general, symptoms have been present 12 to 18 months before the diagnosis is made. The course is progressive, though it may be slow. The usual story is that of an individual over the age of 40, previously in good health, who experiences some anorexia and consequent loss of weight. He does not become alarmed about his mild epigastric distress for weeks or months, but in a year, when the symptoms have progressed or changed character and he has lost 10 to 12 pounds, he seeks medical advice. At this time the symptoms depend on the type and location of the lesion, and the presence and location of metastases.

Epigastric distress, if present, is variable in character. It may consist of merely a fullness or discomfort after eating or of a gnawing or aching occurring a short time after meals, which may be relieved by further ingestion of food or by vomiting. Though the distress may be indis-

tinguishable from that of peptic ulcer, it is different from it in the majority of instances, and is not completely relieved by alkali, food, or vomiting. Nausea and vomiting may occur regardless of the location of the lesion, but more frequently when the gastric outlet is obstructed. The vomitus may or may not contain food, bile, or blood. Hematemesis or melena may be first symptoms, but can occur at any time.

Anemia is frequently present and may be of normocytic or, if there is chronic blood loss, hypochromic microcytic type. There may be a low-grade fever. A higher degree of fever suggests the presence of extensive metastasis to the liver or an abscess as a result of a low-grade perforation.

Physical Findings. Physical examination is frequently negative in the course of the disease. There may be pallor, evidences of loss of weight, a mass in the epigastrium, and nodular enlargement of the liver. Much less frequently there is a firm, hard node in the left supraclavicular area (Ewald's node, Virchow's node, sentinel node), and evidence of metastases to both ovaries (Krukenberg's tumor), to the rectal shelf (Blumer's shelf), to the skin, or to the navel.

Laboratory Examination. The blood count may disclose evidence of normocytic or hypochromic microcytic anemia, and there is present occult blood in the stool or gastric content in a large percentage of cases at one time or another. Free acid is present in the gastric content in about 40 per cent of the cases, and is more apt to be present in lesions of the distal than of the proximal third. Characteristic malignant cell nuclei, when gastric sediment is stained by Papanicolaou's method, may be found when the more cellular types of lesions are present. The electrogastrogram may reveal a pattern characteristic of malignancy.

Roentgenologic Examination. The roentgenologic examination, though not infallible, is probably the most valuable method of determining the presence of gastric carcinoma. The roentgenologic appearance depends on the type of lesion present. The polypoid tumor growing into the lumen is seen as a defect subtracting from the normal outline of the stomach filled with barium, or as a sharply outlined nonopaque area when pressure is made over the site. The ulcer type is detected by the presence of barium in a crater, or by a crater located on a subtrac-

tion defect, or by a crater surrounded by a translucent halo (Carman's meniscus sign). The differentiating roentgenologic signs of benign and malignant ulcer are discussed in Chapter 259. The scirrhous type produces a constant rigid, sometimes ragged, alteration in the contour of the involved portion of the stomach. The normal mucosal pattern is almost invariably destroyed or distorted, as may be seen by mucosal relief studies using small amounts of barium and graded degrees of compression. In the antrum both curvatures are usually involved and the lumen narrowed by infiltration of the wall to give an annular defect. Peristalsis does not pass through the involved portion. The diffusely lesion may give rise to a typical small, contracted stomach sometimes referred to as the "leather-bottle" stomach (fig. 228). Occasionally, a py-

absent or vague and indefinite, one must accept the fact that there is no clinical pattern by which the presence of an early lesion can be suspected. It is not practical to submit every person over the age of 40 to a roentgenologic examination of the stomach, although, if any progress is to be made in arriving at an early diagnosis, any patient at or over the age of 40 who develops indigestion which cannot be otherwise accounted for will have to undergo roentgenologic examination of the stomach and, if necessary, gastroscopy. Further inroad into the early diagnosis of gastric cancer can be made by regarding the so-called precancerous lesions with suspicion and treating them accordingly. The attitude toward gastric ulcer is outlined in a discussion of that subject in Chapter 259. Gastric polyps should be removed as soon as their presence has been determined. Patients with chronic atrophic gastritis should be subjected to gastroscopic and roentgenologic examinations at regular, frequent intervals.

Complications. The complications of gastric carcinoma include perforation, hemorrhage, obstruction, and metastasis. Perforation, rarely acute, may occur into the pancreas, less frequently into the duodenum, jejunum, or colon, late in the course. Roentgenologic evidence of fixation of the involved portion of the stomach wall or even of fistulous tracts between the stomach and other viscera may be found. While oozing and minor hemorrhages from gastric carcinoma are common, as evidenced by presence of occult blood in the stools or of "coffee-ground" appearance of vomitus, massive hemorrhage occurs much less frequently than it does in peptic ulcer. Obstruction occurs when the lesion surrounds either gastric orifice. It occurs more frequently with prepyloric lesions. Obstruction of the lower end of the esophagus gives rise to dysphagia.

Metastases may occur to the omentum, peritoneum, liver, left (occasionally right) supraclavicular nodes, rectal shelf, ovaries, umbilicus, bones, inguinal nodes, lungs, adrenals, skin, or brain.

Treatment. The ideal treatment of gastric carcinoma is complete surgical removal of the early lesion. Laparotomy, with the possibility of extensive resection in mind, should be performed in all cases in which the diagnosis has been made, except in the face of unequivocal evidence of

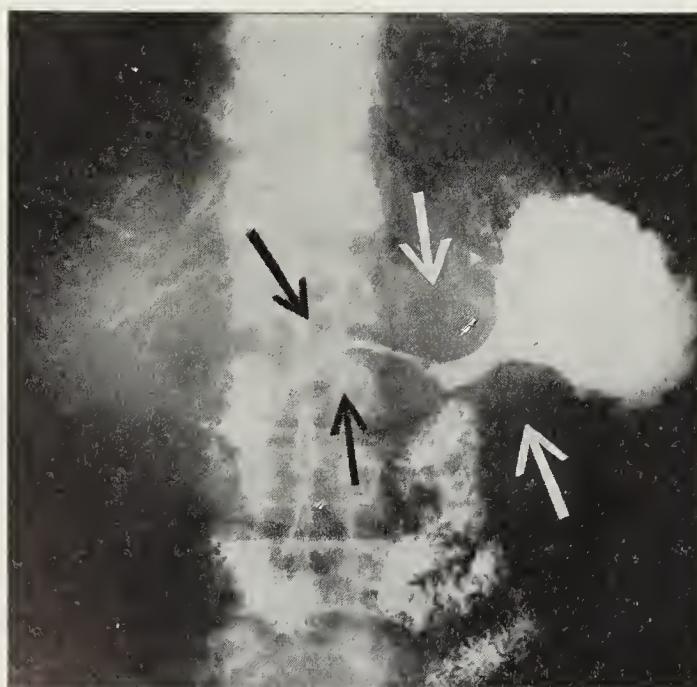


FIG. 228. Roentgenologic appearance of funnel-shaped deformity of the stomach caused by extensive scirrhous carcinoma. The lumen of the distal two-thirds of the stomach has been narrowed by the lesion (arrows).

carcinoma may completely obstruct the outlet of the stomach and not be detectable. The finding is that of a dilated stomach with hyperactive peristalsis. A lesion of the fundus of the stomach may be readily overlooked because of the inaccessibility of the area to palpation.

Gastroscopy is of value in providing additional evidence, the combination of gastroscopy and roentgenograms giving a much higher degree of accuracy than either alone.

Early Diagnosis. In view of the fact that symptoms of early carcinoma of the stomach are

metastases to the peritoneum, bone marrow, and liver. Some amazingly prolonged survivals have been observed following resection, despite the presence of metastases to the liver.

Medical therapy consists of symptomatic and supportive management of the patient with an inoperable lesion or the patient in whom the lesion has been resected. A soft, bland diet is usually tolerated by patients with inoperable lesions. Except in unusual instances, there should be no restrictions on palatable or nutritious foods. Sedatives, analgesics, hypnotics, and narcotics should be used freely but wisely. The diagnosis should not be disclosed to the patient. Not even the most mentally rugged can maintain hope in the knowledge of an inoperable cancer. A stable, responsible member of the family, however, should be informed.

The question of whether roentgen therapy is worth while is a difficult one to answer. No satisfactory proof exists that it has ever cured a case of gastric carcinoma, and the evidence that survival may be prolonged is but suggestive. The anorexia, nausea, and vomiting induced by intensive irradiation appear to accelerate the downward course of the patient.

After resection, medical management should include a nutritious, well-balanced, easily digested diet administered in small amounts, eaten at frequent intervals. The diet should be supplemented with iron and vitamins.

Prognosis. The prognosis depends on the type and location of the lesion, and the tendency to metastasize and infiltrate. The location of the lesion is of importance for several reasons. The more distal the lesion, if it has not infiltrated into contiguous organs, the more readily it is resectable. Pyloric growths produce obstructive symptoms earlier and are more easily resected. Lesions on the greater curvature are more readily resectable than those on the lesser curvature because they are accessible and they tend to involve regional lymph nodes at a later stage.

The duration of life after resection of gastric carcinoma depends on the degree of completeness of the resection and whether or not metastasis to vital organs has occurred. It averages one to two years longer than in those cases treated palliatively. Isolated cases have lived as long as 22 years. Death usually results from inanition as a result of anorexia and vomiting, but may also

occur as a result of perforation or massive hemorrhage.

SARCOMA OF THE STOMACH

The chief differences in the clinical pattern of sarcoma as compared to carcinoma of the stomach are: (1) the occurrence in younger patients; (2) the necessity for biopsy in order that diagnosis may be established; and (3) the greater radiosensitivity. The latter feature is especially important in the case of lymphosarcoma.

BENIGN TUMORS OF THE STOMACH

Several types occur, those of epithelial origin being the more common. The presence of a tumor is established by roentgenologic and gastroscopic methods, but the benign nature of the tumor can only be proved by microscopic examination. Clinical manifestations are usually absent, but hemorrhage, pyloric obstruction, or malignant transformation may occur.

PEPTIC ULCER OF THE STOMACH

See Chapter 259 for a discussion of peptic ulcer of the stomach.

GASTRITIS

Inflammation of the stomach may be acute or chronic, and may be caused by nonspecific substances or specific agents.

ACUTE GASTRITIS

These disorders may be classified into four main groups:

1. Acute Simple Exogenous Gastritis. Alcohol, various drugs, and bacterial toxins (especially those of the *staphylococcus*) constitute the most important etiologic agents. The chief symptoms are anorexia, nausea, and vomiting. The diagnosis is made from the occurrence of these symptoms following the ingestion of one of these irritant substances. Treatment consists of withholding food and administering fluids parenterally when necessary.

2. Acute Corrosive Gastritis. This serious disorder is induced by the ingestion of such highly irritative substances as lye, strong acids, and salts of arsenic or mercury. Profuse vomiting with hematemesis is common. Severe epigastric pains may occur and are commonly associated with circulatory collapse. Death may occur from this or from peritonitis resulting from perfora-

tion. Management consists of gastric lavage and the use of appropriate antidotes (see Chapter 92). The maintenance of proper fluid balance (see Chapter 28) and observation for evidence of peritonitis are particularly important.

3. Acute Infectious Gastritis. This occurs in the course of almost any infectious disease and is manifested by anorexia and, less frequently, by vomiting.

4. Acute Suppurative Gastritis. This may result from the common pyogenic organisms and should be managed by antibiotic therapy and surgical intervention.

CHRONIC NONSPECIFIC GASTRITIS

Study of the mucosa of the stomach by the gastroscopic method has revealed three types of chronic inflammation. One of these (chronic atrophic gastritis) is associated with a grayish discoloration and thinning of the mucosa, the blood vessels being more prominent than normal because of the thinness of the superficial layers of the stomach. The second (chronic superficial gastritis) is characterized by hyperemia and edema. The third type (chronic hypertrophic gastritis) is characterized by granular nodules resembling polyps and a velvety, swollen, and spongy appearance of the mucosa. Shallow ulcerations of varying size may be present. The chronic superficial and hypertrophic varieties are encountered more frequently than the atrophic type. Because gastroscopic findings suggestive of the three types of chronic gastritis may be encountered in the absence of symptoms, many feel that there are no characteristic clinical pictures. One should not, however, be led astray by such reasoning because practically any readily demonstrable lesion of the stomach, such as gastric ulcer, may be asymptomatic at some time in its course. Unlike most observers, the writer is convinced that chronic gastritis may give rise to reasonably characteristic clinical pictures which, when carefully scrutinized, can be diagnosed readily.

Symptoms in the atrophic variety include anorexia, epigastric fullness, and loss of weight. Periods of ill health alternate with periods of well-being. Gross hemorrhage may occur. Physical examination is negative. Roentgenologic examination of the stomach reveals no abnormalities, though it was expected that a carcinoma would have been demonstrated. Gastric analysis

frequently reveals an absolute achlorhydria with a great deal of mucus in the samples.

The clinical pictures of chronic superficial and chronic hypertrophic gastritis are often indistinguishable but are definitely more gastric than

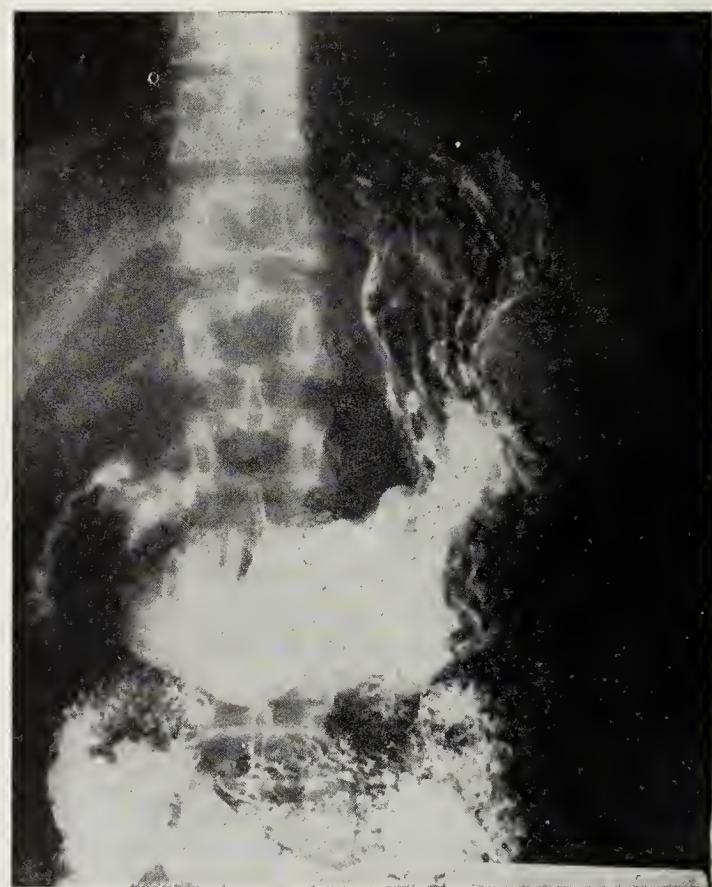


FIG. 229. Roentgenologic appearance of the stomach and duodenum of a patient with gastroduodenitis. The mucosal folds are prominent. Gastroscopy, essential for confirmation of diagnosis, revealed evidence of hypertrophic gastritis.

that of the atrophic type. Both types occur in individuals who are constantly subjected to anxiety states and frustrations of one type or another. The symptoms are characteristically present during the periods of mental distress and dietary and alcoholic indiscretions, and are usually absent during periods of freedom from aggravation. The appetite is usually good, but the patient states he can't eat everything or anything because distress will occur. Most of them, however, must ingest a sufficient number of calories for there is usually little or no loss of weight. There may be a peptic ulcer type of distress if there is actual ulceration of the gastric mucosa or an associated duodenitis. Heartburn and nausea are very common. Vomiting and gross hemorrhage may occur in both types. Physical examination may reveal tenderness

over the accessible portions of the stomach and the duodenum. Roentgenologic examination of the stomach may be negative in both types or may reveal in the hypertrophic variety prominent gastric rugae (fig. 229), shallow ulcerations, prolapsing gastric mucosa, and evidences of inflammation and edema of the mucosa of the duodenal cap. Gastric analysis frequently reveals high values for free hydrochloric acid. Less frequently, a relative achlorhydria is encountered and occasionally, in the hypertrophic type, an absolute achlorhydria. When the gastric samples contain little or no free hydrochloric acid, mucus is usually present in abnormally large amounts.

The diagnosis of all three types of chronic gastritis depends on gastroscopy. Management consists, in the main, of avoiding ingestion of irritating foods and condiments, and the use of a bland diet plus psychotherapy. Interval feedings should be administered in cases with hyperacidity. Patients presenting atrophy of the gastric mucosa should be observed carefully and repeatedly for the possible development of evidences of pernicious anemia and gastric carcinoma, and be treated accordingly.

SPECIFIC GASTRITIS

SYPHILIS

Syphilis of the stomach is extremely rare. The lesion reported most frequently is of a chronic inflammatory nature, causing induration and thickening of the gastric wall, at times resulting in an hourglass deformity. The outstanding symptom in the majority of patients is epigastric pain or discomfort which, unlike that of peptic ulcer, comes on immediately after eating. In a small proportion of cases, especially those with ulceration and hydrochloric acid present, the pain is similar to that of peptic ulcer and is relieved by food. Loss of weight, vomiting, and massive hemorrhage may occur, but perforation is rare. Achlorhydria occurs in about 85 per cent of the cases; the acid may return after specific treatment. The blood or spinal fluid Wassermann test is almost always positive. A positive diagnosis of gastric syphilis is difficult, and practically none of the procedures which are employed, including the demonstration of spirochetes in the lesion, is infallible. The differentiation from carcinoma may be impossible without microscopic examination. The therapeutic test is of

little value because, in spite of adequate antisyphilitic therapy, the roentgenologic deformity may be changed only moderately. Medical treatment is indicated only in early cases. Unless the lesion regresses within a period of two to three weeks on an intensive course of penicillin therapy and a bland dietary regimen, gastric resection should be performed.

TUBERCULOSIS

Tuberculosis of the stomach occurs very rarely, and is encountered more frequently in adults than in children. Primary involvement constitutes a medical curiosity. The vast majority of cases have tuberculosis elsewhere in the body, particularly in the lungs. Three major types may be recognized: ulcerative, miliary, and granulomatous. When present, symptoms may suggest a peptic ulcer or a gastric carcinoma. Extragastric symptoms depend on the site and extent of tuberculous involvement elsewhere in the body. The diagnosis is established by microscopic examination of the lesion removed at laparotomy. When the diagnosis is made, therapeutic measures should include the administration of streptomycin.

MYCOTIC INFECTIONS

These disorders are rare, produce no characteristic or roentgenologic findings, and are diagnosed either by biopsy or by demonstration of the etiologic agent in the gastric secretion. The treatment is that of fungous infections in general (see Part VI, Section 11).

MISCELLANEOUS DISEASES OF THE STOMACH

CASCADE STOMACH

A cascade deformity of the stomach is sometimes found associated with a rather characteristic clinical picture. The cascade appearance is usually due to forward displacement of the vertical limb of the stomach, while the cardiac portion remains posterior. The fundic pouch fills before ingested material can spill over into the antrum, hence the term "cup and spill" sometimes is applied. Symptoms are produced when ingested material fails to empty from the fundic locule and especially if swallowed air also accumulates which may exaggerate the deformity. Symptoms

consist of a sensation of pressure, fullness, or sharp pain in the lower left chest, aerophagia, and belching, the latter not affording relief. The condition occurs more frequently in individuals of nervous temperament and hypersthenic habitus. Many of them believe they are suffering from heart disease because of palpitation during periods of distention of the fundic locule. The diagnosis is made during fluoroscopy by observing the barium fill the cardiac portion of the stomach before it spills over into the antrum. The condition is best demonstrated by a lateral view. The cascade arrangement is sometimes responsible for an inability to intubate the antrum, the terminal portion of the tube curling around the fundic locule. The results of therapy are not always satisfactory. The dietary regimen should consist of three small meals supplemented with interval feedings. Overeating, bolting of food, air swallowing, and constipation should be avoided. The position in which the fundic locule empties most readily should be determined fluoroscopically, and the patient advised to assume that position for a half-hour after meals. Emotional and psychogenic disturbances should be handled by psychotherapy.

DIVERTICULA OF THE STOMACH

The incidence of diverticula of the stomach is low. They are found more commonly in middle-aged individuals. Two types occur; congenital (true) and acquired (false). Congenital diverticula are encountered most frequently on the posterior wall near the lesser curvature below the cardia. Acquired diverticula occur most frequently near the pylorus and are caused by traction of inflammatory lesions of neighboring structures. The majority of diverticula are asymptomatic. A common symptom, however, is a sensation of localized fullness in the epigastrium which feels as if it might be relieved by belching and, at times, by vomiting. Pain may occur as a result of inflammation or retention of material. Massive hemorrhage has occurred in a few cases. The diagnosis is based on roentgenologic demonstration of a barium-containing sac projecting from the normal contour of the stomach. The sac may retain barium for several hours after the remainder of the stomach has emptied. When treatment is indicated, it should include postural drainage after fluoroscopy has demonstrated the best position for evacuation.

If the symptoms are distressing, excision of the sac may be necessary.

HYPERTROPHIC PYLORIC STENOSIS

Hypertrophy of the musculature of the pylorus, similar to that which occurs in the newborn, has been alleged to occur in adults of all ages. In the majority of cases, symptoms of pyloric obstruction suggest a preoperative diagnosis of pyloric peptic ulcer or malignancy, and, indeed, microscopic examination of the resected pylorus usually reveals evidence of a healed peptic ulcer or of a small malignancy. The treatment, in view of the fact that an unsuspected malignancy may be present, is extensive subtotal gastric resection with wide excision of the pylorus.

FOREIGN BODY IN THE STOMACH

A wide variety of foreign objects capable of being swallowed have been found in the stomach. Many of them, such as coins and marbles, rarely cause symptoms and in time are eliminated through the rectum without having done harm. Sharp-pointed objects such as tacks, needles, and especially open safety pins, may penetrate the wall of the stomach or intestine and give rise to peritonitis or abscess formation. Occasionally, a needle may find its way to parts of the body outside the abdomen. Swallowed knives, forks, spoons, and other objects have been known to remain in the stomachs of inmates of mental institutions for years without producing serious symptoms. Occasionally, they may be responsible for ulceration, perforation, or obstruction of the stomach or intestine. The swallowing by children of toys made of lead or of crayons containing lead may give rise to plumbism. Bezoars may attain a huge size and cause symptoms which indicate serious gastric disease. They are conglomerations of swallowed foreign material consisting either of hair (trichobezoar), hair and vegetable fiber (trichophytobezoar), or vegetable fiber alone (phytobezoar), usually due to ingestion of persimmons. The long-continued use of calcium or magnesium powders or tablets may give rise to concretions of these salts in the stomach (gastroliths), especially if there is delayed gastric emptying. Concretions of precipitated shellac may be found in the stomachs of individuals who drink shellac for its contained alcohol.

The diagnosis of foreign body in the stomach is based on the history of swallowing such an object and on roentgenologic examination or gastroscopy.

Treatment is indicated only when definite distress is present or when the presence of a foreign body constitutes a danger, as in the case of a needle or open safety pin. In the removal of such foreign objects, laparotomy is less dangerous, simpler, and more effective than attempted extraction through a gastroscope. Objects such as nails sometimes can be removed through the natural channels by means of a swallowed magnet attached to a string.

PROLAPSING GASTRIC MUCOSA

Occasionally mucosa, the seat of a hypertrophic gastritis, may prolapse through the pylorus and simulate the picture of a polyp prolapsed into the duodenum. Symptoms may consist of epigastric pain, of nausea and vomiting due to gastric retention, or of melena as a result of bleeding from the congested mucosa. The diagnosis is made roentgenologically by the demonstration of negative shadows consisting of extensions of gastric rugae into the duodenal cap. Sometimes the negative shadows result in a "cat's paw" appearance. Gastroscopy usually reveals evidence of chronic hypertrophic gastritis. Most cases respond to conservative management, which should include a bland dietary regimen similar to that used for peptic ulcer. Surgery is rarely indicated, but when decided on should be preceded by a preoperative period of preparation with a bland, high-protein diet and other measures to correct hypoproteinemia if such exists. If this is not done, the suture lines made through inflamed, edematous, and congested gastric and duodenal tissues may result in faulty healing, and give rise to troublesome post-operative complications such as hemorrhage, leakage from the duodenal stump, and failure of the stoma to function properly.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE STOMACH

In this section the differential diagnosis of lesions of the stomach which may simulate the clinical and roentgenologic pictures of carcinoma of the stomach will be considered. Frequently, the differentiation cannot be made except by

microscopic examination of the lesion, but at times careful attention to detail may avoid an unnecessary laparotomy. The differential characteristics of benign and malignant ulcer are discussed in the chapter on Peptic Ulcer (Chapter 259). The diagnosis and differential diagnosis of the various forms of acute gastritis usually present no problem in view of the association of acute gastric symptoms with a history of ingestion of specific irritants and toxic substances, or of their occurrence during the course of an acute infectious disease or a septicemia. The diagnosis of the various forms of chronic gastritis can be established only by gastroscopy; consequently, one must rely on a careful scrutiny of the clinical picture, and usually a negative roentgenologic examination, to justify a rather trying procedure. The more important diagnostic features of chronic gastritis and of miscellaneous conditions of the stomach such as diverticulum, prolapsing gastric mucosa, cascade stomach, and rare specific infections have been described under their respective headings and will not be repeated.

The diagnosis of carcinoma of the stomach which has advanced to the stage where it is producing symptoms is based on the clinical picture, roentgenologic examination, gastroscopy, and, when necessary, laparotomy. The variable clinical picture has been described and yields less precise and exact information than roentgenologic examination and gastroscopy. Gastric analysis, the electrogastrogram, and the iodoacetate index may yield corroborative but not pathognomonic evidence. Gastric sediment stained by a Papanicolaou's method may furnish valuable evidence if malignant cells are found. A negative examination does not eliminate the presence of a neoplasm in the stomach.

The differentiation of gastric sarcoma from carcinoma is usually not possible except by histologic examination. Features of a particular case which may lead one to suspect that the gastric lesion might be sarcoma include a younger age and the demonstration of enlarged lymph nodes not in the usual sites of metastasis from gastric carcinoma. The presence of a crater fleck on top of a rounded, smooth negative subtraction defect may suggest a leiomyosarcoma. Benign tumors are also differentiated best by microscopic section after their complete removal. The clinical and roentgenologic features of Hodgkin's disease of the stomach may defy

differentiation from carcinoma by any procedure short of microscopic examination. Splenomegaly, lymphadenopathy, pruritus, Pel-Ebstein fever, and a peripheral blood picture consisting of leukopenia and eosinophilia, if present, may suggest Hodgkin's disease. Leukemic infiltration of the stomach may give rise to the clinical and roentgenologic characteristics of gastric carcinoma. The diagnosis of leukemia should rarely be missed because of the characteristic clinical, peripheral blood, and bone marrow pictures.

Gastric syphilis is very rare. The finding of a lesion simulating malignancy in a patient with positive serologic reaction by no means should be taken to indicate that the lesion is syphilitic. Rapid involution of the lesion under gastroscopic and roentgenologic observation, when intensified antisyphilitic therapy is administered, should be the only justification for avoiding laparotomy.

Spasm of the antrum due to gastritis in association with a duodenal or pyloric ulcer may at times result in a narrowing of the antrum, so that it is not possible to determine radiologically whether a scirrhous carcinoma is present. Relaxation of the area following a large parenteral dose of atropine under fluoroscopic inspection, followed by disappearance of the defect on rigid medical therapy, might justify the avoidance of laparotomy, but otherwise surgery should be resorted to. Hypertrophic gastritis of the antrum may simulate the roentgenologic appearance of carcinoma of this area, and at times laparotomy must be employed to identify the true nature of

the lesion. Benign hypertrophy of the pylorus in adults can produce in every detail the clinical and roentgenologic picture of a scirrhous carcinoma of the pylorus. Differentiation is not possible by any means except histologic examination.

The presence of a foreign body in the stomach, of the nature of a bezoar, may at times require differentiation from gastric carcinoma. The diagnosis of bezoar can usually be made if a history of chewing hair or eating persimmons can be obtained, if the filling defect noted by x-ray is freely movable, or if examination of the gastric content reveals microscopic evidence of bezoar material.

Extrinsic pressure defects are best differentiated by gastroscopy and by roentgenologic techniques employing insufflation of air into the stomach.

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Peptic Ulcer

Thomas E. Machella

Introduction
Duodenal Ulcer
"Dumping" Syndrome
Postgastrectomy Diarrhea and Failure to Gain Weight
Complications of Duodenal Ulcer

INTRODUCTION

Peptic ulcer is an example of a somatic disease which is greatly influenced by, and probably pre-

Gastrojejunocolic Fistula
Peptic Ulcer of the Stomach
Benign vs. Malignant Ulcer
Primary Jejunal Ulcer
Peptic Ulcer of the Esophagus

cipitated by, emotional disturbances. It comprises one of the commonest organic causes of indigestion. It has been estimated that during a

modern lifetime 5 to 12 per cent of the population become afflicted with the disease. The diagnosis of the uncomplicated case is relatively simple, as it gives rise to a rather characteristic clinical picture. The sites at which peptic ulcer occurs most frequently, such as the lower end of the esophagus, the stomach, the duodenal cap, and the gastrojejunral junction, are accessible to roentgenologic examination, and, in certain instances, to endoscopic inspection. Response to adequate therapy is usually satisfactory providing the physician treats the patient as well as the ulcer. The psychogenic motivating factors in the pathogenesis or aggravation of the ulcer must be discovered and successfully handled in order to obtain the best results.

In this section an attempt will be made to describe the characteristics of peptic ulcer in general and of duodenal ulcer in detail, and to point out the differentiating and special features of ulcer located at various other sites in the gastrointestinal tract.

Etiology. The pathogenesis of peptic ulcer has not been established to the satisfaction of all. The complexity of the problem and the discrepancies in the clinical and experimental literature preclude at the present time a clear understanding of the etiology of the disease. The occurrence of peptic ulcer in individuals who are high-strung, tense, and possessed of more than the average amount of ambition, drive, and responsibility, as well as in persons who are subjected to emotional conflicts and upheavals, strongly suggests that psychogenic influences play an important role in the pathogenesis. A great deal of evidence has accumulated to indicate that such emotional disturbances give rise to gastric hypersecretion, hypermotility, and hypertonus. The association of acute peptic ulcer in the stomach or duodenum with lesions in the central nervous system, as well as the results of the vagotomy operation for the treatment of peptic ulcer, indicate that the impulses responsible for the abnormal gastric physiology arise in the central nervous system and are mediated through the parasympathetic division of the autonomic nervous system. There can be little doubt that acid gastric juice is necessary for the production of a peptic ulcer. The development of peptic ulcer at the sites of heterotopic gastric mucosa in the lower end of the esophagus or in a Meckel's diverticulum, as well

as at the margin of the anastomosis between the stomach and jejunum, clearly demonstrates the role of acid in the production of peptic ulcer at these sites. Similarly, the absence of duodenal ulcer in patients with achlorhydria attests to the importance of hydrochloric acid in the production of duodenal ulcer. However, the reason why a localized area of mucosa in the stomach or duodenum fails to withstand the digestive action of hydrochloric acid and pepsin has not been established and has given rise to a great deal of speculation and animal experimentation. Local ischemia secondary to neurogenic, vascular, and allergic influences; poorly understood hormonal mechanisms; and injury by bacteria, chemical agents, and foreign bodies have been held responsible by some. Others have ascribed the occurrence of the local lesion to a focal loss of protective or neutralizing influences. Recently the role of lysozyme has engaged the attention of investigators, some maintaining that this enzyme, capable of lysing mucus, is present in increased amounts in the gastric juice of peptic ulcer patients and that its production is in part influenced by the central nervous system. The final role of lysozyme in the pathogenesis of peptic ulcer remains to be evaluated.

Certain factors which contribute to the chronicity of peptic ulcer are more universally agreed upon. These include protracted emotional disturbances and psychogenic influences leading to gastric motor and secretory hyperactivity, alcoholism, irritating and coarse foods, gastric retention, and poor nutrition. The pathogenesis of peptic ulcer has also been discussed in a previous chapter (see Chapter 15).

Pathology. Ulcers are usually single but occasionally are multiple. The ulcer results from a penetrating process, beginning in the mucosa, invading the deeper layers beneath, and perhaps perforating them completely. It may be acute or chronic, the essential pathologic difference being the amount of connective tissue present. The border of the ulcer is sharp, and the surrounding mucosa may be normal or slightly inflamed, flat or slightly elevated. The floor of the crater is clean and consists of a thin layer of exudate overlying a deeper layer of granulation and fibrous tissue. In a chronic ulcer the fibrous tissue may be interrupted with thrombosed blood vessels. The ulcer heals by scarring; the crater fills and there remains a smooth surface devoid of mu-

cosa. The scar may contract and distort the surrounding tissue.

DUODENAL ULCER

Duodenal ulcer occurs more frequently in males than in females, the ratio being about 4 to 1. Although it may occur at any age, the majority of patients experience the onset of symptoms in the fourth decade.

Clinical Picture. Pain is the outstanding symptom of duodenal ulcer, the characteristic features of which are its quality, rhythmicity, periodicity, and chronicity. It consists, as a rule, of a gnawing or aching sensation sharply localized to some point in the epigastrium, frequently to the right of the midline. The patient, often and unhesitatingly, will localize the site of the pain with one finger. It is steady and continuous, lasting 15 minutes to an hour or more, unless relieved by the ingestion of food or antacid. Rhythmicity is related to the digestive cycle. The pain appears one to four hours after meals. It may awaken the patient at night, usually between the hours of 12 and 2 a.m., but is frequently absent before breakfast. The periods of pain may last a few days, several weeks, or several months, with intervals of freedom of similar duration. As time goes on, the periods of relapse become longer and those of remission shorter. Sometimes, but by no means in all cases, the distress comes in the spring and the fall. Symptoms may disappear during pregnancy, to reappear after parturition. The chronicity of the disease is evidenced by the fact that the average duration of the period of remissions and recurrence is 6 to 7 years, but in some instances they may extend over a span of 40 to 50 years.

Appetite and weight are usually well preserved, and nausea and vomiting are not common in the absence of complications. The physical examination of the abdomen may be entirely negative, but not infrequently reveals tenderness localized to the site of the ulcer.

Laboratory Findings. Gastric analysis usually reveals high values for volume and for free and total acidity during the interdigestive periods and in response to a standard test meal. The absence of free hydrochloric acid excludes an ulcer of the peptic type. The blood count may reveal a hypochromic microcytic anemia if there has been bleeding from the ulcer. In young males,

the most common cause of such anemia is bleeding from a peptic ulcer.

Roentgenologic Examination. Roentgenologic demonstration of an ulcer crater is the most important single diagnostic procedure. The majority of duodenal ulcers are located in the bulb, only about 5 per cent being located in the postbulbar area. The crater appears as a niche when located on the superior or inferior margins of the bulb, or as a circumscribed collection of barium surrounded by a clear zone when it is located on the anterior or posterior walls. In very active acute ulcers, a crater or niche sometimes cannot be demonstrated, and one has to rely on secondary signs such as spasm, irritability, failure of the cap to fill, and local tenderness. When such secondary signs are due to ulcer, re-examination within a few days after the acute symptoms have subsided will usually reveal the crater. As the ulcer heals, some contraction and deformity may occur; characteristic, when seen, is a "fleur-de-lis" appearance (fig. 230).



FIG. 230. Roentgenologic appearance ("fleur-de-lis") of contracted and deformed duodenal cap caused by repeated episodes of activity and healing of duodenal ulcer.

Diagnosis. The diagnosis of duodenal ulcer is based on the clinical picture and on the roentgenologic demonstration of the lesion or corollary evidence of its presence. Gastroscopy is of no value in demonstrating duodenal ulcer, as visualization beyond the pylorus is not possible. It may, however, reveal the presence of an as-

sociated gastritis which not infrequently accounts for variations from the typical clinical picture. If symptoms suggestive of peptic ulcer are present and there is repeated failure to demonstrate roentgenologic evidence of a lesion in the stomach or duodenal cap, a search for a crater elsewhere in the duodenum and even in the proximal jejunum should be made. The peptic ulcer type of pain may occur also in patients with hypertrophic gastritis or duodenitis, and when heterotopic gastric mucosa is present in a Meckel's diverticulum.

Treatment. Healing of the ulcer is accomplished best by ensuring mental and physical rest, by suppressing gastric motor and secretory hyperactivity, and by improving the nutrition of the patient. The emotional aspects of the patient's life should be analyzed carefully and efforts made to help him handle them successfully. Often this can be managed quite satisfactorily by the physician, but at times the services of a psychiatrist are necessary. When the ulcer has healed, the disease should be considered as arrested and not cured, and measures instituted to prevent a relapse.

1. **HOSPITALIZATION.** The first decision to be made concerns whether the patient should be treated in a hospital, at home, or on an ambulatory basis. Proper management in a hospital is preferable but is not always feasible. The patient should be hospitalized if any of the complications of peptic ulcer threaten, if the domestic environment is not conducive to proper rest, or if the patient has failed to respond to an ambulatory regimen. The second choice is that of bed rest at home if the conditions at home are conducive to mental rest, and if a strict dietary regimen can be carried out. The patient can be permitted to remain working if financial necessity demands, providing the program of frequent feedings can be carried out, the environment is good, and heavy physical duty is not undertaken. Each case must be individualized and that decision made which promises the best results. Most patients can be treated on an ambulatory basis. Removal from a bad environment should be accomplished when possible.

2. **DIET.** Strict adherence to a dietary schedule is essential. The type of regimen to be advised should be individualized.

a. **FOR VERY ACTIVE ULCER.** Equal parts of milk and cream, 100 ml. (total) hourly, 7 a.m. to

9 p.m. If pain persists during the night, the feedings should be continued throughout. After one or two days a soft-boiled egg with cracker or bread and butter may be added to one of the forenoon feedings, and to one of the afternoon feedings, 100 ml. of a cooked cereal. Eggs and cereals are added gradually until at the end of the first week, in addition to the milk mixture hourly, the patient is getting two or three soft-boiled eggs and 200 to 300 ml. of cereal. The cereal and egg should be given alternately but at the same time, and in addition to the milk and cream. Custards, cream soups, vegetable purées and other bland foods may be substituted for the milk and cream at times. Clear jellies may be added if desired.

After one week the feedings may be reduced to every second hour, and, as soon as possible, to six a day—i.e., three regular meals and extra milk and cream between meals and at bedtime. Meat, broiled or boiled, may be permitted within another week. If acute symptoms recur, the original program should be resumed. The diet should be supplemented with 25 mg. of ascorbic acid three times each day.

b. **BLAND DIET FOR AMBULATORY PATIENTS.** The three main meals of the day should be selected from the foods listed below. The patient should, in addition, be given instruction as to intermediate feedings. The spacing of the feedings should be determined by the time when the main meals are taken. The final intermediate feeding for the day should be determined by the time at which the patient retires. If he goes to bed at midnight, he should have intermediate feedings at 9 p.m. and shortly before retiring. The amount of cream in the milk-and-cream mixture may be increased when it is desirable to increase caloric intake.

(1) *Milk and Milk Products.* Including butter, cream, and cheese (cream, cottage, American, "Velveeta," Swiss, and Cheddar).

(2) *Cream Soups Made with Strained Vegetables.* Carrot, corn, pea, potato, spinach, tomato, kidney bean, and beet.

(3) *Cereals.* Cooked farina, "Cream of Wheat," rice, corn meal mush, strained oatmeal, etc. Any dry cereal that does not contain bran. Macaroni, spaghetti, and noodles cooked with butter or cheese (no meat or tomatoes).

(4) *Eggs.* Soft-boiled, poached, soft-scrambled and, if ground or well chewed, hard-boiled.

(5) *Vegetables.* Thoroughly cooked and soft asparagus tips, mashed beets, turnips, carrots, pumpkin; baked or mashed white and sweet potatoes; boiled or baked squash without skins or seeds. The following vegetables may be added if they are thoroughly cooked and mashed through a strainer: spinach, lima beans, peas, corn, kidney beans. Raw, coarse, or stringy vegetables should be avoided.

(6) *Fruits.* Cooked or canned without skins or seeds: apricots, peaches, apples (stewed or baked), pears, plums. Raw fruits and fruit juices, except thoroughly ripe bananas, should be avoided.

(7) *Bread.* Day-old white bread or toast, melba toast, plain crackers, zwieback, Holland rusk, waffles, or pancakes (flour, corn meal, or buckwheat). Pumpernickel, cracked wheat, rye, and whole wheat bread should be avoided.

(8) *Desserts.* Puddings, such as custard, corn-starch, junket, bread, tapioca, rice (without raisins); spanish cream, "Jello" (plain or with cooked skinless fruit added). Clear jellies; no jam or marmalade. Fruit whips (made with strained fruits) of prunes, banana, apricot, peach, etc., using either egg whites or whipped cream. Sponge cake, simple cookies such as "Social Teas," chocolate or vanilla wafers. Ice cream, if eaten slowly.

(9) *Beverages.* Weak tea (hot or cold), cocoa, chocolate, milk eggnogs, milk shakes, malted milk, "Ovaltine," weak coffee with cream.

Meat should not be permitted until after the second week. Meat soups, seasonings, spices, alcoholic or carbonated beverages, and very hot or very cold foods should be avoided.

At least one glass of milk and cream (two parts of milk to one part of cream) should be taken between meals and at bedtime (six feedings or more daily).

When meat is permitted, tender beef, lamb, veal, fowl, or fish that is boiled, broiled, or roasted, but no meat soups, should be used. Gristle or parts that cannot be adequately macerated should be avoided. The food should be chewed thoroughly.

The above diet should be supplemented with 25 mg. of ascorbic acid three times a day. If the patient continues to work, the interval feedings of milk and cream may be carried in a thermos bottle to facilitate obtaining them on schedule.

C. PROTEIN HYPERALIMENTATION. In protein-

depleted patients a high protein intake is desirable. The goal may be attained by substituting the required amounts of milk powder, crude casein, or protein hydrolysate for the interval feedings of milk and cream. If it is desired to institute a program of protein hydrolysate hyperalimentation, the regimen should consist of frequent feedings of a solution of a mixture of equal parts of protein hydrolysate and "Dextromaltose." The amount of the mixture should be calculated on the basis of 20 calories per pound of body weight, and each feeding should consist of 100 to 200 ml. of a 30 to 50 per cent solution administered every hour from 6 a.m. to 10 p.m. The feedings should be continued throughout the night if, and as long as, night pain is present. Vitamins and iron should be supplemented.

The use of protein hydrolysate mixtures in the treatment of peptic ulcer has certain advantages as well as disadvantages; consequently their use should be limited to selected cases. It is perfectly true that under ordinary conditions of satisfactory digestion and absorption 1 Gm. of crude protein is just as adequate nutritionally as 1 Gm. of hydrolyzed protein. However, in the treatment of peptic ulcer, hydrolyzed protein may be used more advantageously than crude protein or milk for the following reasons: (1) It has a more effective buffering capacity. (2) Hypertonic solutions of hydrolyzed protein remain in the stomach longer than equivalent concentrations of crude protein and, consequently, the buffering action lasts longer. (3) A positive nitrogen balance is obtained more readily than when milk is used; this is of importance in protein-depleted patients in whom extensive gastric surgery is contemplated. (4) Clinical experience has demonstrated that ulcers heal more rapidly than when milk and antacid are employed. (5) The use of protein hydrolysate has a certain psychotherapeutic value which is useful in some patients who lack confidence in the more conservative therapeutic methods. Disadvantages in the use of protein hydrolysate include the expense, unpalatability, and the fact that in individuals with rapid emptying time the rapid entrance of hypertonic solution of protein hydrolysate into the duodenum may give rise to diarrhea.

3. DRUGS: a. SEDATION. Apprehensive and mentally tense patients should receive regular small doses of phenobarbital in capsule or tablet form.

b. ANTACIDS. The use of antacid drugs is often unnecessary. They may be used if pain persists or becomes worse on the diet, or if the patient is free of pain during the day while on the diet but experiences pain at night. If it is decided to use an antacid, then that one should be selected which is insoluble, is neutral in aqueous suspension, does not irritate the stomach or intestine, does not affect the acid-base balance, and does not cause diarrhea or constipation. Of the antacids, magnesium trisilicate and colloidal aluminum hydroxide are the least objectionable. Very large doses of aluminum hydroxide should not be used in the presence of gastric stasis due to pylorospasm, because of its tendency to delay gastric emptying. Aluminum hydroxide should not be used when there is bleeding into the stomach or intestine, because of the possibility of intestinal obstruction as a result of formation of masses of blood clot and aluminum hydroxide. For prompt neutralization, calcium carbonate may be used. If constipation tends to occur, small doses of magnesium oxide may be combined with it. The use of antacids, especially the soluble ones, should be discontinued as promptly as possible. The soluble ones may precipitate alkalosis, the initial symptoms of which are distaste for milk, headache, anorexia, thirst, and mental depression.

c. VAGAL DEPRESSANTS. If the dietary program does not suffice to control the pain, if antral or duodenal spasm is present, or if there is night pain, atropine or belladonna may be prescribed throughout the day and at bedtime.

d. ALCOHOL. Alcohol in any form should not be prescribed, as it increases gastric acidity. Its excessive use also encourages dietary and other indiscretions.

e. BOWELS. If the diet and bed rest constipate the patient, regular small doses of milk of magnesia and/or mineral oil may be prescribed.

4. SPECIAL MEASURES. If the dietary, vagal-depressant, and antacid regimen fails to control pain, special procedures may be required. Intractable persistent pain may occur when the ulcer is located in the pylorus or duodenum, and is associated with pylorospasm or edematous and inflammatory narrowing of the outlet of the stomach and high acidity. Severe intractable pain also may occur when the ulcer is penetrating. In such cases one of the following procedures may be employed:

a. CONTINUOUS GASTRIC ASPIRATION. (For cases with pain and vomiting.) A soft-tipped rubber tube is introduced into the stomach by the nasal route and is attached to a source of continuous suction. Protein hydrolysate and dextrose solution, and blood or plasma are administered intravenously in an attempt to correct hypoproteinemia and to supply calories. Physiological saline solution is administered intravenously or subcutaneously in amounts adequate to maintain a satisfactory fluid and acid-base balance. The blood serum chlorides, carbon dioxide, and total base should be checked daily, and deviations from normal corrected as promptly as possible without overloading the circulation. The continuous aspiration of hydrochloric acid may produce a primary alkali excess with alkalosis and tetany. Likewise, there may occur manifestations of potassium deficiency which may be reflected in the serum potassium concentration or by electrocardiographic changes. Usually, within 24 to 36 hours of continuous aspiration, the acute symptoms subside, and the frequent administration of small amounts of milk and cream or protein hydrolysate and "Dextri-maltose" solution can be attempted, the suction being discontinued during the period. If the oral feedings are tolerated, the tube may be withdrawn and the plan of treatment outlined for acute active ulcer instituted.

b. CONTINUOUS DRIP. (For cases with no gastric retention.) If the plan of continuous aspiration of gastric juice fails to afford relief from pain and there is no evidence of gastric retention, a tube is passed (nasally) into the stomach and either a milk and cream mixture or a protein hydrolysate—"Dextri-maltose" solution is introduced by continuous slow drip throughout the 24 hours. Vitamin intake should be supplemented.

Radiation Therapy. Gastric acidity may be reduced for varying periods of time by roentgenologic irradiation of the stomach. Such a plan of therapy for peptic ulcer may be employed in certain selected cases, particularly when surgery is contraindicated and conservative measures have failed and dangerous complications threaten. The effects of irradiation in lowering gastric acidity are not permanent. The intelligent use of this therapeutic measure may salvage a patient who otherwise would be faced with a poor prognosis.

Surgery. Surgery is practically never indicated for uncomplicated duodenal ulcer, but may be required if the ulcer cannot be controlled by a thorough and adequate trial of medical therapy. The main general objective of surgery is to restore the patient to a useful way of life. To accomplish this, subsequent ulceration should not occur, which means that the ability of the stomach to secrete hydrochloric acid must be reduced by the operative procedure selected. In addition, the surgical result must be anatomically and functionally satisfactory. The three main types of operation which have been performed are: (1) gastroenterostomy, (2) vagotomy, and (3) subtotal gastric resection.

1. **GASTROENTEROSTOMY.** The operation of simple gastroenterostomy for the treatment of duodenal ulcer is no longer popular for several reasons: (a) It does not reduce the acid-forming ability of the stomach. (b) Unless the outlet from the stomach is obstructed, gastric content frequently will continue to leave the stomach by way of the pylorus and not through the stoma. This may lead to a continued activity or to a reactivation of the duodenal ulcer. (c) If the outlet of the stomach is obstructed, acid gastric content will leave through the stoma but peptic ulceration at or near the stoma may occur. The incidence of marginal ulcer is as high as 25 to 30 per cent in some series. (d) In some instances a vicious circle is established in which gastric content leaves by way of the pylorus, passes through the duodenum, but re-enters the stomach through the stoma. This gives rise to a rather unfortunate situation wherein appetite is impaired and nutrition suffers.

Simple gastroenterostomy does have a place in the treatment of duodenal ulcer—that of a palliative intervention, particularly in those cases in which, because of general or local conditions, a more radical operation is not feasible.

2. **VAGOTOMY.** The operation of vagotomy at present is on trial and its final evaluation awaits the passage of time. Its objective is to reduce gastric acidity by eliminating the nervous phase of gastric secretion. The operation of vagotomy alone for the treatment of duodenal ulcer has been abandoned in many clinics primarily for two reasons. (a) It is impossible to perform a "complete" vagotomy regularly. To successfully reduce gastric acidity, all of the gastric branches of the vagi must be completely de-

stroyed. If they are not destroyed completely, ulceration may persist or recur. Careful dissections of the vagal branches innervating the stomach in cadavers have revealed that it is highly improbable that a "complete" vagotomy can be performed in more than 85 per cent of the cases. The proportion of patients in whom a "complete" vagotomy is possible must be less than 85 per cent, when one considers that a more thorough dissection is possible in the cadaver than in the patient at operation. (b) If the vagotomy is "complete," undesirable complications may occur, the most troublesome of which is gastric retention as a result of the destruction of the extrinsic motor innervation of the stomach. Gastric retention may require further surgery to ensure an adequate outlet from the stomach or the pharmacologic promotion of gastric evacuation by means of "Urecholine" or "Doryl."

The operation appears to find its greatest field of usefulness in the treatment of marginal ulcer where further gastric resection is not possible or feasible and an adequate outlet from the stomach is already assured. Some clinics have reported favorable results following the performance of vagotomy combined with gastroenterostomy. It is possible that in these cases a large proportion of marginal ulcers will develop.

3. **SUBTOTAL GASTRIC RESECTION.** At the present time the operation of choice in many clinics is adequate subtotal gastric resection. In order to obtain a satisfactory result, from the standpoint of avoiding marginal ulcer, the resection must be adequate. This means that 75 to 80 per cent of the stomach should be removed in order to decrease the hydrochloric acid-secreting area of the stomach which occupies the fundus and the upper half of the body.

