

Tubercles are formed just under the epithelium and become confluent and necrotic. Ulceration of the mucosa which results affects chiefly the vocal cords, false cords, aryepiglottic folds and epiglottis. The latter is sometimes completely eroded away, so that swallowing becomes very difficult. The ulceration of the vocal cords changes the voice to a husky, toneless whisper. If it extends so as to denude the cartilages of the larynx, they may become necrotic and prone to serious secondary infections. In the trachea the infection of the mucosa from the sputum leads to the formation of numerous shallow lenticular ulcerations (Fig. 346).

**Tuberculosis of the Lungs.**—The simplest form of tuberculosis of the lungs is found in children in whom at first no complex resistance and immunity have been developed to impede the course of the infection and modify the result. In recent years we have been able in almost every case to confirm the ideas of Küss, Ghon, Opie, and others as to the primary pulmonary complex which is seen in children. One finds a



Fig. 347.—Primary caseous lesion at base of child's lung with caseous lymph-nodes rupturing into a bronchus producing scattered patches of caseous pneumonia.

caseous mass rounded or pyramidal in form, with base toward the pleura, usually in the lower part of the upper or lower lobe, although it may be almost anywhere in the periphery. Careful search with the palpating finger while the lung is fresh aids one in finding this, and then a section toward the hilum usually shows that the lymph-node in the line of drainage is infected, greatly enlarged and caseous. One must suppose that the bacilli, inhaled deep into the lung, have lodged in the periphery but that many have been carried by the lymphatics, in the lack of the fixation described above, to the lymph-node. Then with the advent of the allergic hypersensitization such great numbers of bacilli have produced complete caseation both of the first area of their deposit and of the lymph-node.

This, then, is the primary pulmonary tuberculosis in the previously uninfected person whether infant or adult. It may be overcome and heal so that, much later, we find an encapsulated calcified nodule at the pleural surface and a corresponding stony lymph-node in the line of drainage. But more commonly, perhaps, there is a further extension of the infection.

The next stage is commonly produced by the invasion of the wall of the adjacent bronchus by the bacilli in the caseous lymph-node so that soon the bacillus-laden material of the softened node is poured into the bronchus and aspirated into the corresponding region of the lung. Indeed, there is nothing to prevent its passage, into other bronchi and even into the opposite lung. Allergic hypersensitization being well de-



Fig. 349.—Primary tuberculous focus in child's lung, secondary infection, and caseation of lymph-node. Scattered patches of caseous pneumonia.

veloped, the entrance of these abundant bacilli into the lung quickly results in the production of lobular areas of caseous pneumonia. Figure 347 shows this course of events half diagrammatically. These areas may be large and confluent and even in young children the complete necrosis and softening of the lung tissue may end in its discharge through the bronchus leaving a ragged cavity.

It is evident that a pulmonary vein might be so eroded that the bacillus-laden caseous material of the lymph-node is emptied into the circulating blood, or this might happen in miniature in many minute venules, so that bacilli distributed everywhere set up a miliary tuberculosis.

Generally upon the death of such infected infants or young children

one is greatly impressed by the extreme enlargement of the lymph-nodes about the hilum of the lung and bifurcation of the trachea and even in the neck, and by their complete caseation. This is in sharp contrast with the condition found in the chronic pulmonary tuberculosis of adults in whom the development of immunity from a former primary infection has accentuated greatly the power of fixation of the bacilli, so that even from extensive pulmonary lesions relatively few bacilli are drained into the lymph-nodes of the hilum—a few tubercles are found there and some scarring, but not the wholesale caseation that is characteristic of infants.



Fig. 350.

Fig. 350.—Caseous primary subpleural lesions in upper and lower lobes of child's lung with secondary caseous bronchial lymph-nodes.

Fig. 351.—Primary caseous lesion at base of child's lung with secondary caseation of bronchial nodes and many small foci of caseous pneumonia.



Fig. 351.

**Tuberculosis of the Lungs of Adults.**—In the lungs of grown persons lesions of the greatest variety and complexity are to be found, and it is often very difficult to trace their sequence since they are formed, no doubt, in progressive order, but under the influence of varying degrees of resistance and allergic reaction and from the transportation of varying numbers of bacilli by various routes.

The type of tuberculosis of the lung found in children is not very often seen in adults because so few persons escape infection so long. It is sometimes seen, however, and doubtless would be regularly found if persons who had lived to adult life in some isolated spot where there was no contact with tuberculosis, were brought to a city and exposed to in-

fection. We have just observed a case in a woman of thirty-six in whose right lower lobe there was a caseous encapsulated and partly calcified nodule about 1 cm. in diameter. Small tubercles could be traced along the lymphatics in the wall of a bronchus toward the glands of the hilum which were partly caseous, and there were minute areas of caseous pneumonia and tubercles scattered through the lungs. Konyevits describes a number of cases of this sort in apparently healthy young men who died in the influenza epidemic.

Generally, however, the primary pulmonary complex is no longer recognizable, either because the primary lesion and those in the lymph-glands of the hilum have been reduced to inconspicuous scars or because they are lost in subsequent extensive lesions.



Fig. 352.—Old apical scar.

It is, therefore, thought by Opie and others that the apical lesions so commonly found in adults, if only in the form of an old scar, are due to a new exogenous infection. The proof of this is difficult, but it seems probable. Such apical lesions which are generally flat, scale-like, depressed scars over the apex of the lung, often with pigment collected about them, are extremely common in persons of middle and advanced age (Fig. 352). They may extend into the lung substance a short way or even lie below the apex, radiating narrow lines of scar tissue into the surrounding lung and sometimes showing a caseous or calcified centre. Usually the bronchial nodes show at most a pigmented scar which may be related to this. These apical scars on microscopical study rather rarely show any distinct tubercles, but there are so many transitions to a more active process that their nature cannot