The operation, if improperly performed, may give rise to undesirable sequelae. These include gastric retention as a result of failure of the stoma to empty satisfactorily; pain and other manifestations as a result of inadequate drainage of the afferent loop; and "dumping" symptoms, diarrhea, and malnutrition as a result of too rapid emptying of the gastric remnant and prompt entry of ingested food into the jejunum.

"DUMPING" SYNDROME

When the gastrointestinal tract has been deprived of the reservoir function of the stomach,

as after a gastroenterostomy or a subtotal gastric resection, the ingested food sometimes enters the jejunum almost immediately and gives rise to unpleasant symptoms, these constituting what has been called the "dumping" syndrome. The symptoms consist of any combination, or all, of the following: a feeling of warmth, weakness, sweating, vertigo, tightness or pain in the epigastrium, nausea, palpitation, and, in some cases, collapse. They vary in severity and in the degree to which they incapacitate the patient, but usually cause him to lie down after a meal until they subside. They occur after all meals in some individuals, but only after certain ones in others. They usually make their first appearance as soon as the patient resumes feedings post-operatively and may trouble him for weeks to years. Some patients learn that the avoidance of certain foods or liquids may result in a failure of the "dumping" symptoms to occur. The writer believes the manifestations are caused by distention of the jejunum, not primarily by the food which enters it, but by the distention caused by fluid pouring into the lumen from the blood stream in response to the osmotic properties of constituents of the food. They are not due to hypoglycemia or to hyperglycemia, but a hyperglycemia is usually present when they occur. They cannot be reproduced by an intravenous injection of glucose. The symptoms, in some cases, may be prevented by administering atropine in physiologic doses, by an injection of tetraethylammonium chloride before meals, or by omitting fluids from meals.

POSTGASTRECTOMY DIARRHEA AND FAILURE TO GAIN WEIGHT

A certain proportion of patients fail to regain lost weight postoperatively or continue to lose weight despite an adequate food intake. Such patients have an increased amount of fat and nitrogen in their stools or even a frank diarrhea containing undigested food particles. The reason for this is a rapid small-intestinal motility caused by the prompt entrance into the jejunum of food materials possessing osmotic properties of hypertonic proportions.

The dietary of such individuals should consist of natural protein foods, fats, and starches. Sugars must be restricted. Fluids should be omitted during the meals, and taken an hour before or after. Measures to increase the digestion

and absorption of fat, such as the administration of pancreatin and "Tween 80," have been disappointing in the writer's experience. In subjects who are unwilling or unable to adhere to a conservative plan of therapy, surgical revision of the stoma, with the object of restoring some reservoir function to the gastric remnant, may be necessary.

COMPLICATIONS OF DUODENAL ULCER

Perforation. Perforation is characterized by a sudden onset of an excruciating and prostrating pain beginning in the epigastrium and, within an hour or two, migrating to the lower right quadrant or even becoming diffuse, depending on the dispersion of the irritating acid gastric content. The tendency is for the material to spill into the right gutter of the abdomen and down into the pelvis. Usually nausea is present and the patient tries to suppress vomiting to avoid jarring the acid-seared abdominal cavity. There is a characteristic facies: the face is pallid, haggard, anxious, and appealing, and is covered with beads of cold sweat. Respiration is shallow in an attempt to restrict the excursions of the diaphragm and the movement of the irritated intraabdominal viscera. The position of the body is frozen for the same reason. Abdominal palpation reveals a characteristic boardlike rigidity. Peristalsis is usually absent but may return if the scattering of gastric content has not been diffuse and peritonitis has not yet set in. A flat plate of the abdomen will frequently reveal the presence of free air in the uppermost portion of the abdomen, depending on the position of the body when the film is taken. The inability to demonstrate pneumoperitoneum does not rule out perforation of an ulcer. The signs and symptoms of shock may occur when peritonitis develops.

DIFFERENTIAL DIAGNOSIS. The diagnosis of acute perforation is rarely difficult. The frozen attitude of the patient and the boardlike rigidity of the abdomen are absent in biliary or renal colic. In mesenteric occlusion and intestinal obstruction, the pain is rhythmic and intermittent. Dissecting aneurysm of the aorta is accompanied by profound shock and, if recovery occurs, may be detected by roentgenograms of chest and abdomen. In tabetic crisis and coronary occlusion there is no rigidity of the abdomen, and there are usually present other signs and symptoms of

differential diagnostic significance. Perforation of the gallbladder usually is indistinguishable from that of the stomach or duodenum; however, it usually occurs during or after an apparent subsidence of an attack of acute cholecystitis. Acute pancreatitis is at times difficult to differentiate. In this disease there is usually marked shock and the abdominal rigidity is less intense and widespread. The serum amylase and lipase are elevated, but they may also be elevated when peptic ulcer has perforated into the pancreas. At times it may be impossible to differentiate perforation of peptic ulcer from perforation of hepatic or splenic flexure or of the transverse colon.

TREATMENT. The treatment of acute perforation, a surgical emergency, is immediate surgery. Delay in operation increases mortality. The procedure to be employed should have as its primary objective the survival of the patient and therefore consists of the simplest, quickest, and safest operation. The procedure of choice in many clinics consists of oversewing the perforation and suturing a tab of omentum to the closure. Treatment for shock, if present, should be instituted promptly. A tube should be passed into the stomach as soon as possible and gastric content aspirated continuously. Following surgery, treatment for peritonitis should be employed. Surgery may be withheld in doubtful cases if rigidity disappears, normal peristalsis returns, and systemic signs of peritonitis do not appear. In such cases continuous gastric aspiration via nasal tube should be maintained and supportive therapy administered parenterally.

Massive Hemorrhage. (See Chapter 17 on Hematemesis and Melena.) Symptoms consist of faintness, weakness, vertigo, and perspiration, followed soon after by the passage of a tarry stool and, at times, hematemesis. Syncope and collapse may occur, depending on the severity of the hemorrhage and the resultant drop in blood pressure. The pulse becomes weak and rapid. The patient complains of thirst. The red blood count and hemoglobin fall as the blood volume is restored by hemodilution. The blood urea nitrogen may be moderately elevated due to absorption of blood from the intestine and diminished blood flow through the kidney as a result of the fall in blood pressure.

TREATMENT. If the patient is not vomiting or in shock, a prompt feeding program should be

instituted, regardless of the severity of the hemorrhage or its continuance. The patient is typed and adequate amounts of suitable blood are made ready. If shock is present, suitable measures to combat it are instituted. The patient should be seen by a surgeon, and his case closely followed by both the physician and the surgeon. The situation represents an emergency which is handled best by close teamwork between physician and surgeon.

Feedings, selected from the bland diet for ambulatory patients, are administered every second hour throughout the waking hours. The patient is allowed as much food as he desires. Withholding of food is indicated only if, and as long as, the patient is vomiting or the degree of shock does not permit alimentation. Morphine should not be administered because of its tendency to produce nausea and vomiting. If pain is severe, "Demerol Hydrochloride" may be used. A barbiturate may be administered if a sedative is indicated for apprehension and restlessness. Atropine should not be administered until after the emergency is over, because of its tendency to increase the pulse rate and thus void one of the vital signs useful in evaluating the status of the patient in so far as the stage of shock is concerned. It also produces gastric and small-intestinal stasis. Transfusions of blood or plasma or intravenous infusions are given according to medical indications, always when the pulse is 120 or more or the blood pressure is 90 or less, or if the erythrocyte count is below 2,500,000. Iron, in liquid form, may be prescribed after hemorrhage has ceased. In some clinics roentgenologic examination is performed before bleeding has ceased. It is safer to delay this procedure until a week or 10 days have elapsed after the acute episode, and the stools no longer contain gross evidence of blood. The roentgenologist should be warned that the patient has recently stopped bleeding, in order that vigorous abdominal palpation procedures be omitted. It is advisable that an intern accompany the patient to and from the x-ray department.

The question of whether or when to operate on a patient who is bleeding or who has bled is an individual one. The mortality in intelligent active medical management is low; nevertheless it exists. The mortality of patients operated on who are in shock or who recently have been in shock is considerably higher. Many factors have

to be considered and weighed carefully. Among these are the age and personality of the patient, the number of previous hemorrhages, the severity of the hemorrhage, the degree of shock,¹ the availability of large amounts of blood for transfusion, the skill and experience of the surgeon and the anesthetist, and the trauma of operation. Surgery is contraindicated when the patient is in shock. It should be delayed when a patient has been in shock and has just recently stopped bleeding, as the trauma of operation may precipitate another period of shock which may be irreversible. If there is evidence of continued massive hemorrhage and the patient is not in shock, surgical intervention will be necessary, especially in sclerotic individuals. After a patient has stopped bleeding, surgery should be recommended if he is over the age of 50, if he has a gastrojejunal ulcer, if he shows evidences of unwillingness or inability to adhere strictly to medical management of his ulcer, or if there has been a previous hemorrhage. In such cases surgery should be performed when the cardiovascular system has become well stabilized and anemia and hypoproteinemia have been corrected.

Obstruction. Obstruction of the outlet of the stomach may be due to spasm, to edema and inflammatory swelling about the ulcer, to cicatricial stenosis, or to a combination of these factors. Symptoms and signs of obstruction include vomiting of food ingested during previous meals, belching of foul odors, and, in individuals with thin abdominal walls, visible peristalsis traveling from the left upper quadrant toward the umbilicus. If vomiting has been pronounced, there may be clinical and laboratory evidence of dehydration and alkalosis. Aspiration of the stomach the morning after an evening meal containing identifiable food will yield the food in undigested or partially digested form. Roentgenologic examination of the stomach gives the most valuable evidence of obstruction, for it permits not only the determination of the site, nature, and extent of the obstructing lesion but also the degree of retention. The barium meal should be aspirated from the stomach as soon as the examination has been completed.

TREATMENT. The stomach should be intubated and constant suction applied. Alimentation should be administered intravenously and should be aimed at correcting dehydration, acid-base imbalance, and hypoproteinemia, as described in

the section on Continuous Gastric Aspiration. After 48 to 72 hours, liquid feedings of milk and cream or protein hydrolysate—"Dextri-maltose" solution may be administered, the suction being discontinued for about 2 hours after each feeding. If the feedings are returned to the suction bottle on resuming suction, the obstruction is still present. If the obstruction has been due to spasm or edema, it will have been relieved partially at the end of 48 to 96 hours, and entirely at the end of a week or 10 days. At the end of this period the stomach should be re-examined roentgenologically. If vomiting occurs or if the stomach is still dilated with little or no barium passing into the duodenum, and aspiration in the evening reveals a quantity of 800 to 2000 ml., surgical intervention should be resorted to and an adequate subtotal gastric resection performed. Surgery should not be performed unless the stomach has been adequately decompressed; otherwise difficulties with the stoma may be encountered after operation.

Gastrojejunal (Marginal, Anastomotic) Ulcer. The term "gastrojejunal ulcer" is used to describe a peptic ulcer which develops at or near the site of anastomosis of stomach and jejunum. It is a complication of gastroenterostomy performed for peptic ulcer, and occurs more frequently after a simple gastrojejunostomy than following subtotal gastric resection. Its occurrence after subtotal gastric resection usually means that the resection has been inadequate. The ulcer is situated more frequently on the jejunal than on the gastric side of the anastomosis.

Symptoms may appear in three weeks to more than 20 years after the gastroenterostomy. Pain is the outstanding symptom, though it may be absent and the first manifestation may consist of melena. The pain occurs early after a meal, and the relief afforded by food and antacid is of short duration because the ulcer is protected from acid for only a brief period. It is experienced most frequently in the left midabdomen, often in the region of the umbilicus, and occasionally in the epigastrium. The pain may be influenced by changes in the position of the body. Positions which permit acid to bathe the ulcer are usually avoided by the patient, as these precipitate the pain, while those which keep acid gastric content away from the ulcer site are favored. Physical examination is usually negative except for tenderness localized to the site of the ulcer. The

complications of gastrojejunal ulcer are similar to those of any other type of peptic ulcer; in addition, a gastrojejunocolic fistula may develop.

DIAGNOSIS. The diagnosis is established by the roentgenologic demonstration of a niche or gasticoscopic visualization of the crater. Failure to demonstrate a niche by roentgenologic means should not be considered too strongly as evidence against the existence of an ulcer in the presence of typical symptoms. The presence of free hydrochloric acid is essential to the diagnosis of gastrojejunal ulcer. In the performance of the gastric analysis the tube tip should be introduced into the stomach under fluoroscopic guidance, and kept there. During the test the patient should assume that position, demonstrated roentgenologically beforehand, which favors retention of gastric secretion in the portion of stomach containing the tip of the tube.

TREATMENT. Once a gastrojejunal ulcer has developed, the likelihood of intractability is greater than in the case of duodenal or gastric ulcer. Medical management must be strict and protracted, preferably in a hospital; otherwise it will not be effective. If the ulcer proves refractory, surgery will be necessary. The nature of the operative procedure to be used will depend on the type of operation previously employed. If a simple gastroenterostomy has been performed, the anastomosis should be taken down and an adequate subtotal gastric resection made. If a gastric resection has been previously performed, the probability is that it was inadequate and a more adequate one should be substituted. If such is not feasible, a vagotomy may yield excellent results.

GASTROJEJUNOCOLIC FISTULA

Gastrojejunocolic fistula occurs most commonly as a result of perforation of a marginal ulcer into the colon. The clinical manifestations, similar to those of a gastrocolic fistula, occur as a result of ingested food by-passing the small intestine and entering the colon. Their severity depends on the size of the fistula. Characteristic are the passage of frequent stools containing undigested food and the belching of gases with a fecal odor. Despite a good food intake, there develops loss of weight, dehydration, anemia, hypoproteinemia, edema, and stigmas of vitamin deficiency. A craving for food, difficult to satisfy, occurs in some cases. When the fistula is large,

the diagnosis is readily established by observing the passage of barium into the stomach during the performance of a barium enema or by the rapid entry of a barium mouth meal into the colon. When the fistula is small, repeated attempts may be necessary to demonstrate its existence. Treatment consists of surgical repair of the defect after the nutritional status has been improved and existing deficiencies corrected. This may be accomplished by parenteral means or by intrajejunal alimentation if a nasal tube can be inserted into the jejunum distal to the site of the perforation.

Somewhat similar clinical manifestations may occur following accidental anastomosis of the stomach to a loop of lower ileum instead of upper jejunum during the performance of a gastroenterostomy. The existence of such a gastroileostomy may be established roentgenologically by observing barium re-enter the stomach hours after the mouth meal has been emptied, or by noting a rapid emptying of the mouth meal into the colon.

Prognosis. Disappearance of symptoms and healing of the duodenal ulcer can be effected in about 90 per cent of the cases, providing the patients are willing and able to adhere to an adequate therapeutic regimen. The problem of keeping the ulcer healed, however, is a more difficult one. One of the reasons for this lies in the inherent human tendency to depart from therapeutic procedures which involve dietary modifications and restriction, as soon as, or shortly after, freedom from symptoms has been experienced. Another reason is a failure on the part of the physician to appreciate, discover, and handle successfully the emotional factors which motivate the disease. Following the healing of an ulcer, the patient should remain on an ulcer regimen as long as he is subjected to these motivating influences. He should continue interval feedings, and when such is not feasible, substitute a nonabsorbable antacid. He should continue abstinence from caffeine and alcohol-containing beverages. The use of tobacco should be abolished if there has been a clear-cut relationship between smoking and aggravation of ulcer symptoms. The writer does not forbid smoking in moderation when the habit affords mental relaxation. In about 10 per cent of the cases, intractability, hemorrhage, perforation, or pyloric obstruction will necessitate surgery.

PEPTIC ULCER OF THE STOMACH

The nature of pain, the signs, the pathologic characteristics, the tendency to recur, the sex distribution, and the complications of peptic ulcer of the stomach (gastric ulcer) are similar to those of duodenal ulcer. Despite the many similarities, certain differences between the two diseases exist.

The peak incidence for gastric ulcer is in the fifth decade, a decade later than that for duodenal ulcer. Gastric ulcer is encountered roentgenologically one sixth to one tenth as frequently

that the patient be hospitalized so that the therapeutic regimen, similar to that for duodenal ulcer, can be more strictly enforced. Roentgenologic examination should be repeated at the end of three weeks and, if necessary, the site of the ulcer inspected gastroscopically. Despite an apparently favorable response, the ulcer site should be submitted to periodic roentgenologic re-examination and, when indicated, gastroscopy, every 3 months for one year, and every 6 months for another 18 months, the exact time intervals depending on the specific case. Lap-

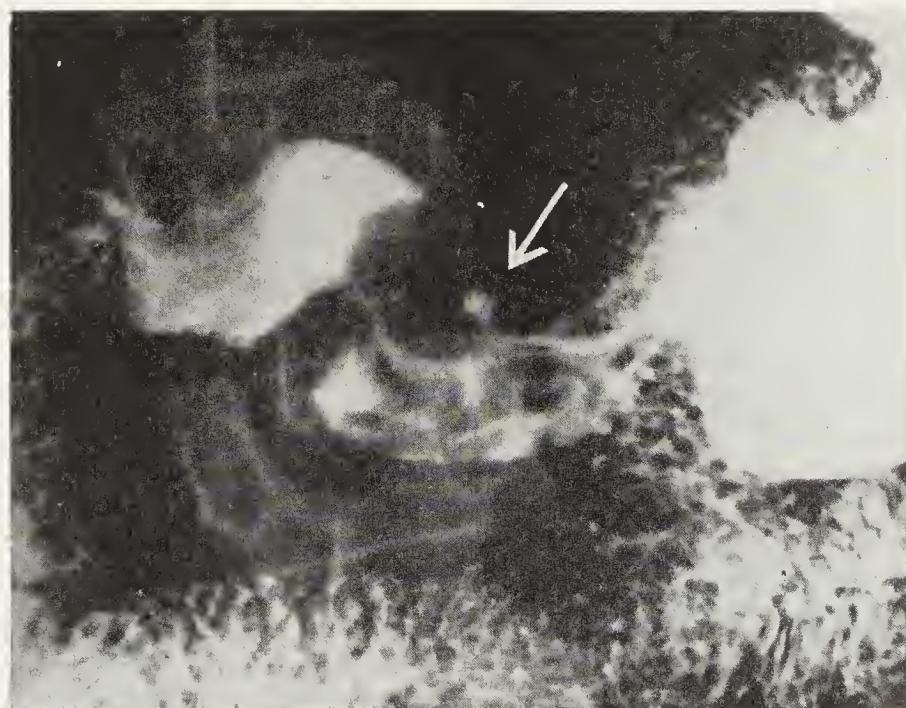


FIG. 231. Roentgenologic appearance of crater (arrow) of benign peptic ulcer projecting from lesser curvature of prepyloric region of stomach.

as duodenal ulcer. Nausea occurs more commonly in gastric ulcer, probably because of the more frequent coexistence of gastritis. Hematemesis is more apt to occur in hemorrhage from a gastric ulcer. Gastric ulcer is usually associated with lower free hydrochloric acid values, although high acid figures are not uncommon when the ulcer is located at or near the pylorus.

The diagnosis of gastric ulcer is established by roentgenologic examination. The majority of ulcers occur near the pylorus and on the lesser curvature. The crater, when seen in profile, is usually visualized as a penetrating niche (fig. 231). Gastroscopy is valuable as a supplementary procedure and may reveal some ulcers, especially superficial ones, not disclosed roentgenologically.

In the nonsurgical management of the uncomplicated gastric ulcer it is highly desirable

rotomy should be resorted to promptly in all instances in which the crater has not permanently disappeared or has recurred, or when there is any doubt as to whether the lesion is benign or malignant. The surgical procedure of choice is that of gastric resection with as wide a removal of the ulcer site as possible. Vagotomy has no place in the treatment of gastric ulcer because of the possibility that the ulcer may be malignant.

BENIGN VS. MALIGNANT ULCER

The differentiation of benign from malignant ulcer may at times be impossible by any procedure short of microscopic examination. Since 10 to 12 per cent of gastric ulcers are malignant, all available clinical and laboratory diagnostic procedures, including at times a therapeutic test, should be employed to arrive at a decision. There are no clinical criteria which can be relied upon

to differentiate the two, though the concomitant presence of a duodenal ulcer argues in favor of the gastric lesion being benign. An absolute achlorhydria strongly favors a malignant ulcer, but the presence of a high degree of gastric acidity does not rule out malignancy. The results of the iodoacetate index and the electrogastrogram, in their present state of development, should not be considered too strongly since false positives as well as false negatives may lead to an erroneous decision. Roentgenologically, an ulcer should be considered malignant and prompt laparotomy resorted to if it is located on the greater curvature, if the crater is located on a subtraction defect, or if the crater is surrounded by a translucent halo (Carman's sign). All other gastric ulcers should be subjected to a three-week trial of closely supervised and intensive therapy in a hospital. If the crater disappears and remains absent when roentgenologic and gastroscopic examinations are made three weeks later, one can assume that the ulcer was benign only if it remains absent. If a decrease in the size of the niche has not occurred at the end of three weeks, malignancy should be suspected and surgery advised.

PRIMARY JEJUNAL ULCER

Primary ulcer of the jejunum, single or multiple, is rare. It is more commonly located in the upper jejunum and on the antimesenteric border, and may be associated with other ulcers in the stomach or duodenum. The diagnosis rarely is made until some complication, such as perforation, obstruction, or hemorrhage, makes laparotomy imperative. Pain, when present, is usually localized in the lower epigastrium, around or immediately below the umbilicus. The diagnosis of primary jejunal ulcer should be considered in all patients who complain of peptic ulcer distress but in whom a duodenal or gastric ulcer or a duodenitis is not demonstrable; in patients with recurrent attacks of unexplained partial upper small-intestinal obstruction; in individuals with acute perforation; and in those with unexplained melena. Surgery is indicated in all cases because of the danger of complications, especially perforation.

PEPTIC ULCER OF THE ESOPHAGUS

Peptic ulcer of the esophagus in most instances is single and occurs in the lower 3 inches. It may

occur as a result of secretion of acid gastric juice by heterotopic gastric mucosa, as a result of the regurgitation of acid gastric juice through a relaxed cardia, or when the cardia is located above the diaphragm, as in congenital short esophagus with thoracic stomach. The chief symptom, pain, occurs within a few seconds of the swallowing of solid food and is experienced at or near the ensiform process or beneath the sternum, and may be referred to the back or anterior chest. Dysphagia may be complained of early or late, depending on whether spasm or stenosis is present. The diagnosis may be established by the roentgenologic demonstration of a niche. Biopsy through an esophagoscope should be performed in all cases to rule out other types of ulcer, particularly carcinoma. The complications are similar to those of duodenal ulcer. An excellent plan of immediate therapy consists of hourly feedings of a solution of equal parts of a protein digest and "Dextri-maltose" mixture, as described in the section on duodenal ulcer. Varying proportions of milk and cream can be used instead. Essential vitamins should be supplemented in liquid form. The liquid diet should be maintained for about 10 to 14 days, after which a gradual resumption of bland food may be permitted. The patient should sleep or rest in a semi-Fowler position. If conservative measures fail, gastrostomy may be required.

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Diseases of the Duodenum and Mesenteric Small Intestine

Thomas E. Machella

Duodenitis
Duodenal Stasis
Chronic Regional Enteritis
Pathology
Clinical Picture
Laboratory Findings
Roentgenologic Findings
Diagnosis
Treatment
Acquired Diverticula
Meckel's Diverticulum
Tumors of the Small Intestine

DUODENITIS

The term *duodenitis* is applied to an inflammation of the mucosa of the first and second portions of the duodenum. Such inflammation may be confined to these areas or may be associated with, or part of, an inflammatory process involving the gastric mucosa. It occurs in individuals who are subjected to emotional disturbances of the type encountered in peptic ulcer or chronic superficial or hypertrophic gastritis. The symptoms may suggest duodenal ulcer. Massive hemorrhage may occur. Gastric acidity is usually increased. The diagnosis is presumed from the roentgenologic demonstration of spasm and irritability of the duodenal cap, and inability to demonstrate an ulcer fleck. When acute symptoms have subsided and irritability has disappeared, roentgenologic examination may reveal coarse mucosal folds. The treatment is similar to that of peptic ulcer.

DUODENAL STASIS

Duodenal stasis most commonly occurs as a result of a disturbance in the motor function of the proximal duodenum in asthenic, viscerotonic, and emotionally unstable individuals. In such cases, a "to-and-fro" action of the barium in the descending limb of the duodenum, associated with delayed gastric emptying, is usually observed during fluoroscopy.

Symptoms appear for the first time following loss of weight after an emotional upset. They consist of a sense of epigastric fullness and gase-

ous distention, flatulence, belching, pain, anorexia, nausea, vomiting, and headache. The pain, which may be severe and colicky, is likely to be precipitated or aggravated by ingestion of food, but may be relieved by lying prone or by assuming a knee-chest position. Loss of weight is progressive.

The ultimate objectives of treatment are weight gain and the successful handling of the psychogenic factors involved. The diet should consist of bland foods, rich in calories. The feedings should be small and administered frequently. Changes in posture, such as elevating the foot of the bed, lying on one side or the other for an hour after meals, or assuming a prone or knee-chest position may relieve postprandial epigastric distress, and facilitate emptying of the stomach and duodenum. A cholinergic drug such as "Urecholine," administered before each meal, may help to relieve stasis. At times, a period of intravenous or intrajejunal alimentation may be required. An intensive psychotherapeutic program should be instituted. A short-circuiting operation, such as an enteroenterostomy, invariably fails to afford relief unless an organic obstruction can be demonstrated.

CHRONIC REGIONAL ENTERITIS

Regional enteritis occurs in both sexes and at any age. The majority of patients are in the third and fourth decades when the diagnosis is first established. Though some deny that the regional enteritis is a psychosomatic disease, others, including this writer, are convinced that it is. Emotionally, the patients are somewhat similar to those with idiopathic ulcerative colitis in that they are frustrated for one reason or another. As a rule, however, they appear to be more intelligent, less dependent, and mentally more mature. Another concept of the etiology maintains that the changes in the bowel wall are secondary to obstruction of the lymphatics

draining the involved segments. However, obstruction of the lymphatics is probably secondary to the primary disorder in the bowel wall.

Pathology. The disease may be confined to the terminal ileum but may also involve additional segments or all of the small intestine. At times, the duodenum or the cecum and ascending colon may be involved. The wall of the diseased intestine is greatly thickened as a result of edema, cellular infiltration, and fibrosis. The lumen is narrowed, and the mucosa shows varying degrees of ulceration, destruction, and hyperplasia. Miliary nodules containing epithelial, round, and giant cells may be found on the serosa.

Clinical Picture. The presenting symptoms are variable; the manifestations may resemble those of acute appendicitis, chronic ulcerative colitis, intestinal obstruction, or a fever whose origin is not readily apparent. Not infrequently the diagnosis is first made during laparotomy for suspected acute appendicitis. In the acute forms, less commonly encountered than the chronic variety, the outstanding symptom may be massive hemorrhage as manifested by melena.

In the typical case, the history consists of mild, continuous or intermittent diarrhea accompanied by abdominal cramps over a period of months or years. Fever is frequently, but not always, present. It is intermittent in type and not always associated with diarrhea. The fever is higher and more persistent when the entire small intestine is involved. Many of the patients also have symptoms of chronic gastritis. During the later stages of the disease, a mass is frequently palpable in the right lower quadrant of the abdomen or elsewhere, depending on the location of the diseased section of the intestine. Evidence of malnutrition may be present. Complications include fistula formation, abscesses at the site of perforation and intestinal obstruction, and, in the acute forms, massive hemorrhage.

Laboratory Findings. Leukocytosis is usually present when the disease is active; otherwise, the leukocyte count is normal or even low. An eosinophilia is encountered in rare instances. Hypochromic anemia on a nutritional basis may occur. Occult blood is found in the stool in the more severe cases and, if diarrhea is marked, mucus also may be present. Gross pus is found only rarely in the stools.

Roentgenologic Findings. In the early stages of the disease, characteristic roentgenologic find-

ings may be absent. In the later stages, the involved portion presents a characteristic appearance which consists of a thin thread of barium often referred to as the "string sign." The segments of the bowel proximal to the constricted areas are dilated. Involvement of the terminal ileum may be demonstrated after a barium meal, as well as after a barium enema. Involvement of other portions of the small intestine is at times more clearly demonstrated by the small-intestinal-enema technic or by the introduction of barium through a Miller-Abbott tube into the segment under suspicion. Involvement of the cecum and ascending colon are best demonstrated by a barium enema.

Diagnosis. The diagnosis of regional enteritis, particularly of the terminal ileum, is not difficult when there is encountered a young person with a mass in the right lower quadrant, fever, anemia, and the characteristic roentgenologic findings. Not infrequently, an appendectomy scar is present. A somewhat similar picture may, at times, be obtained when the terminal ileum is involved in ulcerative colitis, in Hodgkin's disease, in primary sarcomatosis, in primary ileocecal tuberculosis, in sarcoidosis (Besnier-Boeck-Schumann disease), in endometriosis, and by multiple carcinoids.

Chronic ulcerative colitis may be ruled out by the character of the stools, the sigmoidoscopic picture, and the barium enema. Hodgkin's disease and primary sarcomatosis of the small intestine run a more severe and progressive course, and give rise to rapid emaciation and gross hemorrhage. Primary ileocecal tuberculosis is very rare in adults, but occasionally occurs in children and adolescents. Tuberculous involvement of the ileum is more frequently associated with evidence of tuberculosis elsewhere in the body, particularly in the lungs. Differentiation from sarcoidosis may not be possible clinically or by roentgenologic means. The same applies to multiple carcinoids and endometriosis, and microscopic examination must be resorted to. Sprue usually can be readily differentiated by the clinical picture, the large frothy stools, the macrocytic type of anemia, and the absence of stenosing lesions on roentgenologic examination.

Treatment. The type of treatment depends upon the stage and activity of the disease, the location and extent of involvement, and complications. Disappointment in the results of surgery

is gradually leading to the adoption of medical plans of therapy.

Conservative management includes correction of existing deficiencies, a high-protein, low-residue diet supplemented with essential vitamins and iron, and the discovery and successful handling of the emotional problems motivating the disease. An excellent form of alimentation during relapses consists of a solution of a mixture of equal parts of a soluble protein hydrolysate and "Dextri-maltose" administered according to the plan outlined in the section on chronic ulcerative colitis. "Sulfasuxidine," streptomycin, or aureomycin may be given a trial in patients with fever, although these rarely influence the course of the disease. Some writers have been impressed by the results of roentgen therapy. Convalescence should be prolonged and situations which threaten to upset the patient emotionally should be aborted or prevented.

The treatment of choice in the past has been surgery, consisting of either resection of the involved segment or a short-circuiting operation. Both procedures entail a significant operative mortality, and are followed by recurrence in a discouragingly large proportion of patients. Surgery is not feasible nor practical when the disease process involves many segments or all of the small intestine. The entire small intestine and colon should be studied carefully by roentgenologic means for evidence of involvement of segments other than the terminal ileum in all patients in whom surgery is contemplated, so as to determine whether or not "skip" areas are present (i.e., involvement of segments of the intestine with interspersed areas of normal gut). Obstruction and perforation are clear-cut indications for surgery.

ACQUIRED DIVERTICULA

Acquired diverticula of the small intestine occur as herniations of mucosa through weak points in the intestinal wall, and are examples of pulsion diverticula. They are encountered more frequently in the upper small intestine and less frequently as the terminal ileum is approached. They are usually single, and when multiple often occur in association with diverticula elsewhere in the intestinal tract. Most of them are found in individuals beyond the age of 50 years.

Uncomplicated acquired diverticula of the small intestine causes no symptoms as a rule.

The failure to empty properly may result in inflammation and give rise to symptoms, including pain, nausea, vomiting, and tenderness. Perforation or hemorrhage may occur. The sac may become strangulated and gangrenous, and at times be responsible for partial intestinal obstruction. The diagnosis is made by roentgenologic visualization of the gut (fig. 232). As a rule, no

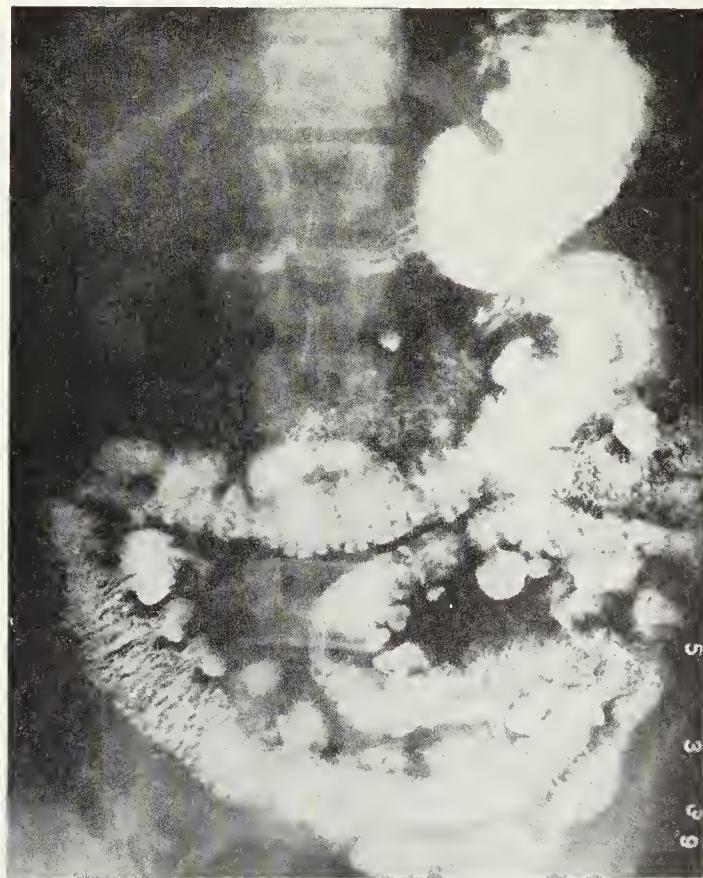


FIG. 232. Roentgenologic appearance of the jejunum following ingestion of barium meal. The barium-filled sacs projecting from the intestine are asymptomatic diverticula.

treatment is necessary. Complications such as inflammation, hemorrhage, obstruction or perforation require appropriate medical or surgical measures.

MECKEL'S DIVERTICULUM

Meckel's diverticulum occurs as a result of incomplete obliteration of the omphalomesenteric duct, its structure depending on the degree of obliteration. Its length varies from 25 to 125 mm. The diverticulum is usually situated on the antimesenteric border of the ileum, 25 to 100 cm. above the ileocecal valve. The lumen is lined with ileal mucosa but heterotopic tissue such as pancreatic rests or gastric, colonic, or duodenal mucosa may also be present. The uncomplicated

diverticulum usually is asymptomatic. Complications include acute inflammation, perforation, intestinal obstruction, volvulus, intussusception, peptic ulceration when heterotopic gastric mucosa is present, and gross hemorrhage. Benign and malignant tumors may originate in the diverticulum. The roentgenologic demonstration of a Meckel's diverticulum is extremely difficult. Most cases are first recognized at laparotomy performed for a suspected acute appendicitis or some other complication.

TUMORS OF THE SMALL INTESTINE

All three types of tumors—carcinoma, sarcoma, and benign lesions—occur in the small intestine, though rarely. Malignant tumors may reach considerable size, are usually single, and spread by lymphatic metastasis or direct invasion. Benign growths are often polypoid, sometimes multiple, and usually, but not always, smaller.

The most common location of carcinoma is the second portion of the duodenum, and the next most frequent is the lower ileum. Adenocarcinoma occurs more frequently in the duodenum, while the scirrhouous or napkin-ring type is more often found in the lower ileum. Bleeding, gross or microscopic, is the most important clinical manifestation. The presenting symptoms may also be those of mechanical obstruction and, rarely, of perforation. Metastasis occurs early, and recurrence within a few months after resection is the rule.

The most common sites of sarcoma are the terminal ileum and jejunum. Pain is a frequent symptom. The tumors tend to grow externally and are less apt to ulcerate, so that bleeding usually does not occur. Mechanical obstruction may occur as a result of either distortion of the lumen or infiltration of the bowel wall. Ascites may develop as a result of mesenteric or peritoneal involvement or of pressure on the main venous trunks.

The most frequent sites of benign tumor are the ileum and the duodenum. Adenomas are the most common, and myomas are next in frequency, with fibromas and lipomas slightly less prevalent. About one half of these tumors give rise to symptoms as a result of hemorrhage, obstruction, or intussusception.

The discovery of all three types of lesions is made by roentgenologic means. Often special intubation procedures may be required. The exact type of lesion is determined by microscopic examination after surgical resection.

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Appendicitis

Thomas E. Machella

Acute Appendicitis

- Incidence
- Etiology
- Clinical Picture
- Laboratory Findings
- Complications
- Diagnosis
- Differential Diagnosis
- Treatment
- "Chronic" Appendicitis or Appendiclausis

ACUTE APPENDICITIS

Incidence. Acute appendicitis can occur at any age but is most often seen between the ages of 10 and 30 years. It has been estimated that 1.8 per cent of the total population of the United States undergo appendectomy yearly.

Etiology. The pathogenesis of appendicitis has not been settled to the satisfaction of all. Some maintain that the disease is primarily of bacterial origin, the bacteria reaching the appendix through its blood supply (hematogenous) or by lodgment in its crypts of swallowed microorganisms (enterogenous). Others maintain that obstruction of the lumen occurs first and that inflammation is secondary. The anatomic nature of the appendix itself is such that substances which enter it may find difficulty in leaving. Though a large variety of mechanical factors can constitute physical handicaps for ready evacuation of the appendix, an appendicolith is probably the most important single cause of obstruction of the lumen. One or more are found in 50 to 80 per cent of cases of appendicitis. Sometimes swallowed foreign bodies such as pins, small bones, or lead shot may lodge in the appendix and give rise to obstruction and even perforation of its wall. Occasionally worms, especially *Enterobius vermicularis* and sometimes *Ascaris lumbricoides*, may lodge in the appendix and provoke colic. Following obstruction due to any cause, the secretory pressure of the appendix produces injury to the tissue with leukocytic invasion, pus formation, and subsequent gangrene and perforation. Practically all of the histologic varieties of the disease can be produced by occlusion of the lumen in animals such as the chimpanzee and

the rabbit, in which the appendix secretes fluid actively.

The results of bacteriologic examination of the contents of inflamed appendixes vary. Undoubtedly the streptococcus plays an important role in the etiology. The fact that colon bacilli may rapidly overgrow other organisms may account for the significance sometimes ascribed to their presence. Other organisms, including anaerobes, have been recovered from inflamed appendixes.

Clinical Picture. The typical attack of appendicitis is characterized by intermittent or colicky pain in the epigastrium or periumbilical region, at times generalized but tending shortly after to become localized in the right lower quadrant. The onset of the pain is frequently followed by nausea and/or vomiting. Anorexia is common; it may precede the pain or it may come on with nausea and vomiting. Localization of the pain in the right lower quadrant is associated with a change in its character. It becomes dull and constant and then gradually increases in severity; nausea and vomiting tend to subside. Complete obstruction of the lumen is usually associated with pain of a colicky nature. The painful episodes are of short duration but recur with increasing severity. Cessation of pain may indicate expulsion of an obstructing substance from the appendix into the lumen of the gut, but also, like "the calm before the storm," may herald the onset of gangrene and perforation with subsequent peritonitis.

In the usual case, the temperature rarely exceeds 100° F. When gangrene develops, it may reach 101° F. Perforation and peritonitis are usually associated with still higher temperatures. An increased pulse rate is usually present but rarely exceeds 100 per minute, unless gangrene or perforation occurs. Children are apt to have a higher fever and pulse rate than adults. In the latter group, both temperature and pulse rate may be normal. Constipation occurs in about 15 per cent of the patients during the acute symptoms, while diarrhea is less common. The incidence of diar-

rhea in children is difficult to assess, as not infrequently laxatives have been administered.

The most important physical sign of acute appendicitis is tenderness over the site of the appendix; this usually coincides with the region in which the pain localizes. The tenderness becomes more diffuse and localization difficult when peritoneal irritation spreads. Rebound tenderness may be elicited when the parietal peritoneum is involved in the inflammatory process. Rigidity of the abdominal wall may occur as additional evidence of peritoneal irritation. Rectal examination, with the patient in the left-lateral position, may elicit tenderness in the right pelvis.

Laboratory Findings. The leukocyte count is usually elevated, the degree of leukocytosis depending on the severity of the inflammation and the presence or absence of suppurative complications. It may vary from 10,000 in mild cases to over 20,000 per cu. mm. when peritonitis is present. A normal leukocyte count, however, may be encountered even in patients with severe inflammation, but in such cases the differential count will usually reveal a marked increase in the number of immature neutrophils, as well as an increase in the total number of cells of the myeloid series. Children tend to develop a greater leukocytosis than adults.

Urinalysis should be performed in all instances of suspected appendicitis and should be especially examined for red blood cells, leukocytes, bacteria, and sugar. In men, the specimen of urine should be obtained before rectal examination is performed. In women, the sample should be collected in such a manner as to avoid contamination with vaginal discharge, preferably by catheterization. Barium enema is contraindicated when acute appendicitis is suspected.

Complications. Peritonitis is a dreaded complication of appendicitis. Its presence is usually heralded by an increase in the area of pain, tenderness, and rigidity, and subsequently by abdominal distention and cessation of peristalsis. Fever and leukocytosis increase as the process spreads.

Perforation of the appendix with extrusion of pus into a pocket formed by adhesions results in an abscess. The localization of pain and tenderness which have been diffuse, and a lessening of fever and degree of leukocytosis with a restoration of a normal number of mature neutrophils indicate that the infection has become localized

with abscess formation. Abdominal palpation may reveal an indefinite, tender mass which may also be palpated by rectum. When the abscessed wall includes part of the cecum, sigmoid, renal pelvis, urinary bladder, ureter, or vagina, fistula formation may result. A sinus may occur if the content of an appendiceal abscess finds its way to the skin surface.

Suppurative pyelophlebitis and liver abscess occur rarely. These serious complications of appendicitis are usually heralded by a severe chill, high fever, sweating, and pain, and also tenderness and rigidity in the right upper quadrant. A mild jaundice may also occur. Excursion of the right dome of the diaphragm is usually restricted. Subdiaphragmatic abscess may also occur, at times, as long as a month after the acute attack. Other complications include pulmonary embolism, adynamic ileus, and partial or complete intestinal obstruction as a result of adhesions.

Diagnosis. The occurrence of epigastric, hypogastric, or periumbilical pain, with subsequent localization in the right lower quadrant, associated with nausea and vomiting and tenderness in the right lower quadrant, justifies the diagnosis of acute appendicitis. Individuals with disease of the spinal cord from any cause, when developing acute appendicitis, may demonstrate none of the clinical manifestations to point to the appendix as the cause of illness. In the aged, in whom the primary process is sometimes vascular occlusion, there is little or no antecedent colic. The process remains almost asymptomatic until local or general peritonitis sets in.

A careful history must be elicited in cases presenting atypical features, as appendicitis can simulate almost any acute disease of the abdomen. A retrocecal appendix may give rise to pain in the right flank or costovertebral area. Location of the inflamed appendix on the psoas muscle may give rise to pain on the anterior and inner aspects of the thigh when the hip is moved. Contact with the ureter may give rise to dysuria or frequency and radiation of the pain into the genitalia or inner aspects of the thigh. Pain low in the back or in the perineum as well as pain on defecation may occur when the appendix is in contact with the sigmoid. Left-sided appendicitis in older persons may be mistaken for acute sigmoid diverticulitis.

Differential Diagnosis: IN THE MALE. The differential diagnostic possibilities in the male in-

clude a mesenteric lymphadenitis, diverticulitis of the colon, carcinoma of the proximal colon and cecum, Meckel's diverticulitis, regional enteritis, and urinary tract disorders.

Unless laparotomy is resorted to, the differential diagnosis between acute mesenteric lymphadenitis and acute appendicitis frequently cannot be made. The symptoms and signs can be quite similar. Suggestive of mesenteric lymphadenitis are: a history of a preceding or associated upper respiratory infection; a history of repeated attacks; a fever and leukocytosis out of proportion to the physical signs; absence of rebound tenderness; a relative lymphocytosis; and, in children, the ability to palpate masses of lymph nodes in the iliac regions, especially on the right side—the termination of the mesentery.

Diverticulitis of the cecum is very rare, particularly in individuals under the age of 40 years. Differentiation from acute appendicitis is difficult and at times impossible. Diverticulitis of the sigmoid, rare under the age of 40 years, can usually be differentiated. Pain at the onset is commonly left-sided. Tenderness can frequently be elicited in the left lower quadrant or by rectum, and often is located over a palpable mass. The presence of gross blood in the feces favors the diagnosis of diverticular disease. Anorectal causes of bleeding should be excluded if reliance is to be placed on this finding. Occasionally, diverticulitis of a redundant loop of sigmoid may give rise to pain and tenderness in the right lower quadrant. Left-sided appendicitis and sigmoid diverticulitis may be extremely confusing, and cannot be differentiated preoperatively readily and safely without resorting to barium enema and sigmoidoscopy. These procedures entail a risk. The differentiation between appendicitis and Meckel's diverticulitis usually cannot be made preoperatively. Regional ileitis may also present diagnostic difficulties, and at times laparotomy must be resorted to if the signs and symptoms are sufficiently suggestive of appendicitis to make roentgen barium studies hazardous. Acute gastroenteritis, as a rule, presents no great diagnostic problem.

Renal lesions should present little confusion when symptoms are typical. Ureteral calculus gives rise to very severe pain in the right loin which radiates to the genitalia, and to frequency, dysuria, and gross or microscopic hematuria. Fever and leukocytosis are usually absent, but reflex gastrointestinal symptoms may be present.

A flat film of the abdomen may disclose an opaque shadow in the course of the right ureter. Occasionally, an inflamed retrocecal appendix in contact with the right ureter may give rise to ureteral type of pain and hematuria, as well as to the signs and symptoms of acute appendicitis. In the initial stages, pyelitis of the right kidney can simulate appendicitis very closely. In such cases, bacteria without pus cells may be present in the urine. Signs of peritoneal irritation and tenderness on rectal examination are absent. Hydro-nephrosis of the right kidney may give rise to fever, leukocytosis, tenderness on palpation, and suggestion of a mass in the right abdomen. The demonstration of an enlarged kidney by physical examination or on a scout film of the abdomen favors the diagnosis of hydronephrosis. A distended and inflamed gallbladder may cause pain low in the right abdomen, while a high-lying inflamed appendix may give rise to pain in the right upper quadrant. A perforated peptic ulcer with seepage of gastric content down toward the pelvis may simulate the signs and symptoms of acute appendicitis, particularly of a ruptured appendix. Usually the onset history is different in the two diseases. Abdominal pain of diabetic acidosis subsides as acidosis is overcome. Right lower lobe pneumonia may give rise to reflex pain, tenderness, and muscle tenseness in the right lower quadrant. The clinical signs of pneumonia, such as flaring alae nasi, cyanosis, herpes labialis, rapid respiratory rate, and expiratory grunt, should arouse the suspicion of the existence of pneumonia, even in the absence of clear-cut physical signs. There is usually a greater degree of fever and leukocytosis in pneumonia. Roentgenologic examination of the chest may reveal the cause of the symptoms in the absence of physical findings in the chest. Perforation of the cecum secondary to carcinoma, ruptured diverticulum, or granuloma may be impossible to differentiate from ruptured appendix.

Other conditions which at times require differentiation include abdominal crises of tabes, rupture of the deep epigastric artery, incarcerated inguinal or femoral hernia, sequelae of abdominal trauma, orchitis in an undescended testis, mesenteric occlusion, acute porphyria, intestinal obstruction, abdominal vein phlebitis, abdominal colic of plumbism, and polyarteritis nodosa.

IN THE FEMALE. In the female, not only most of the diagnostic possibilities occurring in the

male, but also diseases of the female pelvic organs, must be considered. The commonest of these is pelvic inflammatory disease. Generally, the patient has had symptoms for a longer period of time and is sicker, the fever and leukocytosis are greater, and the tenderness on vaginal or rectal examination is more related to the adnexae than to the appendix. Manipulation of the cervix gives rise to pain. The sedimentation of erythrocytes is usually accelerated, in contrast to a normal rate or only a slight increase in appendicitis. The symptoms may come on or be exaggerated at the time of the menstrual period. Rupture of a Graafian follicle may simulate the signs and symptoms of appendicitis. The rupture usually occurs about two weeks before the expected onset of the next period. The severity of the manifestations depends on the amount of blood in the peritoneal cavity. The diagnosis cannot be established on clinical grounds with sufficient reliability to avoid laparotomy, except possibly if the signs and symptoms occur on the left side.

Ruptured ectopic pregnancy may be associated with amenorrhea, sudden onset of severe lower abdominal pain, nausea, vomiting, fever, and leukocytosis. The pain may be referred to the tip of the shoulder. The umbilicus may be discolored bluish green (Cullen's sign). Vaginal examination may reveal signs of early pregnancy. A mass may be palpable in the cul-de-sac. Laparotomy is usually imperative, as profound shock, depending on the degree of hemorrhage, may result from delay. Torsion of a pedunculated uterine fibroid, of a small ovarian or parovarian cyst, or of an ovary with a long attachment, may also simulate the clinical picture of appendicitis. The exact diagnosis is established at laparotomy, which is indicated regardless of the information gained by pelvic or rectal examination.

In the final analysis, a great variety of extra-appendiceal diseases and lesions may mimic the signs and symptoms of acute appendicitis. The mortality of delay is so great, as compared to the mortality of a simple appendectomy, that one is justified in resorting to laparotomy when there is any reasonable doubt as to the diagnosis. Time has not altered the old adage, "a live patient

without an appendix is much better off than a dead person with one."

Treatment. The treatment of the acutely diseased appendix consists of its removal as soon as the diagnosis is suspected and the patient adequately prepared. The time at which surgery should be performed, in the presence of complications of appendicitis, is a matter for decision in the individual case. The administration of cathartics to patients with suspected appendicitis is contraindicated.

"CHRONIC" APPENDICITIS OR APPENDICLAUSIS

The term "chronic appendicitis" has been loosely employed to indicate two different entities. One of these is recurrent acute appendicitis, which has already been discussed except for the feature of recurrence. The other use of the term "chronic appendicitis" is largely a misnomer, and has been applied to unexplained persistent symptoms referable to the right lower quadrant resulting from almost any cause, but usually due to emotional disturbances. Patients in the latter category are often made worse by removal of the appendix, and are rarely relieved except for psychotherapeutic effect. In the absence of clear evidence pointing toward an acute attack, operation for "chronic" appendicitis is unjustified.

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Diseases of the Colon and Rectum

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INTRODUCTION

The diagnosis of the various colonic and rectal diseases is established readily, not only because the clinical pictures are rather distinctive but also because the colon and rectum can be satisfactorily examined. Simple digital examination yields information about the anus and rectum. The interior of the rectum and lower sigmoid is visualized through a sigmoidoscope. The remainder of the colon can be examined roentgenologically. Additional information is obtainable from gross and microscopic inspection and from bacteriologic and chemical studies of the stool.

The reader is referred to Chapter 16 for consideration of general principles in regard to constipation and diarrhea.

SIGMOIDOSCOPY

Sigmoidoscopy is of utmost importance in the detection of diseases of the lower 25 to 30 cm. of the colon and rectum. Its use is indicated in ascertaining the causes of constipation, diarrhea, and hemorrhage from or obstruction of portions of the lower bowel within its reach. The diseases which may be revealed by the procedure

include carcinoma and other malignant diseases, benign polyps, diffuse polyposis, strictures, idiopathic ulcerative colitis, amebic colitis, bacillary dysentery, tuberculosis, proctosigmoiditis due to lymphogranuloma venereum or irradiation, melanoisis coli, diverticulosis, diverticulitis, intussusception, spastic colon, and megacolon. The instrument permits biopsy as well as removal of certain lesions within its reach. The danger of perforation of the bowel should always be kept in mind. This possibility is not great if ordinary precautions are taken. The examination should be delayed in the presence of pain or anal inflammation, fissure, or ulcer.

CANCER OF THE COLON AND RECTUM

Carcinoma of the colon and rectum is responsible for about 15 per cent of all deaths from cancer. Although the lesion has been reported in children, it is primarily a disease of the cancer age and spares neither sex.

Etiology. The carcinoma probably originates either in a preexisting polyp or as an indurated nodule in the mucosa. Polyps, single or multiple (including diffuse polyposis), are regarded as precursors. Pseudopolyps accompanying inflammatory lesions, such as chronic ulcerative or amebic colitis, may also undergo malignant degeneration. An inherited predisposition to carcinoma of the colon is suggested in some instances by its occurrence in relatives of patients with the disease. There is no evidence to suggest that either chronic constipation or diverticulosis is a predisposing factor.

Pathology. About two thirds of malignant tumors of the large bowel occur in the left half, while the remainder occur in the right. The most common sites of involvement, in descending order of frequency, are the rectum, sigmoid, cecum and ascending colon, transverse colon, descending colon, hepatic flexure, and splenic flexure. The majority of these are adenocarcinomas. A few are epitheliomas of the squamous cell variety, most of which are found in the anus and rectum.

Four types of adenocarcinoma occur: nodular, scirrhous, colloid, and papillary. In the proximal colon the lesions tend to be large, bulky, fungating, and friable, and frequently ulcerate. Obstruction is rare because the fecal stream is liquid and the diameter of the colon large. Carcinomas of the narrower distal colon, where the fecal stream is less liquid, are more frequently scirrhous and are more apt to produce obstruction because they tend to encircle the lumen. Metastasis occurs either by direct extension, by hematogenous spread, or by way of the lymphatics, the latter being the most important route. The most common sites for metastasis are the regional lymph nodes, liver, and lungs. Lesions of the rectum and sigmoid tend to metastasize with greater frequency, while those in the cecum do so less often.

Symptoms. The symptoms of carcinoma of the colon depend on its site, the pathologic nature, the extent and location of metastases, and the presence or absence of complications such as perforation or obstruction. The great majority of patients have either abdominal distress, gross rectal bleeding, or a definite change in bowel habits. Rarely, the finding of metastasis at distant sites furnishes the first clue.

Carcinoma of the right colon usually gives rise to clinical pictures which consist of either indigestion and abdominal distress, manifestations of anemia, or an asymptomatic palpable mass. The gastrointestinal complaints consist of anorexia, flatulence, nausea, vomiting, and variable degrees and types of abdominal distress. The distress arising from carcinoma of the cecum and ascending colon is often ill-defined and poorly localized to the right side of the abdomen. An obstructing lesion of the hepatic flexure or transverse colon may be associated with cramps or colicky pains in the right lower quadrant as a result of obstruction. Weakness and fatigue due to anemia, without gross bleeding, as well as weight loss, may also constitute the clinical picture in carcinoma of the ascending colon. In a small proportion of asymptomatic cases, a tumor mass is discovered accidentally. Constipation and/or diarrhea occur less frequently than in lesions of the left colon.

Obstructive manifestations more frequently dominate the clinical picture of carcinoma of the left half of the colon. A common onset symptom is a change in bowel habits. This consists of either

progressive constipation and diarrhea, or, much less frequently, of alternating constipation and diarrhea. Abdominal pain of variable severity may occur. Usually, it is poorly localized in the left abdomen. Relief may be afforded by the passage of flatus or feces. Despite the fact that gross blood in the stools is noted frequently, anemia is not so common or so severe as in carcinoma of the right colon. Weight loss occurs late.

Lesions of the rectum manifest themselves by producing changes either in the character or regularity of the stools. A gradual change from the usual bowel habit is noted frequently. This consists of increasing constipation, diarrhea, or constipation alternating with diarrhea. An urge to defecate frequently, along with a feeling of incomplete evacuation after defecation, is common. Blood may be noted on the outside of the stool, in the toilet bowl or bedpan, or on the toilet paper. The stool, at times, may consist entirely of blood. Some discomfort in the pelvis and/or irritation of the anus during defecation may be complained of. Pain during defecation is more prominent when the growth involves or extends into the sphincter or perirectal structures. A decrease in the caliber of the stools occurs when the anus is involved, or when a lesion higher up causes anal spasm. Loss of weight and strength occur late.

Physical Signs. The general appearance of patients with carcinoma of the colon varies. Some appear healthy while others are cachetic. Pallor may be striking in lesions of the cecum and ascending colon as a result of anemia.

A mass may be palpable in those portions of the colon accessible to palpation. The tumor is as hard "as a turnip," does not dent, and is not tender unless secondarily infected. Obstructive lesions may give rise to visible as well as audibly increased peristalsis and abdominal distention. Enlargement and nodularity of the liver indicate the presence of metastases. Metastases may also occur to the umbilicus, to the inguinal nodes, and, rarely, to the supraclavicular and axillary nodes. Ascites may be present.

Carcinoma of the rectum may be palpated digitally in most instances. Straining by the patient may cause highly situated lesions to descend within reach of the finger. In females care must be exercised not to mistake the cervix for a lesion of the anterior wall of the rectum, and vice versa. Vaginal examination may reveal a lesion in the rectosigmoid not detected by rectal examination.

Laboratory Findings. Anemia is more common and more severe in patients with carcinoma of the cecum and ascending colon than in those with left-sided lesions. It may have some of the features of pernicious anemia; the cause, in the absence of gross bleeding, is not known. The white blood count is usually not elevated unless secondary infection is present. Occult blood is detectable in the stools in most patients with colonic carcinomas.

Roentgenologic Examination. Roentgenologic examination is indispensable for the diagnosis of cancers of the colon that cannot be visualized sigmoidoscopically (figs. 233, 234). Barium enema followed by air contrast studies are diagnostic in the vast majority of such cases. Small lesions in the flexures or cecum may be missed unless carefully searched for.

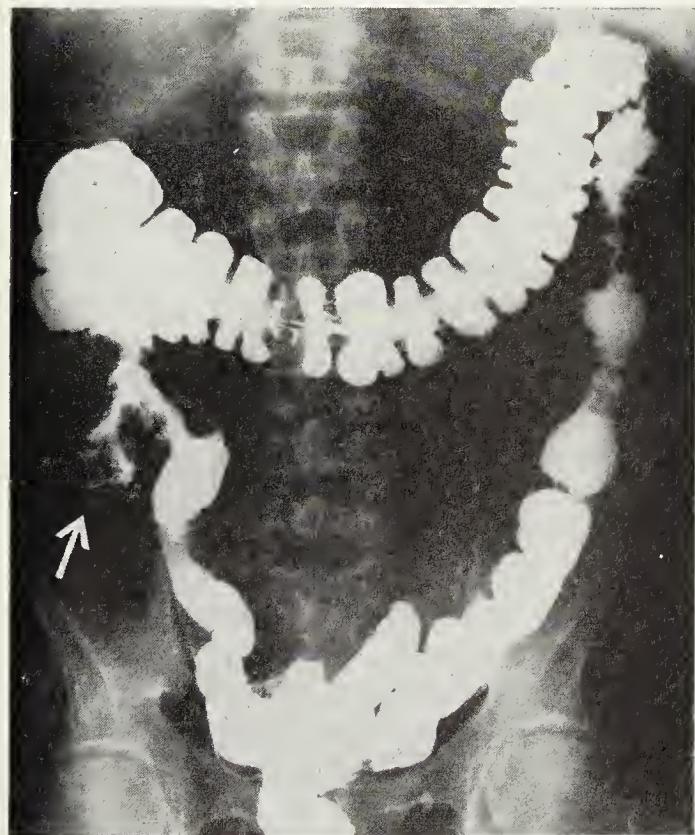


FIG. 233. Roentgenologic appearance (following barium enema) of deformity produced by a large carcinoma of the cecum and ascending colon (arrow).

Diagnosis. The diagnosis of carcinoma of the colon is made on the basis of the clinical picture, physical examination including a digital rectal examination, sigmoidoscopy and barium enema, and, when indicated, a barium-air contrast study. Sarcomas and carcinoma are similar in their clinical patterns in most respects. Sarcomas occur in younger persons, produce obstruction, and

cause hemorrhage less frequently but run a more rapid course.

On the right side of the colon the differential diagnosis includes anemias of diverse etiology, renal neoplasm, regional enteritis, tuberculosis, benign tumors, hydrops of the gallbladder, gastric carcinoma, appendiceal abscess, diverticulitis, and inspissated feces. On the left side, the

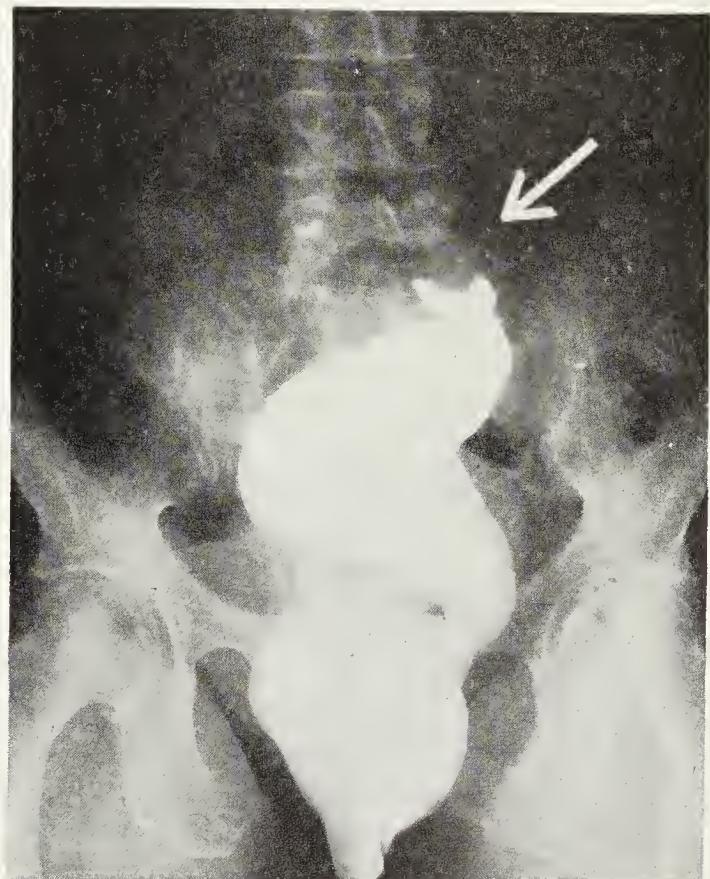


FIG. 234. Roentgenologic appearance of the distal colon and rectum following introduction of barium by rectal enema. The barium failed to flow beyond the sigmoid (arrow), which is the site of an obstructive carcinoma.

lesions to be differentiated include diverticulitis, spasm, fecal impaction, pelvic lesions, lymphogranuloma venereum, metastases to Blumer's shelf, and benign tumors.

Complications. The first manifestation of a carcinoma of the colon not infrequently is the result of a complication. Bleeding, gross or microscopic, occurs when the lesion ulcerates. Fever, leukocytosis, and tenderness occur when the ulcerated tumors become secondarily infected. Perforation, slow or sudden, may occur as a result of either infection or growth of the tumor through the wall of the gut with consequent peritonitis and abscess or fistula formation. The perforation may occur at the site of or proximal to the tumor.

In obstructing left-sided tumors, rupture of the thin-walled cecum may occur as a result of distention and back pressure. Fistulas may form between the colon and the stomach, small intestine, bladder, or vagina. Obstruction of the colon is more characteristic of left-sided lesions. The obstruction usually develops slowly, but occasionally occurs suddenly as a result of occlusion of a narrowed lumen by feces or barium, or as a result of edema, volvulus, or intussusception. Lesions of the sigmoid may invade the bladder or produce hydronephrosis by obstructing a ureter.

Treatment. Surgery is the only treatment. Roentgen therapy has very little to offer. The surgical procedure of choice is a one- or two-stage resection, with primary anastomosis.

Prognosis. The prognosis in carcinoma of the colon is favorable if the lesion can be resected before local and distant metastases have occurred. The number of five-year survivors is greater than for gastric cancer. Prognosis in the untreated case is hopeless, death usually occurring before 12 to 13 months have passed.

BENIGN TUMORS OF THE COLON AND RECTUM

The adenomatous polyp is the commonest variety of benign tumor of the colon and rectum. Other types, less common, include lipomas, endometriomas, myomas, fibromas, hemangiomas, lymphomas, neurofibromas, teratomas, enterogenous cysts, and cholesteatomas. Polyps occur most frequently in the rectosigmoid and rectum and may be asymptomatic for years. They may be single or multiple. Symptoms, when present, are not diagnostic. The commonest is blood in the stools. Lesions in the rectum and rectosigmoid may be associated with tenesmus and a feeling of "still something to come out" after defecation. Physical examination of the abdomen is usually negative, though a large lipoma may be palpable. Each benign tumor, especially a polyp, must be considered a premalignant lesion and should be resected or destroyed by fulguration when resection or excision is not possible. Malignant change not infrequently is found in microscopic sections of a benign-looking polyp. Patients so treated should be re-examined sigmoidoscopically and roentgenologically at regular intervals for evidence of recurrence as well as for polyps elsewhere in the colon. Additional polyps may have

been overlooked because of their small size at the time of the original examination. The incidence of carcinoma in patients with diffuse or multiple polyposis is high. The relatives of such patients should be examined. For diffuse polyposis, ileo-sigmoidostomy with subtotal colectomy is usually necessary.

CHRONIC IDIOPATHIC ULCERATIVE COLITIS

Idiopathic ulcerative colitis is encountered at any age, though the greatest number of cases occurs between the third and fifth decades. Both sexes are involved about equally.

Etiology. A specific etiology has never been established. The disease is not infectious or contagious and does not occur in epidemics. The occurrence of more than one case in the same family is uncommon. Bacteria, viruses, allergy, nutritional deficiency, and lack of specific intestinal factors have been held responsible but have not been proved to play etiologic roles. The recently alleged role of excessive lysozyme production awaits further clarification.

Many, including the writer, believe that the disease is a psychosomatic disorder. Emotional conflicts and frustrations very frequently precede the onset of the disease, and are frequently and intimately related to exacerbations and recurrences. It is seen in high-strung, exacting, emotionally unstable and immature, overly sensitive, fearful, and frustrated individuals. A relationship between stress-producing factors and alterations in the function of the colon has been clearly demonstrated. Furthermore, success in the management of the disease is directly proportional to the ability of the physician to discover and handle the motivating emotional factors.

Pathology. The pathologic picture of idiopathic ulcerative colitis is one of nonspecific inflammation, the degree depending on the frequency, duration, and severity of the attacks. In the majority of instances, the process involves the colon either partially or completely during the initial episode. The rectosigmoid is involved in the majority of cases, and the terminal ileum not infrequently. When the disease spares the rectosigmoid, the terminal ileum is usually involved, and at times other segments of the small intestine.

Early in the onset of the disease the mucosa is hyperemic, glistening, and edematous. Ulcers may not be visible because of edema. Subsequently,

ulcerations may become prominent. In some areas the mucosa is covered with an adherent inflammatory exudate. Coalescence of ulcers results in a denudation of the mucosal surface. Polypoid hyperplasia occurs in some areas. The submucosa and muscular layer are edematous early but subsequently undergo fibrosis. Contraction of the fibrous tissue produces marked narrowing of the lumen. In the acute fulminating types, the mucosa may be so extensively denuded that the wall is very susceptible to perforation.

Clinical Picture. The symptoms in any given case depend on the site, extent, and severity of the involvement. The onset may be gradual or sudden. When gradual, the first bowel abnormality is very often the presence of blood and mucus in the stool. Subsequently, the stools become softer, occur with greater frequency and urgency, and finally become liquid. They now contain fecal material, serous exudate, blood, pus, mucus, and gas, and their passage may be associated with tenesmus. When the onset is sudden, the loose, watery stools containing blood, gas, and mucus are numerous. In the acute fulminating types, liquid discharges consisting of gas, blood, pus, mucus, and serous exudate may be almost continuous. Abdominal cramps are common in all except the very mild cases. They usually precede and are relieved by defecation. Lying on the right side, a favored position of ulcerative colitis patients, tends to decrease the number of stools. Tenesmus and rectal soreness may be very annoying. Fever and tachycardia are usually present during the acute phases. The fever may last for days to months. The temperature curve is of an intermittent and, at times, of a remittent type. Occasionally, fever without diarrhea is the primary manifestation of ulcerative colitis.

In severely ill patients, there are usually pallor, dehydration, and stigmas of vitamin deficiency. In addition there may be acute arthritis and/or erythema nodosum and evidences of loss of weight. Palpation of the abdomen may reveal tenderness over the accessible involved portions of the colon, commonly over the sigmoid and cecum. The liver, and in anemic patients the spleen, may be palpable.

Laboratory Findings. Anemia of a hypochromic normocytic or a hypochromic microcytic type is frequently present, depending on the amount of blood loss and degree of iron and nutritional deficiency. The total leukocyte count may be nor-

mal or elevated. When elevated, the percentage of polymorphonuclear forms may be increased. In some instances a relative increase in lymphocytes or monocytes is found and, rarely, an eosinophilia.

Studies of the electrolytes of the blood may reveal evidence of base deficit, as indicated by the low sum of chloride and bicarbonate. The prothrombin concentration is frequently decreased. Liver function tests show no constant abnormalities except "Bromsulphalein" retention as a result of fever. In severely malnourished cases, the total serum proteins are frequently low; occasionally, the albumin-globulin ratio is reversed.

Sigmoidoscopic Picture. The sigmoidoscopic appearance of the bowel depends on both the stage and severity of the disease. During the acute phase, the earliest change that is detectable consists of minute petechiae and a slightly edematous mucosa. Subsequently, the mucosa becomes more diffusely hyperemic and glistening, and there is an excess of mucus. Swabbing reveals a granular surface which bleeds readily. Ulcerations may not be visible because of edema. If visible, they are small or large, depending on the degree of mucosal edema present. Later, ulceration and denudation are extensive, with little or no normal mucosa and much thick, mucopurulent, adherent exudate. In the severe acute fulminating types, sigmoidoscopy should be delayed until pain, spasm, and irritability have disappeared. The preparation for and the performance of sigmoidoscopy in such patients is dangerous. Perforation occurs readily because the mucosa is extensively denuded and the walls of the gut are very friable.

In the chronic stage, the sigmoidoscopic appearance depends on the activity of the process. During quiescence the lumen is narrowed and the normal architecture is lacking. The surface is pale and firm, and does not bleed readily. There is little exudate. Pseudopolyps may be visible. During acute exacerbations, hyperemia, edema, mucopurulent exudate, and mucosal denudation may be seen.

Roentgenologic Appearance of Colon. The changes visualized on roentgenologic examination of the colon depend on the site and extent of involvement, and on the degree of associated spasm. They do not always parallel the severity of the clinical manifestations.

Early, and characteristic when seen, are the

very fine, irregular, serrated or "saw-tooth" borders of the barium-filled segment (fig. 235). Spasm and irritability are common. When extensive mucosal involvement and destruction are extensive, the normal mucosal pattern is lacking. Changes in mucosa are demonstrated best by the air-barium contrast technic. The haustral markings



FIG. 235. Roentgenologic appearance of the colon of a patient with active chronic idiopathic ulcerative colitis, following barium enema. The colon is narrowed and tubular, the margins are fuzzy or serrated and the mucosal pattern is distorted.

are absent, the colon is shortened, and the lumen narrowed; the appearance is that of "lead pipe." Polypoid hyperplasia is evidenced by the presence of circular, irregularly placed filling defects.

The terminal ileum, when involved, is rigid and dilated, and has lost its normal markings. The small intestine, after a barium meal, may reveal hypomotility or hypermotility. It should be examined in all cases to detect areas of regional enteritis. Failure to detect associated involvement of the small intestine is one of the reasons why some patients have failed to do well after surgical ileostomy and colectomy.

Differential Diagnosis. A history of frequent, liquid, bloody stools in an individual whose stools do not contain amebas or dysentery organisms

should always suggest the diagnosis of idiopathic ulcerative colitis. The diagnosis is established by sigmoidoscopy and barium enema when the patient can safely withstand these procedures.

Differentiation from amebic dysentery is made by the sigmoidoscopic demonstration of discrete, irregular, undermined ulcers with relatively normal mucosa interspersed, by the finding of *Endamoeba histolytica*, and by the response to amebicidal drugs. Bacillary dysentery is differentiated by the isolation of specific dysentery organisms on stool culture. Sigmoiditis of lymphogranuloma venereum is characterized by a predilection for the female sex, a history of enlarged inguinal glands, the presence of a rectal stricture late in the course of the disease, a hyperglobulinemia, and a positive Frei test. Primary tuberculosis of the intestinal tract, a very rare entity, may give rise to ulceration. The more common forms of intestinal tuberculosis are associated with pulmonary lesions. Regional enteritis is characterized by a milder clinical course, absence of gross blood in the stools, normal sigmoidoscopic picture, and a normal roentgenologic appearance of the colon. The disease at times is associated with involvement of the cecum and ascending colon. Involvement of the terminal ileum in such cases is evidenced by a reduction in the caliber of the lumen rather than by a dilatation. Diverticulitis of the colon may simulate some of the features of idiopathic ulcerative colitis, but is readily differentiated roentgenologically, and is encountered in an older age group. Other causes of diarrhea, including uremic colitis and malignant lesions of the colon, are readily differentiated. The association of carcinoma with ulcerative colitis must always be kept in mind.

Complications. Local complications of idiopathic ulcerative colitis include malignant degeneration of pseudopolyps, stricture formation and obstruction, hemorrhage, perforation with localized or generalized peritonitis, perianal or rectal abscesses, and fistula. Other complications include acute arthritis, erythema nodosum, thrombosis of the veins of the extremities, retarded sexual and physical development, amenorrhea, severe acidosis with cerebral damage as result of hemorrhages into the brain, and manifestations of deficiency of minerals such as potassium and calcium.

Course. The disease is characterized by remissions and relapses. The course may be prolonged

if foods to which a gastrointestinal allergy exists are ingested or if the psychiatric aspects of the case are not adequately handled. Induction of a permanent remission depends entirely on the ability of the physician to discover and handle the patient's emotional problems successfully.

Treatment: MEDICAL MANAGEMENT: PSYCHOGENIC. Successful management calls for a sincere, understanding, helpful, and sympathetic attitude on the part of the physician, and his ability to instill confidence and arouse hope in the patient who has been subjected to a variety of emotional frustrations and insults. Most cases can be handled satisfactorily by the physician acting as his own psychiatrist. The relatives and friends of the patient may furnish useful information. The patient usually resents a trained psychiatrist but, at times, his services may be necessary. The emotional problems must be handled carefully; otherwise, the untimely or unwise exposure of the conflicts to the patient may produce a severe reactive depression and culminate in suicide.

DIET. The basic nutritional aim is the administration of a high-calorie, high-protein, high-carbohydrate, low-fat, low-residue diet, adequate in minerals and vitamins, and free of gas-forming, allergenic, and irritating foods. A high protein intake is essential for the restoration of a positive nitrogen balance and to ensure healing of tissues. Regardless of the type of diet used, it should be supplemented with a sufficiency of vitamins, including vitamin K.

One not infrequently finds that adequate nutrition for the patient is at best difficult or even impossible if the ordinary foods are to be relied upon. When faced with a seemingly impossible situation, the problem can be solved nicely by the use of a solution of a mixture of protein digest and a carbohydrate such as "Dextri-maltose." The measured amount of the mixture, calculated on the basis of 20 calories per pound of pre-illness weight, is dissolved in enough boiling water to make a 15 to 25 per cent solution and stored in a refrigerator. Two hundred to 400 ml. of the solution are administered every two hours, from 6 a.m. to 10 p.m. This form of alimentation supplies a high-calorie, high-protein, high-carbohydrate, low-fat, low-residue, and hypoallergenic diet free of irritating materials. Vitamins and iron must be supplemented. The solution is administered for a period of three to six weeks, or until clinical and sigmoidoscopic evidence of sub-

sidence of inflammation is assured, after which a high-calorie, low-residue diet can be proffered gradually, taking care to omit foods to which the patient is allergic. The decision concerning hypersensitivity can be determined best not by skin tests, which are practically valueless in this type of disorder, but by careful interrogation of the patient.

In the acute fulminating types, the patient should be put to bed and given repeated transfusions. Calories and protein are supplied by a slow continuous intravenous drip of a solution containing dextrose and a protein hydrolysate. Vitamins are administered parenterally. Signs of shock should be watched for constantly, and appropriate measures instituted promptly.

SPECIFIC MEASURES. Acid-base imbalance and calcium and vitamin deficiency should be corrected promptly. Anemia is best treated by the transfusion of sufficient whole blood to raise the hemoglobin to a substantial level. Iron, in a form which does not irritate the alimentary tract, should be administered. Occasionally, small doses of opium for a few days may afford relief from diarrhea and abdominal cramps. Severe abdominal cramps may be relieved by an injection of an adequate dose of atropine or dibutoline. Regular doses of phenobarbital are useful to allay apprehensiveness. They should not be so large as to make the patient too drowsy, otherwise involuntary soiling of the bed with feces will complicate the nursing problem.

The sulfonamides and various antibiotics, though of no proved value in the treatment of the primary disease process, may be administered from the standpoint of secondary infection. They should always be administered when perforation of the bowel is suspected and surgery is delayed or not indicated.

The effects of cortisone and ACTH on the course of the disease are still in the experimental stages. In the writer's experience a prompt and dramatic remission can be induced during the administration of cortisone but a relapse may occur when the use of the compound is discontinued unless other principles in the management of the disease are followed.

SURGICAL MEASURES. Surgery should not be undertaken until all other efforts have proved futile, and should be reserved for the complications such as free perforation, hemorrhage, carcinoma, obstructing stricture, and intractability.

The number of cases requiring surgery because of intractability should be very small. The presence of pseudopolyps is not an indication for operation. They disappear in satisfactorily handled cases. When surgery is decided on, the usual procedure is that of ileostomy with or without a subsequent colectomy.

DIVERTICULOSIS AND DIVERTICULITIS

Diverticula are especially common in the sigmoid and descending portions of the colon. They

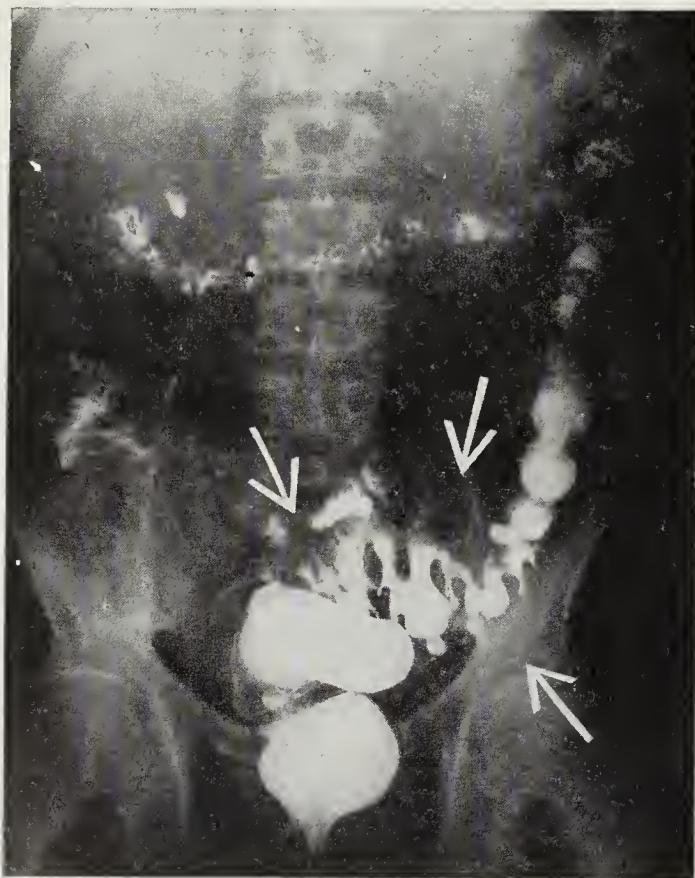


FIG. 236. Roentgenologic appearance of colon following subsidence of an attack of acute diverticulitis. Several diverticula are present in the sigmoid. Site of involvement is indicated by arrows.

produce no symptoms unless complicated by inflammation. Acute diverticulitis mimics acute appendicitis, but the pain and tenderness are mainly in the left lower quadrant, and the relationship of pain to defecation and passage of flatus may be striking. Diarrhea may alternate with constipation. Chronic diverticulitis produces a clinical picture resembling that of carcinoma of the large bowel, but frequently is accompanied by recurrent acute attacks. Gross bleeding may

occur. Perforation may give rise to a localized abscess or, less commonly, to general peritonitis or a fistulous communication with the bladder. The diagnosis of diverticulosis depends entirely upon the roentgenologic demonstration (fig. 236); that of diverticulitis depends mainly upon the clinical picture. Perforation calls for surgical management. Otherwise, the treatment consists of low-residue diet, mineral oil, antispasmodic drugs, and intestinal antiseptics of the sulfonamide group.

HIRSCHSPRUNG'S DISEASE OR MEGACOLON

Congenital dilatation and hypertrophy of the colon is thought to be caused by a derangement of the autonomic innervation. Aside from obstinate constipation, the outstanding symptom, there may be a feeling of fullness, or other manifestations of increased abdominal pressure. The diagnosis is established by the barium enema and sigmoidoscopy. Medical management consists in the use of mineral oil, enemas, and cholinergic drugs (such as "Urecholine," 10 to 25 mg., or "Doryl," 1 to 2 mg., three times daily). Sympathectomy may be employed when symptoms are debilitating and conservative management has failed.

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Diseases of the Pancreas.

Thomas E. Machella

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INTRODUCTION

The diagnosis of pancreatic disease is frequently missed. There are several reasons for this, the most important being a failure to think of pancreatic disease as responsible for the production of the symptoms. Other reasons include the inaccessibility of the gland to palpation, the fact that clinical manifestations are very frequently due to secondary dysfunction of the biliary and gastrointestinal tracts, and the general unavailability of laboratory procedures useful in detecting pancreatic disorders. The latter include the determination of the concentration of pancreatic enzymes in the blood serum and in duodenal content, and the determination of total, neutral, and split fat, and of nitrogen, in the stools. Roentgenologic procedures useful in detecting pancreatic disease are limited to the detection of calcified deposits on scout films of the abdomen, and to the disclosure of encroachment of mass lesions on the normal contour of the barium- or air-filled stomach or duodenum.

ACUTE PANCREATITIS

The term *acute pancreatitis* is used to include acute edematous (interstitial) pancreatitis, acute

hemorrhagic pancreatitis, and acute pancreatic necrosis, as these probably represent different degrees of severity of the same pathologic process. The disease is encountered in both sexes, the peak incidence occurring between the fourth and the seventh decades.

Etiology. The exact mechanism by which the destruction of pancreatic tissue is initiated has not been established. The frequent association of pancreatitis with biliary tract disease has given general acceptance to the theory of intrapancreatic activation of lipase as a result of reflux of bile into the pancreatic duct. The correctness of this view has been questioned. Infections by way of the blood stream, as in cases of mumps or pyemia, have also been ascribed etiologic roles. Cultures made in early cases are frequently sterile, while organisms grown late in the disease are looked upon as secondary invaders. Overindulgence in alcohol is considered a major etiologic factor by some. Acute inflammation of the pancreas may also occur in association with penetrating peptic ulcer.

Pathology. Early in the course of the disease, the pancreas is edematous. Subsequently, hyperemia, hemorrhages, and necrosis occur. The entire pancreas or involved portion is enlarged and either firm or friable. The surface has a dark red, purplish, or black-mottled appearance. A variable amount of fat necrosis is present; it may be limited, in mild cases, to the fat in and about the pancreas, or it may also involve the fat of the omentum, mesentery, and peritoneum. Straw-colored or bloody fluid is present in the peritoneal cavity, depending on the stage of the disease process. In more advanced stages, diffuse suppuration, abscesses, or gangrene with sloughing may occur. The various pathologic changes may heal or be followed by various sequelae such as repeated attacks of pancreatitis, abscess or cyst formation, or calcium deposition.

Clinical Picture. The attack begins with severe pain in the epigastrium or right upper quadrant. The pain is usually persistent but at times is

paroxysmal and colicky, or even intermittent as in intestinal obstruction. It radiates most frequently through to the back, and less commonly to the sternum, lower abdominal quadrants, flanks, and either scapula. Nausea and vomiting are commonly associated, and constipation is almost always present.

There is usually elevation of a degree or two in temperature, with a corresponding increase in pulse rate. In more severe cases the picture of circulatory shock develops, with cyanosis, cold and clammy skin, and low blood pressure, with a rapid, thready pulse and subnormal temperature. Suppuration or gangrene are associated with a spiking fever curve.

The patient with acute pancreatitis looks and feels sick. The abdomen is frequently distended and peristalsis is inaudible as a result of irritation of the peritoneum and intestine by enzyme-containing peritoneal fluid—a chemical peritonitis. Tenderness and rigidity may be detected in the epigastrium or right upper quadrant. Jaundice is common, but its cause has not been determined unanimously. It has been ascribed to a hepatitis due to an increased concentration of pancreatic enzymes in the portal vein, to cholangitis, or to pressure on the common duct by an enlarged head of the pancreas. The skin of the loins or umbilical area may be discolored to a slate blue. Signs and symptoms of tetany as a result of hypocalcemia have been observed in some instances.

Laboratory Findings. The leukocyte count may be normal but is frequently increased, the degree depending on the severity of the disease process. The serum amylase and lipase concentrations are usually increased; the elevation in lipase being more persistent than that of amylase, which is increased only during the early course of the disease, frequently within the first 24 hours. Amylase may be found in increased amounts in the urine at the same time. Other abnormalities which may be encountered include hyperglycemia, glycosuria, bilirubinemia, bilirubinuria, hypoprothrombinemia, hypocalcemia, and positive liver flocculation tests.

Diagnosis. The most important factor in the diagnosis of acute pancreatitis is the awareness of the possibility of the condition as one of the causes of severe upper abdominal pain. The diagnosis very frequently is first made at laparotomy because most patients are admitted to the sur-

gical service as cases of perforated peptic ulcer, peritonitis, biliary colic, or intestinal obstruction. Other conditions with which the disease may be confused include mesenteric thrombosis and coronary occlusion, dissecting aneurysm, and intra-abdominal apoplexy.

Perforation of peptic ulcer may be differentiated by the demonstration of air in the uppermost portion of the abdomen on a survey film. The serum amylase may be elevated if the ulcer has perforated into the pancreas. An attack of biliary colic is usually associated with tenderness localized to the right upper quadrant. Peritonitis due to causes other than perforated peptic ulcer is usually not associated with the severe onset pain of pancreatitis. Intestinal obstruction is associated with distention of the abdomen, normal leukocyte count and temperature, hyperactive peristalsis unless morphine has been administered recently, and the presence of gas-fluid levels on survey films of the abdomen.

Mesenteric thrombosis or occlusion is associated with diminished or absent peristalsis, symptoms of intestinal obstruction, and perhaps melena. Serum enzyme determinations aid in differentiating acute pancreatitis from dissecting aneurysm, intraabdominal apoplexy, and coronary occlusion. The latter has been reported to give rise to electrocardiographic changes suggestive of coronary occlusion during the period of serum amylase elevation.

Complications and Sequelae. An attack of acute pancreatitis is very apt to be followed by subsequent ones. The recurrent attacks may eventually produce sufficient damage to the acinar and islet cells to give rise to manifestations and complications of chronic pancreatitis. The process may remain active until necrosis, profuse gastrointestinal bleeding or septicemia, and multiple abscesses terminate its course.

Treatment. There is considerable difference of opinion as to whether pancreatitis should be treated surgically or medically. Since the diagnosis is rarely made preoperatively and the picture is that of a surgical abdomen, laparotomy is usually performed. The surgical procedures used are cholecystostomy or choledochostomy.

When conservative treatment has been decided upon, management consists of bed rest, nothing by mouth, control of pain (tetraethylammonium chloride may relieve pain), measures to combat shock, penicillin administration, and the

parenteral administration of physiological saline and blood. Gallbladder disease and peptic ulcer, if present, should be treated properly for prophylactic purposes.

CHRONIC PANCREATITIS

Chronic pancreatitis is encountered more frequently in males, the majority of cases occurring in the fifth and sixth decades.

Etiology. The disease may result from any cause of fibrosis of the pancreas, such as repeated attacks of acute pancreatitis; inflammatory disease of the biliary tract, stomach, or duodenum; peptic ulcer penetrating into the pancreas; obstruction of the pancreatic ducts; tuberculosis; syphilis; or arteriosclerosis. Some believe that alcohol is an important etiologic factor in certain cases.

Pathology. There is an increased amount of fibrous tissue which is laid down in either one of two main patterns, the interlobular or the intralobular. In the interlobular variety, the fibrosis is most conspicuous between the lobules. The pancreas is firm and may be enlarged. The acinar tissue is destroyed but the islets are spared until late. In the intralobular form the parenchyma itself is replaced by fibrous tissue. Atrophy of the islets occurs early. Arteriosclerosis, syphilis, hepatic cirrhosis, and, more commonly, hemochromatosis appear to be of etiologic importance in the intralobular type.

Clinical Picture. The clinical manifestations of chronic pancreatitis depend on the nature of the associated organic disease, on the degree to which acinar and islet tissue are destroyed, and on whether or not obstructive jaundice is produced.

In some cases, diabetes or a diabetic type of glucose tolerance curve may direct attention to the pancreas; in others, a change in the character and number of stools. The characteristic stool, seen in advanced stages of the disease, is bulky, frothy, light-colored, glistening, and foul smelling. Marked weight loss, despite a good appetite, occurs because of faulty digestion and absorption of foodstuffs.

Occasionally, there is a silent and progressive jaundice as a result of compression of the common duct by the enlarged head of the pancreas. In such cases, carcinoma of the head of the pancreas is usually suspected clinically and at laparotomy.

Diagnosis. The clinical diagnosis of chronic pancreatitis is based on the findings of hyperglycemia, glycosuria or a diabetic type of glucose tolerance curve, a decreased volume and concentration of pancreatic enzymes in aspirated duodenal juice, and an increased amount of nitrogen and of total and unsplit fat in the feces while on a Schmidt diet. The detection of opaque shadows due to calcification in the region of the pancreas on survey films of the abdomen is very helpful.

In the differential diagnosis of chronic pancreatitis with fatty stools, other causes of steatorrhea must frequently be considered. Sprue is associated with a flat oral glucose tolerance curve, a normal curve following administration of glucose intravenously, an increased amount of total and split fat in the stools while on a Schmidt diet, and a normal concentration of pancreatic enzymes in the duodenal juice. A preoperative differential diagnosis between chronic pancreatitis and carcinoma of the pancreas causing obstructive jaundice may not be possible on the basis of duodenal enzyme concentration and fat content of stools. Roentgenologic demonstration of actual invasion or distortion of the duodenum or stomach, gastrointestinal bleeding, and signs of metastasis support the diagnosis of carcinoma. Intestinal lipodystrophy (Whipple's disease) may be associated with steatorrhea as a result of deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. Manifestations consist of flatulence, diarrhea, achlorhydria, loss of weight, anemia, edema, ascites, arthritis, and cutaneous pigmentation. There may be associated a low-grade inflammation of the pleura, pericardium, and peritoneum.

Treatment. Prophylaxis consists of the proper management of predisposing diseases of neighboring organs, and abstinence from alcohol. The diet should be high in carbohydrate and readily assimilable protein, but low in fat. In cases with gastric hyperacidity, measures to neutralize gastric juice should be employed in an attempt to prevent peptic ulceration of the duodenum, as the amount of bicarbonate in pancreatic juice is usually reduced. The administration of protein hydrolysates aids in maintaining a positive nitrogen balance. Sufficiency of minerals and vitamins should be assured. An active preparation of pancreatin should be administered in adequate amounts if steatorrhea and crætorrhea are present. The average dose of a preparation of 4 U.S.P.

strength should be at least 3 to 4 Gm. to be taken with meals. The amount should be increased if necessary. If the diarrhea cannot be controlled by pancreatin, small doses of powdered opium or paregoric may be prescribed on occasions when access to facilities for stool evacuation is not available. Choline or methionine should be administered to prevent fatty infiltration of the liver. Insulin is essential when diabetes is present. When obstructive jaundice is manifested, some surgical procedure, such as a cholecystenterostomy or cholecystogastrostomy, is indicated.

PANCREATIC LITHIASIS

The concretions are believed to be the result of precipitation of calcium in areas of fat necrosis. The resulting obstruction of ducts leads to fibrotic replacement of glandular tissue. Although symptoms may be absent in some cases, in others there may be severe recurrent colic which requires opiates. The parenteral injection of tetraethylammonium chloride may relieve severe pain in some cases. The attacks may produce all the features of acute pancreatitis. In chronic cases, steatorrhea, diabetes mellitus, or both, may occur. Duodenal ulcer occurs in a significant number of cases as a result of a deficient amount of

bicarbonate available for neutralization of acid gastric juice. The diagnosis depends upon the roentgenologic demonstration of opacities in the region of the pancreas (fig. 237). The other features are those of the associated acute or chronic pancreatitis or of diabetes mellitus. The manage-

CARCINOMA OF THE PANCREAS

Carcinoma of the pancreas occurs more frequently in males.

Pathology. The malignant process may originate in the parenchyma of the gland or in the pancreatic ducts. The most frequent type of tumor is adenocarcinoma, although scirrhous forms are not infrequent. Most pancreatic carcinomas are primary in the pancreas, but a few originate in the biliary tract or duodenum and invade the pancreas secondarily. The head of the pancreas is involved in the majority of cases. In some, the malignant process is spread diffusely through the pancreas. Less frequently, the lesion involves only the tail and body of the pancreas.

Metastases occur early. The routes by which the tumor spreads include: direct extension to neighboring organs and structures including the celiac plexus and large veins; along the lymphatics to regional lymph nodes; at times to mediastinal or supraclavicular nodes, and through the portal vein to the liver and thence into the systemic circulation by way of the heart and lungs. Metastases are found most frequently in the liver.

Clinical Picture. The disease is rapidly progressive, death usually occurring about eight months after the onset of symptoms. Indefinite symptoms such as vague epigastric discomfort or flatulence may be present early. When present, the most significant early symptom is pain in the epigastrium. It is variable in type but when characteristic is usually dull, boring, and penetrating, and radiates through to the back. It is usually intensified by lying supine, as a result of pressure or tension on the celiac plexus. Relief may be afforded by curving the spine forward in the "fetal" position. A history of pain at night is frequently obtained. Accompanying the pain there may be nausea, vomiting, epigastric fullness, and abdominal distention. Weight loss occurs rapidly.

Occasionally, jaundice is the first symptom, but in many cases weeks and months elapse before it is noted. The length of the interval from the time of the first evidences of carcinoma to the appearance of jaundice depends on the location of the tumor in the gland and its relation to the



FIG. 237. Roentgenologic appearance (survey film) of the abdomen of a patient with attacks of severe epigastric pain, diabetes, and steatorrhea. The opaque shadows indicated by the arrow are caused by calculi in the head of the pancreas.

bicarbonate available for neutralization of acid gastric juice. The diagnosis depends upon the roentgenologic demonstration of opacities in the region of the pancreas (fig. 237). The other features are those of the associated acute or chronic pancreatitis or of diabetes mellitus. The manage-

common duct. It does not appear at all in some instances, particularly in lesions of the tail and body. Intractable pruritus, usually evidenced on inspection by presence of scratch marks on the skin, frequently accompanies jaundice. Firm and nontender hepatomegaly may occur as a result of common-duct obstruction, metastases, or both. A dilated gallbladder can be seen occasionally, and more often palpated (Courvoisier's sign). Relaxation of the abdominal musculature while the patient is under the influence of a short-acting intravenous barbiturate may aid in palpating the distended viscera. Only rarely can the lesion itself be palpated. Some cases, for unknown reason, develop multiple venous thromboses. The thrombi do not contain malignant cells. Ascites, as a result of metastasis to the peritoneum or of compression or thrombosis of the portal vein, may be present.

Laboratory Findings. A mild degree of anemia may be present. The serum lipase may be increased during the early stages of the disease if the pancreatic ducts are obstructed. It falls as the amount of acinar tissue is progressively destroyed. The total amount and concentration of pancreatic enzymes in aspirated duodenal juice before and after the injection of secretin, "Mecholyl," or "Urecholine" is decreased, depending on the degree of duct obstruction, and on the extent to which the parenchyma of the pancreas is damaged.

The serum bilirubin is elevated in jaundiced patients as a result of common-duct obstruction. The concentration rises steadily and then levels off. It does not decrease unless a fistula develops between the distended portion of the biliary tree and the intestine, or unless an obstructing piece of tumor tissue is dislodged. Occasionally, fluctuations in the degree of icterus may occur as a result of intermittent partial obstruction of the biliary tract if the common duct is so situated that it is kinked, rather than compressed, by the enlarging head of the pancreas. Liver tests show findings characteristic of obstructive jaundice, and do not reveal evidence of hepatic cell damage until such has occurred as a result of back pressure. When obstructive jaundice is present, the prothrombin concentration of the blood may be decreased as a result of failure of bile salts to enter the intestine. The amount of biliary constituents in the stools and urine depends on the degree to which the entrance of bile into the in-

testinal tract is impeded. The amount of bile entering the intestine is best determined by aspiration of duodenal content rather than by the amount of bile pigment in the stool. Presence of blood in the aspirated material is suggestive of invasion of the duodenum. The sediment, when stained by the Papanicolaou technic, may reveal the presence of carcinoma cells. The stools contain an increased amount of neutral fat and nitrogen, depending on the degree to which the external secretion of the pancreas is lacking, and on the amount of bile entering the intestine. They may also contain gross or microscopic blood if the malignant process has invaded the stomach or duodenum.

Either hyperglycemia and glycosuria or an impaired glucose tolerance curve is present in less than half of the cases. In the majority of these, the diabetic state is a result of destruction of islet tissue.

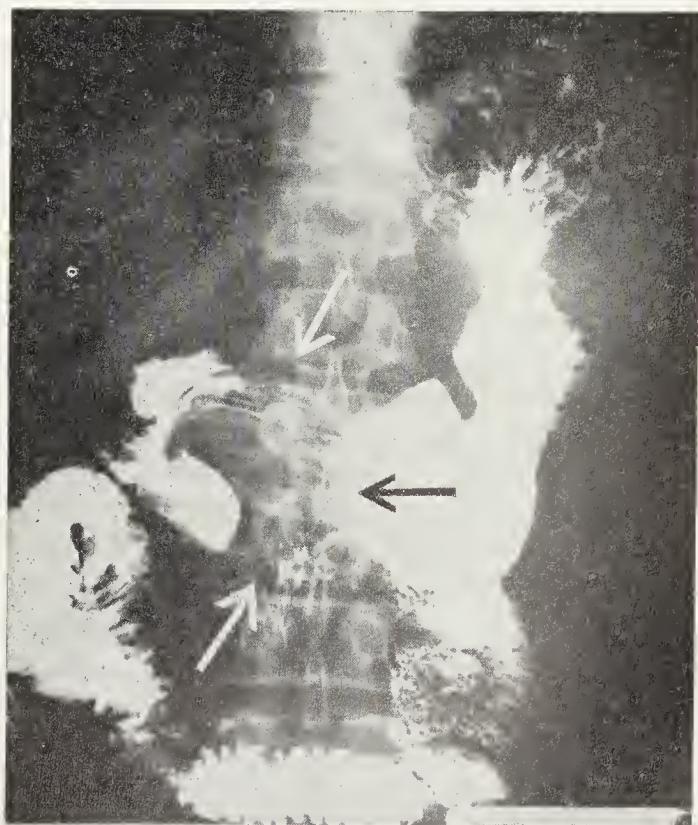


FIG. 238. Roentgenologic appearance of the stomach and duodenal loop of a patient with a large carcinoma of the head of the pancreas. The lesion has compressed the antrum of the stomach and the proximal transverse duodenum and has narrowed the descending duodenal limb by infiltration and compression (arrows).

Roentgenologic Findings. The roentgenologic diagnosis of carcinoma of the pancreas is based on finding evidence of encroachment, displacement, or invasion of barium- or air-filled neighboring structures (fig. 238). Findings which are

suggestive include: enlargement or widening of the duodenal loop; obstruction of the duodenum, pylorus, or antrum by compression; irregularity or distortion of the duodenum or stomach by actual infiltration; or a filling defect shaped like an inverted "3" on the inner aspect of the descending limb of the duodenum. Pancreatic tumors may be outlined in lateral and anteroposterior films after distending the stomach with air or gas. The roentgenologic examination in carcinoma of the pancreas is not infrequently negative.

Diagnosis. The occurrence in a middle-aged male of digestive disturbances, pain, and loss of weight should suggest the diagnosis of carcinoma of the pancreas when disease elsewhere in the gastrointestinal and biliary tracts has been ruled out. The demonstration of impaired carbohydrate metabolism and of abnormalities in the enzyme concentrations in the duodenal content and blood is highly suggestive. Unexplained hiccup may, at times, furnish a useful clue to the presence of a carcinoma in the tail of the pancreas with metastasis to lymph nodes in the region of the diaphragm. The development of unexplained peripheral vein thrombosis may be similarly helpful.

The diagnosis of the well-advanced case of pancreatic carcinoma with weight loss, pain, progressive jaundice, palpably distended gallbladder, or palpable mass in the epigastrium with characteristic roentgen pressure defects on barium-outlined neighboring structures, is readily made. Other diagnostic possibilities must always be considered. These include carcinoma of the stomach, duodenum, colon, bile duct, liver, and ampulla of Vater; retroperitoneal sarcoma; pancreatic cyst; chronic pancreatitis; stone in the common duct; hepatitis; peptic ulcer; and calculous cholecystitis.

Treatment. In the presence of inoperable growths, relief from jaundice may be produced by cholecystostomy or cholecystojejunostomy. Radical surgery offers the only hope for cure in early cases. Total pancreatectomy has been performed successfully on a number of occasions. The management of a patient so operated on is similar to that outlined in the section on Chronic Pancreatitis. It includes replacement therapy and measures aimed at preventing the development of a peptic ulcer at the site of the gastroenterostomy. Successful surgical excision

of carcinoma involving the body or tail of the pancreas is possible.

CYSTS OF THE PANCREAS

Pancreatic cysts are rare. Although they are occasionally congenital (dermoids or in association with polycystic disease of the kidneys) in origin, cysts are usually due to obstruction of the pancreatic ducts, to trauma or inflammation and, occasionally, to invasion of the pancreas by parasites (tapeworms, echinococcus, cysticercus). The cysts are more frequently unilocular than multilocular. They vary tremendously in size, are usually filled with either colorless or sanguineous fluid, and may or may not contain pancreatic enzymes.

Pain of variable character and severity is the most common symptom. It is usually located in the epigastrium or left hypochondrium and may radiate to the back. Pressure on neighboring structures such as the stomach, duodenum, common duct, or vena cava may give rise to manifestations of obstruction of these structures. Destruction of pancreatic tissue may cause manifestations of a deficiency of the external and internal secretions of the pancreas. Loss of weight and asthenia are common.

Physical examination of the abdomen may be negative or may reveal a nontender, fluctuant mass in the upper abdomen. Roentgenologic examination may reveal signs similar to those produced by carcinoma of the pancreas, except that the defects produced are smooth as a result of compression and displacement rather than of invasion.

The treatment is surgical—marsupialization or complete removal.

MISCELLANEOUS DISEASES OF THE PANCREAS

The head of the pancreas may be annular and surround the descending portion of the duodenum. As a result of compression of the latter, injury to the pancreas sometimes occurs and is associated with rupture. In such cases the symptoms and signs of peritonitis and of acute pancreatic necrosis may occur. An external pancreatic fistula may drain part or all of the pancreatic juice externally. Complete fistulas give rise to severe disturbances of nutrition and metabolism. Tuberculosis of the pancreas is very uncommon and rarely, if ever, primary. Syphilis

of the pancreas is exceedingly rare. The most common lesion in the pancreas attributed to syphilis is interstitial pancreatitis with varying degrees of interlobular and intralobular involvement. Benign solid tumors of the pancreas are rare and present no characteristic clinical manifestations. Adenomas of the islets of Langerhans may be associated with hyperinsulinism and produce the syndrome of hypoglycemia. (See Chapter 60 for a more complete discussion.) Carcinoma of the islets of Langerhans is a rapidly growing tumor which occurs more commonly in males, is more frequent in middle age, may or may not produce hypoglycemia, arises most often in the tail of the pancreas, and metastasizes quickly and widely to neighboring and distant structures, but more often to the liver and to near-by lymph nodes. The usual histologic criteria are not applicable to an islet-cell tumor. It is only the presence of metastasis that reveals its malignant nature. Sarcomas of the pancreas are very rare. The clinical features are essentially those of carcinoma with some of the findings which occur in association with cysts of the pancreas. Cystic fibrosis of the pancreas is seen

mainly in children, probably is present at birth in all instances, and not infrequently is associated with bronchiectasis.

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Section 6—The Liver, Gallbladder, and Bile Ducts

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Diseases of the Liver

Daniel Harvey Labby

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PORTAL CIRRHOSIS

(Laennec's Cirrhosis, Alcoholic Cirrhosis,
Atrophic Cirrhosis)

The stony-hard liver with dropsy was described nearly three centuries B. C., by Erasistratus of Alexandria. In the centuries intervening, the condition has been described in the excellent writings of John Brown, Morgagni, Matthew Baillie, and others. The first adequate account of portal cirrhosis was written in 1819 by Laennec, who was attracted to the fawn or "yellowish russet" color of the projecting nodules on the liver, and thereby named the disease *cirrhosis*, deriving the term from the Greek work *kirrhos*, meaning orange-colored or tawny. The fibrosis of the liver, however, is considered more important, since the color simply depends upon the amount of hyperemia, hemosiderosis, necrosis, fat, and jaundice; but the term *cirrhosis* has become too universally established to be displaced.

Incidence and Etiology. The incidence of portal cirrhosis shows great geographic variability, although statistics are markedly conditioned by diagnostic standards in various parts of the world. Such low incidence as 0.02 per cent of all

autopsies for Moscow stands in contrast to the high incidence of 12.5 per cent in Zurich. Portal cirrhosis is more frequent in the larger cities of the United States, as is alcoholism, but the overall incidence is usually given as 2 to 3 per cent of all autopsies. At least one form of cirrhosis (Wilson's hepatolenticular degeneration) is hereditary and familial, but environmental (alcoholism and nutritional deficiency) rather than constitutional factors probably influence the higher incidence of cirrhosis among persons of Italian and Irish descent. Males are affected two to three times as frequently as females. This may be attributed to the higher incidence of chronic alcoholism in men. Portal cirrhosis occurs most often in occupational groups with ready access to alcoholic beverages. Thus liquor handlers, brewery workers, bartenders, and salesmen are most commonly represented, although the exact role of alcoholism in the etiology of cirrhosis is still obscure. During the early years of prohibition in the United States, there was a decline in the mortality rate of cirrhosis of the liver from the preprohibition level of 13 to 14 per hundred thousand population to about 7 per hundred thousand, and a parallel decline in the incidence of death from alcoholism. Approximately 70 per cent of all patients with portal cirrhosis give a history of chronic alcoholism, but, at a maximum, only 30 per cent of all chronic alcoholics develop cirrhosis. While undoubtedly a common precursor of portal cirrhosis, alcohol is neither the only nor necessarily the most important predisposing cause.

The clinical studies of recent years have placed more emphasis upon the coexistence of alcoholism and nutritional deficiencies in patients with portal cirrhosis, in a manner completely analogous to alcoholic beriberi and alcoholic pellagra. This concept could explain the development of cirrhosis of the liver in both alcoholic and non-

alcoholic patients. The common occurrence of the disease in India, Java, and Ceylon, where, because of religious custom, chronic alcoholism is almost unknown, indicates that alcohol is far from being the sole cause. Infections such as acute infectious (virus) hepatitis, malaria, and syphilis; and toxic agents such as arsenic, lead, and copper, as well as cleaning fluids and halogenated hydrocarbons, have at times been suggested as important predisposing causes. Characteristically, portal cirrhosis is a disease of late middle life, but may occur at any age. Most often the first symptoms appear in patients between 35 and 65 years of age, with a peak incidence earlier in females than in males.

Pathogenesis. Portal cirrhosis has been generally regarded as a response to injury, which may take any of the various forms mentioned previously. The primary injury may be a chronic nutritional deficiency combined with alcoholism, producing the fatty liver considered by many pathologists as an essential prerequisite to cirrhosis. The diet of patients with cirrhosis is frequently deficient in protein and amino acids known to be important in preventing the fatty liver experimentally. The essential amino acid methionine, and the substance choline have been termed lipotropic, since they prevent the accumulation of fat in, and accelerate its removal from, the liver. Experimental studies with animals have indicated that absence of the lipotropic substances from the diet leads to a form of fatty liver and cirrhosis closely analogous to portal cirrhosis. Both fatty liver and cirrhosis are reversible in rats when these substances are resupplied in the diet. The relationship between choline and methionine, and animal cirrhosis has not been established, and it would be unwise to translate this experience directly to human cirrhosis. The exact role of the fatty liver in human cirrhosis requires further elucidation.

A timely clinical problem is the relationship between attacks of acute infectious hepatitis and the subsequent development of cirrhosis as the end result of acute injury by inflammation. Although still the subject of controversy, it has been considered that the transition of acute hepatitis through chronic active hepatitis to cirrhosis may pursue a course indistinguishable from hypertrophic or cholangiolitic cirrhosis. Numerous serial tissue studies offer pathologic confirmation, but, as stated by Watson, "The end

stages of the cholangiolitic cirrhosis following prolonged hepatitis may be indistinguishable, anatomically, from ordinary atrophic or portal cirrhosis."

More often the progression of chronic active hepatitis to cirrhosis is similar to the healing of subacute yellow atrophy and produces the pathologic picture of healed "toxic" cirrhosis with coarse, irregular nodules (coarsely nodular cirrhosis, postnecrotic cirrhosis). Intermediate cases between these various forms of cirrhosis and portal cirrhosis exist, indicating variable pathways from common etiologic factors to common end point, but this is of more pathologic than clinical importance.

Pathology. At autopsy the liver is usually small, nodular, firm, leathery, and atrophic, weighing less than 1600 Gm. Less often it is hypertrophic and of greater weight than normal. The organ is pale brown or brownish yellow in color, covered by fairly uniform nodules projecting above the surface, varying from a millimeter to a centimeter in diameter. The smaller nodules represent original parenchyma of reduced volume, whereas the larger nodules are masses of proliferative hepatic cells, or the so-called "regeneration foci." Bands of connective tissue form an irregular broad network across the surface.

Microscopically, there is disorganization of the hepatic architecture, consequent to the fibrosis that spreads from the portal spaces to include a varying number of lobules. Degeneration of the peripheral cells of the liver lobules, accumulation of fat droplets, and some necrosis occur early in the process. As necrotic cells are absorbed, the stroma collapses and the spared hepatic cells regenerate. The resulting expansion compresses the stroma and vascular channels, leading to repeated degeneration and removal of the parenchymal cells by hyperplasia. Many repetitions of this process result in complete distortion of hepatic architecture. Further impairment of the circulation is produced by contraction of the connective tissue about the terminal twigs of the hepatic and portal veins and extensive accumulations of fat. There is eventually such a great increase in the fibrous connective tissue that a rigid cage is formed about the masses of liver lobules, mechanically limiting the space for the hepatic cell. Immediately under the capsule this limitation is not so great, and nodules of proliferating cells may expand and bulge above the

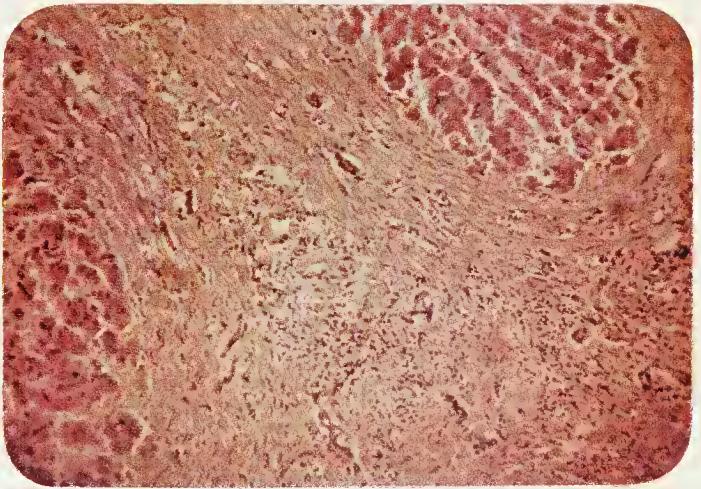
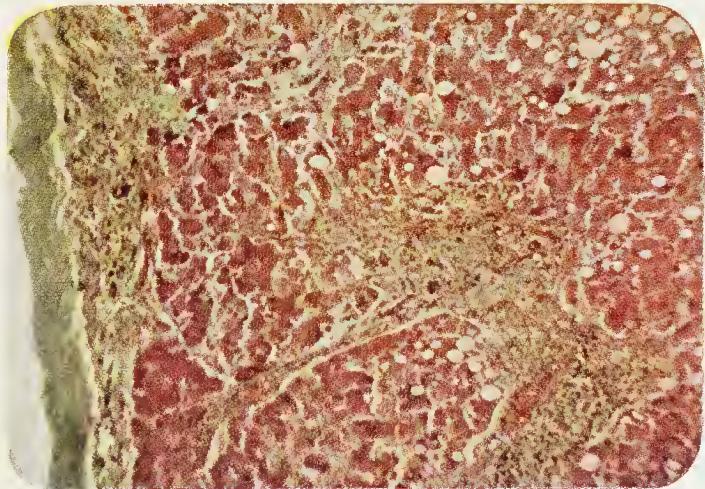
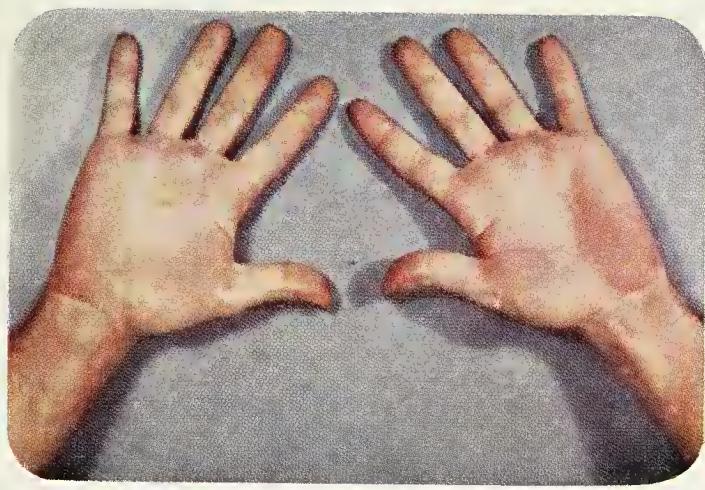


PLATE IV

(A) Hands of a 56 year old patient with portal cirrhosis held overhead showing "liver palms" with erythema of thenar and hypothenar eminences and finger pads.

(B) Numerous spider angiomata scattered over the right shoulder area of the same patient. Note large solitary spider with central "body" and hairlike "feet."

(C) Gross appearance of liver of same patient showing fine, even nodularity or "hob-nailing" and shrunken appearance.

(D) Same specimen in cut section showing even size of nodules and yellow color of increased fat content.

(E) Microscopic section (Masson stain). Note thickness of liver capsule, increased amount of fibrous tissue in portal area and presence of fatty infiltration.

(F) "Toxic" nodular cirrhosis (postnecrotic cirrhosis) following acute infectious hepatitis and chronic "active" hepatitis. Note great thickness of connective tissue bands and isolation of parenchyma into small concentric hyperplastic nodules. A mild inflammatory cellular infiltration persists and the small bile ducts show active hyperplasia. Fat is inconspicuous.

surface, producing the characteristic nodular "hobnailed" appearance. The impaired portal circulation and the contraction of the fibrous connective tissue contribute eventually to the breakdown of liver function.

Symptoms and Signs. The liver possesses so great a reserve that 80 per cent or more of its substance must be attacked by disease before symptoms and signs of hepatic insufficiency develop. In the symptomatic stage, therefore, less than 20 per cent of the patient's liver is functioning adequately. Since cirrhosis is a disease of great chronicity, the symptoms may develop with great subtlety. A bout of acute alcoholism or an intercurrent infection such as a common cold, pneumonia, or dysentery may precipitate a patient headlong into a state of hepatic insufficiency. Symptoms of hepatic failure may begin by slight equivocal departures from health. Unexplained lassitude should direct attention toward the possibility of hepatic disease. In the early stages, easy fatigue, dyspepsia, anorexia, nausea, and vomiting may occur. A sensation of heaviness with distention after meals, and gaseous eructations, are common. Bowel irregularities alternating between constipation and looseness may be accompanied by yellowness or muddiness of the conjunctiva. A fatty and foul diarrhea is not uncommon. Bleeding phenomena also may be present in the form of epistaxis, purpura, bleeding gums and hemorrhoids, menorrhagia, and metrorrhagia. Weight loss and evidences of tissue wasting are almost constant signs, and are often the presenting complaints. Diffuse abdominal pain is not a rare early symptom. It may have the quality of a dull, dragging ache in the right hypochondrium and be accompanied by a high right lumbar backache.

If ascites is not present, the liver may be felt below the right costal margin as a firm, non-tender, rounded, irregular edge. During an acute bout of hepatic decompensation, slight tenderness of the liver edge may appear and persist. Jaundice is ordinarily mild in the early stages of cirrhosis, and unaccompanied by pruritus. When present in moderate severity it constitutes a poor prognostic sign, especially if accompanied by ascites. A splotchy brown form of cutaneous pigmentation occurs occasionally in portal cirrhosis. This may be diffuse but is usually darkest over the exposed parts of the body. The pigment is free of iron and is probably a form of melanin; a

relationship to disturbances in porphyrin metabolism has been suggested.

A vascular "spider" or angioma is common in cirrhosis. Its exact etiology is unknown, but it is thought to be related to altered estrogen metabolism. It occurs with greatest frequency over the skin of the face, cheek, neck area, upper shoulders, and trunk, but rarely below the umbilicus. A typical spider angioma is a bright red lesion, characterized by a central point or "body" from which there radiate many fine hairline "feet" for a distance of about 1 cm. or more. When the central area is compressed with a pencil point the structure will blanch completely, and it refills from center to periphery when pressure is released. If the angioma is compressed by a glass slide, a distinct arterial pulsation will be seen. A brilliant red erythema of the thenar and hypothenar eminences of the hand and the finger pads has been noted and given the term "liver palm"; this same coloration may occur in the toes. Clubbing of fingers is not infrequent in portal cirrhosis, but is more frequent in biliary cirrhosis. Fever due to no apparent cause occurs more often in the course of active cirrhosis than is appreciated. This usually takes the form of nocturnal elevations to 100° to 101° F., but may rise to 103° F. with or without a chill. This is particularly frequent in patients with ascites, and is often accompanied by drenching night sweats. Infected ascites and tuberculous peritonitis or enteritis must be considered when fever occurs. Hepatic necrosis has been suggested as a cause of fever, after the previous conditions have been ruled out.

A peculiar sweet odor of the breath commonly occurs in cirrhosis, and resembles the odor of autolyzed liver tissue in vitro. This so-called "liver breath" may develop late or early in cirrhosis, and may persist throughout the course of the disease. Its cause is unknown. Oligomenorrhea and amenorrhea are common in the female with cirrhosis, and a juvenile cirrhotic individual may fail to develop secondary sex characteristics. In men, loss of libido and impotence are common; true gynecomastia and fibrosis and atrophy of the testes are much less frequent. Defective dark adaptation, osteoporosis, and osteomalacia occur occasionally. The neurologic manifestations of cirrhosis are usually those of peripheral neuritis, on the basis of the accompanying nutritional deficiency and chronic alcoholism. Toxic delirium due to alcoholic toxicosis is frequent, as well as

mania and delirium tremens, Korsakoff's psychosis, and various delusional states. Euphoria and progressive mental confusion may alternate, as well as states of muscular spasticity and other evidences of cerebral irritation and degeneration. Coma usually appears terminally.

In addition to these indications of hepatic insufficiency and failure of liver cell metabolism, there may be accompanying symptoms and signs arising from mechanical obstruction of the portal venous blood stream. These may further intensify the state of hepatic failure.

A palpable and enlarged spleen occurs in more than half of the cases of cirrhosis, and has been found in as many as 80 per cent of some groups. In 10 per cent of cases, hematemesis is the first sign of hepatic disease, and tarry stools may be the earliest indication of bleeding esophageal varices. The elevation of portal venous pressure resulting from the progression of cirrhosis serves to enlarge the venous communications between the gastric veins and the esophageal veins, since the rising pressure is first felt in these channels. These facts, together with the poor structural support offered by the esophageal submucosa and the aspirating effect of negative intrathoracic pressure during inspiration, all favor the formation of large, fragile varicosities of the esophageal veins in cirrhosis. Hemorrhoids and dilated abdominal veins are frequently encountered in patients with rich collateral circulations. The most frequent and characteristic sign of cirrhosis of the liver is undoubtedly ascites, which occurs in at least 80 per cent of cases, and is often associated with umbilical hernia. Edema often precedes ascites, and may be noted first in the ankles. At this stage in the natural history of cirrhosis, a decrease in the serum albumin concentration is almost always encountered. Absolute values of 3 to 3.4 Gm. % or less are typical. A moderate rise of the serum globulin level is frequently seen at this time. However, the development of fluid retention in cirrhosis in the form of ascites and edema does not alone depend upon alterations in serum proteins. The increased pressure of the portal venous bed and altered state of portal capillary permeability undoubtedly contribute to the appearance of ascites. In addition, hormonal factors in the form of antidiuretic substances much like the posterior pituitary principle have been found to be present in increased amounts in the urine of patients with cirrhosis and ascites.

For further exploration of these concepts the reader is referred to papers dealing directly with these mechanisms.

Laboratory Signs of Hepatic Failure. Normochromic anemia is common, but occasionally a macrocytic anemia is seen, and is thought to be due to failure of the liver to form or store the anti-pernicious anemia principle. Hypochromic anemia may be present if there has been chronic blood loss from leaking esophageal varices. In the so-called "Banti's disease" which occurs in young adults, there may be depression of the white count, and anemia of marked degree. Leukocytosis does not occur ordinarily. More commonly, a slight leukopenia is present with white blood cell counts less than 5000. A tendency to thrombopenia is seen occasionally. One of the most constant findings is the alteration of serum protein. In early hepatic insufficiency due to cirrhosis, the serum globulin will rise, producing little change or a slight rise in the total protein values. Later, the serum albumin will decrease also, lowering the total protein unless the globulin has shown a proportionate rise. The prothrombin time is prolonged and unresponsive to the parenteral injection of vitamin K. A rise in icteric index and serum bilirubin occurs with jaundice, especially the direct-reacting or one-minute fraction.

The cephalin-cholesterol flocculation test frequently shows a 3+ or 4+ reaction in cirrhosis, but the thymol turbidity reaction may be only slightly elevated, especially in alcoholic cirrhosis. In the presence of an elevated serum globulin, particularly the gamma-globulin fraction, the thymol turbidity reaction is of greatest intensity. For reasons poorly understood, this is encountered more often in cirrhosis following acute infectious hepatitis than in the alcoholic variety. One of the most useful tests is the "Bromsulphalein" excretion test. In cirrhosis more than 5 per cent of this dye is found retained at the end of the 45-minute interval (5 mg. per kg. test). These tests are discussed in greater detail in Chapter 18. The urobilinogen content of the urine is often high normal or only slightly increased, there may be slight glycosuria, and tyrosine and leucine crystals appear in the urinary sediment. Esophageal varices are demonstrable radiologically in approximately half the cases by the utilization of a thick barium swallow.

Diagnosis. The ease of diagnosing portal cirrhosis will depend upon the stage to which the process has advanced. Diagnosis is rarely difficult in the stage of "decompensation" when ascites, jaundice, and liver and splenic enlargement are found. It is more important, however, to establish the diagnosis with certainty before this advanced stage of decompensation is reached, since proper therapy, if instituted early, will forestall decompensation and prolong life. In any patient with a history of alcoholism and chronic dietary deficiency, in whom weight loss and anorexia are accompanied by mild jaundice and enlargement of the liver and spleen, the diagnosis of portal cirrhosis should be easily established. Icterus may be overlooked unless an icteric index or total serum bilirubin determination is done. The presence of "liver palms" and spider angiomas in a malnourished patient exhibiting the above symptoms and signs is valuable confirmatory evidence of an underlying portal cirrhosis. It may be necessary to perform an abdominal paracentesis to ascertain the exact size of the liver and spleen. This useful and highly important procedure also permits an examination of the ascitic fluid for the characteristics of a transudate and a study of the sediment for malignant cells, in an attempt to rule out an underlying carcinoma. Following paracentesis, the rounded, irregular liver edge will frequently be found well below the right costal margin, if the cirrhosis is in an early hypertrophic or fatty stage. If the edge is not felt and the liver is small and atrophic, it can often be percussed above the right rib margin. The spleen is frequently palpable and enlarged during the stage of liver atrophy. An x-ray flat plate of the abdomen may assist in determining organ size, but is not highly accurate. The presence of large irregularities and nodules over the liver should lead to consideration of carcinoma.

In any patient suspected of having cirrhosis, measurements of liver function should be undertaken to evaluate the remaining functional capacity of the liver. The most useful tests for this purpose are the measurement of the total serum proteins and the albumin-globulin ratio, with particular attention directed to the absolute level of serum globulin in the presence of a large liver. Serum globulin values of 3 Gm. % or greater point strongly to cirrhosis, especially if there is an accompanying depression of the serum albumin

level. In the presence of ascites, distortions in the serum proteins are almost always found. In the absence of jaundice, a retention of more than 5 per cent of "Bromsulphalein" at the end of 45 minutes is excellent evidence of underlying cirrhosis. Measurements of the serum alkaline phosphatase are useful but never critical. If the prothrombin time is found to be prolonged, vitamin K should be administered in dosages of 10 mg. or more daily, to ascertain whether the prothrombin time will shorten. In the presence of advanced cirrhosis there is a slight or indifferent decrease in prothrombin time with fixation to a subnormal level often within the bleeding range. The demonstration of esophageal varices should confirm the impression of cirrhosis, and the presence of a collateral venous circulation over the abdominal wall, spider angiomas, and "liver palms" are further confirmation.

Gallbladder disease frequently accompanies cirrhosis. Attacks of gallbladder colic in patients with liver and splenic enlargement do not exclude the additional diagnosis of cirrhosis of the liver. Patients with cirrhosis frequently have great difficulty in clearing and concentrating gallbladder dye, so that a negative gallbladder shadow in a patient with a large liver and spleen need not necessarily mean underlying gallbladder disease. In the presence of hematemesis without ascites, peptic ulcer may be suggested. However, pain has a definite relationship to eating in the latter condition, and enlargement of the liver or spleen does not usually occur. Fluoroscopic examination for the presence of ulcer will also exclude the possibility of peptic disease or a malignant lesion of the gastrointestinal tract. If thick barium is used in this procedure, esophageal varices frequently can be detected, even though recent hemorrhage may have occurred. Biopsy of the liver by needle punch peritoneoscopy or laparotomy is not often necessary, but is the ultimate means of establishing the diagnosis.

Course and Prognosis. Up to 10 years ago, the outlook for patients with cirrhosis was poor. After the onset of ascites, approximately 80 per cent of patients would be lost within two years, and an additional 10 per cent by the end of three years. The development of jaundice or hematemesis in the presence of ascites exaggerated these statistics. Since the establishment of the concept of dietary deficiency as an important etiologic factor in cirrhosis, these figures have

been greatly altered by the application of nutritional therapy. To some extent, the course of cirrhosis may be conditioned by active alcoholism and dietary deficiency: the disease may run a rapid course from ascites to death in one or two months, or the patient may linger for many years. Death may occur from esophageal hemorrhage, but does not do so frequently. The threat of such hemorrhage is a constant menace, regardless of the improvement which may follow therapy, so that prognosis must always be guarded.

Since the patient with portal cirrhosis is easy prey to intercurrent infection, the commonest cause of death before the antibiotic era was pneumonia. With modern antibiotics and plasma and blood transfusion, more elaborate support is available to these patients during periods of decompensation and emergency surgery or crisis. The cause of death in Laennec's cirrhosis is most frequently stated to be "cholemia," an ill-defined state in which sudden intensification of signs and symptoms of cirrhosis appear. Stupor and delirium progress into coma, and are accompanied by intense jaundice. It is rare that a patient can be recalled from such an advanced state. Esophageal bleeding may also precipitate cholemia, and the entire picture of hepatic failure may develop following such minor operations as dental extractions, which can result in uncontrollable bleeding. An occasional patient may enter a state of circulatory collapse following the initial abdominal paracentesis. No reasonable explanation has been forthcoming for this phenomenon. Refinement in diagnostic methods has meant more early diagnoses, so that the outlook for prolonging life is no longer considered hopeless.

Treatment. Since the modern concept of cirrhosis is that of a nutritional deficiency syndrome, therapy should be aimed at measures which ensure an adequate food intake of the widest type. To accomplish this aim, the patient's individual tastes, dislikes, and religious preferences must be respected. Lack of appetite is a common problem in cirrhosis and must be overcome before the patient can be expected to eat heartily. It has been the tradition to prohibit fat in the cirrhosis diet because of the possibility of further liver injury. This has served only to decrease palatability. Until adequate experimental evidence indicates that moderate amounts of fat are injurious in cirrhosis, it seems unwise to

prescribe diets which provide as little as 25 to 30 Gm. of fat daily. The inclusion of adequate fat carries no unusual risk if balanced by the protective action of protein, and will not only enhance taste but also supply essential fatty acids and lipid-bound proteins. The most biologically active and digestible forms of fat are to be found in milk, cream, butter, cheese, ice cream, and other milk products. Fried fats are usually restricted because of difficulty in digestion. It is desirable to plan a diet which contains at least 125 to 130 Gm. of protein and 250 to 350 Gm. of carbohydrate daily, and sufficient fat to preserve taste and appetite appeal. This usually amounts to 80 or 90 Gm. daily.

Appetite may be stimulated in the anorectic patient in a number of ways. Simple withdrawal of alcohol in a patient who has been drinking liberally very often restores appetite. Large amounts of parenteral vitamin B, crude liver extract (2 to 3 ml. daily, intramuscularly), or a special crude liver extract for intravenous use in large doses are all useful supplements. Ten units of insulin 20 minutes before each meal has been helpful but should be used with some caution. The discontinuance of alcohol is probably advisable but not critical. The appetite stimulation of a small amount of alcohol before each meal may lead to so appreciable a gain in caloric intake as to offset any injurious effects. Ascites must be removed if it interferes with a gastric filling at mealtime, but not more often than is necessary because of the accompanying protein loss.

Supplementary vitamins have been greatly exploited in the treatment of cirrhosis. The frequent occurrence of cirrhosis of the liver in a setting of nutritional deficiency does not signify that vitamins should be prescribed routinely. In the presence of beriberi, pellagra, or ariboflavinosis, specific vitamins of the B group are indicated; and in the presence of marked malnutrition, there is rationale for their use. Ordinarily, they need not be continued long beyond the time necessary for the reversal of the obvious clinical deficiency syndrome, particularly if the patient has resumed eating an adequate diet. There is sufficient reason, however, to regard cirrhosis of the liver as an intrinsic deficiency disease in which faulty metabolism of certain essential dietary components may give rise to a syndrome resembling deficiency disease outwardly but which, unlike the ordinary deficiency disease,

does not respond in a striking or specific manner to one or a combination of vitamins. Thus, in cirrhosis, the prothrombin time responds incompletely to large amounts of vitamin K because of faulty utilization of this vitamin to produce prothrombin. Night blindness occurs in 50 per cent of patients with cirrhosis, but additional vitamin A does not effect complete reversal, probably because the conversion of carotene to vitamin A and the storage of this vitamin are defective in cirrhosis. Osteoporosis and osteomalacia, which are seen occasionally in cirrhosis, are neither prevented nor cured by vitamin D. The less severe intrinsic deficiencies are seen early in hepatic failure, and are more easily reversed when the liver is large. Later in the stage of atrophy the deficiencies are clinically more apparent and refractory.

In general, the outlook in cirrhosis therapy is better when the liver is hypertrophic. The use of lipotropic substances, such as methionine and choline, is still controversial. Ordinarily, these substances are present in most general diets in amounts adequate to complete fat transportation in the liver. However, the intake of food and lipotropic substances is generally poor in the chronic alcoholic with cirrhosis and fatty liver. Therapy may be instituted with 2 to 5 Gm. of choline chloride or dihydrogen citrate, in addition to the high-protein, high-caloric diet indicated previously. Excellent protein concentrates are now available to amplify and supplement the diet of the patient who is too ill to eat satisfactorily.

Intravenous feedings in the forms of 5 per cent or 10 per cent glucose, with added vitamins of the B group, may be given to advantage, particularly during acute episodes of nausea, vomiting, and diarrhea. Plasma and blood transfusions offer excellent sources of nitrogen because the protein is preformed and homologous, but the risk of transmitting homologous serum hepatitis in the infused plasma or blood is an important consideration. In the presence of blood loss or marked anemia, however, blood transfusions are a necessity. Solutions of human serum albumin have shown great promise in the control of ascites and edema and the correction of hypoproteinemia, and may be administered in combination with glucose. Until albumin solutions are generally available, however, they cannot be included in the general routine.

In the presence of decompensated liver disease,

it is important to reduce the functional demands on the liver—an effect which cannot be achieved short of absolute bed rest. The importance of rest cannot be overemphasized, especially during decompensation and in the presence of fever, icterus, hemorrhage, or ascites, when the weight and burden of the fluid accumulation may exhaust the ambulant patient. In cases of massive ascites the patient may be obliged to support an additional 15 to 20 pounds if allowed unrestricted activity on the ward. The use of morphine and barbital derivatives is to be discouraged in patients with chronic liver disease, because their action will be unusually prolonged, and may lead to undesirable consequences. They have occasionally precipitated irreversible coma. Sedation is frequently necessary, particularly in unmanageable alcoholics. Paraldehyde, chloral hydrate, and small amounts of bromide are to be preferred. Mercurial diuretics may be effective, but often act indifferently or not at all. An occasional patient is seen who can be kept moderately free of ascites by weekly or semiweekly injections of a mercurial diuretic. The gastric irritation that frequently accompanies the adjuvant use of ammonium chloride contraindicates its use in the patient with cirrhosis when anorexia is a problem. The use of these diuretics is never critical and should not be continued if ineffectiye. It is often desirable to restrict salt in patients with cirrhosis in order to achieve control of fluid storage. Since saltless foods are unappetizing and compromise food intake, artificial salting agents should be used freely.

Numerous surgical measures have been devised for the control of esophageal bleeding and ascites. The splenorenal shunt is one of the most promising, and offers a reduction of at least 25 per cent in portal venous pressure. In a selected series of cases it has produced marked relief in esophageal bleeding and ascites. An incomplete Eck's fistula has been performed in many cases in which the portal vein is anastomosed side-to-side to the inferior vena cava but allowed to remain patent through the liver. This will decrease portal pressure by 50 per cent but, like the above procedure, is an operative undertaking of great magnitude and should be performed only by an experienced surgeon. The injection or ligation of esophageal varices is successful occasionally, and the acute bleeding of an esophageal varix has been controlled by local pressure ap-

plied through a distended balloon. The use of a "button" to create a communication between the peritoneal cavity and the abdominal subcutaneous tissues has been advocated. In this manner the patient with ascites receives a constant clysis into the tissue of the abdominal wall. Occasionally, remarkable benefit is seen, but in the majority of instances it has not been of practical benefit, since the large bleb formed in the abdominal wall endothelializes or fails to absorb fluid actively.

BILIARY CIRRHOSIS

This term is a matter of clinical convenience. In loose application, it indicates that the cause of cirrhosis is to be found in the bile ducts; and in the etiologic sense, infection, inflammation, and obstruction in any combination within the biliary tract are important in the production of fibrosis and nodular parenchymal degeneration. For simplicity, therefore, two distinct types may be classified: (1) nonobstructive (hypertrophic) biliary cirrhosis (Hanot's cirrhosis, cholangiolitic cirrhosis); and (2) obstructive (benign or malignant) biliary cirrhosis.

NONOBSTRUCTIVE BILIARY CIRRHOSIS

In 1875 the French physician Hanot described a type of liver involvement characterized by severe jaundice, a chronic febrile course, the absence of ascites or acholic stools, and a very large, smooth liver and spleen. This is an uncommon condition usually involving young people between the ages of 20 and 30 years. There is some tendency for a severe form of the disease to occur in families.

Pathology and Pathogenesis. The disease is undoubtedly infectious in origin and probably represents an ascending cholangitis and cholangiolitis of the bile ducts. As indicated in the previous section, a type of liver lesion, in many ways similar to that described by Hanot, may result from prolonged chronic active infectious hepatitis. An increasing number of cases are being documented illustrating this relationship. The common occurrence of fever and lymph node and spleen enlargement substantiates the concept of an underlying infection which theoretically could reach the liver by the blood stream, producing a descending cholangitis, or ascend into the liver from the duodenum. As a result of spreading in-

faction along the bile ducts, inflammation occurs both inside and outside the duct. Therefore, the connective tissue becomes infiltrated with inflammatory cells and proliferates, leading to atrophy of the liver cells at the periphery of the lobule and the production of a dense periportal zone of fibrous tissue. The general architecture is well preserved and the central lobular area remains intact. The liver is enormously enlarged, weighing from 3000 to 4000 Gm.; the surface is finely granular and dark green in color.

Symptoms and Signs. The symptoms at onset are variable, and may lie outside the gastrointestinal system. Malaise, rhinitis, upper respiratory infections, and chilliness are usually accompanied by abdominal discomfort and pruritus and followed by jaundice. The onset is frequently insidious, and dismissed as an attack of "grippe" or "intestinal flu." Diarrhea is a frequent early sign and often precedes the onset of jaundice. By the time the patient is seen in an acute "attack," the spleen is enlarged and itching is a prominent and distressing complaint. Mild jaundice, fever, and leukocytosis are common. The entire episode may subside and not recur for several weeks or months. With each renewed attack the intensity of symptoms increases. There is finally enormous liver and spleen enlargement with the smooth, even, nontender liver edge extending to the umbilicus. With repeated attacks, the jaundice deepens and assumes a characteristic olive green. Clubbing of the fingers and toes, spider angiomas, and liver palms are frequent. Ascites and esophageal varices do not develop until late in the course of the disease. Nonspecific neurologic complaints may take the form of delirium, agitation, tremor, dystonic movements, and tetanoid spasms. The onset of coma marks the terminal phase.

Diagnosis. The important diagnostic features are the absence of a history of alcoholism, the persistence of bile in the stools despite marked jaundice, and the enormous enlargement of liver and spleen in the absence of ascites, esophageal varices, or hematemesis. There is marked elevation of the alkaline phosphatase, reduction in the esterified cholesterol fraction, and distortion of the serum proteins with early elevation of the serum globulin level and later depression of the serum albumin. The prothrombin time may be unduly prolonged and produce severe hemorrhages from the gums and mucous membranes.

Only an imperfect response to vitamin K injection is obtained.

Treatment. No effective form of treatment exists. The measures indicated in the section on Portal Cirrhosis are of value in the general support of the patient. The accompanying cholangitis does not respond to any known chemotherapy.

OBSTRUCTIVE BILIARY CIRRHOSIS

This term is applied to the hepatic lesion resulting from long-standing extrahepatic biliary tract obstruction, and reflects a fibrosis spreading from the bile ducts around the liver lobules. Secondary infection is usually present in the large bile ducts, and may ascend.

Etiology. This lesion is seen most frequently in strictures of the common duct following gallbladder surgery, in congenital obstruction of the bile ducts in children, and in biliary obstruction in the adult due to a stone in the common bile duct or cancer of the head of the pancreas.

Pathology. In the early stages the liver is enlarged and intensely dark green in color. The surface shows an irregular granularity in contrast to the smooth surface of the hypertrophic liver of nonobstructive biliary cirrhosis. The larger bile ducts are dilated, and there is proliferation of the bile duct epithelium with elongation and tortuosity of the smaller bile ducts, but there is little formation of new ducts. A progressive increase of portal connective tissue appears, followed by infiltration with lymphocytes and mononuclear cells. The bile may become inspissated and bile thrombi develop, leading to rupture of the canaliculi.

Symptoms and Signs. The fundamental clinical picture depends on the causative factor: "stone in the common duct with a history of intermittent jaundice, chills, and fever; or carcinoma of the head of the pancreas with persistent relatively painless jaundice (in 15 to 20 per cent), progressive in intensity, and accompanied by signs of a general deterioration of health. The spleen may become moderately enlarged. Jaundice remains marked throughout the course of the disease. Esophageal varices and hematemesis, as well as ascites, develop occasionally in this form of cirrhosis, but are not common. There is eventual marked depletion of liver function, with a terminal course marked by severe "cholemia."

The average duration of life after the first appearance of jaundice has been stated to be 3.8 years for patients with benign obstruction, and six months for those with neoplastic obstruction.

Treatment. Treatment consists obviously in the removal of the obstruction, either stone, carcinoma, or stricture. Under the latter circumstances the area around the porta hepatis is often distorted, and the anatomic landmarks so completely destroyed that palliative surgery is frequently ineffective in diminishing the amount of biliary obstruction. Removal of a benign obstruction, once biliary cirrhosis has developed, will restore liver function in only the occasional case.

CARCINOMA OF THE LIVER

Although the liver is the commonest site of secondary metastatic carcinoma in the abdomen, it is probably one of the rarest sites of primary carcinoma.

Incidence. Primary carcinoma of the liver is seen more often in males than in females, in contrast to gallbladder carcinoma which is more common in females. This may be related to the more frequent occurrence of gallstones in the female sex. Primary carcinoma occurs in individuals in the 50-year age group. Secondary carcinoma develops in 50 per cent of all cases of abdominal malignancy. It is a curious fact that the yellow race shows the greatest tendency to develop primary carcinoma of the liver. In the United States primary carcinoma is seen particularly among Chinese. Dietetic factors may be of etiologic importance. Experimentally, the azo dye, butter yellow, has been found to be carcinogenic in mice and rats—an effect which can be offset by the administration of casein and riboflavin in the diet. The relationship of these observations to human primary carcinoma of the liver is unknown. Since cirrhosis frequently accompanies primary liver carcinoma, it is considered by some pathologists as a premalignant lesion. This matter has been a point of perennial debate, and is far from a settled issue. The facts indicate that primary carcinoma of the liver, of the hepatic cell type of hepatoma, is found in association with cirrhosis in about 87 per cent of cases, and with cholangioma or bile duct carcinoma in about 51 per cent of cases. How often cirrhosis develops into carcinoma is, of course, a matter of conjecture.

Primary carcinoma of the liver cell, or hepatoma, occurs in two main forms: (1) a solitary massive carcinomatous nodule with a few small outlying nodules; and (2) multiple nodules scattered through the liver substance. These masses are as a rule soft, slightly hemorrhagic in appearance, and show a tendency to central necrosis. The type of cirrhosis accompanying the multiple nodular type is fibrous and dense; with the solitary massive carcinoma, cirrhosis, if found, is usually of microscopic dimensions. There may be invasion of the adjacent circulation, but distant metastases from primary carcinoma of the liver are extraordinarily infrequent. A third form of primary carcinoma of the liver has been described in which the entire liver is infiltrated by small microscopic nodules and surrounded by thick connective tissue hyperplasia. It is difficult to distinguish this lesion from cirrhosis without careful microscopic study. The massive form of solitary liver carcinoma frequently shows such extensive central necrosis that the organ may attain enormous size and occupy almost the entire abdominal cavity.

Microscopically, the liver cells of hepatoma are arranged in irregular fashion, and show great variation in cell type. Giant cells, multinucleated cells, and mitoses are common, and in some areas an alveolar or adenomatous arrangement may be seen. The primary bile-duct carcinoma or cholangioma appears in the form of scattered nodules, and produces an intensely jaundice-enlarged liver. Secondary carcinoma should probably be the first consideration in every case of suspected carcinoma of the liver, so that distant sources of carcinoma may be ruled out first. The most common sites of origin of metastatic carcinoma of the liver are the stomach, large bowel, pancreas, breast, uterus, lung, eye (melanoma), kidney, adrenal, and prostate.

Symptoms and Signs. Carcinoma of the liver pursues the classic course of any intraabdominal malignancy. The onset is characterized by indigestion, anorexia, nausea, and vomiting, followed by a gradual disintegration of health. Weight loss and weakness are extreme, and accompanied by a progressive anemia. In secondary carcinoma of the liver, the initial symptoms are most often those arising from the site of the primary tumor, although not infrequently the first sign of abdominal cancer may be liver enlargement due to metastases.

In any form of carcinoma of the liver, symptoms rarely result from impairment of liver function since, in contrast to cirrhosis, carcinoma is present in addition to the liver but not at the expense of it. Discomfort in the right upper quadrant, jaundice, and ascites constitute the usual progression. If the patient is seen at a late stage, it may be impossible to distinguish primary malignant disease of the liver from the secondary type unless there is evidence of a primary growth elsewhere. One of the most dependable signs, especially in the massive solitary nodular type of primary carcinoma, is eccentric enlargement of the liver with irregular bulging in the right hypochondrium or epigastrium. Jaundice appears in over 50 per cent of cases, and is usually due to adjacent pressure of malignant nodules upon the intrahepatic bile ducts. Pressure of invaded periportal glands upon the common duct, although frequently described, is rare. There is usually no splenic enlargement unless invasion of the portal vein and its tributaries has occurred. Ascites is common and may be due to tumor thrombosis of the portal vein, to extension of the carcinoma to the peritoneal wall, to pressure of carcinomatous nodules on the portal vein, or to the associated cirrhosis. A common and dependable finding is that of irregular fever, which may be due to central necrosis of the carcinomatous nodule. Eosinophilia of 25 per cent may also occur. Fluoroscopy may disclose a solitary nodule bulging into the right chest, producing a central dome-shaped protrusion upward against the right diaphragm.

Diagnosis. Clinically, carcinomatous livers are properly considered the site of metastases until all suspicious distant sites have been ruled out. The greatest difficulty lies in distinguishing cirrhosis from carcinoma of the liver. The usual clinical picture of cancer of the liver is much like that of a rapidly progressing cirrhosis. If the cirrhosis accompanying liver carcinoma is not severe, liver function may be preserved up to the last, but often a marked elevation of the serum alkaline phosphatase will be present, even though jaundice is minimal or absent. If the serum albumin is not depressed when ascites appears, carcinoma of the liver—either primary or secondary—should be suspected. Examination of the ascitic fluid for malignant cells may be decisive. Needle biopsy, laparotomy, or peritoneoscopy with liver biopsy may provide final proof.

Difficulty may be encountered in distinguishing biliary cirrhosis from primary cholangioma, since icterus is so common in both diseases. The former condition, however, occurs in younger individuals, is accompanied by marked enlargement of the liver and spleen and early jaundice, and runs a chronic course. Hepatic abscess can be distinguished by the presence of the classic signs of infection with chills and fever, marked leukocytosis, and night sweats. Examination of the stools for amebas will rule out amebic liver abscess. Enlargement of the spleen may accompany primary carcinoma of the liver if there is invasion of the portal system or an accompanying severe cirrhosis.

Course. The average course from onset to death is stated to be 3.2 months, varying from 2.5 months for hepatoma to 4.2 months for cholangioma. These figures are approximations, since death may occur rapidly if there is severe cirrhosis, and be delayed if the cirrhosis accompanying the malignant process is not rapidly progressive.

Treatment. This is purely symptomatic and supportive. X-ray has been of little value in the treatment of primary hepatic carcinoma. Recently, partial resection of the liver for primary carcinomas has been successfully carried out. Since this procedure involves partial hepatectomy, it is of sufficient magnitude to be undertaken only by an experienced surgeon.

LIVER ABSCESS

There are two important types of liver abscess: pyogenic and amebic.

Pyogenic Liver Abscess. Although infection may reach the liver by way of the portal vein, the lymphatics, the bile ducts, or the hepatic artery, collections of pus in the liver most commonly result from extension of nearby purulent lesions of the gallbladder, peritoneum, or pleura. Hematogenous extension of infection may occur through hepatic arterial emboli as in bacterial endocarditis, or directly from penetrating stab and bullet wounds. The usual origin of septic emboli to the liver is a suppurating appendix, though it is remarkable that this condition is not more common. Abscesses are nearly always multiple and, because of "streaming" within the portal vein, are found most often in the right lobe of the liver. If of long duration, they attain considerable size. The most common pathogens

producing abscess are staphylococci, streptococci, *Escherichia coli*, Friedländer's bacillus, and the dysentery bacillus. Multiple abscesses of microscopic size are occasionally found in the liver as a metastatic extension of other intraabdominal abscesses. These are small and can be detected grossly only if the cut section of the liver is compressed, forcing purulent material to ooze from numerous small areas on the cut liver surface. Occasionally, a suppurative ascending cholangitis may result from gallbladder disease and give rise to multiple abscesses.

The cardinal clinical picture is that of underlying infection: chills, fever, drenching sweats, and local pain due to expansion of the liver substance. If encapsulation of the abscess occurs, these symptoms may disappear. Pain over an enlarged liver, accompanied by chills, spiking temperature elevation, nausea, and vomiting are all highly suspicious. Since the right lobe of the liver is involved most frequently, upward enlargement of the dome of the liver into the diaphragm may occur. This lesion and primary carcinoma are the two commonest conditions in which enlargement of the liver occurs upward. Right lumbar backache and tenderness of the right costovertebral angle and over the liver on percussion and deep palpation are common. Elevation and immobility of the right diaphragm over the abscess may be noted fluoroscopically. Irritation of the diaphragm and overlying pleura produces cough, pain in the right chest, and referred pain to the right shoulder. Rupture of the abscess through the diaphragm into the pleural space or lung will result in empyema or lung abscess with purulent sputum. Rupture may occur into the peritoneal space and cause peritonitis. Subphrenic abscess is frequently a result of liver abscess rupturing into the subdiaphragmatic space on the right. In the chronic, encapsulated liver abscess the general signs of chronic infection, cachexia, weight loss, and weakness are prominent features. Jaundice is rare and a late alarming sign. Elevations of the white blood count from 15,000 to 30,000 and an extremely fast sedimentation rate point to abscess formation. If a diffuse inflammatory hepatitis accompanies the localized infection, there may be impairment of liver function, as noted by the "Bromsulphalein" test.

Treatment with full doses of antibiotic agents to limit the spread of infection is strongly in-

Table

MISCELLANEOUS

	<i>Age and Sex</i>	<i>Etiology and Pathogenesis</i>	<i>Symptoms and Signs</i>
Fatty liver	No predominance	In obesity, tuberculosis; hepatotoxins such as phosphorus and arsenic; chronic alcoholism and nutritional disturbances (avitaminosis B); lack of lipotropic substances, choline, methionine, and lipotaeic. May develop as a preliminary phase of portal cirrhosis; uncontrolled diabetes mellitus. Huge fat droplets in liver cells of periphery of lobules	Vague gastrointestinal distress with fullness and discomfort over liver; absence usually of icterus, pain, or ascites unless severe. Predominant symptoms those of fundamental disease. Enlarged liver but small spleen
Acute yellow atrophy	20-30 yr. either sex	Pregnancy, fulminant acute infectious hepatitis, malaria, yellow fever, typhoid, arsphenamine, acute alcoholism, cinchophen. Liver shrunken, atrophic, yellow-green. Cells around central vein area necrotic. If process is subacute, regeneration and repair evident with fibrosis and production of healed "toxic" cirrhosis	Mild onset like acute hepatitis, or violent and fulminant from start with nausea, vomiting, progressive icterus, hemorrhages (prolonged prothrombin time), restlessness, delirium, coma, temperature rise before death. Liver small and not palpable, spleen enlarged. Icterus may not appear until patient pre-terminal
Congestive ("cardiac") cirrhosis	Young and middle-aged cardiac patients	Most common in association with rheumatic mitral and tricuspid disease, chronic constrictive pericarditis, and occasionally in hypertensive heart disease. Occurs in 4-7% of congestive cardiac deaths. Liver enlarged, red to brown color, with discrete and confluent nodules. Microscopically hyperemic with degeneration and necrosis of cells around central vein. Compact acellular fibrosis in portal zones. Numerous regenerative foci	Predominant clinical picture of circulatory (right heart) failure, pain and liver discomfort, nausea, anorexia, ascites, and edema. Hepatomegaly always; splenomegaly may also occur
Hepatolenticular degeneration (Wilson's disease)	10-25 yr. either sex	Etiology unknown; familial and hereditary. Symmetric degeneration of putamen and caudate nucleus associated with portal type of cirrhosis	Hepatic failure with nausea, vomiting, transient icterus, and ascites with hepatosplenomegaly usually appear before neurologic signs of extrapyramidal disease such as contractures, tremor, rigidity, dystonic movements, and later mental deterioration. Brown-green pigment ring around cornea (Kayser-Fleischer ring) is pathognomonic
Sarcoma of liver	Primary type in children under 10 or adults over 70. Males 3:2	Primary sarcoma well circumscribed with either massive solitary lesion (most common) or scattered nodules. Pseudocysts may form and there is hemorrhagic tendency, especially into peritoneal cavity. Spindle- or round-cell types of fibroblastic sarcoma. Metastatic sarcoma of liver common in melanoma from retina or pigmented mole of skin, osteogenic sarcoma, etc.	Clinical features are same as sarcoma, though liver enlargement is usually huge in primary type

* Other forms of liver disease are included elsewhere under specific etiologic disorders.

LIVER CONDITIONS*

<i>Diagnosis</i>	<i>Course and Prognosis</i>	<i>Treatment</i>
Association of known etiology with large, smooth, soft, painless liver, and absence of icterus. Minimal disturbance of "Bromsulphalein." Rule out cirrhosis, chronic passive congestion, lymphosarcoma, and ptosis	Usually reversible if fundamental etiology can be controlled. Alcoholic type may progress to cirrhosis but diabetic type may be less influenced and show no measurable hepatic dysfunction	Correct known etiology if possible. High-protein, high-calorie diet; choline and methionine probably useful in alcoholic type with supplements of B vitamins
Association of hepatitis picture with known etiology. Late appearance of jaundice and conspicuous central nervous system features. Marked disturbances in tests of liver function. Persistence of nonpalpable or small liver	Usually fatal in 14 days or less. Subacute variety may persist 6-8 weeks. Prognosis bad with pregnancy	Elaborate nutritional support with high-protein, high-carbohydrate diet. Vitamin supplements plus vitamin K. Intravenous alimentation
Diagnosis difficult because of lack of distinctive features beyond simple passive congestion. Liver function tests usually normal or minimally impaired	Course determined by fundamental circulatory problem; death not reported from hepatic failure alone	Treatment of circulatory failure
Familial history in patient with signs of cirrhosis, extrapyramidal disease, and Kayser-Fleischer corneal ring (50% of cases). Liver function tests may be normal until decompensation occurs	Downhill course with death due to intercurrent disease more often than hepatic failure. Course runs variably from several months to years	No known therapy except for hepatic failure
	Death in 1-2 yr.	No known therapy

dicated, and should be followed by surgical incision and drainage. Exploratory aspiration with a needle, while sometimes successful, is dangerous, and inferior to surgical laparotomy. It is wise to give a trial course of emetine therapy in any case of primary liver abscess, though amebas may not be recovered from the bowel.

Amebic (Tropical) Liver Abscess. Abscess of the liver may be the first sign of intestinal infestation with *Endamoeba histolytica*. Since this parasite produces bowel ulceration, it is probably carried to the liver via the portal vein and produces a true hepatitis or hepatic abscess. Amebic liver abscess is much more common in the tropics and subtropics than in temperate climates. The number of cases of intestinal amebiasis which develop liver abscess must be extremely small. Males suffer from this complication more often than females, the ratio being 7:1. The age group from 21 to 40 is most commonly afflicted; the previous state of nutrition and the number of preceding attacks of amebic dysentery are important predisposing causes. Frequently, no previous history of diarrhea or dysentery can be obtained. An amebic liver abscess may develop in individuals who have recovered from acute amebiasis months to years before.

The abscess is usually solitary but is not infrequently multiple. In many instances the content of the abscess is necrotic or caseous. The causative agent is not a pyogenic organism, but secondary infection may occur and produce true suppuration. The abscess may attain huge size and be of great chronicity. Fresh abscesses usually show no definite abscess wall, but contain grayish brown areas of cytolyzed and necrotic liver tissue. The huge old abscesses have a definite wall of great thickness and enclose liquefied hepatic substance containing necrotic liver tissue, strands of connective tissue, and old blood. Since the connective tissue reticulum of the liver substance is more resistant to the cytologic action of the amebas than the parenchyma of the liver, the abscess is frequently crisscrossed by strands of connective tissue which stretch across the cavity. The contents of the amebic liver abscess are chocolate brown in color, and contain the above elements together with trophozoites of *E. histolytica*. Pus cells appear when secondary infection occurs, at which time the contents of the cavity may assume the color of the infecting organism and lose the typical "anchovy sauce"

appearance. It is difficult to demonstrate the trophozoites of *E. histolytica* in the older abscesses with thick walls, since a secondary bacterial infection will cause them to disappear.

The clinical picture of a patient with an amebic liver abscess is essentially that described above for pyogenic liver abscess, except that the onset is more insidious and the course milder. A definite "presuppurative stage" occurs, and is recognized as a mild amebic hepatitis. The liver is tender, slightly enlarged, and accompanied by a dragging, aching pain in the right hypochondrium which may be referred to the right shoulder, axilla, or back. Fever is mild, chills are unusual, and, in contrast to pyogenic abscess, there is only moderate leukocytosis. Marked elevation of the sedimentation rate often occurs. There may be drenching night sweats, and if the infection is allowed to run uncontrolled for a long period of time it may eventuate in marked emaciation and disability. In this respect it will resemble malignant liver disease.

The treatment of amebic liver abscess and amebic hepatitis is medical, and consists of emetine hydrochloride or other effective amebicide drugs, as discussed in Chapter 181. Medical treatment very often will correct even the largest of amebic liver abscesses, although needle aspiration or surgical intervention is occasionally necessary. Relief by the use of antiamebic treatment is often so striking that a similar clinical picture which remains uninfluenced by antiamebic therapy may be considered not to be an amebic abscess or hepatitis. In the presence of secondary infection, antibiotic agents can be employed with success.

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Diseases of the Gallbladder and Bile Ducts

Andrew B. Small and C. A. Moyer

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The gallbladder is a dispensable organ. Its congenital or induced absence in man is compatible with a normal existence. Some animals, such as the deer, horse, and elephant, do not possess a gallbladder. In these animals bile enters the intestine continuously. In those animals that do possess a gallbladder, the entrance of bile into the intestine is intermittent and more or less coincides with eating.

The known functions of the gallbladder are the concentration and storage of bile, and the secretion of mucus. Water is absorbed by the mucosa of the gallbladder. The absorption of water continues until the concentration of biliary solutes reaches 20 to 25 Gm. per 100 ml. Because of its ability to concentrate solutes by the absorption of water, it can receive and store the entire daily output of liver bile.

As was intimated previously, the gallbladder empties during the entrance of mixed foods into the intestine. The act of emptying is not a simple one. Repeated contractions of the gallbladder, associated with the relaxation of the sphincter of Oddi, are necessary for the complete evacuation of its contents. Ivy showed that the emptying of the gallbladder, when food enters the intestine, is actually accompanied by the stimulation of the gallbladder by a hormone, cholecystokinin. This substance is produced within the mucosa of the duodenum, when fats or fatty acids come in contact with it. Besides stimulating the gallbladder, cholecystokinin effects relaxation of the sphincter

of Oddi. Many agents affect the gallbladder and contractile elements of the sphincter of Oddi in various ways.

1. Relaxation of the sphincter without stimulation or relaxation of the gallbladder usually follows the impingement of hypertonic magnesium sulfate and sodium chloride solutions upon the duodenum, and the inhalation of amyl nitrite.

2. Relaxation of the gallbladder and sphincter attends the administration of nitroglycerin, and toxic doses of atropine.

3. Contraction of the gallbladder and sphincter may be induced with morphine, pericholedochal inflammation, and emotional disturbances.

4. Contraction of the gallbladder and relaxation of the sphincter are effected only by cholecystokinin, the production of which is dependent upon the ingestion of food.

The constituents of bile are described in Chapter 18.

The gallbladder is afflicted by some of the ills affecting its parent tract, the intestine, such as obstruction of its duct, bacterial inflammatory disease, and neoplasms. The most common abnormality of the gallbladder is the containment of concretions of cholesterol or bile pigments (gallstones), with or without significant admixture with calcium salts. The conditions necessary for the production of stones of cholesterol within the gallbladder are really unknown. Because of certain positive correlations—namely, with pregnancies and obesity—it is felt that the development of a majority of these stones is incident to metabolic disturbances that affect the formation and excretion of cholesterol and bile salts.

The pigment stones are hard, small, black concretions of calcium bilirubinate. Their formation is generally associated with the hemolytic anemias.

The imposition of an infection within the stone-containing gallbladder effects a deposition of calcium carbonate upon the pigment or cholesterol nucleus.

The pure pigment and cholesterol concretions are radiolucent. When they are covered or mixed with calcium carbonate they become radiopaque.

The most common affliction of the gallbladder is cholecystitis. The etiology of cholecystitis is presumably not primarily bacterial, as implied by the name. It appears that interference with the emptying of the gallbladder by stone or a

malfunctioning cystic duct is the most frequent cause of the disease.

ACUTE CHOLECYSTITIS

Experimentally, acute cholecystitis can be produced readily by the injection of concentrated bile or bile salts into the gallbladder while the cystic duct is partially or completely obstructed by a ligature. Cholecystitis produced experimentally and that which occurs in man are indistinguishable one from the other.

Pathologic Findings. When the abdomen is opened and the gallbladder is examined within 36 hours of the onset of cholecystitis in man or in the experimental animal, the gallbladder is usually dilated. Its wall is thickened by edema. The serosa is dull and varies in color from yellow to red, black, or green, depending upon the extent of damage. It is usually covered by a fibrinous exudate.

Upon opening such a gallbladder the fluid content often resembles pus, but pus cells are not present in large numbers when this material is examined microscopically. It is usually a mixture of old partly inspissated bile, cellular debris, cholesterol crystals, and bile pigment. The mucosa is inflamed, hemorrhagic, ulcerated, or infiltrated with bile. The villi are flattened.

Histologic examination of this early process reveals three prominent changes in the gallbladder wall: edema, hyperemia, and hemorrhage. The edema is striking and involves mostly the subserous layer. Many vessels are dilated and hyperemic. Hemorrhage at times is localized to the vicinity of vessels, or it may be spread through a large section of the wall. The mucosa is sometimes spared.

In the more rapid or fulminating cases the gallbladder wall, in part or in its entirety, may be necrotic. The mucosa shares in this damage with the other layers.

The cells of an acute inflammatory exudate do not appear in great numbers in the gallbladder wall until about the fourth day of the disease, or later. At first, a scattering of leukocytes is noted, and then small isolated collections appear in the subserosa. In many instances the inflammatory process progresses, and frank suppuration begins first as intramural abscesses, which later may become confluent so as to involve most of the wall. It is most probable that the inflammation up to this stage in acute obstructive cholecystitis

is not due to the presence of any microorganism. This is quite different from acute inflammatory disease of other organs.

Later, however, bacterial invasion of the chemically damaged gallbladder may occur. Occasionally, cholecystitis may be of bacterial origin.

Whatever the exact etiology of cholecystitis may be, it is a recurrent progressive disease of middle and old age, and of obesity. It affects women more frequently than men. Evidence of previous attacks may be obtained from a carefully taken history. Nearly all sufferers will complain of some previous abdominal discomfort or of indigestion. This is especially true of patients over 50 years of age.

Symptoms and Signs. A constant severe abdominal pain usually marks the onset of acute cholecystitis. This pain may wax and wane slowly, but does not cease. It is usually situated in the epigastric region, with reference to the right posterior chest below the scapula. Occasionally, primary reference of the pain is to the left upper or lower quadrants of the abdomen. Occasionally, this pain is not relieved by morphine but may be relieved by amyl nitrite or nitroglycerin.

Although very early in the course of the disease the pain is usually felt only in the epigastric and lower substernal regions, sooner or later the acute, severe epigastric pain subsides and a constant aching pain makes its appearance over the region where the gallbladder is located, most often in the right hypochondriac region. It is presumed that the early severe epigastric pain is caused by mechanical obstruction of the cystic duct and that the later appearing, less severe right hypochondriac pain is produced by the consequent pericholecystic inflammation. The early epigastric pain is not particularly aggravated by movement, as is the hypochondriac ache. Occasionally the pain will be located in the right hypochondriac region from the onset.

Tenderness in the upper abdomen and lower right anterior chest is usually elicitable; very early it may be sharply localized to the area overlying the gallbladder. Occasionally the tender area can be outlined only by sharp, light percussion. This is especially true when the gallbladder is high and is overlaid by the lower right chest cage. Nausea, vomiting, anorexia, and a sense of fullness or distention usually accompany the pain. Fever is usually present. Spasm of the ab-

dominal muscles varies with the severity of the inflammatory process and the proximity of the gallbladder to the abdominal wall. Very early in the course of acute cholecystitis, the spasm is of the voluntary type and tends to be present over the whole upper abdomen. Later the spasm becomes involuntary and localized to that part of the abdomen overlying the inflamed gallbladder.

The palpability of an inflamed, tender gallbladder depends upon the degree of obstruction and the distensibility of its wall, as well as upon the position of the gallbladder in relation to the anterior parietes.

Right-sided inspiratory distress in the form of a pleuritic-like pain unaccompanied by a pleural friction rub is a common sign and is of diagnostic value in the differentiation of acute cholecystitis from other upper abdominal diseases, but it may mislead one into making a diagnosis of pneumonia when cholecystitis is actually present.

Differential Diagnosis. The early signs and symptoms of acute cholecystitis are often superficially similar to those of volvulus of the small intestine, of appendicitis, of acute pancreatitis, of myocardial infarction, of pneumonia, of rupture of a peptic ulcer, and of an obstructive neoplasm of the transverse colon. The late signs and symptoms of acute cholecystitis are so much like those of a neoplasm of the hepatic flexure of the colon that many a stone-containing gallbladder has been removed only to have the symptoms persist, and months later the real trouble—a carcinoma of the colon—is discovered. Occasionally, when the epigastric pain is slight and is referred to the left lower quadrant, and meteorism is present, one is misled into making a diagnosis of an obstructive lesion of the sigmoid colon, and a sigmoidal obstruction may be demonstrated with a barium enema. The obstruction is, of course, of the spastic type, but it may be so complete as to lead to performance of a decompressive operation upon the large intestine.

It is evident that the differential diagnosis of acute cholecystitis is often difficult. It might be said that when something is missing from the diagnostic triad of acute cholecystitis—namely, the typical pain, the tenderness and spasm beneath the right costal margin, and the palpation of a mass—the diagnosis of acute cholecystitis cannot be made with certainty.

Whenever the diagnosis of acute cholecystitis is not clear, one should take pains to rule out

those diseases which cannot be treated surgically, such as pneumonia, myocardial infarction, acute infective pericarditis, and acute pancreatitis.

Clinical Course. There are three different and approximately equally frequent courses of the acute disease:

1. Progression associated with necrosis of the gallbladder and perforation thereof.
2. Static condition (symptoms and signs persist relatively unchanged for a week or more).
3. Remission.

A rising leukocyte count, increasing and spreading pain and tenderness, increasing fever, and the appearance or growth of a palpable mass are signs of progression of the disease, and herald impending perforation of the gallbladder. The leakage of bile through the gallbladder wall occurs to some extent during 14 to 20 per cent of the attacks of acute cholecystitis.

Perforation into the free peritoneal cavity induces a peculiarly lethal form of peritonitis. It must be remembered that bile peritonitis can occur without actual physical perforation of the gallbladder wall. It is presumed that leakage of bile per diapedesis through the necrotic gallbladder wall is responsible.

Perforation of the gallbladder into the duodenum may occur. This sets the stage for the passage of stones into the gut, and if the stones are large enough, obturation of the intestine follows. About 50 per cent of the individuals who suffer intestinal obstruction by gallstones die.

Treatment. The treatment of acute calculus cholecystitis of the progressive or static type is fundamentally surgical. Since it is not infectious or functional in origin in the majority of cases, and suppuration does not occur until late (three to four days after onset), early operation should be done in order to prevent suppuration and the severe complications which occur.

The positive indications for operation during the early course of disease are: (1) pain which is difficult to relieve; (2) a firm, tender mass; and (3) a rising fever or leukocyte count.

It is occasionally necessary to resort to cholecystostomy (drainage of the gallbladder) when an initial delaying program has been carried out. It is the operation of second choice. It is lifesaving, however, and is indicated when the patient is a bad risk; when perforation and abscess exist; when the brawny edema, which comes late, obscures the structures in the hepatoduodenal liga-

ment; and when jaundice is present in a very ill person.

It must be understood that cholecystostomy does not terminate the disease, but only interrupts it. A large proportion of patients who have undergone cholecystostomy have subsequent attacks of cholecystitis, and when cholecystectomy is then performed the mortality in this group is relatively high.

The supportive therapy is directed toward the control of pain, the correction of fluid imbalances if they exist, and the relief of tympanites by duodenal intubation.

CHRONIC CHOLECYSTITIS

The remission of acute cholecystitis followed by residual cholezystic or pericholezystic disease is called chronic cholecystitis.

Pathologic Findings. The pathologic findings in chronic cholecystitis vary, depending upon the duration of the process, the amount of cystic duct obstruction, the chemical injury, the presence or absence of stones, and the severity of the complicating infection.

Patients suffering many attacks of severe acute cholecystitis, and especially those who have stones in a nonfunctional gallbladder, have gallbladders which show the most severe pathologic changes. The gallbladder is often small, shrunken, fibrotic, and thick-walled. It may contain stones of which the so-called mixed or infective type predominate.

Symptoms and Signs. Chronic cholecystitis is a progressive disease having remissions and exacerbations. The exacerbations are characterized commonly by the symptoms and signs of acute cholecystitis. Occasionally, however, the symptoms of chronic cholecystitis are insidious in onset, being manifested by disturbances of digestion, and the symptom complex which we ordinarily associate with acute cholecystitis is absent. These people complain of all of the symptoms known as "indigestion."

Diagnosis. The diagnosis of chronic cholecystitis should be based upon the evaluation of three findings: (1) the history of attacks of acute cholecystitis; (2) stones demonstrated radiographically either as positive calcium stones or as negative shadows with the Graham-Cole test; and (3) cholecystographic evidence of a nonfunctioning gallbladder, which (provided that liver damage does not exist) signifies that the

gallbladder does not fill or that it has lost its concentrating ability.

Treatment. The indications for cholecystectomy are the same as the criteria for the diagnosis of chronic cholecystitis, namely: (1) pain of extrahepatic biliary tract origin; (2) nonfunctioning of the gallbladder, as determined by cholecystography, or positive evidence of stones in the gallbladder.

Without a history of the typical pain of gallbladder colic or evidence of stones, it has been found that cholecystectomy generally fails to relieve the symptoms presumably attributable to chronic cholecystitis, even though the gallbladder may have failed once to fill with dye. However, whenever typical attacks of pain have been suffered and stones are shown to be in the gallbladder, or the gallbladder does not visualize at all after repeated administrations of the dye, one can expect cure by cholecystectomy.

Medical measures such as the elimination of offending foods and the use of antispasmodic drugs are indicated whenever the presence of chronic organic disease of the gallbladder cannot be established with certainty. The above measures are also valuable for controlling the dyspepsia often experienced for three to six months following cholecystectomy. However, these measures are not indicated when the diagnosis of chronic cholecystitis can be established definitely; then, surgical measures should be used.

"Faint" visualization of the gallbladder and/or delayed or "incomplete" emptying thereof, after the administration of a fatty meal, do not constitute adequate evidence for making a diagnosis of chronic cholecystitis *unless* typical attacks of pain have been suffered and the physician has actually observed the typical physical signs of acute cholecystitis. Dyspepsia and fatty food intolerance do not constitute adequate corollary evidence to enable one to infer that a poorly visualizing gallbladder is the seat of disease. The delayed emptying of a dye-filled gallbladder has no diagnostic significance. Modern cholecystography employing orally administered "Priodax" is a fairly definitive test for the evaluation of the physiologic status of the gallbladder, provided that there is no jaundice, hepatic insufficiency, vomiting, dehydration, diarrhea, or pyloric obstruction. The dye may be administered intravenously whenever enteral absorption cannot be depended upon. When the

precautions are taken, the gallbladder that does not visualize at all after two proper administrations of "Priodax" is likely to contain stones 9 times out of 10, even though there are no other physical signs or symptoms of cholelithiasis.

Whenever one is tempted to ascribe indigestion and intolerance to fatty foods to chronic disease of the gallbladder, without anamnestic evidence of rather typical attacks of acute cholecystitis or radiographic evidence of a nonfunctioning or a stone-containing gallbladder, he should remember that people born without gallbladders may have the same symptoms, and that they certainly have a "nonfunctional" gallbladder using the Graham-Cole test. In other words, dyspepsia and, more especially, intolerance to fatty foods are grossly overrated signs of gallbladder disease.

CHOLELITHIASIS

Gallstones are associated with three different types of clinical problems: (1) acute or chronic cholecystitis; (2) obstruction of the common duct; and (3) asymptomatic cholelithiasis. In view of the potential dangers of the asymptomatic stones (i.e., neoplasm, acute cholecystitis, and common-duct obstruction), it is now deemed preferable to remove such stone-containing gallbladders, provided that no contraindication to elective operation exists, and the surgeons within the locality are capable of performing the operation with a mortality rate of less than 1 per cent. Should the mortality rate following elective cholecystectomy in the locality exceed 1 per cent, the removal of the asymptomatic stone-containing gallbladder constitutes a greater danger to life than reserving operation for complications while maintaining a careful watch over the individual.

TUMORS OF THE GALLBLADDER

CARCINOMA

Incidence. Adenocarcinoma of the gallbladder comprises about 3 per cent of all malignant tumors of the body. It develops during the later decades of life. Women suffer from it four times as frequently as do men.

Its cause is unknown. However, the almost invariable association of carcinoma of the gallbladder with cholelithiasis is presumptive evidence that chronic cholecystitis with cholelithiasis is one of its prime causes. It has been estimated

that carcinoma of the gallbladder occurs in about 2.5 per cent of people having stones in their gallbladders.

Symptoms and Signs. The early symptoms are those of chronic cholecystitis with stone. Fifty to 70 per cent of patients give a history of previous dyspepsia and "biliary" colic.

The pain is either dull, boring, and progressive, or spasmodic, and is usually located in the epigastric and hypochondriac regions. As time passes, it becomes increasingly more difficult to relieve with opiates.

Pain and weight loss are the commonest manifestations, but indigestion, anorexia, jaundice, and vomiting may occur.

Diagnosis. The earliest symptoms of carcinoma of the gallbladder are those of chronic cholecystitis with stone. Unfortunately, most patients are seen late, and the presenting signs and symptoms at that time are those of obstructive jaundice and tumor. Therefore, the condition is confused most frequently with carcinoma of the head of the pancreas or of the common bile duct.

Prognosis. The prognosis is usually very grave. Only about 5 per cent of people having a grade II carcinoma live for five years. No one suffering from highly anaplastic carcinoma of the gallbladder lives that long.

It is obvious that prevention of carcinoma of the gallbladder is the only solution to the problem. The removal of gallbladders which contain stones during early adult life and middle age should reduce the number of deaths from carcinoma of the gallbladder.

SARCOMA

Sarcoma of the gallbladder is very rare. The symptoms and prognosis are similar to those of carcinoma of the gallbladder.

BENIGN TUMORS

Papillomas have been reported in 8 per cent of surgically removed gallbladders at the Mayo Clinic. Many of the small papillomas, however, are only hypertrophied mucosal villi, and may be associated with cholesterolosis.

Myoma, fibroma, lipoma, and adenoma occur in the gallbladder, and are rare. Benign tumors rarely produce symptoms, and are found accidentally by cholecystography, or by palpation of

the gallbladder during manual intraabdominal exploration.

OBSTRUCTION OF COMMON BILE DUCTS

Diagnosis. The only constant sign of obstruction to the flow of bile through the common bile duct is jaundice. Pain, vomiting, itching, and fever are variable accompaniments thereof. Because pain is often a relatively minor complaint with extrahepatic obstructive jaundice, the differentiation of hepatic jaundice from that accompanying a mechanical obstruction of the common duct is frequently very difficult. However, it is very important that one be able to separate extrahepatic biliary obstruction from the intrahepatic types quickly, so that definitive surgical measures can be undertaken to relieve the obstruction of the extrahepatic ducts before serious impairment of liver function occurs. The mortality rate associated with the surgical relief of obstruction of the common bile duct rises as the liver fails, and since the liver failure associated with common bile duct obstruction increases with the passage of time, it is obvious that the differential diagnosis of jaundice should be considered so pressing as to lead to the performance of diagnostic laparotomy after the other differential diagnostic measures have been exhausted. The subjection of an individual to anesthesia, and the exploration of the common duct while he suffers from a hepatic jaundice, is attended by high morbidity and mortality rates. Therefore, accuracy of differentiation is to be sought after as well as speedy diagnosis.

The differential diagnosis of jaundice is discussed at length in Chapter 18. The more important diagnostic features of the commoner causes of obstruction to the flow of bile through the common duct are listed in table 109. It should be emphasized that cholecystography is a useless procedure in persons with obstructive jaundice.

Symptoms and Signs. As stated earlier, jaundice is the only constant sign of obstruction to the flow of bile through the common duct. When a choledolith causes the obstruction, the intensity of the jaundice tends to vary because the obstruction is usually incomplete and its degree of completeness changes from day to day. However, when a stone becomes tightly fixed in the ampulla of Vater, no bile enters the intestine and the jaundice tends to deepen steadily. When the ob-

struction is caused by neoplastic growths within the common hepatic duct, the common duct, or the head of the pancreas, the jaundice deepens steadily and the obstruction to the flow of bile into the intestine is complete. Carcinomas of the ampulla of Vater, because of their tendency to ulcerate, are associated with a varying jaundice early; later, however, the obstruction becomes complete and the jaundice increases steadily.

The pain associated with obstructions to the common duct varies in intensity. Sudden obstruction by stone is attended by an acute, agonizing pain in the epigastrium which radiates straight through to the back. It is relatively constant and often subsides slowly; however, it may cease suddenly, and when it does so the stone can often be found in the feces passed during the next few days. Not all common ducts which contain stones become acutely obstructed by them and, consequently, some people may have choledocholithiasis without pain. However, many of these have mild jaundice intermittently and *develop hepatomegaly and splenomegaly*. In other words, they show a clinical picture which is very much like that of the preascitic stage of Laen-

nec's cirrhosis. Consequently, when hepatomegaly, splenomegaly, and mild jaundice are discovered, even though little or no pain has been suffered, it should always be remembered that chronic intermittent, incomplete common-duct obstruction by stone may be the cause, and steps should be taken to rule in or out that possibility.

The pain associated with the slowly progressing obstructive lesions of the large bile ducts is usually mild compared to that produced by sudden obstruction with stone. The pain may be of the aching type and located over the whole epigastric and right hypochondriac regions; it is presumably caused by enlargement of the liver. This is often the only type of pain suffered when inflammatory or traumatic strictures, or neoplasms of the ampulla or of the ducts, cause the obstruction. Neoplasms of the head of the pancreas are associated with varying intensities of epigastric and back aches. The backache is generally located by the individual beneath the area lying between the tenth thoracic and second lumbar vertebrae. These aches are often at their worst between midnight and morning, and may not be felt during the day.

Table 109

THE MORE IMPORTANT CAUSES OF COMMON DUCT OBSTRUCTION IN ADULTS

Cause	Common Symptoms	Character of Jaundice*	Other Findings	Preferred Treatment†	Liver Damage
Stone	Pain, vomiting, intermittent fever	Intermittent Incomplete	History of cholecystitis	Removal	
Neoplasms	1. Head of pancreas	Progressive pain in epigastrium and back	Progressive Complete	Resection or palliative biliary short circuit	Evidence of impaired liver function appears late unless there is accompanying cholangitis as shown by chills and fever. Impaired function at early stage without high fever suggests a hepatic cause for the jaundice
	2. Common duct	Pain minimal Chills and fever	Progressive Complete	Resection or palliative biliary short circuit	
3. Ampulla of Vater	Pain minimal Chills and fever	Intermittent and incomplete early; later, progressive and complete	Occult blood in stools	Resection	
Stricture	1. Traumatic	Minimal	Progressive Complete	Repair	
	2. Inflammatory	Recurrent fever and jaundice	Intermittent Incomplete	Early evidence of liver damage Prolonged external drainage	

* The jaundice is always of the obstructive (regurgitative) type.

† Vitamin K administration is indicated in all instances of obstructive jaundice.

Acute common-duct obstruction by a stone ("ball-valve stone") is often attended by intermittent chills and fever, the so-called Charcot's intermittent hepatic fever. It is generally believed that these chills and fever do not represent a bacterial invasion of the duct system of the liver, provided that the jaundice increases during the bouts of fever. However, the surgeon views these febrile episodes with apprehension, and considers that they constitute positive indications for the surgical removal of the obstructive agent as soon as possible.

When amebic hepatitis can be excluded, an intermittent or remittent fever attended by an enlarging, tender liver, physical and roentgenologic signs of right basilar, pleural, and pulmonary inflammation, and a relatively mild jaundice which does not increase appreciably with the febrile episodes, signifies that a suppurative cholangitis exists. Unless surgical drainage of the duct systems is instituted very soon, recovery practically never takes place. Multiple parenchymal abscesses develop within a relatively short time. However, chances of complete recovery are good if the duct system is drained early and external diversion of the bile is carried out for 6 to 12 months. During this period of time, the T tube or catheter draining the duct never should be closed. As long as the external drainage of bile is taking place, 4 to 10 Gm. of salt and 1 Gm. of dehydrocholic acid ("Decholin") are given daily, 20 mg. of menadione is injected intramuscularly once a week, and meat should be eaten at every meal. These measures serve to prevent the development of deficits of sodium salts, vitamin K, cholic acid, and porphyrins while the bile is diverted from the bowel. Suppurative cholangitis more often attends ductile obstruction by neoplasms and strictures than ductile obstructions by stones.

Itching is a prominent accompaniment of common-duct obstruction, provided that the liver has not been damaged badly. The itching is caused by the retention of the bile salts. Since the formation of bile salts within the liver is a conjugative process and requires a fairly normal liver to carry it out, itching constitutes a fairly good clinical measure of liver function. If the jaundice deepens or remains static while itching decreases in intensity, the liver is probably suffering rapid functional impairment. If the jaundice is intense and itching is absent or minimal,

then, too, the liver function is likely to be poor by most of the other criteria. Should the itching subside with the jaundice and no significant fever obtain, then the subsidence of itching has no meaning in relation to the changes in hepatic function. However, should the itching diminish as fever and other general signs of illness increase, a fulminant destruction of the liver is probably taking place.

If the gallbladder is palpable and complete obstruction of the common duct is present, carcinomatous obstruction of the duct is most likely. Should the gallbladder not be palpable with a complete obstruction of the common duct, obstruction by stone is likely. This is the essence of Courvoisier's law. It is now realized that there are many exceptions to this rule, and consequently much of its diagnostic emphasis has been lost.

Treatment. Surgical procedures are the only definitive means of treating obstructions of the common bile ducts. Gallstones cannot be dissolved, strictures cannot be softened, and neoplasms cannot be treated by chemical or dietary measures (fig. 239). One is justified in watching an individual who passes a cholelith per rectum and has a gallbladder which is demonstrated by x-ray and has no stones in it. However, early operation is indicated whenever the jaundice does not recede quickly or the gallbladder does not visualize or contains stones after the jaundice has subsided, provided that the individual is better than a fair operative risk. Enfeebled old age, recent myocardial infarction, a recent or an extensive apoplexy, and advanced renal disease warrant watchful waiting, provided that the signs of obstruction disappear within a reasonable length of time. However, the continuance of the signs of obstruction for longer than two weeks, the rapid deterioration of the individual, or the development of suppurative cholangitis is sufficient to warrant the risks of surgery, even in the face of myocardial infarction without cardiac failure, enfeebled old age, etc. The surgery of today is better than that of yesterday, and the "bad operative risk" of yesterday is the "fair risk" of today and, it is hoped, the "good risk" of tomorrow. The reduction of the risk of an operation upon the biliary tract is due largely to advances in the techniques of the preoperative and the postoperative care and in anesthesia.

Before the discovery that a deficiency of vita-

min K was responsible for the occasional preoperative and common postoperative hemorrhagic diathesis associated with regurgitant jaundice, uncontrollable operative and postoperative hemorrhage was the commonest cause of death dur-

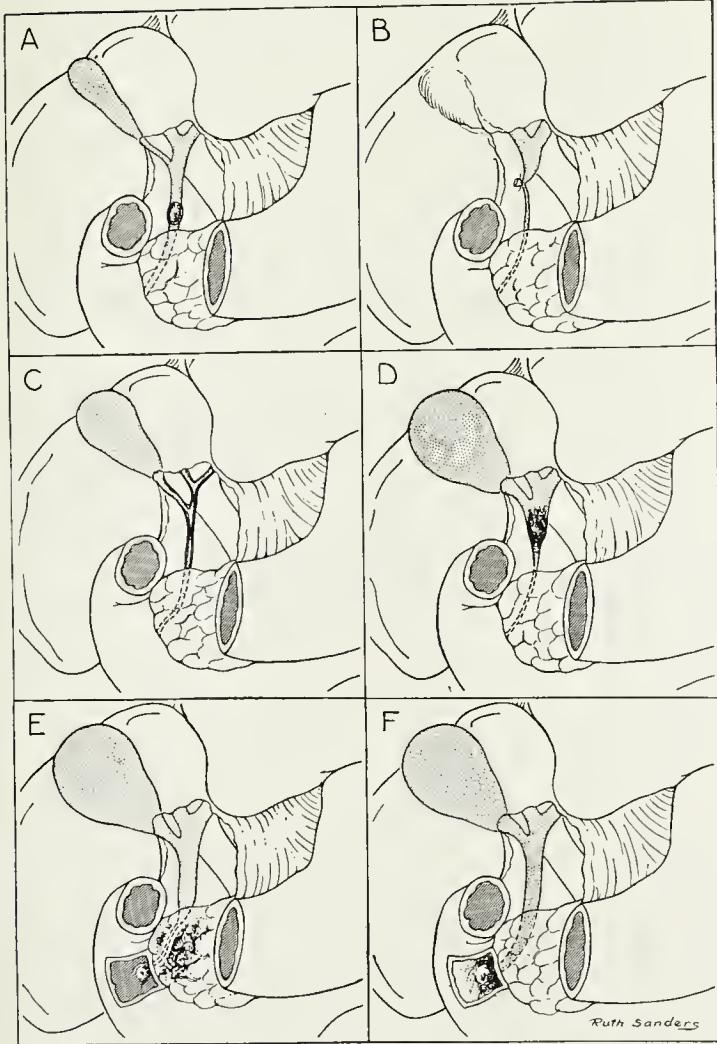


FIG. 239. (A) Stone in the common duct. (B) Post-operative traumatic stricture. (C) Inflammatory stricture. (D) Neoplasm of the common duct. (E) Carcinoma of the head of the pancreas. (F) Ampullary carcinoma.

ing and following operations on the common bile duct. Today, death from operative hemorrhage is a rarity, *provided that* vitamin K is given parenterally, preoperatively and postoperatively; 2 to 20 mg. of menadione, intramuscularly, should be given daily, and the prothrombin level should be followed.

Operation should not be undertaken until the prothrombin level is greater than 60 per cent of normal. The administration of calcium salts intravenously is entirely ineffective in the control of the hemorrhagic diathesis accompanying jaundice.

Since he who starves before he is operated upon does not withstand anesthesia and surgical trauma

as well, nor do his wounds heal as well, as he who has not starved, the use of high-caloric, high-protein, liquid interval oral feedings in conjunction with the parenteral administration of 10 or 15 per cent solution of glucose in distilled water should be regularly employed preoperatively, whenever the spontaneous intake of food is insufficient to maintain body weight.

Whenever anemia exists it should be corrected by the transfusion of blood before surgical relief of the obstruction to the common duct is attempted. In addition, the blood which is lost during the operative procedure should be replaced as it is being lost. The loss of blood during choledochostomy and resections of tumors of the ducts and pancreas is usually of such magnitude that these operations cannot be undertaken safely without provision for the transfusion of blood during the operation.

No operative procedure upon the biliary tract should be undertaken unless one is assured that the stomach is empty and that it will remain empty during the entire anesthetic period. A gastroduodenal tube inserted into the stomach and attached to an appropriate suction apparatus will accomplish this. When the stomach is kept empty during and immediately following operation upon the biliary tract, the deadly aspirational chemical pneumonia and troublesome postoperative ileus and vomiting occur rarely. However, if provision for the removal of air and fluid from the stomach is not made, then postoperative ileus, meteorism, and vomiting occur commonly, and occasionally chemical pneumonia will kill.

Significant deficits of sodium, water, and potassium tend to accompany obstructions of the common duct whenever profound anorexia and vomiting are associated with it. These deficits are to be corrected (Chapter 28) before the operation is performed, or peripheral circulatory failure is likely to occur, even though the blood that is lost is adequately replaced.

After the removal of the obstruction to the common duct, temporary external drainage of the bile through a catheter or T tube is commonly practiced. This provides for the continuous loss of extracellular fluid which may amount to as much as 2 liters daily. If this loss is not made up accurately by the administration of an appropriate salt solution, peripheral circulatory failure, oliguria, and anuria are likely to occur,

even though adequate or even excessive amounts of water may be given. Because this biliary drainage contains appreciable amounts of bicarbonate and potassium, Hartmann's solution (lactated Ringer's solution) is superior to isotonic sodium chloride for the replacement of the extracellular fluid lost through the drainage tubes.

The external biliary drainage, besides providing for the continuous loss of extracellular fluid from the body, also increases the rate of loss of the cholic acid conjugates. The losses of these substances may be effectively made up by the oral administration of 2 to 3 Gm. of methionine and 1 to 2 Gm. of dehydrocholic acid ("Decholin") daily.

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Introduction

H. Houston Merritt and Daniel Sciarra

The approach to a neurologic problem, as in other medical specialties, is usually twofold. Since many systemic diseases may involve the nervous system, often the method of approach is similar to that in general medicine. A patient in uremia with neurologic manifestations is best explored with the methods and tools available to general medicine. The genesis of the spinal cord signs of subacute combined degeneration is best made clear through blood and gastric studies. Even in such a relatively rare disease as hepatolenticular degeneration (Wilson's disease), the liver picture may overshadow the neurologic signs, and only an active search for deficiency of liver function may elucidate the diagnosis.

The second approach in cases with nervous system disease is by methods and means which are especially applicable to this field. Important among these is a history of the patient's illness directed toward the analysis of neurologic symptoms. Especially worthy of note may be changes in the state of consciousness, the appearance of weakness, or loss of the special senses. The type of course that the illness follows may be of great help in establishing neurologic diagnosis. Thus, in patients with a cerebrovascular accident the onset of symptoms is sudden and the subsequent course is stationary or remitting. Patients with a brain or spinal cord tumor will present a progressive, inexorable course. Patients with degenerative diseases of the nervous system tend to show a slowly progressive course.

A general physical examination may often reveal the cause of neurologic disturbance. The finding of a high blood pressure may be the clue to the cause of the appearance of a sudden hemiplegia in a patient. The finding of a mass in the breast may make clear the cause of a patient's headache. However, often a more detailed neurologic examination is needed to clarify a neurologic problem. The neurologic examination is, in fact,

a physical examination with more emphasis laid on the nervous system. A systematic approach to the neurologic examination is desirable, and one of two methods of examination is recommended. The patient can be examined according to systems: thus, the cranial nerves, the motor system, the reflexes, and the sensory system can be examined in order. Or the patient may be examined topographically, each area of the body being examined for the various modalities before moving on to another area. In any case a systematic approach is essential to the elucidation of a neurologic problem.

The general principles of diagnosis in neurology are usually twofold. First, localization of the lesion is important. Initially, an effort is made to locate the process either at peripheral nerve, spinal cord, or cerebral level. Then, more precise localization is attempted. Having established the level of the lesion, clarification as to its nature is necessary. The constellation of symptoms together with the course will in most cases give a tentative diagnosis. The neurologic findings on examination serve to clarify what seemed otherwise obscure from history alone. In any case, determination of the location and nature of the lesion makes for a definitive diagnosis and hence indication for therapy.

As with history and physical examination, laboratory investigation of neurologic problems includes those which are used in the study of all patients. Urinalysis, blood counts, and blood chemical and serologic tests may give valuable diagnostic aid. However, in many cases with neurologic disorder some more specific tests directed toward the nervous system may be needed.

X-ray examination of the skull is particularly valuable when the signs and symptoms suggest that the lesion is in the brain. Examination of the fluid removed by lumbar puncture is of particular aid in the diagnosis of infections of the nervous

system. An increase in the leukocyte count and a reduction in the sugar and chloride content of the cerebrospinal fluid are the usual changes with pyogenic infections of the meninges. Lumbar puncture is also of diagnostic and prognostic value in cerebrovascular accidents and in trauma to the central nervous system. In the latter condition blood may be found, and the amount of bleeding offers some guide as to the seriousness of the brain injury and to prognosis. In neoplasms lumbar puncture may also be of considerable help. A high cerebrospinal fluid protein and a manometric block are cardinal signs of a spinal cord tumor, while a high pressure and an elevated protein content are characteristic of tumors of the brain.

Mediums of different densities may be introduced into the nervous system for better visualization of its component parts. In general, radiopaque substances such as "Pantopaque" or "Diodrast" are injected into the spinal canal for visualization of the spinal subarachnoid spaces. This procedure is of particular value in outlining spinal cord tumors or ruptured intervertebral disks. Gases that are radiolucent, such as air, oxygen, or helium, may be introduced into the subarachnoid space and thus into the cerebral ventricles. Pneumoencephalography is of importance in the more definitive localization of brain tumors or in outlining cerebral atrophy. When the spinal fluid pressure is elevated, a ventriculogram may be done with introduction of air directly into the ventricles.

Of late years, angiography has been introduced as another method of outlining the cerebral structures. This method, which consists of injecting a radiopaque oil (35 per cent "Diodrast") into the cerebral circulation, is of particular value when the site of the lesion is known. Angiography is of value in the demonstration of the location and nature of intracranial lesions which have an abnormal vascularity or displace the large vascular channels. The procedure is of particular importance in the diagnosis of aneurysms, vascular anomalies, and intracranial tumors.

The nervous system may be explored in several ways by electrical methods. The electrical potentials of the cerebral cortex can be recorded. Electroencephalography (Chapter 31) is of particular value in demonstrating generalized abnormalities of the cortical activity in patients with encephalitis, head injury, or diffuse cerebral damage from

any cause. Focal damage to the brain by tumors, vascular lesion, or trauma can be localized by the appearance of focal alterations in the electrical activity of the cortex. Electroencephalography is perhaps most widely used as an aid in the diagnosis of epilepsy. Recording of the electrical potentials of the muscles, electromyography, is of value in the diagnosis of conditions which are accompanied by abnormal movements or wasting of the muscles. In addition, the level of an intraspinal lesion can be located by this method. The integrity of individual muscles and of the nerves supplying them can be tested by electrical stimulation of the nerves.

Examination of visual fields is indicated in many patients with cerebral symptoms. The character of the defects in the peripheral field of vision is of value in determining the site and location of the lesion. Enlargement of the blind spot is strong evidence in favor of a generalized increase in intracranial pressure.

Careful testing of the hearing and labyrinthine function is indicated in all patients with tumors, loss of hearing, dizziness, or vertigo, and whenever a lesion of the brain stem is a diagnostic consideration. These tests are of particular importance in the diagnosis of Ménière's syndrome and tumors of the cerebellopontine angle.

Treatment of diseases of the nervous system is a steadily expanding field. The sulfonamides and the antibiotics are as effective in the bacterial infections of the meninges and central nervous system as they are in similar infections elsewhere in the body. Penicillin is replacing the arsenicals and fever therapy in neurosyphilis. Streptomycin is effective in arresting the progress of tuberculous meningitis and has effected a complete cure in a small percentage of cases. Effective methods of therapy are available for the paroxysmal diseases, epilepsy, migraine, and Ménière's syndrome. The severity of the symptoms which result from vascular lesions of the nervous system can be modified in some cases by sympathetic block or by modification of the clotting time of the blood. Intracranial tumors, aneurysms, and vascular malformations can in many instances be extirpated or treated by x-ray irradiation. Intractable pain is relieved by section of appropriate nerve roots or spinal tracts, or by frontal lobotomy. Static defects in the control of muscular action may be effectively treated by physical methods and by re-education.

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Disorders of the Cranial Nerves

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First Cranial Nerve
Second or Optic Nerve
Third, Fourth, and Sixth Cranial Nerves
Fifth or Trigeminal Nerve
Seventh or Facial Nerve
Eighth Cranial Nerve
Ninth, Tenth, Eleventh, and Twelfth Cranial Nerves

FIRST CRANIAL NERVE

Disturbance of the sense of smell may occur as a result of injury to the nasal mucosa, the olfactory bulb, its filaments, or its central connections. Injuries to the central connections are not usually accompanied by any detectable loss of olfaction. Occasionally, however, olfactory hallucinations of a transient and paroxysmal nature occur in patients with lesions in the temporal lobe.

Loss of smell is often accompanied by an impairment of the sense of taste, since the latter is dependent to a great extent upon the volatile substances in foods and beverages.

Temporary impairment of the sense of smell is frequently seen in connection with the common cold or other diseases of the nasal mucosa. Inflammatory or neuritic lesions of the olfactory bulb or nerve are uncommon, although these structures may be involved in syphilitic or tuberculous meningitis or in the course of a generalized polyneuritis. The filaments of the olfactory nerve may be torn from the cribriform plate or the bulb contused or lacerated in injuries to the head. The olfactory bulb may be compressed by meningiomas, metastatic tumors, or aneurysms in the anterior fossa, or by infiltrating tumors of the frontal lobe.

SECOND OR OPTIC NERVE

Examination of the optic nerve and its functions in neurologic disorders is of primary im-

portance. Since the optic nerve head can be considered as a direct outpouching of the brain, it will often reflect cerebral conditions. This is particularly true in patients with tumors or abscesses of the brain where an increase in the intracranial pressure is manifested by a swelling of the optic disk (choked disks). Damage can occur anywhere intracranially along the optic nerves or tracts, and be evidenced by visual field defects. Pituitary tumors and other growths in the sellar region often yield bitemporal visual field defects, while lesions posterior to this region tend to give homonymous hemianopsia.

Neurosphilis, and especially tabes or taboparesis, may be attended by optic atrophy. This is usually due to an interstitial neuritis of the optic nerve leading to a secondary optic atrophy. Some involvement of the optic nerve may be expected in fully three quarters of the cases of multiple sclerosis. Here it is often evidenced by pallor or atrophy of the optic disks. An intrinsic affection of the optic disk called retrobulbar neuritis may occur in young people and be attributed to disease of the nasal sinuses. In many cases of this sort an etiologic agent is difficult to trace. Some patients will later show symptoms or signs indicating that the visual symptoms were the prelude of multiple sclerosis. The optic nerve may be damaged by various drugs and toxic agents, including tryparsamide, thallium, methyl alcohol, tobacco, and ethyl alcohol.

THIRD, FOURTH, AND SIXTH CRANIAL NERVES

These nerves innervate the extrinsic and intrinsic musculature of the eyes. Because of simi-

larity of function and similar liability to disease, they are best discussed together.

Diphtheria often involves the third nerve, paralysis of accommodation and internal rectus weakness being common. Diabetes, on the other hand, when it affects the cranial nerves, shows



FIG. 240. Total ophthalmoplegia with a right internal carotid aneurysm.

preference for the sixth. Graves's disease associated with exophthalmos may lead to ocular palsies which at times can be complete. Myasthenia gravis frequently involves the extraocular muscles. These ocular palsies tend to occur with exertion of eye muscles and tend to be transient. Multiple sclerosis may also give rise to ocular palsies which usually remit.

Infection in and about the face can cause ocular palsies. Thus, infection of the cavernous sinus may involve the third nerve, and petrositis the sixth cranial nerve.

Cerebral trauma and increased intracranial pressure may also cause ocular palsies, the sixth cranial nerve being most commonly involved. Ocular paralyses are present in brain stem tumors, though usually not as isolated phenomena. Aneurysm or vascular malformation may involve cra-

nial nerves, most commonly the third (fig. 240). These cases are often associated with recurrent bouts of unilateral headache (ophthalmoplegic migraine).

FIFTH OR TRIGEMINAL NERVE

The sensory portion of the fifth nerve is subject to a functional disturbance known as trigeminal neuralgia. This painful affection, usually unilateral, may affect any or all branches of the fifth nerve, but involvement of the maxillary division is most common. The etiology is unknown, though focal irritation in and about the teeth, nose, and sinuses may play a significant role. The pain is often precipitated by certain trigger mechanisms such as chewing, brushing the teeth, or washing the face. The pain is sudden, excruciating, and paroxysmal. Each attack lasts seconds or minutes, and may recur over a period of minutes, hours, or days. A bout will usually remit in days or weeks, but the patient lives in constant dread of recurrence. There is no adequate structural lesion, and all forms of medical treatment are of little or no value. Surgical therapy consists of injection of the various branches of the Gasserian ganglion or severance of the sensory roots proximal to the ganglion. Alcohol injection of the affected branch is the treatment of choice in debilitated or elderly patients who are unable to withstand a major surgical operation. Recurrence of symptoms within six months or a year is likely. Section of the sensory root in the middle or posterior fossa gives permanent relief. In the differential diagnosis, tumors of the fifth nerve or Gasserian ganglion or aneurysm of the internal carotid must be ruled out. In these, objective sensory loss and motor weakness will usually be found, whereas in trigeminal neuralgia, no objective evidence of fifth nerve involvement can be made out.

SEVENTH OR FACIAL NERVE

Of all the cranial nerves, the seventh is most liable to injury by trauma, especially when there is a fracture of the base of the skull. Tumors of the posterior fossa may also involve this nerve. Parotid gland tumors and operation on the parotid gland, on the mastoid bone, or for trigeminal neuralgia may damage the seventh nerve. The newborn child may have facial palsy due to forceps pressure at the parotid gland level.

Any infection involving the parotid gland, such as mumps or uveoparotid fever, can cause facial palsy. In addition, facial paralysis may en-

sue in the course of other infections such as herpes zoster, diphtheria, acute meningitis, and poliomyelitis. Infectious polyneuritis commonly gives rise to a facial diplegia. The facial nerve may be involved in the course of multiple sclerosis, diabetes, and myasthenia gravis.

The most common form of facial palsy is known as Bell's palsy. The cause of the paralysis of the facial muscles in these cases is unknown, although in some cases exposure to cold is advanced as an etiologic factor. The severity of the paralysis is subject to some variation. Usually all of the muscles of one half of the face are weak or completely paralyzed, and in most cases there is a loss of taste on the anterior portion of the tongue on the side of the facial palsy. Complete recovery in the course of three to six weeks is the rule, but a partial paralysis may persist. Treatment consists of splinting of the weak facial muscles, together with massage and electrical stimulation.

EIGHTH CRANIAL NERVE

The auditory and vestibular nerves have diverse origins and terminations, but a common course. During this course they form the eighth cranial nerve. Symptoms of peripheral involvement of this nerve consist of varying degrees of deafness, vertigo, tinnitus, nystagmus, and disturbed equilibrium. Tumor of the cerebello-pontine angle (neurofibroma or meningioma), often involves this nerve early or selectively. The eighth nerve is frequently affected in the course of acute or chronic infections of the meninges. It may be damaged by various drugs or toxic agents including quinine, acetylsalicylic acid, and streptomycin.

The eighth nerve is involved in a paroxysmal disorder known as Ménière's syndrome (chapter 275). In addition, nonrecurrent attacks of vertigo, tinnitus, and slight loss of hearing of unknown cause may occur. These cases of so-called acute labyrinthitis differ from those described by Ménière in that the duration of the attack is longer and there is no recurrence of the symptoms once they have cleared.

The vestibular nuclei in the brain stem may be involved in tumors, vascular lesions, and in the course of multiple sclerosis.

NINTH, TENTH, ELEVENTH, AND TWELFTH CRANIAL NERVES

Though each of the glossopharyngeal, the vagus, the spinal accessory, and the hypoglossal

nerves may be involved separately, more commonly several of them are involved concurrently. Within the brain stem, tumors, syringobulbia, amyotrophic lateral sclerosis, and multiple sclerosis may affect combinations of these nerves. Diphtheria and myasthenia gravis are systemic diseases that also involve these cranial nerves. Tumors, trauma, and surgical intervention in the neck may be followed by similar paralyses. Neoplasms from the nasopharynx may invade the base of the skull and involve these nerves (Schmincke's tumor).

The ninth (glossopharyngeal) nerve may become the seat of a neuralgia which is the counterpart of a trigeminal neuralgia except for location. The pain originates in and about the tonsils and shoots to the ear and throat. Division of the nerve close to the medulla is the treatment of choice.

The tenth (vagus) nerve in particular may be involved in the chest, the recurrent laryngeal branch being most commonly implicated either by tumor, inflammation, or aortic aneurysm. Unilateral paralysis may often be followed only by hoarseness and some difficulty with speech. On the other hand, bilateral complete vagal paralysis leads to inability to talk, swallow, or breathe effectively, and is usually incompatible with life.

The eleventh (spinal accessory) nerve is perhaps more commonly damaged in the neck than either of its neighbors. The sternocleidomastoid and trapezius muscles are then affected. These muscles, however, are commonly affected in progressive muscular dystrophy and myotonia atrophica, and these conditions must be differentiated.

The twelfth (hypoglossal) nerve may be involved by aneurysm of the vertebral artery, fracture dislocations of the atlas, or tumors in the posterior fossa, or in the course of multiple sclerosis, poliomyelitis, polyneuritis, basilar meningitis, amyotrophic lateral sclerosis, or syringobulbia. With unilateral involvement there is atrophy of one half of the tongue and impairment of its movements. With bilateral involvement the tongue lies useless in the floor of the mouth and there is an impairment of phonation and deglutition.

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Congenital Disorders

H. Houston Merritt and Daniel Sciarra

Cerebral Palsy of Children

Pathogenesis
Symptoms and Signs

Diagnosis
Treatment

Hydrocephalus

Definition
Pathogenesis
Symptoms and Signs

Diagnosis
Treatment

Spina Bifida

Definition
Pathogenesis
Symptoms and Signs

Diagnosis
Treatment

Amyotonia Congenita

Definition
Pathology
Symptoms and Signs

Diagnosis
Treatment

Neurodermatoses (Phacomatosis)

Definition
Pathogenesis
Symptoms and Signs

Diagnosis
Treatment

In patients with congenital disorders of the nervous system, the neurologic defects may be present at birth or they may not become evident until some months or years later when the child fails to show evidence of normal physical or mental development. Thus, for example, a defect of the cerebellar, pyramidal, or extrapyramidal system may not be manifested until the age at which the child should normally begin to sit erect, walk, or talk.

CEREBRAL PALSY OF CHILDREN

Commonly called congenital diplegia or Little's disease, cerebral palsy of children includes those cases with bilateral, symmetric, nonprogressive disturbance of motility which are the result of developmental defects in the nervous system or of trauma at birth.

Pathogenesis. About 0.5 per cent of patients admitted to pediatric hospitals have cerebral palsy. The common cause is a developmental defect or intrauterine cerebral degeneration. Often a history of abnormal labor, birth trauma, or neonatal asphyxia is elicited. Though these latter

factors may be of etiologic significance, pathologic investigation indicates that the developmental defect responsible for the cerebral palsy is often also the basis of the obstetric difficulties.

Symptoms and Signs. In the more severe instances symptoms are evident from birth. Vomiting, irritability, and difficulty in nursing may be noted. The patients are susceptible to intercurrent infection and may succumb early in infancy. In milder instances, initial awareness of motor difficulty may not occur until the child fails to perform the expected acts at certain months. Thus, the infant may not sit up at six months or begin to talk and walk at one year. About 25 per cent of cases have convulsions. Athetoid movements of the limbs are common but do not usually appear until the second or third year of life.

The signs will depend on the part of the brain affected. Spastic weakness of the extremities is the most common manifestation. This is usually symmetric, and the legs are involved more severely than the arms. A characteristic "scissors gait," exaggerated tendon reflexes, and extensor plantar responses are present. In the mild forms there may be only exaggeration of tendon reflexes, extensor plantar responses, and slight contractures of the calf muscles leading to talipes equinovarus. The most severe cases have marked spasticity of all extremities and involvement of the bulbar muscles with dysarthria and dysphagia. Involuntary or athetoid movements, cerebellar signs, or mental retardation may also occur.

About 70 per cent of cases show some degree of mental retardation. This often appears to be more severe than is actually the case, due to the difficulty which these patients have in expressing themselves.

Diagnosis. When the symptoms and signs are present from birth, diagnosis is not difficult. When the difficulty is noted at a later date, distinction must be made from the progressive degenerative disorders such as cerebromacular degeneration (Tay-Sachs disease) and diffuse sclerosis (Schilder's disease). These are characterized by inexo-

rable progression. Amyotonia congenita and the muscular dystrophies are childhood diseases distinguished by widespread flaccidity of muscles.

Treatment. Treatment will depend on the extent and type of involvement. The mild cases may proceed through a fairly normal life. In the moderately affected group, muscle re-education, speech training, and corrective orthopedic procedures should be employed. A careful evaluation of mentality is advisable since many children with cerebral palsy are brighter than they appear, their slowness often being due, in great part, to their physical handicap. Special courses of study and vocational guidance to fit individual capability may be of great benefit.

Curare has been given for the spasticity, but usually only with transient benefit. Phenobarbital or "Dilantin Sodium" should be used as needed for convulsions.

HYDROCEPHALUS

Definition. *Hydrocephalus* is the term used to describe an enlargement of the head which results from an increase in the volume of the cerebrospinal fluid within the skull.

Pathogenesis. Cases of hydrocephalus may be divided into two types: obstructive hydrocephalus and communicating hydrocephalus.

Obstructive hydrocephalus may be caused by blockage of the cerebrospinal fluid circulation at any point in its course. Tumors in the third ventricle may obstruct the outflow from the lateral ventricles; the passage of fluid from the third to the fourth ventricle may be prevented by compression or stenosis of the aqueduct of Sylvius. Tumors, meningeal adhesions, or absence of the normal foramen may obstruct the flow from the fourth ventricle into the subarachnoid spaces of the basal cisterns.

In communicating hydrocephalus, free communication exists between the ventricles and the subarachnoid space of the basal cisterns. The hydrocephalus is usually due to blockage of the fluid in the basal cisterns or to a deficiency in the absorption of cerebrospinal fluid. Maldevelopment of the absorptive channels (Pacchianian bodies), adhesions of the leptomeninges of the basal cisterns following cerebral infection, thrombosis of the intracranial venous sinuses, and compression of the meninges by subdural hematomas are the most common causes of communicating hydrocephalus.

Symptoms and Signs. Enlargement of the head is one of the cardinal symptoms of hydrocephalus and is most prominent in the very young. Because of the expansibility of the skull in infancy, signs and symptoms of increased intracranial pressure may be slight or absent. Visual disturbances and convulsions are common.

In children and adolescents, when hydrocephalus is usually due to acquired causes rather than congenital, the signs of increased intracranial pressure are common, with headache, vomiting, and papilledema as presenting symptoms and signs. A "cracked pot sound" on skull percussion may be present. Enlargement of the head is not conspicuous. X-rays of the head will show signs of increased pressure. Air studies of the head will show dilated ventricles.

Diagnosis. Diagnosis is usually not difficult, especially in congenital hydrocephalus when the head may be enormously enlarged. The hydrocephalus of late childhood can be demonstrated by pneumoencephalography.

Treatment. The treatment of hydrocephalus is aimed at relieving the excess of fluid by opening up the passages or cutting down the rate of formation of the fluid. In the majority of the cases of congenital obstructive hydrocephalus the obstruction is not complete, and, similarly, in the communicating type the absorptive mechanisms are not completely nonfunctioning. Therefore, methods of reducing the amount of fluid formation, such as excision or coagulation of the choroid plexuses, are often of definite value.

The obstructive hydrocephalus secondary to compression of the outlets by tumors or complete atresia of the aqueduct of Sylvius can be relieved by creating a new channel for the fluid. Both third ventriculostomy and the insertion of a tube which connects the lateral ventricles with the posterior fossa (Torkildsen's operation) are suitable procedures.

SPINA BIFIDA

Definition. Spina bifida is a defect in the normal closure of the spinal column at any point. It may or may not be associated with hydrocephalus, meningocele, meningomyelocele, extraspinal tumors, spinal cord abnormalities, or defects in the muscular and cutaneous structures overlying the spinal defect.

Pathogenesis. In embryonic development the neural tube fuses dorsally to form the spinal cord.

Failure of such fusion may be associated with similar failure of fusion of the overlying vertebral canal leading to a spina bifida, or the latter defect may occur without any failure of closure of the neural tube.

Symptoms and Signs. The commonest site for a spina bifida is in the lumbosacral area, although it can occur anywhere along the vertebral axis. When the bony defect is associated with a neural defect, a meningocele or meningomyelocele may result with protrusion of the neural contents out of the bony canal. A severe lesion of this sort shows loss of bladder control and paralysis of lower limbs, and may be incompatible with life.

The importance of spina bifida lies in its milder forms, when external evidence of the defect may be lacking (*spina bifida occulta*) or may be limited to a dimpling of the skin or a patch of long hairs over the site of the spinal defect. These cases may be associated with weakness or atrophy of the lower extremities, abnormalities in development of the feet, and urinary difficulties. The reflexes may be absent when the roots of the cauda equina are involved in the meningocele. Increased reflexes and abnormal plantar responses may be present when the spinal cord is also involved.

Other abnormalities are often associated with spina bifida, such as hydrocephalus, Arnold-Chiari malformation of the brain stem and cerebellum, harelip, and cleft palate.

Diagnosis. When the sac of a meningocele or meningomyelocele presents itself in an infant whose lower limbs are paralyzed, diagnosis is not difficult. In spina bifida occulta with symptoms, differentiation from cauda equina or other spinal cord tumor must be made by x-rays of the spine or surgical exploration.

Treatment. In spina bifida occulta, treatment is usually palliative. Enuresis may be helped by drugs of the belladonna group. Physiotherapy may be of assistance in obtaining full usefulness of the legs. In cases with protruding meningocele or meningomyelocele, surgical intervention may be attempted. If neural tissue is involved in the sac, results are not favorable, and even when a pure meningocele exists, surgical resection may lead to hydrocephalus.

AMYOTONIA CONGENITA

Definition. Amyotonia congenita (*Oppenheim's disease*) is a congenital disease evident from birth

and characterized by marked hypotonia and weakness of muscles.

Pathology. Atrophy and degeneration of the anterior horn cells are found in the spinal cords of infants who do not survive this illness. The cranial nerve nuclei may be similarly affected. The muscles show simple atrophy with fat replacement.

Symptoms and Signs. From birth the infant may be noted to be feeble in its actions, though the condition may go unnoticed until directed motion such as holding up the head or sitting up is expected. The muscles are markedly hypotonic and weak. Tendon reflexes are absent.

Diagnosis. This can usually be made without difficulty, since there is only one other disease, infantile progressive muscular atrophy or Werdnig-Hoffmann disease, in which hypotonic muscular weakness is present from birth. These two diseases are considered by many authors to be identical. The only clinical difference between the two conditions, which has been advanced by some, is that amyotonia congenita is nonprogressive while infantile progressive muscular atrophy is always progressive and fatal.

Treatment. Treatment consists of keeping muscles in as good condition as possible. Contractures should be avoided by passive motion and massage. Prognosis is good if the intercurrent infections to which these patients are liable can be controlled. These patients usually recover a considerable degree of strength, though complete recovery is rare.

NEURODERMATOSES (PHACOMATOSIS)

Definition. The neurodermatoses are a group of diseases that regularly show involvement of at least two main organ systems, the skin and the nervous system. These syndromes are neurofibromatosis, von Hippel-Lindau disease, Sturge-Weber syndrome, and tuberous sclerosis.

Pathogenesis. Since the skin and the nervous system are both derived from ectoderm, the neurodermatoses are probably due to a developmental defect in the ectoderm. As would be expected, these diseases may show marked variations and diversity of form. All of them may be associated with other congenital abnormalities.

NEUROFIBROMATOSIS (von Recklinghausen's disease) consists of cutaneous pigmentation associated with tumors in various parts of the body. Multiple fibromas of the peripheral nerves and

cranial nerves, meningiomas, and gliomas may occur, and at times several types of tumors may occur in one individual.

VON HIPPEL-LINDAU DISEASE consists of vascular malformation of the retina (hemangioblastoma) and subtentorial hemangioblastoma, usually in the cerebellum. Other abnormalities such as pancreatic and mesenteric cysts, other tumors in the nervous system, and syringomyelia are also common.

STURGE-WEBER SYNDROME consists of the association of facial nevi with homolateral cerebral vascular malformation.

TUBEROUS SCLEROSIS is a disease characterized by facial adenoma sebaceum and congenital tumors in the cerebral cortex. Like the other neurodermatoses, it may also be associated with other multiple congenital anomalies.

Symptoms and Signs. In general, the cutaneous stigmas of these diseases may be present from birth. The neurologic manifestations may vary greatly in nature and time of development.

NEUROFIBROMATOSIS. The skin manifestations of neurofibromatosis, usually present from birth, vary from spots of discoloration (*café au lait* spots) to huge subcutaneous neurofibromas. The neurologic manifestations usually do not appear until later in life. The spinal cord or the brain may be the site of neurofibromas or associated meningiomas or gliomas, and the symptoms will vary according to location. A favorite site of the neurofibromas is along the course of the eighth cranial nerve.

VON HIPPEL-LINDAU DISEASE. The common manifestations of von Hippel-Lindau disease are skin telangiectases and angioblastomas of the retina and of the cerebellum, although symptoms of spinal cord disease may be present due to associated tumors or syringomyelia. The syndrome, when full blown, is easily discernible, but fragments of the syndrome are more common than the whole picture.

STURGE-WEBER SYNDROME. In the Sturge-

Weber syndrome, nevi are found on the face, along the distribution of the fifth cranial nerve. Convulsive seizures, hemiplegia, and mental retardation are the common manifestations. X-rays of the skull may show the characteristic curvilinear intracranial calcifications.

TUBEROUS SCLEROSIS. Tuberous sclerosis is a definitive clinical syndrome consisting of convulsive disorder, mental retardation, and facial adenoma sebaceum. The cerebral neoplasms are usually small and consist of small groups of abnormal glial and nerve cells. These may at times be visualized by pneumoencephalography as candle-like gutterings in the walls of the lateral ventricles.

Diagnosis. All four syndromes, when fully developed, are characteristic. Neurofibromatosis and von Hippel-Lindau disease will often have to be differentiated from other cerebral or cord neoplasms. Sturge-Weber syndrome may have to be differentiated from other cerebral vascular malformations; the facial Port wine mark is of great diagnostic value. In tuberous sclerosis, distinction will have to be made from other mentally enfeebling conditions with seizures. Again the facial stigmas may be the definitive clue.

Treatment. In these diseases of congenital origin the treatment will be that of their various manifestations. Primarily this consists of tumor removal if the tumors are producing symptoms. All four diseases may involve seizures, and these should be treated with anticonvulsant medication.

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Disorders of the Blood Vessels of the Brain and Spinal Cord

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Cerebral Vascular Lesions

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CEREBRAL VASCULAR LESIONS

Cerebral vascular lesions are the most common cause of focal disturbances of the brain, whereas primary vascular lesions play a quite insignificant role in the production of disease of the spinal cord. The onset of symptoms in a patient with a cerebral vascular lesion is sudden and dramatic and is usually described by the terms *stroke* or *shock*. Although there are differences in the mode of onset, the symptomatology and the clinical course in the various types of cerebral vascular lesions, the general picture may be quite similar, and it is often difficult to determine the nature of the lesion in any individual case from the clinical data. The most common types of cerebral vascular lesions are cerebral thrombosis, intracerebral hemorrhage, primary subarachnoid hemorrhage, and cerebral embolism.

Definition. These diseases have in common a

sudden, apoplectic disturbance of cerebral circulation as result of disease of the blood vessels.

Pathogenesis. Arteriosclerotic damage to the intima of a blood vessel is the most common cause of cerebral thrombosis. It has also been postulated, but not proved, that cerebral spasm may be the prelude to thrombosis if the spasm lasts long enough. Cerebral thrombosis may result from inflammatory changes in the vessels associated with meningitis, encephalitis, or primary disease of the vessels, or from changes in the viscosity of the blood (polycythemia).

Intracerebral hemorrhage is usually the result of a rupture of an arteriosclerotic vessel. It may also result from the rupture of an aneurysm or vascular malformation, or may follow cerebral trauma.

Primary subarachnoid hemorrhage in the vast majority of cases is due to rupture of an aneurysm. Most aneurysms are of the congenital "berry" variety, though a few are syphilitic, arteriosclerotic, or mycotic in origin.

Cerebral embolism is due to a plugging of a blood vessel with an embolus which is dislodged from elsewhere in the body. The most common sites for the origin of a cerebral embolus are the heart and lungs. Thus cerebral embolism is a complication of rheumatic or bacterial endocarditis, auricular fibrillation, coronary thrombosis, and septic foci in the lungs. Cerebral emboli may be a complication of septic or thrombotic processes in the pelvis or lower extremity, or of fractures of the long bones (fat embolism). Such emboli are very rare and small unless a congenital anomaly of the heart permitting a right to left shunt exists (see Chapter 236).

Incidence. It is difficult to obtain accurate data regarding the relative frequency of the various types of cerebral vascular lesions. Autopsy statistics are not valid because of differences in the mortality rate, whereas figures based on clinical diagnosis are unreliable due to the diffi-

Table 110

INCIDENCE OF THE VARIOUS FORMS OF CEREBRAL VASCULAR LESIONS

Lesion	Necropsy- Controlled Cases		Clinically Controlled Cases*	
	Num- ber	Per Cent	Num- ber	Per Cent
Cerebral hemorrhage.....	116	47	127	21
Cerebral thrombosis.....	106	43	398	66
Cerebral embolus.....	23	10	32	5
Primary subarachnoid hemor- rhage.....	0	0	47	8
Total.....	245	100	604	100

* Diagnosis made on the basis of clinical data alone.

culties in establishing an accurate diagnosis. In a large series of cases (table 110), cerebral hemorrhage constituted almost 50 per cent of 245 autopsy-controlled cases, whereas they represented 21 per cent of 604 cases in which the diagnosis was based on the clinical findings. Cerebral thrombosis was found in 43 per cent of the autopsy-controlled cases and in 66 per cent of the cases diagnosed on clinical findings. Primary subarachnoid hemorrhage was diagnosed in 8 per cent and cerebral embolism in 5 per cent of the clinical cases.

All types of cerebral vascular lesions may occur at any age (table 111). However, intracerebral hemorrhage and cerebral thrombosis are uncom-

mon before the age of 40. Cerebral thrombosis reaches its peak incidence in the sixth to eighth decades as compared to the fifth to seventh decades for cerebral hemorrhage. The incidence of primary subarachnoid hemorrhage and cerebral embolism is spread more evenly over the various decades, occurring most frequently in the fifth to seventh decades.

Symptoms and Signs. Premonitory symptoms of an impending cerebral vascular accident are infrequent. When they occur, they may be non-specific or focal in nature. Nonspecific symptoms include headache, dizziness, drowsiness, and mental confusion. One or more of these symptoms is not infrequent in patients with cerebral vascular disease, and their occurrence does not necessarily presage an impending vascular accident.

Focal premonitory symptoms are uncommon and, when present, usually presage the onset of a thrombosis rather than a hemorrhage. A transient loss of speech, hemiplegia, or paresthesias in one half of the body may precede the onset of a severe paralysis by a few hours or days. These fleeting symptoms have been explained on the basis of spasm of the vessel. They could, however, be due to thrombosis of small terminal twigs of the parent trunk. Paralysis of one of the cranial nerves as the result of compression by an aneurysm may be present for several weeks or months before rupture of the aneurysmal sac.

In the vast majority of the cases the symptoms of a cerebral vascular accident are of sudden onset and reach the maximum intensity within a few minutes or a few hours at the most. These symptoms may again be divided into two groups, focal and generalized. The focal neurologic symptoms, such as paralyses, sensory loss, and speech defects, are related to the site of the hemorrhage or infarct. These will not be discussed in detail since they are of only secondary importance in regard to the differential diagnosis.

The generalized symptoms include headache, vomiting, convulsions, and coma. These symptoms may occur in any type of cerebral vascular accident, but they are more common in patients with an intracerebral or subarachnoid hemorrhage.

Coma, the most dramatic initial symptom of cerebral vascular accident, occurs at the onset in 51 per cent of the patients with a cerebral hemorrhage, in 33 per cent of those with cerebral thrombosis, in 25 per cent of those with a cerebral

Table 111

AGE INCIDENCE (IN PERCENTAGES) OF CEREBRAL VASCULAR LESIONS IN AUTOPSY-PROVED CASES

Age in Years	Intra- cerebral Hemor- rhage	Throm- bosis	Embolism	Primary Subarach- noid Hemor- rhage
Under 20....	1	0	9	11
20 to 29....	0	0	9	17
30 to 39....	3	1	14	19
40 to 49....	21	7	14	20
50 to 59....	27	24	27	18
60 to 69....	26	36	22	10
70 to 79....	20	25	0	4
Over 80....	2	7	5	1
Total....	100	100	100	100

embolus, and in 30 per cent of those with a primary subarachnoid hemorrhage.

~~X~~ Convulsions, usually generalized but occasionally Jacksonian in character, occur at the onset or within a few hours in 15 per cent of the patients with cerebral hemorrhage, in 7 per cent of those with cerebral thrombosis, in 9 per cent of those with a cerebral embolus, and in 15 per cent of those with subarachnoid hemorrhage.

~~X~~ Vomiting is present at the onset in about 50 per cent of the noncomatose patients with a cerebral or subarachnoid hemorrhage, in 25 per cent of those with a cerebral embolus, and in only 16 per cent of those with cerebral thrombosis.

~~X~~ Headache as an initial symptom occurs in approximately 63 per cent of the noncomatose patients with a cerebral hemorrhage, in 25 per cent of those with a cerebral embolus, in 6 per cent of those with cerebral thrombosis, and in almost 100 per cent of those with a primary subarachnoid hemorrhage.

If the hemorrhage is a small one or if a minor vessel is occluded by a thrombus or embolus, there may be no change in the vital signs. With a large hemorrhage or occlusion of a major vessel, the temperature is elevated, the pulse rate is increased, and the rate and depth of the respirations are altered. Failure of the vasomotor and heat-regulating centers is a constant finding in patients with any type of fatal cerebral vascular accident. There is a uniform rise of temperature, pulse rate, and respiratory rate several hours or days before death occurs.

Since arteriosclerosis and hypertension are the most frequent causes of both intracerebral hemorrhage and thrombosis, evidence of sclerosis of the peripheral and retinal vessels, abnormalities in the heart, and changes in the blood pressure are common findings. Clinical signs of cardiac enlargement or auricular fibrillation are present in over 90 per cent of the patients with a cerebral embolus. Cardiac enlargement is present in approximately two thirds of the patients with a cerebral hemorrhage or thrombosis, but auricular fibrillation is relatively rare. Arteriosclerosis and hypertension are common findings in the patients with a primary subarachnoid hemorrhage after the age of 40.

The blood pressure is within normal limits in the majority of patients with a cerebral embolus, but it is usually elevated in patients with a cerebral hemorrhage, subarachnoid hemorrhage, or

thrombosis. However, these lesions may occur in a patient with a normal blood pressure.

~~X~~ Pupillary findings in cases of cerebral vascular lesions are quite variable, depending on the time the examination is made and the presence of other complicating factors, such as syphilis and changes in the pupillary reactions associated with old age. Inequalities in the size of the pupil are common, and the larger pupil is usually on the side opposite to the cerebral lesion. The reaction of the pupils to light is lost or greatly impaired in over 25 per cent of the patients with a cerebral hemorrhage and in less than 10 per cent of those with cerebral thrombosis. Conjugate deviation of eyes alone or of the head and eyes together is frequently present in the patients with evidence of a severe cerebral lesion. It is more common following an intracerebral hemorrhage than after other types of lesions. The deviation is almost always toward the side of the lesion and is associated with impairment of the movements of the head and eyes to the opposite direction. The deviation of the head and eyes tends to disappear with improvement in the general condition of the patient.

~~X~~ Stiffness of the neck is an almost constant finding in patients with an intracerebral or primary subarachnoid hemorrhage and is related to the presence of blood in the cerebrospinal fluid. It is rarely present in patients with a cerebral thrombosis or embolus.

~~X~~ Mental symptoms and signs—confusion, disorientation, and impairment of memory—are frequently present in the period immediately following a cerebral vascular accident. These are related in part to the generalized disturbance of cerebral function associated with the vascular lesion and in part to cerebral arteriosclerosis.

The presence of signs of focal brain damage—hemiplegia, aphasia, hemianopia, and the like—is related to the site of the lesion. Changes in the tendon reflexes and the plantar responses can usually be explained on the basis of the focal lesion. All of the tendon reflexes may be lost when the patient is in the comatose state immediately following the onset of the vascular lesion, but it is more common for the reflexes to be hyperactive on the side opposite to the focal cerebral lesion. Bilateral extensor plantar responses (Babinski's sign) are present in 25 per cent of the patients with blood in the cerebrospinal fluid, and in approximately 15 per cent of

the patients with a cerebral thrombosis or embolus in the period immediately after the onset of the lesion.

Laboratory Findings. Albumin and casts are found in the urine in a high percentage of the patients, regardless of the type of the vascular lesion. This is usually due to associated renal disease and may be accompanied by an elevation of the serum nonprotein nitrogen content. Transient hyperglycemia and glycosuria in the absence of diabetes mellitus are not infrequent. They are probably due to a temporary disturbance in the sugar metabolism as a result of the cerebral injury. They cannot be correlated with the site of the lesion, but are noted more frequently in patients with a hemorrhage than in those with thrombosis or embolism. A leukocytosis of 12,000 or over is present in over 50 per cent of the patients with a cerebral or subarachnoid hemorrhage, and in approximately 10 per cent of the patients with a cerebral thrombosis. A leukocyte count greater than 20,000 is diagnostic of a hemorrhage unless there is a concomitant infection.

XThe cerebrospinal fluid pressure is usually normal in patients with a cerebral embolus or thrombosis. Pressures between 200 and 300 mm. are present in a small percentage of the cases, but readings greater than 300 are rarely seen. In contrast, the pressure is greater than 200 mm. in the majority of the patients with an intracerebral or primary subarachnoid hemorrhage.

XThe cerebrospinal fluid is bloody in all of the patients with a primary subarachnoid hemorrhage, in 85 per cent of the cases of cerebral hemorrhage, and in 15 per cent of the cases of cerebral embolism. The fluid is clear in cerebral thrombosis, although there may be a slight xanthochro-

mic tinge with a few erythrocytes on microscopic examination.

The Wassermann or other specific tests for syphilis are negative in the clear cerebrospinal fluids unless syphilis of the central nervous system is present. The presence of a positive reaction in a bloody fluid cannot be accepted as evidence of syphilis of the nervous system, since it may be due to the presence of syphilitic reagins in the blood serum present in the fluid. The test should be repeated after allowing an interval sufficient for the cerebrospinal fluid to become clear.

Course and Prognosis. The course of patients with cerebral vascular lesions depends on the type and extent of the lesion and the presence or absence of other complicating factors. The prognosis for life is grave if there has been a hemorrhage of any appreciable size or if a major vessel is occluded by a thrombus or an embolus. When a small vessel is the site of a thrombus or an embolus, the patient is usually able to survive the insult unless the complicating factors are serious enough to cause death.

In the fatal cases the duration of life after the onset varies from a few hours to two months. Cerebral vascular accidents, except as noted below, are not a cause of sudden death (within minutes). Death may occur within a few minutes when a large aneurysm ruptures into the subarachnoid space, and death within 12 hours is most common in this type of cerebral vascular accident (table 112). Death occurs within 3 to 12 hours in a few cases of cerebral hemorrhage, but as a rule it is delayed for a period varying from 1 to 14 days. Occasionally, a patient with a cerebral hemorrhage may live several months and die as a result of the hemorrhage. Death within 24 hours is rare in patients with a cerebral throm-

Table 112
LENGTH OF SURVIVAL IN 243 CASES OF FATAL CEREBRAL VASCULAR LESIONS (IN PERCENTAGES)

Length of Life After Onset	Hemorrhage (115 Cases) %	Thrombosis (89 Cases) %	Embolism (21 Cases) %	Primary Subarachnoid Hemorrhage (18 Cases) %
Less than 12 hours.....	4	0	0	22
12 to 24 hours.....	3	1	0	11
1 to 4 days.....	41	30	38	28
5 to 14 days.....	39	39	38	11
2 weeks to 2 months.....	12	23	19	22
2 months to 6 months.....	1	7	5	6
Total.....	100	100	100	100

bosis or embolus. Death in these cases most commonly occurs several days to several weeks after the onset, but it may occur several months later as the result of complications.

The vascular accident is the chief or sole cause of death in the various types of cerebral vascular accidents as follows: intracerebral hemorrhage, 40 per cent; primary subarachnoid hemorrhage (first attack), 35 per cent; cerebral thrombosis, 25 per cent; and cerebral embolus, 30 per cent. The common contributory causes of death in patients with an intracerebral hemorrhage, primary subarachnoid hemorrhage, or cerebral thrombosis are bronchopneumonia, cardiac failure, uremia, lobar pneumonia, diabetes mellitus, and pulmonary infarct. Additional contributory causes of death in patients with cerebral embolus include vegetative endocarditis and embolic phenomena in other parts of the body.

As a rule, the general symptoms are also most intense immediately after the onset, but occasionally in the fatal cases there may be an increase in the depth of coma or a lapse into coma several hours after the onset.

The focal neurologic symptoms are most severe immediately following the onset of the cerebral vascular accident. There are a few exceptions to this rule. In a small percentage of the cases of cerebral hemorrhage there may be an increase in the severity or extent of focal neurologic symptoms over a matter of a few hours. This progress in neurologic signs can be explained by an increase in the size of the hemorrhage. Progression of focal neurologic signs is rare in patients with a cerebral thrombosis or embolus. Progression in such cases can be explained by an independent involvement of other vessels or by the propagation of the thrombus to the point of origin of another branch of the thrombosed vessel.

The prognosis for return of function of paralyzed members cannot be predicted with any degree of certainty in the first few days or weeks. In the nonfatal cases there is usually some improvement in the focal neurologic signs. In some cases this improvement may be very dramatic, with complete resolution of all signs within a few hours or a few days. The hypothesis of a cerebral vascular spasm is used by some authors to explain the fleeting nature of the symptoms in such cases. More commonly, the improvement of symptoms takes place slowly, over a period of several months. Usually, the patient is left with some

permanent residual symptom, such as stiffness and difficulty in the use of the leg in walking, awkwardness in the use of the hand, or some degree of speech defect. In an occasional case there will be no improvement for several weeks but a gradual and appreciable improvement in the following months. For this reason, treatment of the neurologic defect should not be given up as hopeless until at least 12 months have elapsed.

Diagnosis. The differential diagnosis in patients suspected of having a cerebral vascular accident is twofold. First, the condition must be differentiated from other lesions of the nervous system; second, an attempt should be made to determine which form of cerebral vascular accident is present.

The differential diagnosis from ~~other lesions of the nervous system~~ is usually not difficult when the complete history of the patient's illness is known, but it is often extremely difficult when the patient is found in a comatose state and there is no adequate history of the onset of the coma. In such cases a careful examination of the patient and the judicious use of certain laboratory tests are necessary (see Chapter 8). ~~The laboratory procedures of greatest value are the examination of the urine, the determination of the nonprotein nitrogen and sugar content of the blood, examination of the cerebrospinal fluid, and x-rays of the skull.~~

The patient's head should be examined carefully for evidence of external injury, and the size and reactions of the pupils and the odor of the breath should be noted. The optic disks should be examined. The character of the respirations, the temperature, the pulse rate, and the blood pressure are important. The presence or absence of stiffness of the neck should be noted.

It is of paramount importance to determine ~~X~~ whether a hemiplegia is present. This is not simple in a comatose patient, but usually can be done. The face should be carefully observed, and, if there is a puffing out of one cheek with each expiration, there is a paralysis of that side of the face. Paralysis of the extremities can be determined by lifting each extremity and allowing it to fall. If the coma is not too deep, the paralyzed limb will fall heavily, while the unparalyzed limb will gradually sink to the bed. When the patient is in deep coma, all limbs may fall heavily to the bed. Vigorous stimulation of the soles of the feet by a blunt stick or key will cause a withdrawal of the

unparalyzed limbs, while the paralyzed limb will remain inert.

A hemiplegia of sudden onset together with a marked degree of hypertension is presumptive evidence of ~~cerebral vascular lesion~~. The diagnosis of an expanding lesion in the cerebrum, such as brain tumor, brain abscess, and subdural hemorrhage, cannot definitely be excluded, however. If there is no hemiplegia and the blood pressure is normal, coma due to diabetes, acute alcoholism, extradural or subdural hemorrhage, or drug poisoning must be considered.

The odor of acetone on the breath and the presence of sugar in the urine (which may have to be obtained by catheterization) point to diabetes. It must be remembered, however, that transient glycosuria and hyperglycemia occur in a definite percentage of the cases of cerebral hemorrhage or thrombosis. The determination of the sugar content in the blood will aid in establishing or excluding the diagnosis of ~~diabetic coma~~, since the rise in blood sugar which occurs with cerebral vascular accidents is rarely as high as that commonly seen in diabetic coma.

The presence of albumin and casts in the urine is indicative of ~~uremia~~, but the diagnosis cannot be established definitely without a determination of the nonprotein nitrogen content of the blood. It must also be remembered that cerebral vascular lesions are a common complication of uremia.

An alcoholic odor to the breath, a normal blood pressure, no evidence of a hemiplegia, and a normal cerebrospinal fluid are the characteristic findings in cases of coma due to acute alcoholism. The cerebrospinal fluid pressure in these cases may be slightly elevated (200 to 300 mm.).

Cases of ~~extradural hemorrhage~~ are usually easy to distinguish from cases of cerebral vascular lesions. The differentiation is important since the treatment is immediate operation with removal of the clot and ligation of the middle meningeal artery. The presence of contusions or lacerations of the scalp indicative of a head injury is important. It must be remembered, however, that a patient with a cerebral hemorrhage or thrombosis may fall and injure his head. X-rays of the skull and an examination of the cerebrospinal fluid are often of aid. The typical sequence of events in patients with ~~an extradural hemorrhage resulting from trauma~~ is as follows: An immediate period of coma from which the patient

recovers; a lucid interval of several hours' duration which is followed by a gradually increasing stupor; and the development of a hemiplegia. This classic history is present in only about one half of the cases, because there may be sufficient trauma to the brain to produce a prolonged coma which merges with the coma resulting from the pressure of the extradural clot. If there is a fracture of the skull which passes through the groove of the middle meningeal artery, the diagnosis of extradural hemorrhage should be made.

The diagnosis of ~~subdural hemorrhage~~ is often difficult. It is important that the diagnosis be made promptly because immediate operation is necessary to save the patient's life. The differential diagnosis is further complicated by the fact that the head injury which produced the subdural hemorrhage may have been only a slight or moderate one, and an interval of several days or weeks may separate it from the symptoms produced by the hematoma. In addition, the coincidence of hypertension and subdural hematoma is frequent. If there is a history of a recent head injury and there are fluctuations in the patient's state of consciousness, the diagnosis of subdural hematoma should be considered. The frequent association of subdural hematoma with chronic alcoholism should be kept in mind. X-ray examination and examination of the cerebrospinal fluid is of value in the differential diagnosis. The presence of a fracture of the skull or displacement of a calcified pineal gland are in favor of the diagnosis of a subdural hematoma. The finding of a bloody or xanthochromic cerebrospinal fluid under increased pressure excludes the diagnosis of cerebral thrombosis, but does not differentiate between subdural hematoma and intracerebral or primary subarachnoid hemorrhage. Whenever the diagnosis of subdural hematoma cannot be excluded by the history and the findings on examination, small trephine openings should be made in the temporal region of the skull on both sides. It is not uncommon to have false localizing signs in subdural hematomas; and, in addition, it is not rare to find a clot in both the subdural spaces.

In cases of brain tumor or brain abscess the onset of the hemiplegia is usually gradual and preceded by a history of headaches, vomiting, or convulsions for several months. The presence of "choked disks," a normal blood pressure, an increased cerebrospinal fluid pressure, and a clear

or slightly yellow cerebrospinal fluid with a normal cell count and an increased protein content are the characteristic findings in cases of brain tumor. Exactly similar findings are present in cases of ~~brain abscess~~ except that the cerebrospinal fluid usually shows a mild or moderate pleocytosis.

The history of numerous previous convulsions and the occurrence of a convulsion before the onset of the coma, together with a normal blood pressure and a normal cerebrospinal fluid, are in favor of the diagnosis of epilepsy.

The differential diagnosis between the various types of cerebral vascular lesions is important chiefly in regard to the prognosis as to recovery from the "shock" and as to the degree of recovery from the focal neurologic signs. The diagnosis of the cerebral hemorrhage or primary subarachnoid hemorrhage carries with it a grave import as to the life of the patient and the chance of complete recovery from any paralysis that may be present.

The diagnosis of ~~cerebral embolism~~ is indicated whenever there is a sudden onset of neurologic symptoms in a patient with an acute or chronic endocarditis, auricular fibrillation, a recent coronary thrombosis, septicemia, or a septic focus. These cases often present clinical evidence of embolic phenomena elsewhere in the body.

~~X Primary subarachnoid hemorrhage~~ must be differentiated from intracerebral hemorrhage. Headache is a prominent symptom, and signs of meningeal irritation, stiffness of the neck, and Kernig's sign develop rapidly, but focal neurologic signs, such as hemiplegia or aphasia, occur in less than 20 per cent of the cases. The presence of a bloody spinal fluid and a hemiplegia indicates that there has been an intracerebral hemorrhage and is against the diagnosis of a primary subarachnoid hemorrhage. It must be remembered, however, that an aneurysm may be so located that it bleeds into both the subarachnoid space and the cerebrum when it ruptures. Paralysis of the third or other cranial nerves points to the diagnosis of primary subarachnoid hemorrhage.

~~X The differential diagnosis between cerebral hemorrhage and thrombosis~~ is difficult since focal neurologic signs are similar in both and since both occur in patients of the same age group and in patients with arteriosclerosis and hypertension. A bloody cerebrospinal fluid is diagnostic of ~~cerebral hemorrhage~~. In the absence of

blood in the cerebrospinal fluid, or if a lumbar puncture is not performed, there are several points in the history and physical examination that will make this differentiation possible in the majority of the cases. The presence of the following signs and symptoms favors the diagnosis of ~~X an intracerebral hemorrhage~~: (1) convulsions at the onset; (2) the occurrence of severe headache, nausea, or vomiting at the onset; (3) Cheyne-Stokes or labored respirations and conjugate deviation of the eyes; and (4) stiffness of the neck, quadriplegia, and bilateral Babinski toe sign.

Treatment. The treatment of patients with cerebral vascular accidents is separated into two parts: first, the treatment in the immediate period after onset, which is mainly devoted toward saving the life of the patient; and, second, the treatment of residual defects.

In the first stage, skillful nursing care is essential. The patient should be kept in a quiet room. Fluids and liquid nourishment should be given by mouth if the patient is conscious. If the patient cannot swallow, glucose solution (5 per cent) should be given subpectorally or into the thighs. The bladder should be emptied by catheterization if necessary and the bowels kept open by enemas or cathartics. The position of the patient in bed should be changed frequently to prevent the development of hypostatic pneumonia or bedsores. The bed sheets should be changed immediately when they are soiled by urine or feces. Sedatives should be used with care and the opiates avoided, since they tend to depress the respiratory centers.

There is no very satisfactory medical treatment for the cerebral lesion. Gilbert and de Takats recommend blocking the cervical sympathetic trunk with procaine on the side of the lesion in an effort to relieve the collateral stasis, vasoparalysis, and edema which accompany the vascular insult. The increased intracranial pressure which often accompanies an intracerebral or subarachnoid hemorrhage can be treated by removal of fluid by lumbar puncture or by the administration of hypertonic solutions by vein or by rectum. Care should be taken not to dehydrate the patient excessively.

The chief danger in patients with cerebral hemorrhage is death from collapse of the vital centers, which is almost certain to occur if the bleeding continues. There is no known method of hastening the cessation of the hemorrhage from a rup-

tured vessel. Venesection, which was formerly recommended, is of no value unless it is used to combat polycythemia or congestive heart failure. Special treatment, such as transfusions or the administration of vitamin K, is of little value unless the bleeding is related to systemic diseases such as purpura.

The therapeutic value of lumbar puncture in patients with an intracerebral hemorrhage is unproved. It is unlikely that the removal of cerebrospinal fluid will increase the bleeding, and it may be of considerable value in relieving the increased intracranial pressure, especially when a large amount of blood has been extravasated into the subarachnoid space. If, however, the mass of the clot is confined to the substance of the cerebrum, the removal of cerebrospinal fluid is not effective in reducing the intracranial pressure. Lumbar puncture can be performed as a diagnostic measure, and it may be repeated at intervals of 12 to 24 hours if large amounts of bloody fluid can be removed.

Since cerebral hemorrhage usually results in death and since the clot is slowly absorbed and is apt to behave like a tumor, the question of operative removal of the clot should be considered in all patients who survive the initial shock of the hemorrhage. Such operations have proved of lifesaving value in a number of cases and are of benefit in decreasing the severity of the neurologic defect. Unfortunately, the extremely poor general condition of the patient is a deterrent to a widespread use of this form of treatment. At the present time, operative removal of the clot is most suitable in those patients who have survived the initial shock of the hemorrhage and who continue to show evidence of increased intracranial pressure.

There is some disagreement as to the value of lumbar puncture in the treatment of patients with a primary subarachnoid hemorrhage. Experience has shown, however, that improvement in the clinical state of the patient follows the removal of cerebrospinal fluid and the reduction of cerebrospinal fluid pressures. Punctures should be repeated as frequently as required to keep the cerebrospinal fluid pressure down to normal level.

Since recurrence of the bleeding is apt to occur in patients with a primary subarachnoid hemorrhage, consideration should be given to measures directed at localizing and treating the aneurysm.

If the site of the aneurysm is not evident from the clinical signs, it must be localized by cerebral angiography. In general, there are two methods of relieving pressure on the aneurysmal sac. The first and least serious method is ligation of the internal carotid artery on the side of the aneurysm. The second is exposure of the aneurysm by craniotomy and ligating the vessel on both sides of the sac (trapping). Ligation of the internal carotid artery should not be performed until it has been shown that occlusion of the carotid artery by manual compression for periods as long as 30 minutes can be tolerated by the patient without the development of symptoms. Even with this assurance of competency of the collateral circulation, ligation of the internal carotid artery may be followed by the development of a contralateral hemiplegia. Ligation of the aneurysm at craniotomy is a major surgical procedure and is accompanied by a high mortality rate. The decision regarding the applicability of either type of operation is a delicate one, and although no set rule can be established, it would seem wise to defer operation until there is evidence of one recurrence of the bleeding.

After the patient has recovered from the "shock" of the cerebral vascular accident, the therapy should be directed toward restoration of function in the paralyzed limbs. Light massage of the muscles and passive movements of the affected limbs are useful in maintaining the proper circulation and nutrition of the paralyzed muscles, and help to prevent the development of arthritic changes in the joints. It is of great importance to encourage the patient to try to use the paralyzed muscles. The first voluntary movements should be aided by simultaneous passive movements of the joints. Systematic passive movements of all the joints of the affected arm and leg should be made for a few minutes several times a day. The patient should be encouraged to try to move the joints while the physiotherapist is doing so. These exercises should not be unduly prolonged, as the patient will tire and become discouraged. The patient should be given a soft rubber ball to hold in his hand, and be instructed to exercise the fingers by squeezing the ball and by placing it on the bed or table and picking it up. With return of function, more skillful actions should be tried. If there is any tendency toward the development of contracture in the extremities, well-padded removal splints should be applied.

These splints need be kept on only a portion of each day.

When the patient has regained sufficient strength and his general condition permits, he should be allowed up in a chair for a few minutes. This interval can be increased daily as the condition of the patient warrants. Attempts at walking should be aided at first by allowing the patient to lean on an attendant's shoulder. A cane should be substituted as soon as practicable, and this discarded only when the strength of the trunk and leg muscles is sufficient to support the patient.

The treatment of aphasia or disorders of speech is difficult and requires infinite patience on the part of the physician and persistent effort on the part of the patient. Best results are obtained when re-education exercises are given by a trained speech therapist. Fortunately, in the majority of the cases the lesion is not centered in the speech areas, and complete or nearly complete return of the power of speech may occur.

In the cases of cerebral thrombosis due to or associated with a syphilitic infection of the cerebral vessels, antisyphilitic therapy (penicillin) should be given.

INTRACRANIAL SINUS THROMBOSIS

Definition. Intracranial sinus thrombosis is the occlusion of an intracranial venous sinus by thrombus formation.

Pathogenesis. Thrombosis of the intracranial venous sinuses may occur in intracranial infection, in cerebral trauma, or in debilitated states. By far the most common cause is the extension of infection from contiguous structures. The lateral sinus is most often involved in cases with mastoid infection. The superior longitudinal sinus is most often thrombosed in childhood, either following intracranial infection or following ventricular puncture. Cavernous sinus thrombosis may follow infection in and about the face and sinuses.

Symptoms and Signs. The symptoms will be those of the predisposing condition plus those superimposed by involvement of a particular venous sinus.

In lateral sinus thrombosis, complaints may be centered about one ear. Headache is common. Focal signs are rare; when present they lead to the consideration of the presence of an intracere-

bral abscess. Extension may occur to the homolateral jugular vein.

Cavernous sinus thrombosis is usually made evident by severe pain over one eye. The orbital contents and adjacent structures are edematous. Ocular palsies are common, and homolateral papilledema may be present.

Thrombosis of the superior longitudinal sinus may lead to a considerable increase in intracranial pressure. Headache, nausea, and vomiting are prominent early symptoms. The scalp veins may be full and papilledema may be present. Hemiplegia or paralysis of one or both legs, together with convulsions, sometimes Jacksonian in type, may occur.

Lumbar puncture will reveal a cerebrospinal fluid under increased pressure. In thrombosis of the superior longitudinal sinus, increased protein and at times red blood corpuscles may be found in the fluid. Leukocytosis may also be present, indicating extension of infection to the meninges. The Queckenstedt test is positive on the side of a lateral sinus thrombosis.

Diagnosis. Lateral sinus thrombosis yields so few focal signs that it may be indistinguishable from other extension of mastoid infection such as epidural or subdural empyema or even intracerebral abscess. Furthermore, it may coexist with such lesions. Since the latter are the more serious diagnoses, such patients may have to be explored and treated as for serious intracranial infections.

Aneurysm of the cavernous sinus, orbital tumor, or sphenoid wing meningioma may all be confused with cavernous sinus thrombosis. None will have symptoms and signs of infection. The aneurysm is usually on a traumatic basis, and associated with a bruit and pulsation in the eye. The symptoms in patients with orbital tumor and sphenoid wing tumor are of gradual onset.

Treatment. Since most cases of intracranial venous sinus thrombosis are associated with infection, treatment of the underlying infections with chemotherapy and antibiotics is of primary importance. The jugular vein may have to be ligated in cases of lateral sinus thrombosis to prevent spread of the possibly infected thrombus down the neck.

Prognosis with the use of antibiotics has improved remarkably. Patients who recover from a superior longitudinal sinus thrombosis may be left with a hemiplegia or may develop hydrocephalus.

VASCULAR MALFORMATIONS

Definition. Vascular malformation usually consists of a tangled mass of arteries and veins, often forming an arteriovenous shunt in the brain.

Pathogenesis. Vascular malformations are congenital developmental anomalies. They may occur anywhere in the brain, but are most characteristically found lying over the surface of the cerebral cortex. Though often composed of both arterial and venous components, they are, in the main, made up of tortuous, thin-walled, venous channels. They may show wide variation in size, some being almost microscopic while others may lie over the convexity of a whole hemisphere, forming a formidable tangled mass of pulsating vessels.

Symptoms and Signs. The symptoms and signs may be of great variety because of the variations in size and location of the vascular malformations. Recurrent headaches or convulsive seizures are probably the most common symptoms and are often the only manifestation of the malformation. The convulsion may be focal or generalized in nature. Hemiplegia or visual field defects are other common neurologic signs.

A small vascular malformation lying in a so-called silent area of the brain may give no neurologic signs or symptoms. Even lesions of considerable size may be silent until adulthood, when one of the vessels ruptures. The patient may then evidence for the first time the syndrome of subarachnoid or intracerebral hemorrhage.

The use of angiography, especially in cases with a clear-cut focus, is of great aid in elucidating the role of vascular malformations in neurologic disorders.

Treatment. Most cases of vascular malformations are best treated symptomatically. This is especially true if seizures are the predominant manifestations, in which case adequate anticonvulsant therapy should be maintained. An occasional case will show neurologic signs and symptoms that are marked enough so that exploration is indicated. In these cases, however, the malformation is usually so extensive that surgical attack is prohibitive. Collateral circulation is so extensive and so well ramified that vessel ligation is usually not successful. An occasional malformation may be excised en bloc if suitably located and restricted in extent.

INFANTILE HEMIPLEGIA

Definition. Infantile cerebral hemiplegia is a syndrome occurring in the early childhood years characterized by sudden onset of hemiplegia usually associated with or followed by convulsions.

Pathogenesis. Quite commonly, infantile hemiplegia occurs in association with some febrile illness or marasmus. The lesion is usually a vascular one, thrombosis of the cerebral arteries or of the venous sinuses being present.

Symptoms and Signs. The history of sudden onset of hemiplegia alone in a child is usually indicative of the diagnosis. Often this is associated with a loss of consciousness. Convulsions, at times confined to the paretic side, are almost a constant part of the picture. The seizures may occur at the onset of the illness, the patient may then lapse into coma, and the hemiplegia may become apparent only after consciousness is regained.

At times later in life a patient may develop seizures which may be focal. History may indicate a transient hemiplegia in childhood, associated with a febrile illness. Examination of the patient may reveal vestiges of an old hemiparesis, such as smaller limbs on one side, increased tendon reflexes, or an abnormal plantar response. Should pneumoencephalography be resorted to, atrophy of the contralateral cerebral hemisphere will often be revealed.

Diagnosis. The syndrome is a destructive one and should be readily apparent. It may at times have to be differentiated from acute poliomyelitis. This is seldom limited to one arm and leg, is not associated with convulsions, and is accompanied by flaccidity and loss of deep tendon reflexes. A cerebral vascular abnormality may produce a similar clinical pattern. However, the acute picture is due to a hemorrhage, and the presence of blood in the cerebrospinal fluid will help to differentiate this from infantile hemiplegia.

Treatment. During the acute phase, treatment should be directed toward the unconsciousness and the convulsions. Maintenance of the fluid balance and subcutaneous injections of phenobarbital for the seizures may be needed. Treatment of the chronic neurologic deficit is directed toward re-education of the paretic limbs. Convulsions will be treated by adequate amounts of "Dilantin Sodium" or phenobarbital. If suffi-

cient cerebral tissue is destroyed, mental inadequacy may ensue, and this may greatly influence the program of re-education and rehabilitation planned for the patient.

HEMATOMYELIA

Definition. Hematomyelia is the term used to describe the signs and symptoms which occur with destruction of the spinal cord as a result of hemorrhage into the substance of the spinal cord.

Pathogenesis. Petechial hemorrhages in the cord may be found in a variety of toxic and inflammatory states. Massive hemorrhage into the cord is usually the result of contusion and laceration of the cord by trauma or fracture-dislocation of the spine. Occasionally, it may follow a minor external trauma to the body, such as falling onto the buttocks or forcibly extending the spine. The cervical and lumbar enlargements are the commonest sites of hematomyelia. The central gray matter of the spinal cord is most severely involved.

Symptoms and Signs. The onset of symptoms is sudden. With a lesion in the cervical cord, the patient may complain of severe pain in the neck radiating down the arms. There is a flaccid paralysis and loss of reflexes in the arms and a spastic weakness or paralysis of the legs. Because of involvement of anterior horn cells, atrophy of the arm muscles will subsequently develop. The amount of sensory loss will depend on how far the hemorrhage has dissected into the white matter. If the damage is limited to the area around the central canal, loss of sensitivity to pain and temperature may be expected for several segments below the level of the lesion. With involvement of the dorsal columns, deep sensibility below the level of the lesion will also be affected.

The onset of lumbar hematomyelia may be evidenced by sharp pain in the low back. A flaccid paraplegia then ensues, with sensory loss below the level of the lesion. Urinary retention is common. The cerebrospinal fluid is usually normal. Subarachnoid block may be present if there is fracture dislocation of the spine. The spinal fluid may be bloody if there is contusion of the cord.

Diagnosis. In no other spinal cord disease apart from spinal contusion and laceration is onset so rapid. Transverse myelitis from whatever cause is slower in appearance. Acute anterior poliomyelitis has febrile onset, is slower to develop, does not involve sensory loss, and has a pleocytosis in the cerebrospinal fluid. Softening of the spinal cord due to thrombosis may be most difficult to differentiate from hematomyelia. When the thrombosis is due to syphilis, the history of infection and the serologic tests will make the distinction clear. Thrombosis due to spinal arteriosclerotic disease is rare. Symptoms and signs will depend on the particular spinal vessel involved. A sensory level may be regularly expected.

Treatment. Treatment in the initial stage is limited to treatment of the spinal cord injury. Laminectomy with decompression of the cord is necessary if subarachnoid block is present. Late treatment includes physical therapy and muscle training.

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Infections of the Nervous System

H. Houston Merritt and Daniel Sciafra

Intracranial Abscess

Definition

Pathogenesis

Symptoms and Signs

Diagnosis

Treatment

Epidural Spinal Abscess

Definition

Pathogenesis

Symptoms and Signs

Diagnosis

Treatment

Herpes Zoster

Definition

Pathogenesis

Symptoms and Signs

Diagnosis

Treatment

Herpes Zoster

The nervous system and its coverings (meninges) are subject to invasion by most pathogenic organisms. Some of these organisms are common invaders of other parts of the body; thus the spirochete may involve both the nervous system and any other system, and the pyogenic bacteria may do likewise. Other pathogens may be solely neurotropic; e.g., some of the filtrable viruses.

In general, the diseases that are caused by pathogens common to the rest of the body (i.e., neurosyphilis and meningitis) are discussed elsewhere. Infectious diseases of the nervous system that are caused by specific neurotropic viruses are also considered elsewhere. This chapter is chiefly concerned with the pyogenic infections of the brain (abscess) and extradural or subdural collections of pus.

INTRACRANIAL ABSCESS

Definition. Intracranial abscess is a collection of pus within the skull.

Pathogenesis. An abscess may localize anywhere within the cranial cavity. Conveniently, the different areas of localization can be listed as extradural, subdural, and intracerebral. Extradural abscess is usually due to extension of infection from an osteomyelitis of the skull. The infection passes through the bone to the dura, separates the dura from the bone, and forms a localized pocket extradurally. In subdural abscess or empyema, the source is also usually an osteomyelitis, the infection having gone a step

further and penetrated the dura to form a subdural pocket of suppuration. Intracerebral abscess may occur as the next step in spread of infection from an osteomyelitis of the skull. However, intracerebral abscess may also occur as an extension of an infection in the head without the development of osteomyelitis, or may follow a septicemia. Intracerebral abscess is usually single, but may be multiple, especially if of septicemic origin. Usually, the abscess is localized and eventually walled off. Occasionally, the process may become widespread so as to form a suppurative encephalitis.

The most common cause of intracranial abscess is infection of the middle ear or mastoid. In these cases the intracranial infection is either a collection of pus around the dura adjacent to the mastoid, or an abscess in the temporal lobe or the cerebellum. The next most common cause of intracranial abscesses is infection of the nasal sinuses. Such abscesses tend to localize in the subdural and extradural spaces over the anterior half of the cerebral hemisphere, or within the frontal lobes. Abscesses from a hematogenous spread may occur anywhere in the brain, but in general are supratentorial in location. Intracerebral abscess may be indicative of a focal suppuration elsewhere rather than a general septicemia. In such cases the lungs are usually the source, bronchiectasis or lung abscess being present. Occasionally, intracranial abscess may follow fracture of the skull, especially when the injury is a penetrating wound. Patients with those types of congenital heart disease which produce right-to-left shunt (Chapter 236) are particularly prone to develop cerebral abscess.

Though any of the common pyogenic organisms may cause an intracranial abscess, the most common are the staphylococcus, streptococcus, and pneumococcus.

Symptoms and Signs. In the acute stage of an intracranial abscess the symptoms and signs are those of an infection plus focal damage to the brain. If the infection does not remain localized,

then the signs of suppurative encephalitis will supervene. Usually, however, the infectious process does localize and becomes walled off and encapsulated. In this more chronic stage the evidence of infection may be minimal, and the lesion may act as a tumor mass.

The cerebrospinal fluid examination may be of great diagnostic aid. Pressure may be increased. Protein content is usually high. A leukocytosis is present, with lymphocytes predominating.

Diagnosis. In the acute stage, the diagnosis of intracranial abscess can usually be made without difficulty. The combination of ear or sinus infection, osteitis, or other focus of infection, with signs of cerebral involvement in the form of a hemiplegia, convulsions, or choked disks, suggests the presence of an abscess. It is usually in the acute stage that epidural and subdural abscesses are found, and at such time the distinction from an intracerebral abscess may be difficult.

In the chronic stage, diagnosis of intracerebral abscess may be more difficult. Signs of the primary infection may not be apparent. The clinical picture may resemble that of brain tumor. However, even if clinical signs of infection are gone, the cerebrospinal fluid will usually show some increase in cells indicative of an infectious process.

Treatment. The use of chemotherapy and antibiotics in the treatment of ear and sinus infections has markedly cut down the incidence of intracranial abscess. In the presence of an acute abscess the therapy of choice is chemotherapy. It is possible that a certain number of abscesses may clear up under such therapy, and the treatment will hasten encapsulation and facilitate surgical intervention. The development of coma or an increase in focal neurologic signs, in spite of adequate chemotherapy of an acute abscess, is an indication for surgical intervention.

In chronic, walled-off abscesses, surgical intervention is indicated for drainage of the abscess. Seizures are a common residual effect of intracerebral abscess.

EPIDURAL SPINAL ABSCESS

Definition. Epidural spinal abscess is a localized suppuration in the extradural space of the vertebral canal.

Pathogenesis. Spinal epidural abscess is usually a metastatic infection secondary to a pyogenic infection, usually in the skin. Thus furuncles or skin abscesses on the back may metastasize

to the spinal vertebrae, causing an osteomyelitis of the spine and an abscess in the epidural space.

Symptoms and Signs. The presenting symptom is usually pain in the back and around the trunk in a root distribution. Weakness of the legs and urinary retention soon follow. On examination there may be no residua of the primary infection. There is usually stiffness of the neck and localized tenderness of the vertebral column. In the initial stages there may be no weakness of the legs. With cord compression there is weakness of the legs, increased reflexes, and bilateral Babinski sign. When there is thrombosis of the spinal vessels there is a flaccid paraparesis with complete loss of all forms of sensation, loss of reflexes below the level of the lesion, and loss of bladder and rectal control.

A lumbar puncture may be necessary to establish the diagnosis. If this is done, the needle should be inserted slowly, the stylet withdrawn, and suction applied to the needle as the epidural space is approached. If pus is obtained, the needle should be withdrawn before puncturing the dura and infecting the subarachnoid space. If no pus is obtained, the subarachnoid space is punctured, dynamics tested, and fluid removed for examination. There is usually complete or incomplete subarachnoid block. The fluid is clear or cloudy, with a cell count of 50 to 500 per cu. mm., and with polymorphonuclears predominating. The protein content is increased. The sugar content is normal unless the infection has spread to involve the leptomeninges.

Diagnosis. Spinal epidural abscess must be differentiated from an acute transverse myelitis or the acute development of symptoms in patients with a spinal cord tumor. Transverse myelitis is usually differentiated by the absence of spinal subarachnoid block. Spinal cord tumor cannot be differentiated except by exploration.

Treatment. Spinal epidural abscess is an acute neurologic emergency. As soon as the diagnosis is made, or even if it is seriously suspected, laminectomy should be performed. Delay in evacuating the abscess may result in thrombosis of the spinal vessels with consequent myelomalacia and a permanent paraplegic patient. Chemotherapy should precede and follow surgical therapy.

HERPES ZOSTER

Definition. Herpes zoster is an acute infection affecting dorsal root ganglions and their corresponding areas of supply to the skin.

Pathogenesis. Herpes zoster is an infection presumably caused by a virus which has a predilection for posterior root ganglions and the sensory ganglions of the cranial nerves. Occasionally, the infection may involve other parts of the spinal cord and its coverings, and rarely the cerebrum, and produce a myelitis, a meningitis, or an encephalitis. Herpes zoster appears to occur as a spontaneous infection, at times in a mild epidemic form, or it may be the so-called symptomatic form. In the latter case a latent infection seems to erupt when a particular sensory ganglion is traumatized. Thus it may be a complication of other diseases of the spinal cord, or may follow operations on the trigeminal nerve for trigeminal neuralgia.

Symptoms and Signs. General mild symptoms of a systemic infection may precede the vesicular eruption which is characteristic of herpes. The initial symptoms of involvement of the ganglions is a severe, sharp pain in the distribution of the affected root. This is followed within 24 to 48 hours by an eruption located in the dermatomes supplied by the affected ganglions. When the Gasserian ganglion is affected, the vesicular eruption appears in the distribution of the trigeminal nerve. Particularly troublesome may be involvement of the first division of the trigeminal, leading to ophthalmic zoster with corneal eruptions and subsequent scarring. Herpes zoster may also involve the geniculate ganglion, with eruptions in the auricle and facial paralysis (Hunt's syndrome). The vesicular eruption lasts a few days to a week and subsides. In its wake it usually leaves areas of scarring and decreased sensibility. Pain, however, may persist and may even be more intense following the herpetic rash.

Almost all cases of herpes zoster show in-

creased lymphocytes and protein in the cerebrospinal fluid, thus indicating some degree of meningeal involvement. Occasionally, clinical signs of meningitis may supervene and even signs of myelitis and encephalitis may be found.

Diagnosis. Usually the diagnosis of herpes zoster is made with little difficulty. Early in the disease a vesicular eruption associated with pain and hyperalgesia is diagnostic. Herpes simplex is easily distinguishable by its distribution near a mucous membrane, the absence of associated pain, and the absence of aftermaths of scarring. Postherpetic neuralgia is distinguished from other root pains by the preceding clinical picture and the associated scars.

Treatment. The therapy of the vesicular eruption lies in attempting to dry up the lesions and preventing secondary infection. Recent reports indicate that aureomycin and "Chloromycetin" are of value in arresting infection in the nervous system. X-ray therapy to the affected segment, and intramuscular injection of surgical "Pituitrin" or bismuth have been recommended but their value is unproved. Postherpetic neuralgia may be a very troublesome condition, and it may tax the therapeutic resources at hand. X-ray radiation of the affected dorsal nerve roots may be of aid. Surgical section of the affected sensory roots may be resorted to, or even intraspinal section of ascending pain fibers (chordotomy).

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Trauma of the Brain and Spinal Cord

H. Houston Merritt and Daniel Sciarra

Head Injury
Concussion
Cerebral Contusion and Laceration
Extradural Hematoma
Subdural Hematoma
Posttraumatic Syndrome
Spinal Cord Injury
Definition
Pathogenesis
Symptoms and Signs
Diagnosis
Treatment

The central nervous system is encased in sturdy bony structures, the skull and vertebral column, which serve as excellent protectors. But, owing to the fragile nature of the tissues of the central nervous system, severe and often irreversible damage may occur when they are injured by traumatic forces.

HEAD INJURY

Patients with injuries to the head may be divided into two groups, according to the severity of the damage to the bony covering. The first group, or open head injuries, comprises those in which the ~~skull has been penetrated~~ or has suffered a compound fracture. The second group, or ~~closed head injuries~~, includes those in which the brain has been injured without any significant damage to the skull, with the possible exception of a simple linear fracture. The damage in the latter group of cases is due to the striking of the brain against the unyielding skull, usually as a result of the sudden arrest of the forward movement of the head, such as occurs in falling against the pavement or other hard objects.

Pathogenesis. In general, the severity of the injury is related to the force of the blow. A more specific relationship exists, however, between the relative speeds with which the head and the striking object are traveling at the time of contact, and the severity of the head injury. Penetrating or crushing blows also tend to cause more cerebral damage than does a pure striking force, and penetrating explosive objects, such as a bullet, may leave even greater relative injury in its wake. Severe cerebral injury may be incurred without

skull fracture. Conversely, skull fracture does not predicate severe, or even any, cerebral injury. Compound skull fracture, especially if the nasal sinuses or the mastoid areas are involved, carry an additional risk of introducing infection into the meninges or cerebrum. Further, the possibility of posttraumatic convulsions is greatly increased in compound or open head injuries.

Obviously, all degrees of head injury may be incurred. The immediate effects of head injury may be discussed under the three headings: concussion, contusion, and laceration. ~~The complications of head injury~~ include paralysis of the cranial nerves, infections of the meninges or substance of the brain, and hemorrhage into the extradural or subdural spaces and into the substance of the brain. The late effects of head injury include convulsive seizures and a group of symptoms (headache, dizziness, easy fatigability, etc.) described by the term *posttraumatic syndrome*.

CONCUSSION

Definition. Cerebral concussion is a transient functional disturbance of the brain following head injury.

Pathology. In general, cerebral concussion follows mild head injury. The nature of the pathology is not clear, though it has been ascribed to acute cerebral anoxia from edema and other unknown factors, which are the result of the sudden movement of the brain within the bony skull.

Symptoms and Signs. There is a transient loss of ~~unconsciousness~~ of several minutes' duration. During the period of coma there may be an alteration of the respiratory or pulse rates. Following recovery of consciousness there may be ~~retrograde amnesia~~ for the injury and at times for the events preceding injury. ~~Headache and dizziness~~ are the usual symptoms. These commonly persist for only a few days, but they may recur with increased severity when the patient returns to his usual activities (*posttraumatic syndrome*).

Diagnosis. In patients with cerebral concussion the loss of consciousness is brief and the

cerebrospinal fluid is clear and under normal pressure. ~~Prolonged loss of consciousness~~, the presence of focal neurologic signs, or changes in the cerebrospinal fluid indicate a more serious degree of injury to the brain, and exclude the diagnosis of concussion.

Treatment. Cerebral concussion in general needs no specific therapy. Rest in bed for 36 to 72 hours is usually sufficient. Considerable psychologic damage to the patient may occur and post-traumatic symptoms are prone to develop if the physician gives the patient the impression that the injury is of a serious nature.

CEREBRAL CONTUSION AND LACERATION

Definition. Cerebral contusion is the term used to describe the condition which develops in patients with a head injury in which the injury to the cerebral substances is greater than in cerebral concussion. It implies that the cerebral substance has been contused or lacerated by the force of the blow.

Pathology. Diffuse punctate hemorrhages throughout the cerebrum have been found in the cases of contusion that do not survive. These hemorrhages may be particularly prominent at the poles of the cerebral hemispheres, where the cortex may be torn. A diffuse and marked cerebral edema may develop either as a response to the hemorrhages or concomitantly with them.

Symptoms and Signs. Although mild cerebral contusion may occur without loss of consciousness, in the majority of the cases the period of coma is prolonged for many minutes or even for hours. With minor degrees of cerebral contusion the patient recovers consciousness within a few minutes and the subsequent course is similar to that in patients with cerebral concussion. When the injury is more severe, the period of coma is prolonged. The patient may pass through various stages of stupor and confusion before complete consciousness is regained. He may become disoriented, noisy, and at times violent. Focal paralyses, cranial nerve palsies, or convulsive seizures may occur as result of the brain damage.

~~X~~The cerebrospinal fluid is usually under an increased pressure and is bloody. The blood may clear up in about one week, but xanthochromia and increased protein may persist for two to three weeks.

Diagnosis. If unconsciousness persists for more than a few minutes following head injury, or if unconsciousness is followed by mental confusion or neurologic signs, then it can be concluded that the patient has suffered contusion or laceration of the brain.

Treatment. Patients with cerebral contusion should be kept inactive and in bed for several weeks, usually for the period in which it takes the cerebrospinal fluid to clear up. Sedation may be needed, but morphine and the barbiturates should be avoided if possible. Paraldehyde and chloral hydrate may be employed somewhat more safely. Headache should be treated by appropriate analgesics. The ~~increased intracranial pressure~~ can be controlled by repeated lumbar puncture or by dehydration with intravenous saline or glucose solution. The former method is preferable because it allows for the proper maintenance of fluid and electrolyte balance and avoids the untoward side effects of severe dehydration. ~~Decompression operations~~ are necessary only in rare cases where other methods fail to reduce the intracranial pressure.

EXTRADURAL HEMATOMA

Definition. Extravasation of blood between the dura and the inner table of the skull is known as extradural hematoma.

Pathogenesis. Extradural hemorrhage is usually the result of laceration of one of the meningeal arteries (usually the middle meningeal) or the large dural sinuses with separation of the dura from the inner table of the skull. The extravasated blood forms a large clot which gradually compresses the underlying cerebral tissue.

Symptoms and Signs. The characteristic sequence of events in a patient with an extradural hematoma is a brief period of coma, followed by a recovery of consciousness (lucid interval) and a subsequent relapse into coma. Coincident with the relapse into coma there may be signs of focal compression of the cortex in the form of a hemiplegia. This orderly sequence of events may be absent when there is severe injury to the cerebral substance and the coma of the initial injury is prolonged to merge with that due to the pressure of the extradural hematoma on the cerebral cortex.

Diagnosis. The differential diagnosis between extradural hematoma and contusion and laceration of the brain is somewhat difficult, especially

when there is no lucid interval. The presence of a fracture line which crosses the groove of one of the meningeal arteries, or a displacement of the pineal gland in the roentgenograms of the skull is an important diagnostic aid.

Treatment. The diagnosis of extradural hematoma calls for immediate craniotomy with evacuation of the clot and ligation of the bleeding vessel.

SUBDURAL HEMATOMA

Definition. The term *subdural hematoma* is used to denote the collection of extravasated blood between the dura and the pia mater.

Pathology. It is now commonly agreed that subdural hematoma is due to the rupture of small veins which bridge the space between the pia-arachnoid and the dura. Since the subdural space has no adequate mechanism for the absorption of extravasated blood, it remains in the subdural space, and is gradually liquefied and organized by the proliferation of fibroblasts from the inner surface of the dura. Subdural hematomas may occur over any portion of the brain, but they are most common in the frontoparietal region. Not infrequently they are bilateral.

Symptoms and Signs. There are no symptoms or signs that are pathognomonic of the presence of an acute subdural hematoma. This diagnosis should be considered in all patients with a minor or severe injury to the head in which the recovery of the patient is delayed longer than should be expected from the nature of the injury. Fluctuations in the level of consciousness from hour to hour or from day to day are common in patients with an acute subdural hematoma. Occasionally, the symptoms which are due to a subdural hematoma may not develop until weeks or months after the injury. In these patients the signs and symptoms are similar to those in patients with expanding lesions of other types—tumor, abscess, etc.

Diagnosis. The diagnosis of an acute subdural hematoma is often very difficult. It should be considered whenever there is fluctuation in the level of consciousness in the first few days after a head injury. Displacement of the pineal gland in the roentgenogram or focal abnormalities in the electroencephalograms or pneumoencephalograms are, of course, helpful. These are usually not necessary, since it is easier to make small burr holes in the skull in search for a hematoma

whenever this diagnosis is considered. The frequency of subdural hematomas in chronic alcoholic patients should always be kept in mind. The diagnosis of a chronic subdural hematoma is established by the same diagnostic procedures as are used for the diagnosis of other intracranial tumors.

Treatment. Once the diagnosis of subdural hematoma is made, surgical exploration and evacuation of the encysted fluid are indicated. Exploration should also be undertaken when the diagnosis is suspected and distinction from other disease is not clear, as in chronic alcoholics. If there is not prompt recovery after evacuation of a hematoma on one side, the other side should be explored.

POSTTRAUMATIC SYNDROME

Definition. Following head injury, a symptom complex of headache, dizziness, difficulty in concentration, and nervous instability may occur. This is termed the *posttraumatic syndrome.*

Pathogenesis. The pathogenesis of the post-traumatic syndrome is not clear. It can follow any degree of head injury. Various observers would ascribe it to organic damage to the brain. Others would put the syndrome more definitely on a psychogenic basis. It is clear that certain environmental factors do affect the syndrome. For example, the question of compensation in a head injury case will often delay recovery.

Symptoms and Signs. Headache is most common. It is intermittent and is commonly made worse by physical effort or bending over. Dizziness is also prominent and also tends to get worse with sudden changes in posture. Intolerance to noise, difficulty in concentration, and irritability are also present and may be evidence of a general nervous instability. These symptoms are more likely to occur in a person whose nervous temperament predisposes him to such responses. There are no signs indicative of the syndrome. Of course, any signs may be present due to the head injury.

Diagnosis. Some form of emotional lability is the most common sequela of head injury. When headache, dizziness, and lack of concentration occur following an injury, the diagnosis of post-traumatic syndrome may be made. Of the other head injury complications, subdural hematoma must be differentiated. It too may involve headache and dizziness, but the focal signs, changes of consciousness, and progression of symptoms

and signs set it apart from posttraumatic syndrome.

Treatment. This syndrome is usually of limited duration, lasting several months. Occasionally it may be protracted into several years. Mild sedation should be prescribed. Reassurance in regard to the head injury should be given. Clarification and settlement of any litigation and compensation in regard to the head injury should be accomplished as soon as possible.

SPINAL CORD INJURY

Unlike the cerebrum, where late effects are not uncommon, the effects of injury to the spinal cord are usually maximal immediately after the occurrence of the injury.

Definition. Spinal cord injury connotes that the spinal cord has been injured by either direct or transmitted violence.

Pathogenesis. The spinal cord may be injured directly by penetrating objects such as bullets or sharp instruments which inflict stab wounds. Such injuries are common during combat. In civilian life the spinal cord is much more likely to be damaged by transmitted violence, such as in fracture dislocation of the vertebrae. Also lifting, falling, or straining may lead to herniation of an intervertebral disk. Though this usually produces a sciatic syndrome, it can at times produce a picture of cord compression. The commonest locations of injury are the lower cervical spine, the upper cervical spine, and the thoracolumbar junction.

Concussion of the spinal cord may occur as a result of a blow to the spine, without actual trauma to the cord. More commonly, however, the symptoms in patients with spinal cord injuries are due to compression of the cord by fracture or dislocation of the vertebral bodies or by extravasation of blood into the substance of the cord (hematomyelia).

Symptoms and Signs. Any degree of damage to the spinal cord may present the picture of complete transection—i.e., flaccid paralysis, with loss of sensation and reflexes below the level of the lesion, and paralysis of bladder and rectal function. The degree of recovery after a period of several weeks may indicate whether the symptoms are due to an anatomic severance of the

cord or to physiologic interruption of the function by edema or hemorrhage.

Mild injuries may lead to less marked disturbances of the cord. Thus minimal pyramidal signs may appear as incomplete sensory loss. If only one half of the cord is affected, Brown-Séquard syndrome may be expected, with motor loss on one side of the body and sensory loss on the other.

The location of the injury will also determine the symptoms and signs that may be expected. Cervical trauma tends to cause a quadriplegia. If the cervical cord is injured high enough, the injury may be incompatible with life because of respiratory paralysis. Trauma below the cervical cord leads to a paraplegia.

Diagnosis. The dramatic onset of symptoms following an injury makes the diagnosis relatively easy. Roentgenograms of the spine will usually give evidence of fracture or fracture-dislocation of the vertebrae at the level of the injury. The cerebrospinal fluid may be bloody and there is partial or complete subarachnoid block when the cord is compressed by dislocation of the vertebrae.

Treatment. In general, the treatment of spinal cord injuries is conservative and symptomatic. When there is x-ray evidence of bony displacement, of bone fragments pressing on the cord, or when spinal subarachnoid block is present, the cord should be decompressed by laminectomy. If the cervical cord injury is associated with dislocation of the vertebrae, traction in the neck may be needed to secure proper realignment. The aftercare of patients with paraplegia and disturbance of vesical or rectal function is similar to that of patients with like symptoms of other causes. Tidal drainage is an important factor in securing return of function in a paralyzed bladder. Physiotherapy, muscle re-education, and the application of proper braces are all important in the rehabilitation of the patient.

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Tumors of the Brain and Spinal Cord

H. Houston Merritt and Daniel Sciarra

Brain Tumors

- General Symptoms and Signs
 - Special Symptoms and Signs
 - Types of Brain Tumors
 - Laboratory Tests
 - Treatment
- Spinal Cord Tumors**
- General Symptoms and Signs
 - Location of Cord Tumors
 - Types of Spinal Cord Tumors
 - Laboratory Tests
 - Treatment
 - Prognosis

The tumors of the brain and spinal cord are histologically the same. The different clinical pictures, however, make necessary separate consideration.

BRAIN TUMORS

The etiology of brain tumors is as obscure as that of neoplasms elsewhere in the body. The symptoms and signs in patients with cerebral neoplasms are chiefly related to the size and location of the tumor. They are influenced to some degree by the histologic nature of the tumor. The signs and symptoms may be separated into two groups: first, those which are due to the presence of an expanding mass within the skull; and second, those which are due to a local destruction of cerebral tissue.

GENERAL SYMPTOMS AND SIGNS

Headache is probably the most common symptom of brain tumor. It is probably due to pressure on, or displacement of, pain-sensitive structures within the skull. It tends to come on in bouts, particularly on arising in the morning. The headaches are made worse by exertions that raise the intracranial pressure, such as coughing or sneezing. The headache may be made worse by lying down, and may be associated with nausea and vomiting. Occasionally, the headache is unilateral, usually being limited to the side of the neoplasm. In posterior fossa tumors, the headache may be suboccipital.

Seizures are common accompaniments of brain tumors, occurring in approximately 50 per cent of the patients with tumors in the cerebral hemispheres. Focal or Jacksonian seizures may at

times give evidence in regard to the location of a cerebral tumor, but more often the seizures are generalized and are not of localizing value. A seizure which is followed by a transient hemiplegia or aphasia indicates a focal lesion in the cortex. This focal lesion is not uncommonly due to a new growth.

Mental symptoms may occur as result of specific involvement of the cerebral cortex or to generalized cerebral dysfunction secondary to increased intracranial pressure. The changes in mental state due to increased pressure may vary from slight irritability to marked mental deterioration. Consciousness may be disturbed to some degree in many cases of brain tumor. This state may vary from drowsiness to stupor or coma.

Papilledema (choked disk) is present in a high percentage of the patients in the late stages, but may be absent in the early stage. It develops early when the cerebrospinal fluid pathways are obstructed, as with tumors in the third ventricle or posterior fossa. It is absent, or constitutes a late manifestation, with tumors which are confined to one lobe of one cerebral hemisphere. Accompanying the swelling of the optic disks there is enlargement of the blind spots and constriction of the peripheral fields of vision, and, when long continued, there may be optic atrophy and blindness.

Weakness of the ocular muscles is not uncommon in brain tumors. The sixth cranial nerve is most commonly involved, usually as a result of pressure on the nerve from increased intracranial pressure.

SPECIAL SYMPTOMS AND SIGNS

The special symptoms and signs of brain tumors are related to the local destruction or interruption of function of cerebral tissue which they produce. These symptoms do not differ from those produced by similarly placed lesions of other causes. It must be remembered that tumors are rarely confined strictly to any lobe of the brain, and that the dysfunction produced by a

tumor is not localized to the invaded or destroyed areas. The symptoms and signs of tumors in various locations as described below are subject to the above limitations.

Frontal Lobe Tumors. In tumors lying in the anterior part of the frontal lobe region, headache tends to occur early, though papilledema is a late sign. Mental symptoms are common and consist of deterioration, change of affect, and loss of sense of propriety. Urinary incontinence may develop. Pseudocerebellar signs are not uncommon, especially ataxic gait. Tumors of the olfactory groove may produce homolateral anosmia, optic atrophy, and contralateral choking of the optic disk (Kennedy's syndrome).

Tumors lying in the precentral convolution of the frontal lobe are characterized by the appearance of contralateral hemiplegia (fig. 241). If the



FIG. 241. Left facial palsy in a right frontal lobe tumor. (Courtesy, Merritt, Mettler, and Putnam: "Fundamentals of Clinical Neurology," Philadelphia, The Blakiston Company.)

tumor is located parasagittally and compresses both cerebral hemispheres, the paralysis may be bilateral and especially prominent in the legs. Jacksonian seizures are common with tumors in this area, and are often followed by a transient paralysis.

Parietal Lobe Tumors. Sensory defects are the

most prominent signs of tumors in the parietal lobe, but some degree of paralysis is usually present. There may be some loss of tactile sensation on the contralateral half of the body, but more commonly the sensory defect is limited to an impairment of finer discrimination—i.e., two-point discrimination, exact localization of stimuli, and stereognosis. Lesions in the posterior portion of the parietal lobe of the dominant hemisphere may cause some disturbance in the speech function.

Temporal Lobe Tumors. Tumors of the temporal lobe, especially the right, may be present without any focal symptoms. Generalized seizures are common with tumors of the temporal lobes. These may be preceded by dreaming states or hallucinations of smell, taste, or sight (hippocampal fits). Visual field defect (contralateral hemianopsia) is present when the optic radiations in the temporal lobe are compressed, and aphasia, particularly anomia, when the first temporal convolution of the dominant hemisphere is affected.

Occipital Lobe Tumors. Tumors of the occipital lobe are accompanied by a defect in the field of vision, more commonly of a quadrantic nature rather than a complete hemianopsia. Convulsive seizures are not uncommon with tumors in this lobe, and may be preceded by a visual aura. This aura is in the nature of flashes of lights, rather than hallucinations of formed images which are common with involvement of the optic radiations in the temporal lobe.

Optic Chiasma Tumors. Several types of tumor may be found in the region of the optic chiasma, and produce symptoms by compression of the optic chiasma, the hypothalamus, and the pituitary gland. The most common tumor in this region is the pituitary adenoma. Other types include meningiomas, gliomas of the optic nerve or frontal lobe, and craniopharyngiomas. The visual field defect produced by tumors in this region is usually in the nature of a bitemporal hemianopsia. Unilateral blindness or a homonymous hemianopsia may occur if the optic nerve or the optic tract is compressed.

Tumors of the Cerebellum. The cerebellum is a common location for primary tumors in childhood. In adults cerebellar tumors are usually of metastatic origin. Symptoms of increased intracranial pressure occur early and may be severe. Midline cerebellar tumors (medulloblastomas) cause marked ataxia of gait and nystagmus. With

tumors located in the lateral lobes of the cerebellum there may be hypotonia and ataxia confined to the ipsilateral side of the body. Rapid alternating movements are poorly performed. Gait is also unsteady. Cerebellar tumors may disturb the lower cranial nerves by compression.

Tumors of the Medulla and Pons. Tumors in these regions produce signs and symptoms by destroying the nuclei of the cranial nerves and by injury of the long fiber tracts. In the early stages the signs may be confined to one half of the brain stem, but bilateral signs soon develop.

TYPES OF BRAIN TUMORS

The diagnosis of brain tumor should include not only the location but also some attempt to determine the probable nature of the tumor, because the type of therapy is to some extent influenced by the type of tumor.

Meningiomas. Tumors which arise from the coverings of the brain have been variously labeled as meningiomas, arachnoid fibroblastomas, and dural endotheliomas. They compress but do not invade the brain. They commonly develop in adult life and are more frequently found in the female sex. They are most common above the tentorium, particularly in the parasagittal region, in the olfactory grooves, or near the wings of the sphenoid bone. Lying close to the skull, they may erode or stimulate the adjacent bone to overgrowth. This, together with the increase in vascularity of the affected bone, makes the diagnosis of a meningioma possible in many instances from the x-ray pictures of the skull.

Gliomas. Tumors which arise from the glial elements have been subdivided into a number of groups according to the stage of development of the tumor elements. The most common of the subtypes are the astrocytoma, glioblastoma multiforme, oligodendrogloma, and medulloblastoma.

ASTROCYTOMA. This tumor is composed of glial cells of the more differentiated type, and is therefore relatively slow-growing and often undergoes cystic degeneration. It is found in the cerebellar hemisphere in childhood and in the cerebral hemispheres in adult life.

GLIOBLASTOMA MULTIFORME. The most malignant of the gliomas is the glioblastoma multiforme (spongioblastoma multiforme). This type of tumor is most commonly found in the cerebral hemispheres of adults.

OLIGODENDROGLIOMA. This relatively uncommon form of glioma occurs in the cerebral hemispheres of young adults. It is relatively slow-growing and tends to show flecks of calcification.

MEDULLOBLASTOMA. This is a rapidly growing glioma of childhood involving the midline structures of the cerebellum. Signs of increased intracranial pressure develop early. Vestibular and cerebellar signs are common.

Pituitary Tumors. The initial signs and symptoms of pituitary tumors are related to the type of tumor, and are often of endocrine nature. In chromophobe adenoma, the endocrine effects are due to hypopituitarism. Thus, in a female, menstruation may become scanty and disappear. In a man, impotence and loss of facial hair may be early signs. In chromophile adenoma, hyperpituitary symptoms predominate. If the tumor arises before growth has ceased, gigantism may result. If it arises in adult life, acromegaly develops. The subcutaneous tissues, especially of the face, undergo fibrous hyperplasia. Bony overgrowth is particularly evident in the face, jaw, and hands. Pituitary tumors produce visual field defects by compression of the optic chiasma, nerves, or tracts. They usually enlarge and erode the sella turcica.

Neurofibromas. Tumors may arise from the sheath of any of the cranial nerves and are called neuromas or neurofibromas. They are most commonly found on the vestibular portion of the eighth cranial nerve. In this location the characteristic symptoms are tinnitus and loss of hearing. With growth of the tumor the fifth, seventh, and other cranial nerves may be compressed. Damage to the cerebellum and the brain stem may also occur.

Metastatic Tumors. Tumors of any of the organs of the body may metastasize to the brain, but the lungs and the breasts are most commonly the origin of metastatic tumors of the brain. The development of symptoms is rapid and the duration of life after onset of symptoms is short. Occasionally, cerebral symptoms will precede those from the primary site.

Angiomas and Hemangioblastomas. Angiomas are not true tumors but are congenital vascular malformations. They are most commonly found on the surface of the cerebral hemispheres. Hemangioblastomas are true vascular tumors which are found almost exclusively in the cerebellum. At times they may be associated with retinal

hemangioblastoma and congenital malformations elsewhere in the body.

LABORATORY TESTS

It may be possible to localize and determine the nature of an intracranial tumor from the clinical symptoms and signs, but in the majority of the cases this cannot be done without the aid of certain special examinations.

X-rays. X-rays of the skull may give indirect evidence of the presence of an intracranial tumor by producing the changes in the skull characteristic of increased intracranial pressure in the form of an increase in the digital markings on the vault of the skull and erosion of the clinoid processes of the sella turcica. Localized erosion or overgrowth of the skull, increased vascularity, and areas of calcification and ballooning of the sella turcica are the common findings in the roentgenograms which indicate the presence of a tumor. Displacement of the normally calcified pineal gland indicates an expanding lesion.

Cerebrospinal Fluid. The examination of the cerebrospinal fluid may be of assistance in indicating the presence of a brain tumor. The presence of increased intracranial pressure is usually made evident by an increased cerebrospinal fluid pressure. The protein content of the fluid may be increased in brain tumors, especially if the tumor is near a ventricular surface. Lumbar puncture can be performed without danger in patients with tumor, except when there is an excessive increase in intracranial pressure.

Encephalography and Ventriculography. Injection of air into the lumbar subarachnoid spaces or into the cerebral ventricles is of great aid in diagnosing the presence of a tumor and in determining its exact location. If there is no increase in pressure, injection of air by the lumbar route (encephalography) can be performed. X-rays of the skull taken after the introduction of air will demonstrate the presence of a tumor mass by changes in the size and shape of the ventricles and subarachnoid cisterns.

Ventriculography, or the introduction of air into the ventricles through trephine openings in the skull, is the procedure of choice when there is an increase in the intracranial pressure. Ventriculography is a major surgical procedure and should be performed only by neurosurgeons.

Cerebral Angiography. The cerebral vascular tree can be visualized in x-ray films after the

injection of radiopaque substances ("Thorotrast" or "Diodrast") into the carotid artery. This procedure is, of course, valuable in detecting the presence of vascular abnormalities. It is being employed with increasing success in detecting the presence of brain tumors either by the vascularity of the tumor or by the displacement of parts of the vascular tree by an avascular neoplasm.

Electroencephalography. Studies of the electrical activity of the cerebral cortex may reveal abnormalities which indicate the presence of a focal lesion and thus may be of value in localizing a tumor.

TREATMENT

The treatment of choice in brain tumors is complete removal of the tumor by operation. This is often possible with meningiomas, neurofibromas, hemangioblastomas, and pituitary tumors. In the noncircumscribed or more malignant tumors, surgical extirpation may not be possible. In these cases deep therapy with the roentgen ray may inhibit the growth of the tumor and give the patient several or many years of useful life.

SPINAL CORD TUMORS

Tumors which occur in the spinal canal are, in general, similar to those which are found within the cranium. The relatively small amount of available extra space in the spinal canal leads to the development of symptoms before the tumor reaches the size of that commonly encountered within the cranium. An additional significant difference is the relatively greater frequency of benign encapsulated tumors in the spinal canal.

General Symptoms and Signs. Spinal cord tumor produces symptoms by compressing the nerve roots or the substance of the cord or by interfering with its blood supply. The onset of symptoms is gradual and the course is slowly progressive when the damage is due to direct compression. The onset of the symptoms may be sudden when the blood supply of the spinal cord is compressed or invaded by the neoplasm. It is usually not possible to determine from the clinical signs and symptoms whether the tumor is located within the substance of the cord (intramedullary) or on the outside (extramedullary).

At the level of the tumor there are symptoms and signs of compression of nerve roots (pain,

localized muscular weakness and wasting) and below the level of the tumor there is evidence of damage to the long tracts of the spinal cord. In the early stages there is spastic weakness and some impairment of sensory modalities below the level of the lesion, together with dysfunction of the vesical and rectal sphincters. The deep reflexes are increased, and there is an extensor toe sign on both sides. With progress of the damage to the cord by compression, the symptoms and signs of a complete physiologic transection of the cord may develop. This state is common at the onset when the damage to the cord is due to occlusion of its vascular supply by the tumor. Occasionally, the Brown-Séquard syndrome may be found in patients with small laterally placed extramedullary tumors.

Location of Cord Tumors. The site of the tumor can be determined, in the majority of the cases, by the site of the original root pains and by the level of the motor weakness and sensory loss. It is usually not possible to determine whether the tumor is located within or outside the cord substance. Localized muscular atrophy and a syringomyelia type of sensory loss extending over several spinal segments, when present, indicate an intramedullary tumor. Sudden onset of a paraplegia with normal cerebrospinal fluid dynamics is an indication that the tumor is extramedullary and has compressed the blood supply of the cord. This is most common with metastatic and granulomatous tumors.

Types of Spinal Cord Tumors. The most common extramedullary tumors are neurofibromas and meningiomas. Other tumors which are commonly found in the subdural or extradural spaces of the spinal cord are the metastatic and granulomatous tumors (Hodgkin's disease and the like), and leukemic deposits also may be found in the extradural region.

Intramedullary tumors are usually composed of primitive glial elements, most commonly ependymomas or astrocytomas.

Laboratory Tests. X-rays of the vertebral spine should be taken in all cases of suspected

spinal cord tumor. Erosion of bone, angulation or collapse of the vertebrae, or separation of the pedicles may be found, indicating the presence of a tumor.

Lumbar puncture is of the greatest assistance in the diagnosis of cord tumors. Complete or incomplete subarachnoid block is present in all cases except when there is a small laterally placed tumor which is not compressing the cord. The protein content of the fluid is moderately or greatly increased.

When the diagnosis of a spinal cord tumor cannot be made with certainty from the clinical findings, the presence or absence of a tumor can be determined by the intraspinal injection of radiopaque dyes ("Lipiodol" or "Pantopaque"). When a tumor is present, its exact location can be demonstrated by blockage or interference with the flow of the dye when the patient is examined fluoroscopically on the tilt-table. The dye should be removed after the examination is completed.

Treatment. As in brain tumors, the ideal aim in spinal cord tumors is complete removal. This is possible with benign encapsulated extramedullary tumors. Intramedullary tumors are usually not amenable to surgical excision. Some of the tumors in this location may be arrested by radiation. Metastatic and granulomatous extradural tumors usually are not amenable to surgery.

Prognosis. The prognosis is poor in patients with intramedullary or malignant extramedullary tumors. Partial or almost complete recovery of function may result when benign extramedullary tumors are entirely removed. This is particularly true when the operation is performed before there is evidence of complete physiologic transection of the cord.

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Demyelinizing Diseases

H. Houston Merritt and Daniel Sciarra

Multiple Sclerosis (Disseminated Sclerosis)

- Definition
 - Pathogenesis and Pathology
 - Symptoms and Signs
 - Laboratory Data
 - Diagnosis
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- Definition
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 - Laboratory Data
 - Treatment

There are several diseases of the nervous system of unknown etiology in which the principal pathologic finding is a loss of the myelin sheaths. Numerous subdivisions of the demyelinizing diseases have been made according to the site and extent of the involvement and the age of onset of symptoms. It is not known whether all of these diseases represent variations in distribution and severity of one and the same pathologic process. Among the syndromes which have been described are: Cerebral sclerosis of Merzbacher and Pelizaeus, cerebral sclerosis of Scholz, cerebral sclerosis of Krabbe, neuromyelitis optica, multiple sclerosis, and diffuse sclerosis (Schilder's disease). Only the two last-named conditions, which are the most common, will be discussed. The reader is referred to the literature for description of the other syndromes.

MULTIPLE SCLEROSIS (DISSEMINATED SCLEROSIS)

Definition. Multiple sclerosis is a disease of the nervous system characterized clinically by the subacute onset of signs and symptoms of damage to several or many parts of the nervous system. Remissions and exacerbations of the symptoms over a period of months or years occur in the majority of the cases.

Pathogenesis and Pathology. Although numerous theories as to the cause of multiple sclerosis have been advanced, none of them has received general acceptance. In the light of our present knowledge, it is not profitable to discuss any of them.

On pathologic examination there are many small areas in which the myelin sheaths have been destroyed. These areas of demyelination are usually circumscribed, and are seen more commonly in the white matter of the brain and spinal cord than in the gray matter. In the cerebrum the lesions are often in close proximity to the ventricles. The optic nerves, the brain stem, and the spinal cord are also favorite sites of the patches, though any region of the nervous system may be affected. There is usually very little inflammatory reaction. The axis cylinders and other elements of the tissue are less severely damaged than the myelin sheaths, and in some of the lesions the axis cylinders are relatively intact. In the older lesions there is a proliferation of the macroglia with the formation of a glial scar (gliosis).

Symptoms and Signs. Onset of the disease may occur at any age, but over two thirds of the cases have their first symptom in the third and fourth decades of life. The two sexes are equally affected. The disease occurs in all races, but it is more common in temperate climates. The onset of symptoms is usually subacute. The character of the initial symptoms is quite variable, though diplopia, weakness of the legs, or paresthesias in one or more extremities are quite common. The most frequent over-all symptoms are diplopia, loss of visual acuity in one or both eyes, weakness of extremities, and incoordination. In over half of the cases these symptoms, and particularly the initial symptoms, may remit to some degree or entirely disappear. After a period of improvement or relative freedom of symptoms lasting for a few weeks or many years, the old symptoms recur or new symptoms develop and the patient becomes progressively more disabled with each new attack. In some patients there are no remissions; the initial attack is followed by a period of varying duration in which the symptoms remain static, and is followed by the onset of new symptoms. Rarely, the disease is progressive, with death in less than one year.

The most common signs in multiple sclerosis are those of leg weakness, visual difficulties, tremor, ataxia, reflex changes, and loss of position and vibratory sense. Among visual difficulties, nystagmus, optic atrophy, and scotoma on visual field examination are most common. Sphincter control is often impaired. Mental signs and symptoms, either euphoria or mental deterioration, are not uncommon and usually offer a poor prognosis. Not uncommonly there may be signs and symptoms of a complete or incomplete transverse lesion of the spinal cord. When both motor and sensory modalities are involved, the prognosis is poor.

The duration of the disease varies from a few months to many decades. Only rarely do the patients die of the disease, the majority of cases succumbing to intercurrent infections. The average duration of life after the onset of symptoms in hospitalized patients is 12 years. This figure is probably applicable only to the more severe cases, and there are statistics which indicate that the average span of life after the initial attack is longer.

Laboratory Data. The findings on the routine laboratory examination are normal except for those in the cerebrospinal fluid. A slight or moderate pleocytosis is found in approximately 30 per cent of the cases, and a slight or moderate increase in the protein content in about 25 per cent. A cell count greater than 100 per cu. mm. or a protein content greater than 100 mg. per 100 ml. is rare. Changes in the colloidal gold reaction are not uncommon. A first-zone curve is found in approximately 25 per cent of the cases, and minor changes in the reaction in another 25 per cent. An absolute or relative increase in the gamma-globulin fraction of the total protein content is present in about 90 per cent of the cases.

Diagnosis. The diagnosis of the disease can usually be made on the basis of presence of symptoms and signs of involvement of various portions of the nervous system and the variation of the character and severity of the symptoms from time to time. When this occurs, little difficulty in diagnosis is encountered. However, early in the course of the illness the symptoms may heavily outweigh the objective findings and a diagnosis of hysteria is not uncommon. If the disease shows a steadily progressive course and the symptoms seem to be related to a single lesion, the diagnosis may be difficult. However, a careful

examination will usually elicit some indication of dissemination of lesions or there may be a history of previous symptoms which have entirely remitted. X-ray examination of the skull and spine and examination of the cerebrospinal fluid will usually serve to exclude neurosyphilis, brain tumor, spinal cord tumor, and other diseases with symptoms which may simulate those of multiple sclerosis. Only rarely will it be necessary to resort to myelography or pneumoencephalography.

Treatment. At the present time there is no specific therapy. Various methods of therapy, based as a rule on some particular hypothesis as to the pathogenesis of the disease, have been tried. None of them has proved to be of any benefit in regard to the cure of existing symptoms, or the prevention of new symptoms. Physical therapy directed toward rehabilitation is desirable when the disease appears to be static. The patient should be encouraged to carry on as normal a routine as is possible with his deficiencies. When the patient becomes bedridden, especially if paraplegic, care of the skin, bladder, and rectum will be necessary. Intercurrent infections can be cured with the antibiotic agents available, thus prolonging the life span of these patients.

DIFFUSE SCLEROSIS

Definition. Diffuse sclerosis is a demyelinizing disease, most common in children, characterized by the progressive development of signs and symptoms of destruction of the cerebral hemisphere. The demyelinization, unlike that of multiple sclerosis, is diffuse and involves the entire white matter of one or more lobes of the brain or of one or both cerebral hemispheres. Several diseases may well be grouped under this heading. Schilder's disease is probably the best known of the group.

Pathogenesis and Pathology. The cause is unknown. The pathologic changes are similar to those of multiple sclerosis, except that the patchy nature of the demyelinization is not evident. The white matter is destroyed in a diffuse manner and there is a greater degree of destruction of the axis cylinders and other elements of the nervous parenchyma. The myelin sheaths of the fibers which connect adjacent convolutions (U fibers) are often spared.

Symptoms and Signs. Diffuse sclerosis is a relatively rare form of the demyelinizing diseases. It occurs in both sexes and is most common in child-

hood, about 50 per cent of the cases having their onset before the age of 10. Onset after the age of 30 is rare. Loss of visual acuity, affecting both eyes, is the most common early symptom. Mental deterioration, together with spastic paralysis of the extremities, completes the distinctive triad of the disease. Other focal cerebral symptoms and signs which may occur include convulsive seizures, aphasia, cortical sensory loss, and pseudobulbar palsy. The blindness is usually of the cortical type but there may also be optic atrophy or an optic neuritis with swelling of the optic disks. The course of the disease is progressive and usually leads to death within a period of a few months to two years. Remissions may occur, but they are uncommon.

Diagnosis. The diagnosis of Schilder's disease is made on the basis of the development of blindness, mental deterioration, and spastic weakness in childhood. Occasionally the signs may be unilateral and, if coupled with swelling of the optic disks, may suggest the presence of a brain tumor. In these cases the findings on pneumoencephalography will be those of cortical atrophy rather than those of a space-occupying lesion. Diffuse

sclerosis may at times present a clinical picture similar to multiple sclerosis. The onset of symptoms before the age of 10, complete blindness, and severe mental deterioration are unusual in multiple sclerosis. Cerebromacular degeneration (Tay-Sachs disease) is excluded in infants by the absence of the cherry red spot in the macula, and in children by the absence of retinitis pigmentosa.

Laboratory Data. Abnormalities in the laboratory findings, similar to those of multiple sclerosis, are confined to the cerebrospinal fluid. These are similar to those of multiple sclerosis except that a greater degree of pleocytosis and of increase in the protein content of the fluid is occasionally found.

Treatment. There is no specific therapy. Anticonvulsant medication may be used to control the seizures that occur.

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Degenerative Diseases

H. Houston Merritt and Daniel Sciarra

Cerebromacular Degeneration	
Presenile Dementias	
Parkinsonism (Paralysis Agitans)	
Definition	Diagnosis
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Symptoms and Signs	
Diagnosis	
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Huntington's Chorea	
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Amyotrophic Lateral Sclerosis	
Syringomyelia	

The nervous system is subject to a number of diseases of unknown etiology which are characterized by degenerative changes of a widespread nature or localized to a particular portion of the neuraxis. Many of these diseases are rare and do

not merit discussion. For the sake of completeness, a list of these conditions is given in table 113, but discussion in the text is limited to the degenerative diseases which are encountered most frequently.

Table 113

CLASSIFICATION OF THE DEGENERATIVE DISEASES OF
THE NERVOUS SYSTEM ACCORDING TO THE SITE
OF THE PRINCIPAL PATHOLOGY

- A. Cerebral:
 - 1. Cerebromacular degeneration (Tay-Sachs disease)
 - 2. Presenile dementias
- B. Basal Ganglia:
 - 1. Parkinsonism (paralysis agitans)
 - 2. Hepatolenticular degeneration
 - 3. Huntington's chorea
 - 4. Dystonia musculorum deformans
 - 5. Status marmoratus and status dysmyelinisatus
 - 6. Other congenital or hereditary diseases of the basal ganglia
- C. Cerebellum and Spinal Cord:
 - 1. Hereditary spinal and cerebellar ataxia (Friedreich's ataxia)
 - 2. Hereditary cerebellar ataxia with spasticity (Marie's ataxia)
 - 3. Olivocerebellar and olivopontocerebellar atrophy
 - 4. Parenchymatous cerebellar degeneration
 - 5. Myoclonus epilepsy
- D. Spinal Cord:
 - 1. Amyotrophic lateral sclerosis (progressive muscular atrophy, progressive bulbar palsy)
 - 2. Syringomyelia
- E. Cranial or Spinal Nerves:
 - 1. Hereditary optic atrophy (Leber's disease)
 - 2. Hereditary degeneration of the macula
 - 3. Peroneal muscular atrophy (Charcot-Marie-Tooth disease)
 - 4. Hypertrophic interstitial neuritis (Déjérine-Sottas disease)
 - 5. Polyneuritis (multiple peripheral neuritis)

CEREBROMACULAR DEGENERATION

Cerebromacular degeneration (Tay-Sachs disease, amaurotic familial idiocy) is a rare familial disease of unknown etiology, characterized by loss of visual acuity, enfeeblement of the mental faculties, paralyses, and other neurologic symptoms. The pathologic changes in the nervous system are due to a disturbance in the lipid metabolism with excessive deposition of lipid pigment in the nerve cells.

Several variations in the clinical forms of the disease have been described, mainly related to the age at which the symptoms develop. The infantile form occurs predominantly in infants of Jewish parentage. The symptoms develop in the first or second year of life. Blindness with cherry red spot in the macula, convulsive seizures, and regression from the previous stage of mental and physical development are the common clinical symptoms. Death usually occurs within one to three years after the onset of the disease.

Occasionally the onset of the disease may be delayed to early childhood or early adult life.

In these cases there is no racial predilection and there is retinitis pigmentosa instead of the cherry red spot in the macula. In addition, mental deterioration and paralysis are not such prominent features as in the infantile form. Cerebellar or other neurologic symptoms may also occur. The course of the disease extends over several or many years.

PRESENILE DEMENTIAS

The presenile dementias are characterized by the development of progressive mental deterioration in middle or early old age in the absence of cerebral arteriosclerosis, neurosyphilis, or other known causes of cerebral degeneration. Two forms of presenile dementia have been described: Alzheimer's disease and Pick's disease. The clinical picture is similar in the two but there are differences in the pathologic findings. In Alzheimer's disease the pathologic changes are superficially similar to those which occur in senility, but the cortical atrophy is localized sharply to the anterior portion of the frontal and temporal lobes. The ganglion cells in the affected areas are decreased in number and numerous argentophilic bodies (senile plaques) are found.

The cortical degeneration in Pick's disease has a distribution similar to that of Alzheimer's disease, except that the first temporal convolution is spared. There is a laminar degeneration of the nerve cells in the affected convolutions. Senile plaques are scanty or entirely absent.

It is not possible to distinguish between the two forms of presenile dementia from the clinical picture. Progressive impairment of the mental faculties is the most distinctive feature. Various types of aphasic speech disturbances or psychotic manifestations are common. Convulsions may occur, but hemiplegia, hemianopsia, or other focal neurologic signs are uncommon. Both diseases are chronically progressive, with death within 2 to 10 years after the onset.

The presenile dementias are differentiated from cerebral arteriosclerosis by the earlier age of onset and the lack of other signs of cerebral vascular diseases, particularly apoplectiform episodes. Occasionally ventriculography or encephalography may be needed to exclude the presence of a tumor of the frontal lobes. Dementia paralytica is excluded by the results of examination of the cerebrospinal fluid.

There is no specific treatment. Confinement to

an institution is usually necessary in the later part of the disease's course. Anticonvulsant drugs are indicated for the control of seizures.

PARKINSONISM (PARALYSIS AGITANS)

Definition. Parkinsonism or paralysis agitans is a symptom complex characterized by the presence of abnormal movements, rigidity, and various signs of involvement of the structures in the diencephalon.

Pathogenesis and Pathology. The pathophysiology of the symptoms of the disease is unknown. Various authors have attempted to explain the symptomatology on the basis of injury of one or more nuclear masses, specifically the substantia nigra, but such explanations are unsatisfactory. In the vast majority of the cases, "the lesions in the central nervous system are diffuse, and involve the cortex, brain, and cerebellum as well as the basal ganglia. In addition, the symptomatology of paralysis agitans is rarely seen when there is only an isolated circumscribed lesion in any part of the nervous system.

Parkinsonism may follow injury to the nervous system by a variety of disease processes and noxious agents. It occasionally develops in young people on the basis of hereditary influences, but it is most common in adults. It is a frequent complication of encephalitis lethargica, either developing during the course of the acute illness or appearing several or many years later. Parkinsonism may follow injury to the nervous system by carbon monoxide, manganese, or other anoxemic or metallic poisoning, and it is seen frequently in elderly individuals who display symptoms and signs of cerebral arteriosclerosis. In addition, there is a group of cases in which the onset of symptoms occurs in early middle life without any apparent cause. Some neurologists divide the cases into three groups—the "postencephalitic", the "idiopathic", and the "symptomatic" (those due to known injury of the nervous system by arteriosclerosis or noxious agents)—on the basis of differences in the symptomatology. Although the appearance of some symptoms, such as oculogyric crises and respiratory ties, are almost entirely confined to the postencephalitis group, this plan of division is generally unprofitable. The clinical picture, as a whole, is quite similar in all cases, and in many it is impossible to determine whether the symptoms develop without any

known cause or whether the patient had an unrecognized attack of encephalitis lethargica several or many years previously.

Symptoms and Signs. The symptoms usually develop insidiously and progress very slowly. The disease is not fatal, but may lead to complete incapacitation. However, progress may be so slow that death occurs from some other cause before the patient is seriously handicapped.

The disability of the patient is due to the rigidity of the muscles or to the presence of tremors and other abnormal movements. In the majority of patients both rigidity and tremor are present, but, occasionally, one or the other may predominate.

In the moderately advanced cases the posture is stooped, the head is flexed and bent forward, the trunk and knees are flexed, and the arms are adducted and flexed at the elbow. The gait is slow and shuffling, with short steps. There is difficulty in initiating locomotion, but in many cases there is a tendency for the pace to become faster and faster and the patient is unable to arrest his progress without grasping the table, chair, or some other article of furniture. There is loss or impairment of associated movements. The facial expression is relatively fixed (masklike facies), and blinking of the eyelids occurs infrequently (fig. 242). If a smile is evoked, the facial muscles relax slowly to their previous passive state. There is a loss or decrease of other associated movements, such as the swinging of the arms in walking, crossing of the legs after sitting down, and using the arms to assist in rising from the sitting position. The skin is usually oily and excessive perspiration is common. The patient may complain of pains in various parts of the body, which may be due to the rigidity of the muscles. Nocturnal incontinence may occur. There may be excessive somnolence. There is no complete paralysis of any of the muscles innervated by the cranial nerves, but difficulty in convergence and irregularity of extraocular movements (cogwheel type) are common. In addition to the masklike facies, rigidity of the laryngeal and pharyngeal muscles may cause a mild degree of dysphagia and dysarthria. In some cases, the dysarthria is so severe that the patient is speechless or can make only unintelligible utterances.

There is no wasting of the muscles of the trunk or extremities, and their motor power is relatively well preserved, except when the degree of rigidity

is great enough to impair their movements. In some instances this is so extreme that the patient is paralyzed for all practical purposes. ~~The rigidity~~ may involve all of the muscles of the body or may be confined to restricted groups. Not infrequently, the muscles of one half of the body may be involved to a much greater extent than those of the opposite half (hemi-Parkinsonism).

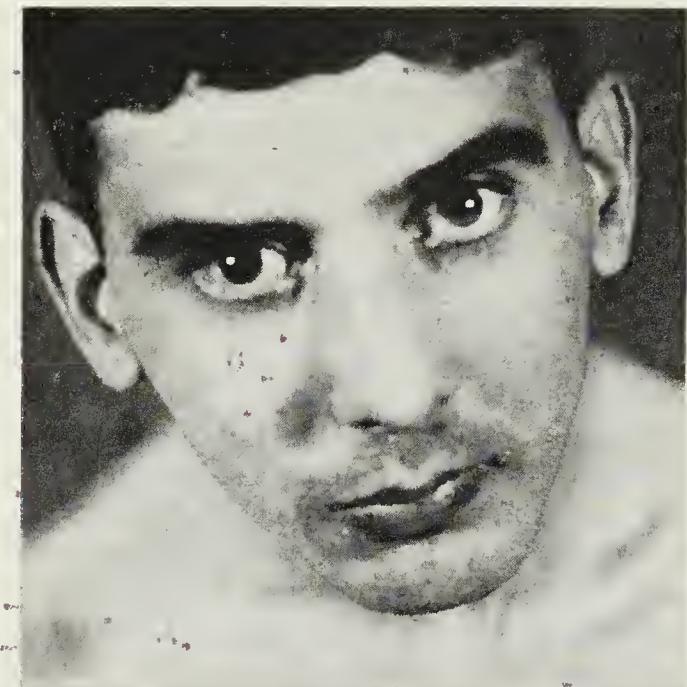


FIG. 242. Facial expression in Parkinsonism. (Courtesy, Merritt, Mettler, and Putnam: "Fundamentals of Clinical Neurology," Philadelphia, The Blakiston Company.)

The function of the muscles also may be impaired by the tremor. ~~The tremor~~ is of the alternating type, and usually is confined to the muscles of the extremities, the neck, the lips, or the tongue. The movements may be gentle, but occasionally they are so forceful that a tremor of one extremity shakes the whole body. In addition to the tremor, there may be other involuntary movements, especially in patients with Parkinsonism as a result of encephalitis lethargica. ~~Fie-like movements~~ of the facial and respiratory muscles may occur and produce snorting or grunting noises. Dystonic movements of the facial or neck muscles, with torticollis, also occur. In occasional cases there are spasmodic movements of the ocular muscles. These movements ~~(oculogyric crises)~~ occur at irregular intervals and in attacks. During an attack, there is forced movement of the eyes and occasionally of the head, in any direction, but usually upward. The patient is in good contact with his environment, but is unable to bring the eyes into normal position, except

with great effort and then only for a moment. The duration of an attack varies from a few minutes to several hours.

The deep reflexes are within normal limits in patients with Parkinsonism, except when there is restriction due to rigidity of the muscles. ~~The plantar responses~~ are usually flexor, but, in an occasional case, they may be of the extensor type. In such cases, it is assumed that the lesions have involved the cortex or fibers of the internal capsule.

There is no impairment of the patient's cutaneous and deep sensibility.

Diagnosis. The fully developed syndrome of Parkinsonism can hardly be mistaken. Early in its course Parkinsonism can, however, be confused with other neurologic disorders. ~~Senile tremor~~ is usually a finer tremor, occurs equally at rest or in motion, and is not associated with rigidity. ~~Cerebellar tremor~~ is differentiated by its predominance on motion, and its association with ataxia and incoordination. Increase in the tone of the muscles due to lesions of the corticospinal tract usually affects the antigravity muscles and is not of the cogwheel type. On the contrary, it tends to be maximal at the beginning of a passive movement and decreases suddenly as the movement proceeds (clasp-knife like).

Treatment. The normal routine and tenor of a Parkinsonian patient's life should be maintained for as long as possible. Activity should be encouraged. Physical therapy is of value in maintaining maximal function. Drugs of the belladonna group have a beneficial effect on the rigidity and lessen the tremor. The latter, however, usually is not greatly influenced by therapy. Attempts have been made to relieve the symptoms by various surgical procedures, such as removal of area 6 in the frontal lobe, removal of portions of the caudate nucleus, section of the ansa lenticularis, and division of "extrapyramidal" tracts in the spinal cord. Amelioration of tremor is usually obtained by the addition of a mild or severe hemiplegia, but rigidity and weakness are seldom benefited.

Administration of the drugs of the belladonna group is still the treatment of choice. Compounds ("Rabellou," "Vinobel," etc.) which have a mixture of the various alkaloids are usually more easily administered than the individual alkaloids. Success in the treatment depends on the skill of the physician in the administration of the drug, and the amount of encouragement which the patient experiences from his contact

with the therapist. The initial dosage should be small and gradually increased to tolerance. Excessive dryness of the mouth and difficulty in convergence are the chief limiting factors in the dosage. In recent years, attempts have been made to treat the symptoms with preparations which do not contain belladonna. Among the drugs which have been used are "Artane," "Diparcol," "Parpanit," and the antihistaminics. The method of administration of these compounds is similar to that of the belladonna preparations. In some cases they have proved more effective than the belladonna drugs.

HEPATOLENTICULAR DEGENERATION

Hepatolenticular degeneration (Wilson's disease) is a disease of childhood or early adulthood characterized by signs and symptoms due to degeneration of the corpus striatum of the brain and a partial cirrhosis of the liver. The latter may be present without any symptoms of liver failure.

Pathogenesis and Pathology. The etiology of hepatolenticular degeneration is unknown. The combination of the cerebral damage with cirrhosis of the liver has naturally led to the supposition that the cerebral changes are in some ways related to the liver disease (fig. 243). The changes in the nervous system consist of a degeneration of nerve cells mainly in the putamen and caudate nuclei. The cerebral hemispheres and the cerebellum are also affected to a lesser degree. The disease is often familial.

Symptoms and Signs. The onset may occur at any age from childhood to early middle life, but is most common in the second or third decade of life. Tremor of one or both upper extremities is often the first sign. This may occur when the extremity is at rest or occur only when it is moved or put under tension. The tremor of the arms may often be brought out in a particular position, as when the arms are held extended in front of the body. Thus, a flapping or "wing beating" of the hands or arms may be noted. Muscular rigidities may develop and the trunk or extremities may assume distorted postures. Speech and swallowing may be impaired early. The facies may assume an empty, vacuous expression. Mental deterioration is also common.

A greenish brown pigmentation of the cornea is found in approximately 50 per cent of the patients. This pigmentation, known as the Kayser-

Fleischer ring, is located on the posterior surface of the limbus of the cornea. It may be visible only on slit lamp examination, and may be present before the development of any neurologic symptoms.

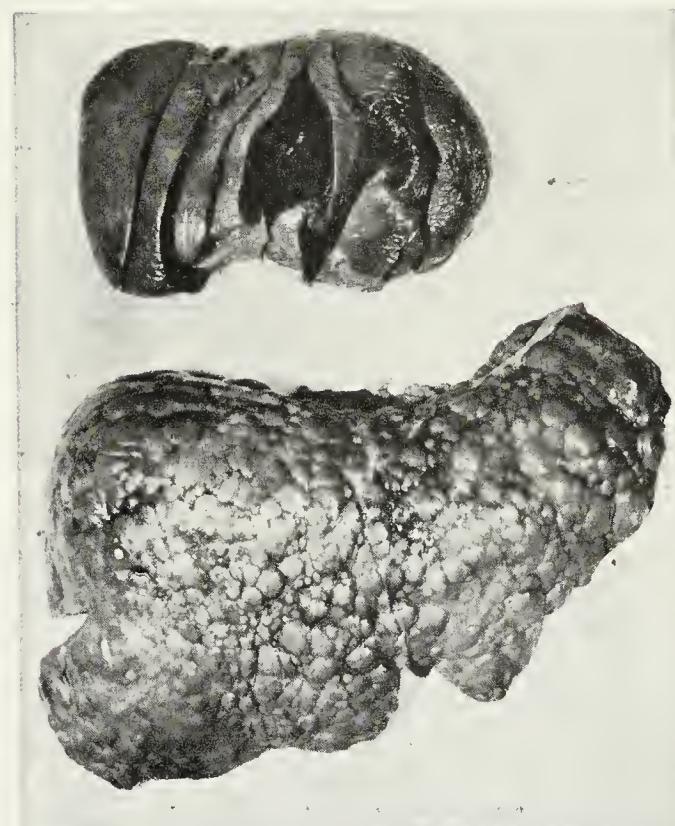


FIG. 243. Cirrhotic liver and enlarged spleen in Wilson's disease.

The cirrhosis of the liver is not uncommonly entirely asymptomatic. Symptoms of liver failure may, however, develop at any stage of the disease. Occasionally they may precede the onset of neurologic symptoms by several or many years. Death may often be caused by the liver disorder.

The course of hepatolenticular degeneration is chronically progressive, with death within 3 to 10 years in the majority of cases. Remissions are rare and are seldom complete.

Diagnosis. The occurrence of tremors of the extremities and muscular rigidity in association with corneal pigmentation and cirrhosis of the liver is pathognomonic of the disease. Early in the course of the disease difficulty may be encountered in the differential diagnosis of other diseases of the basal ganglia or cerebellum. The rigidity and choreoathetoid movements of double athetosis are present from infancy. Parkinsonism, except the form which follows encephalitis lethargica, is rarely seen before the age of 40 years.

Treatment. No therapy is known to affect the course of hepatolenticular degeneration. Dietary regimens have been given because of the liver disease, but they have not appreciably affected the course of the disease.

HUNTINGTON'S CHOREA

Definition. Huntington's chorea is a heredo-degenerative disease of the nervous system manifested by the occurrence of bizarre involuntary movements of the muscles of the trunk and extremities and a progressive dementia.

Pathogenesis and Pathology. The pathogenesis of the disease is unknown. It is highly hereditary in nature. The pathologic changes in the nervous system are widespread. The caudate nuclei are severely shrunken and there are degenerative changes in the ganglion cells throughout the cerebral cortex.

Symptoms and Signs. The involuntary movements are rapid and may involve any of the muscles of the body. Facial grimacing, fidgety movements of the fingers and toes, throwing movements of the arms or legs, and bowing movements of the trunk are common. At the onset these movements are mild and may be mistaken for tics or nervousness. As the disease progresses the movements become more violent and interfere with locomotion, eating, and other essential movements. In the terminal stages the patient becomes bedridden and there may be severe dysarthria. Psychotic episodes may precede or follow the onset of the choreiform movements. Progressive mental deterioration is the rule. The symptoms usually have their onset between the ages of 30 and 45 years, but onset at an earlier or a later age is not uncommon. The duration of the disease after the onset of symptoms is usually 10 to 20 years.

Diagnosis. The diagnosis can be made without difficulty when involuntary movement and signs of mental deterioration appear in adult life in a patient with a history of similar symptoms in other members of the family. Difficulty in diagnosis may occur when the family history is negative, especially when the symptoms develop in late life. The term senile chorea is often used to describe these cases, but it is probable that they represent only sporadic cases of Huntington's chorea. Huntington's chorea is distinguished from Sydenham's chorea by the early age of incidence and transient nature of symptoms in the latter.

Treatment. No therapy is known to affect the course of the disease. Psychotic episodes or evidence of severe mental deterioration may necessitate institutional care. Control of the spread of the disease is essentially a matter of eugenics.

CEREBELLAR AND SPINAL CORD DEGENERATION

The heredodegenerative diseases of the cerebellum and spinal cord are divided according to the age of onset of symptoms and the various features of the clinical picture.

FRIEDREICH'S ATAXIA

Hereditary spinal and cerebellar ataxia (Friedreich's ataxia) is the most common form of cerebellar degeneration. It is a familial and hereditary disease characterized clinically by the appearance in the first or second decade of life of ataxia of the extremities and trunk, absence of the deep reflexes, loss of proprioceptive sensations in the extremities, and an extensor plantar response. Clubfoot and scoliosis are present in a high percentage of the cases. Dysarthria, muscle atrophies, and degeneration of the optic nerve are not uncommon in the latter stages of the disease.

The pathologic changes are most severe in the dorsal half of the spinal cord where there is degeneration of the posterior funiculi, the lateral corticospinal tracts, and the spinocerebellar tracts. Shrinkage of the cerebellum and atrophy of the Purkinje cells is also found in some of the cases.

The ataxia, which is the cardinal symptom, develops slowly over the course of 5 to 15 years and ultimately leads to complete incapacitation. In the course of the disease there may be nystagmus, muscular wasting and weakness, oculomotor palsies, dysarthria, and mental deterioration. Death usually occurs as the result of intercurrent infections, but may be due to paralysis of the bulbar centers. Abortive or atypical forms, which do not lead to incapacitation and which are compatible with a relatively normal life span, are not uncommon. In addition, the atypical forms may present some of the features which are characteristic of progressive muscular dystrophy, peroneal muscular atrophy, familial spastic paralysis, or hereditary optic atrophy.

There is no treatment which is known to influence the course of the disease.

Other Forms of Cerebellar Degeneration. These include the following:

1. HEREDITARY ATAXIA WITH MUSCULAR ATROPHY. In this disease there is impairment of the equilibrium in walking and standing, loss of knee and ankle jerks, and wasting of the muscles of the legs and sometimes of the hands, and the occurrence in occasional cases of extensor plantar responses and kyphoscoliosis. Typical cerebellar signs and nystagmus do not occur. The symptoms develop early in childhood, progress slowly, and, in a large percentage of the cases, become arrested before the development of severe disabilities.

2. HEREDITARY CEREBELLAR ATAXIA WITH SPASTICITY (MARIE'S ATAXIA). The clinical picture in these cases differs from that of Friedreich's ataxia in the late onset (fourth to sixth decades of life), more definite hereditary character, exaggeration of the tendon reflexes, the frequent occurrence of optic atrophy and oculomotor palsies, and the relatively slow course of the disease.

3. OLIVOCEREBELLAR AND OLIVOPONTOCEREBELLAR ATROPHY. This is a disease characterized by the development in adult or middle life of progressive cerebellar ataxia with nystagmus and tremors of head and trunk. Pathologically, the degenerative changes are most severe in the cerebellum, pons, and olives. The reflexes are usually normal, but loss of the knee and ankle jerks or an extensor plantar response may occur. Rigidity of the muscles, immobile facies, Parkinsonian tremor, and mental deterioration may also occur. The course is slowly progressive, with the development of incapacity in 5 to 10 years.

4. PARENCHYMATOUS CEREBELLAR DEGENERATION. This is a sporadic disease of the cerebellum characterized by the development in middle life of cerebellar ataxia which is limited to, or is most severe in, the lower extremities. The pathologic changes are limited to the cerebellum, with disappearance of the Purkinje cells and atrophy of the folia. The etiology of the disease is unknown, but chronic alcoholism or antecedent illnesses have been stressed as presumed etiologic factors. The course of the disease is slowly progressive, extending over several decades. Arrest of the progress of the symptoms may occur.

AMYOTROPHIC LATERAL SCLEROSIS

Definition. Amyotrophic lateral sclerosis is an inexorably progressing disease characterized by degeneration of the motor cells of the spinal cord

and medulla with atrophy, paralysis, and fibrillation of the muscles innervated by the affected cells.

Pathogenesis. The pathogenesis of amyotrophic lateral sclerosis is unknown. The pathology is essentially a degeneration of the motor cells in the spinal cord and brain stem. There is a decrease in the number of the large pyramidal (Betz) cells in the motor cortex and a degeneration of the corticospinal tract, particularly in the spinal cord.

Symptoms and Signs. Amyotrophic lateral sclerosis is a disease of middle or late life. The morbid process may begin in any portion of the spinal cord or in the medulla. When the symptoms are mainly limited to the spinal cord, the condition is usually termed progressive muscular atrophy. Conversely, when the initial symptoms are localized to the medulla, the condition is described by the term progressive bulbar palsy. Regardless of the mode of onset, symptoms and signs of both spinal and medullary involvement are present in the majority of the cases before death. In addition, degeneration of the corticospinal tract is found at necropsy in all of the cases, even though signs of this involvement may have been masked by the muscular atrophy. There are no sensory disturbances.

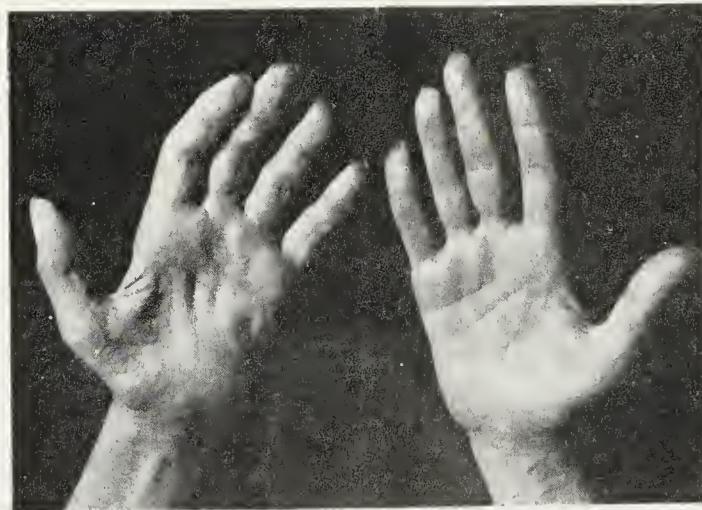


FIG. 244. Wasting of small hand muscles in amyotrophic lateral sclerosis.

The characteristic symptoms and signs of amyotrophic lateral sclerosis are weakness and atrophy with fibrillation and fasciculation of the affected muscles (fig. 244). The frequency of the various sites of initial involvement are approximately as follows: medulla, 21 per cent; cervical cord, 31 per cent; lumbar cord, 38 per cent; mixed or generalized, 10 per cent. With involvement of

the medulla, there is atrophy and fibrillation of the tongue muscles, and difficulty in talking and swallowing. Involvement of the medulla or cervical spinal cord is usually accompanied by an increase in deep reflexes in the legs and an extensor plantar response. The course of the disease is chronically progressive, with death from intercurrent infection or bulbar paralysis in one to five years.

Diagnosis. The diagnosis of amyotrophic lateral sclerosis is made without difficulty when there is generalized muscular atrophy with fibrillations. Difficulty is encountered mainly early in the course of the disease when the atrophy may be limited to one or both upper extremities and there is a spastic weakness of the lower extremities. Syringomyelia is differentiated by the dissociated sensory loss and the trophic disturbances. Muscular dystrophy can be distinguished by the early age of onset and the absence of fibrillations. Tumors of the cervical spinal cord or medulla and other causes of cord compression, such as arthritis of the spine or ruptured intervertebral disk, are differentiated by the x-ray findings and the result of examination of the cerebrospinal fluid, or by myelography.

Treatment. There is no specific therapy. Treatment is entirely symptomatic. Avoidance of infections is important, as respiratory infection added to a bulbar palsy may cause death.

SYRINGOMYELIA

Syringomyelia is a disease of the spinal cord and of the medulla (syringobulbia) of unknown cause, in which there is gliosis, necrosis, and cavity formation. The disease has a predilection for the gray matter of the cord in the cervical and lumbar regions. Occasionally the entire length of the cord and parts of the medulla may be involved.

Pathogenesis. Cavitation of the cord may develop secondary to necrosis in association with intramedullary tumors, vascular lesions, and trauma of the cord and inflammatory processes in the meninges; but primary syringomyelia is considered to be a developmental defect because of its occasional association with other heredo-degenerative defects, such as cervical ribs, scoliosis, webfeet, clubfeet, congenital anomalies of the cervical spine and base of the skull, etc.

Symptoms and Signs. The symptoms and signs of syringomyelia may develop at any age, but

their onset is most common in the third or fourth decade of life. Since the central portion of the cervical cord is the most common site of the cavity, the crossing fibers of pain and temperature are destroyed early in the course of the disease with resulting segmental anesthesia to pain and



FIG. 245. Chareot joints of elbows in syringomyelia.

temperature in the shape of a shawl, but with preservation of the sense of touch in the upper extremities. In consequence, painless burns and injuries of these members are common. Other symptoms and signs of cervical syringomyelia are weakness and atrophy of the muscles of the hands and arms due to destruction of the motor

cells in the ventral horns; loss of reflexes in the upper extremity as a result of interruption of the reflex arc; spastic weakness and increased reflexes in the lower extremity from involvement of the corticospinal tract; and loss of vibratory sense in the legs from involvement of the posterior columns. Lumbosacral syringomyelia is accompanied by weakness and atrophy of the muscles of the lower extremities, disturbance in the control of the rectal and vesical sphincters, loss of reflexes in the legs, and a segmental loss of pain and temperature sensations. A segmental anesthesia to all forms of sensation may result from destruction of the posterior roots at their point of entry to the cord. Occasionally there may be trophic symptoms, such as spontaneous fractures, Charcot joints (fig. 245), and painless felonies. Nystagmus, atrophy of the tongue, difficulty in talking and swallowing, Horner's syndrome, and loss of pain and temperature sense in the face are common symptoms when the cavity involves the medulla (syringobulbia). The progress of the symptoms of syringomyelia is usually very slow, extending over several or many years.

Treatment. The treatment is symptomatic. Instruction should be given in the care of the extremities to prevent burns, injuries, and infections; and orthopedic treatment of fractures and

Charcot joints should be instituted. Treatment directed toward the syringomyelic process has yielded only doubtful results.

X-ray treatment to the cord, in an effort to halt the overgrowth of glia which in many cases apparently precedes the cavitation, has been advocated. Diffuse treatment should be given over the entire spine, with concentration over the apparent sites of the lesion (usually cervical or lumbar cord). While the results of x-ray therapy are not very dramatic, this form of treatment should be tried in all cases.

Drainage of the cavity by splitting the cord in the dorsal median raphe after laminectomy has been tried in a few patients. Transient improvement has been reported, but it is doubtful whether such treatment has any appreciable effect on the course of the disease. The rare patient in whom there is complete subarachnoid block is probably best suited for surgery.

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Paroxysmal Disorders

H. Houston Merritt and Daniel Sciarra

Migraine
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 Definition

Pathogenesis
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The central nervous system is subject to several morbid conditions in which the symptoms occur at periodic or irregular intervals, and the

patient is entirely or relatively free of all symptoms in the interval between attacks. These diseases are epilepsy, migraine, Ménière's syndrome,

and narcolepsy. The pathophysiology of none of these diseases is known, but the paroxysmal nature of the symptoms in all of them suggests that there may be some common etiologic factors. Epilepsy is discussed in Chapter 8, under the heading of Convulsions.

MIGRAINE

Definition. Migraine is a symptom complex characterized by recurrent attacks of headaches, with or without associated visual, gastrointestinal, and other symptoms, in an individual who is in good health in the interval between attacks.

Pathogenesis. The etiology of migraine is unknown, and there are no pathologic changes in the nervous system. The various theories as to the causation of the symptoms include reflex irritation, cerebral edema due to disturbances in the circulation of the blood or cerebrospinal fluid, allergy, duodenal stasis, transitory swelling of the pituitary gland, endogenous or exogenous toxins, endocrine dysfunction, and vasomotor disturbances.

At the present time the most widely accepted theory as to the pathogenesis of the symptoms is that the prodromal symptoms (visual scotoma, hemianopsia, paresthesias, etc.) are due to a function disturbance in the intracerebral circulation (vasospasm or vasodilatation), and that the headache is due to dilatation of the vessels in the dura or in the tissues of the head outside of the cranial cavity.

Migraine is a relatively common disease occurring in approximately 5 per cent of the general population. It is slightly more common in the female than in the male sex. The symptoms may have their onset at any age, but in the vast majority of the cases the first attack occurs in the second or third decade of life. The hereditary nature of the disease is demonstrated by the fact that similar symptoms are present in near relatives of over 50 per cent of the cases.

Symptoms. The most prominent feature of the migraine syndrome is the periodic attacks of headaches, which may be unilateral or generalized. The pain may be localized to the front, back, or side of the head, and varies in intensity from a mild discomfort to a prostrating, throbbing pain. In the severe attacks the headaches are associated with irritability, nausea and vomiting, and photophobia. Other somatic symptoms include abdominal distention, cyanosis of ex-

tremities, vertigo, tremors, pallor, dryness of the mouth, excessive sweating, chilliness, and diarrhea or constipation. The duration of an attack varies from a few hours to many days. Most commonly the symptoms are present for 6 to 18 hours.

In the majority of the patients the headache is the presenting symptom, but in a small percentage the headache is preceded by visual, somatic sensory, or rarely somatic motor symptoms, or severe vertigo. The visual symptoms include flashes of lights, scotomas, and quadrantic or hemianoptic field defects. Sensory symptoms, commonly in the nature of paresthesias, may be widespread and involve one entire half of the body, or they may be localized to the finger tips, tongue, lips, or face. Dysphasia and weakness of one or more of the extremities are rare prodromal symptoms. When the prodromal symptoms are confined to one half of the body, the headache is usually on the opposite side of the head. Since migraine is a functional disorder, it is rare for either the prodromal symptoms or the headache to recur in the same location in every attack. When the headache is hemicranial in nature, the pain is present on the right side in some attacks and on the left side in other attacks.

The prodromal symptoms may last only a few minutes or they may be prolonged for several hours. In the first instance there is usually an interval between these symptoms and the onset of the headache. In the second instance the head pain begins before prodromal symptoms recede.

Migraine Equivalents. Occasionally in a patient who has had migraine attacks and associated phenomena for many years, the headache attacks may alternate or be replaced by the periodic recurrence of some other bodily disturbance. These so-called migraine equivalents may consist of attacks of abdominal pain associated with nausea, vomiting, and diarrhea (abdominal migraine); pain localized in the thorax, pelvis, or extremities; or bouts of fever. Transient psychic disturbances and disorders of mood occurring in episodic bouts have been reported as psychic equivalents of migraine.

Signs. In the interval between attacks there are no significant physical abnormalities. During the attack the patient appears acutely ill. The extremities are cold and cyanosed, and the patient is irritable and desires seclusion. The arteries on the surface of the head are prominent and the amplitude of their pulsations is increased.

Considerable attention has been given to the personality make-up of patients with migraine headaches. According to Wolff, the personality features and reactions dominant in individuals with migraine are feelings of insecurity with tension, manifested as inflexibility, conscientiousness, meticulousness, perfectionism, and resentment.

Studies in the blood, urine, feces, and cerebrospinal fluid during an attack or in the interval between attacks have not shown any constant deviation from the normal. Although minor abnormalities have been found in the electroencephalograms of patients with migraine, it is the consensus that there are no specific abnormalities in the electrical activity of the cortex during, or in the interval between, attacks of migraine except in rare cases where abnormalities are found in connection with the prodromal symptoms.

Diagnosis. The diagnosis of migraine can be made without difficulty when paroxysmal attacks of generalized or unilateral headache preceded by visual scotomas and accompanied by nausea and vomiting occur in a patient with a history of similar symptoms in other members of the family. If the headache always occurs on the same side of the head, the possibility of the presence of a vascular malformation in the cerebrum should be considered.

Treatment. The treatment of patients with migraine is divided into two parts: (1) treatment of the acute attack, and (2) treatment directed toward decreasing the frequency of the attacks.

TREATMENT OF ACUTE ATTACK. The commonly used analgesics which elevate the pain threshold may be effective in relieving the symptoms in patients with attacks of relatively mild severity. A dose of 0.6 Gm. (10 gr.) of acetylsalicylic acid, with or without the addition of 25 mg. of citrated caffeine or 60 mg. of codeine, can be given in such cases.

In the patients with severe attacks the above drugs are usually of no avail and ergot is the only recourse. The preparations of ergot which are most effective are "ergotamine tartrate" and "dihydroergotamine methane sulfonate." These drugs are most effective when administered parenterally early in the course of the attack.

Dihydroergotamine methane sulfonate is administered intravenously in a dose of 1 mg. The injection can be repeated in one hour if necessary. This drug is preferable to ergotamine tartrate

in patients in whom the use of the latter is regularly accompanied by nausea and vomiting.

Abortion of the attack or relief from the symptoms results in approximately 90 per cent of the cases if either of the above ergotamine preparations are administered parenterally within an hour of the onset of the attacks. They are less effective when given by mouth, and much larger doses are required. In addition, if nausea and vomiting has developed, it will probably not be possible for the patient to retain any drug administered by mouth. When given orally, the dose of ergotamine tartrate is 5 mg. at the onset of symptoms, followed by 2 mg. every half hour until the headache is relieved or until a maximum of 11 mg. has been taken.

PREVENTION OF ATTACK. Numerous therapeutic procedures have been recommended for preventing or decreasing the frequency of migraine attacks. None of them are specific or universally effective. Cessation of attacks has followed such operative procedures as section of the middle meningeal or the temporal arteries, but these operations are of value only in selected cases. Psychotherapy, directed toward relief of anxiety and the improvement of personality or situational difficulties, is the most effective form of preventive therapy.

MÉNIÈRE'S SYNDROME

Definition. Ménière's syndrome is a paroxysmal disorder characterized by recurrent attacks of vertigo associated with tinnitus and deafness.

Pathogenesis. The pathogenesis of the symptoms is unknown. In most of the cases there are no pathologic abnormalities. In some patients the symptoms may occur in association with chronic otitis media. Allergy, vasomotor disturbances, and hydrops of the endolymphatic system have been proposed as possible pathogenic factors.

Symptoms and Signs. The cardinal symptom of Ménière's syndrome is recurrent attacks of vertigo. Tinnitus and some impairment of auditory acuity are usually present before the onset of the attacks. These symptoms are increased in severity during the attack of vertigo. The onset of the vertigo is sudden; the environment seems to spin around the patient, though occasionally the patient will feel himself rotating. Nausea and vomiting soon develop. The attack lasts a few minutes to several hours, subsiding gradually.

During the attack there may be nystagmus, especially on looking to the affected side. In the intervals between attacks the patient is usually symptom free, but occasionally there may be a slight sensation of giddiness. Usually the hearing loss is progressive and the attacks of vertigo cease when there is total loss of hearing in the affected ear.

Diagnosis. The diagnosis of Ménière's syndrome is made on the basis of the recurrent attacks of vertigo associated with tinnitus and impairment of hearing. The dizziness and vertigo associated with tumors of the acoustic nerve, cerebellum, or brain stem is not paroxysmal in nature. In addition, these lesions are accompanied by signs and symptoms of injury to other structures in the nervous system.

Treatment. Rest in bed is the only treatment during an attack. The good results which have been reported with various forms of treatment in regard to the prevention of subsequent attacks are an indication of the relapsing nature of the disease and its tendency to disappear with the passage of time. Among the recommended forms of therapy are the administration of nicotinic acid, histamine desensitization, salt-free diet with the administration of ammonium chloride, and the administration of potassium chloride. The latter is probably the simplest and most effective form of therapy. Potassium chloride is given in doses of 6 to 8 Gm. daily for a period of months or years.

If success is not obtained by medical therapy, permanent relief from the attacks of vertigo can be obtained by surgical destruction of the labyrinth or section of the vestibular portion of the eighth cranial nerve intracranially.

NARCOLEPSY

Definition. Narcolepsy is a symptom complex characterized by the occurrence of frequent attacks of an irresistible desire to sleep. These may be combined with sudden attacks of loss of muscular tone in association with emotional stimuli such as laughing.

Pathogenesis. The pathogenesis of narcolepsy is not known. Although narcolepsy has been

known to follow injury to the nervous system by trauma and diseases such as encephalitis lethargica, the symptoms more commonly develop without any preceding injury to the nervous system, and there are no pathologic changes which can be related to the symptoms.

Symptoms and Signs. In the attacks of narcolepsy the patient falls into an apparently normal sleep from which he can be aroused without difficulty. Although the attacks of sleep may occur at inappropriate times, they are most apt to occur under conditions conducive to normal sleep, such as reading, riding in trains or motor vehicles, or the performance of dull tasks. The duration of the attacks of sleep vary from a few minutes to several hours, and they may occur once or many times a day. The nocturnal sleep may be normal, but not infrequently it is accompanied by disturbing dreams. In the majority of the patients with narcolepsy there are, in addition to the attacks of sleep, sudden episodes in which there is partial or complete loss of muscular tone, or sudden transient paralyses in association with emotional stimuli. For example, hearty laughter may cause the patient to fall to the ground or his head to slump on his chest.

Diagnosis. Narcolepsy must be distinguished from simple syncope and epilepsy. The circumstances in which the attacks occur and the ease of arousing the patient makes the diagnosis of narcolepsy relatively simple.

Treatment. Amphetamine sulfate and other sympathomimetic drugs are effective in controlling the sleep attacks. The dose should be regulated so that diurnal sleep is prevented and nocturnal sleep is normal. Doses of 10 to 20 mg. of amphetamine sulfate three to five times daily are usually sufficient.

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Polyneuritis

H. Houston Merritt and Daniel Sciarra

Definition
Etiology
Pathology
Symptomatology
Laboratory Data
Course
Treatment

Definition. Polyneuritis (multiple peripheral neuritis) is the term used to describe the clinical syndrome characterized by widespread involvement of the peripheral nerves, with resultant weakness, sensory loss, and impairment of reflexes.

Etiology. Polyneuritis may be associated with a great number of toxic and metabolic disturbances (table 114). The exact cause of the degenerative changes in the peripheral nerves is unknown, but it is possible that both toxic and metabolic disturbances may produce an alteration in the system of enzymes concerned with the nutrition of the nerves.

Pathology. In the majority of the forms of polyneuritis the pathology is mainly a noninflammatory degeneration of the peripheral nerves. In the initial stages there is swelling and fragmenta-

tion of the myelin. With progress of the destructive process the axis cylinders are also injured. Retrograde changes may be found in the cells of the ventral horns (axonal reaction) and, in chronic cases, in the fibers of the posterior funiculi.

Symptomatology. The clinical picture of polyneuritis is uniform regardless of the cause, but there may be variations in the distribution of paralysis and in the degree of sensory loss, which are related in some way to the underlying cause. Cases of polyneuritis may be divided into three groups according to the severity of the damage to the nerves: (1) mild, with subjective pains and paresthesias, but with little or no weakness, sensory loss, or reflex disturbances; (2) moderate, with subjective pain and paresthesias, slight weakness of the lower or upper extremities, diminution of vibratory sense, hypesthesia in the distal portion of the extremities, and decrease or loss of the deep reflexes; and (3) severe, with complete paralysis of the muscles of the extremities, weakness of the trunk muscles and occasionally of the facial, palatal, and pharyngeal

Table 114
PRINCIPAL CAUSES OF NEURITIS*

Virus	Generalized Polyneuritis				Localized Neuritis	
	Bacteriotoxic	Metabolic	Chemical	Heredodegenerative	Mechanical	Infectious
1. Exanthemas	1. Acute infectious polyneuritis †	1. Diabetes	1. Heavy metals	1. Peroneal muscular atrophy	1. Pressure	1. Diphtheria
2. Mumps	2. Septicemia	2. Pernicious anemia	2. Alcohols	2. Progressive hypertrophic neuritis	a. Tumors	2. Leprosy
3. Herpes zoster	3. Diphtheria	3. Malnutrition	3. Various organic drugs and compounds		b. Saturday night paralysis	3. Tetanus
4. Rabies	4. Acute febrile illness	4. Porphyria			c. Meralgia paresthetica	
					d. Cervical rib	
					e. Herniated nucleus pulposus	
					2. Trauma	

* Modified after Cobb and Coggeshall: Neuritis, *J.A.M.A.*, 103:1608, 1934.

† Also called Guillain-Barre syndrome.

muscles, loss of sensation in the distal portion of the extremities, and absence of all deep and superficial reflexes.

Polyneuritis may occur at any age, but it is most common in young or middle-aged adults. Men are affected much more frequently than women. The symptoms develop slowly over a period of several weeks in the majority of the cases, although the onset is apparently sudden in a few cases of alcohol-vitamin deficiency polyneuritis, and rapid evolution of symptoms (i.e., within 24 to 72 hours) is the rule in "infectious" polyneuritis.

The symptoms of polyneuritis are pains, paresthesias, weakness, and sensory loss. Pains are usually mild in character, but occasionally they may be sharp and burning. The paresthesias are usually a sensation of numbness or tingling. The paresthetic areas are sometimes exquisitely sensitive to touch or pressure.

Muscular weakness is greatest in the distal part of the extremities in the majority of the cases. Rarely, the proximal muscles of the extremities may be more severely affected than the distal muscles. In the moderately severe cases there is paralysis of the digits and weakness of the movements at the ankle and wrist joint with wrist and foot drop. In the severe cases the patient is completely bedridden, with paralysis of all four extremities and weakness of the trunk muscles. Involvement of the cranial nerves is rare, but paralysis of the facial, pharyngeal, and other cranial muscles is not uncommon in diphtheritic or so-called "infectious" polyneuritis. Weakness of the muscles of accommodation is frequent and characteristic of the diphtheritic form. Sphincter disturbances may occur in the severe cases. A mild sensory deficit, especially for vibration, is common in all forms of polyneuritis, but an extensive loss of cutaneous sensation is most frequent in arsenical or the alcohol-vitamin deficiency types of polyneuritis. The cutaneous sensory loss, when present, consists of a hypesthesia or anesthesia to all forms of sensation in an irregular glovelike or stocking-like fashion. Frequently there is a diminution of the threshold to painful stimuli, but a delayed and greater than normal reaction to such stimuli. Pressure along the course of the nerve produces pain and the muscles are tender to pressure. The deep reflexes are absent in a polyneuritis of moderate or severe degree. The plantar response is absent when the

toes are paralyzed, and the abdominal skin reflexes are diminished or absent when there is weakness of the abdominal muscles. Vasomotor and trophic disturbances may also be present. The skin may be smooth and shiny and the secretion of sweat may be disturbed.

The syndrome of confusion, disorientation, amnesia, and confabulation (Korsakoff's psychosis) is occasionally seen in any form of polyneuritis, but is most common in the alcohol-vitamin deficiency form and in the form which occurs with pregnancy.

Laboratory Data. The cerebrospinal fluid may be altered in any form of polyneuritis. The most common abnormalities are a slight increase in pressure when there is weakness of the muscles of respiration, and an increase in the protein content. Rarely, there is a slight pleocytosis. The increase in protein, when present, is usually of only a slight degree (45 to 75 mg. per 100 ml.), but occasionally the protein values may be over 100 mg., and values greater than 1000 mg. per 100 ml. may occur. High values are most common in the diabetic, diphtheritic, and so-called infectious types, but they may occur in any form of polyneuritis.

Other than the changes in the cerebrospinal fluid noted above, there are no clinical pathologic abnormalities in the majority of the cases of polyneuritis. Specific changes in the blood or urine are present in certain forms—for example, the excretion of porphyrins in hematoporphyrinuric neuritis, an elevated blood sugar in the diabetic polyneuritis, or an excessive amount of lead or arsenic in the blood and urine of patients with polyneuritis associated with poisoning by these metals.

Course. Complete or incomplete recovery is the rule in the usual form of polyneuritis. The mortality rate is high (20 to 50 per cent) in the "infectious" or hematoporphyrinuric forms, but death is infrequent in the other types unless complicated by bronchopneumonia, severe vitamin deficiency, or cerebral changes (i.e., Korsakoff's psychosis or polioencephalitis superior hemorrhagica). The course of patients with polyneuritis depends upon the extent to which the destruction of the nerves has progressed before treatment is instituted. With removal of the toxic agent or correction of the metabolic defects which are responsible for the neuritis, recovery may be fairly rapid if the continuity of the nerves

has not been interrupted. On the other hand, the signs and symptoms may continue to progress for some days or weeks and recovery will be delayed for many months when the myelin sheaths and axis cylinders have been destroyed. In the latter case muscular wasting is severe and recovery is incomplete, and there may be a residual weakness, muscular wasting, and impairment of reflexes.

Treatment. The treatment of patients with polyneuritis can be divided into two phases: (1) removal or treatment of the condition which is responsible for the development of the neuritis; and (2) symptomatic therapy.

The administration of BAL (British anti-lewisite) is recommended by some authors for all forms of polyneuritis. There is no indication, however, that it is of any value except in the forms of polyneuritis due to the metallic poisons which are amenable to this form of therapy. The symptomatic treatment of the patient with polyneuritis consists of general supportive measures and physiotherapy. The patient should be kept in bed and the extremities protected from the bedclothes by means of a cradle. The diet should be nutritious and palatable. Tube feeding may occasionally be necessary. It is customary to supplement the diet with vitamins. This is essential when there is evidence of vitamin deficiency, but there is little evidence to indicate that vitamins in excess of the amount contained in a well-

balanced diet have any appreciable effect on the clinical course. The bed should be kept clean and the sheets smooth to prevent injury to the anesthetic skin, although pressure sores rarely develop. The paralyzed extremities should be splinted to prevent stretching of paralyzed muscles. Bivalved plaster shields can be applied to the arms and legs. These can be removed for physiotherapy, which should be started as soon as the painful paresthesias subside. Physiotherapy should include daily or twice daily massage of all the weak muscles, and passive movements of all joints to their fullest extent. There is still some disagreement as to the value of electrical stimulation of the muscles, but the evidence indicates that this form of therapy does assist in maintaining the normal status of the muscles and speeds the recovery of function. When voluntary movements begin to return, muscle-training exercises should be given daily. Care should be taken not to overstrain weak muscles. It is, therefore, unwise to allow the patient to get out of bed or attempt to walk before the results of muscle testing indicate that he is prepared for these exertions.

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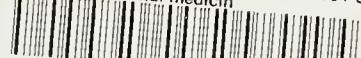
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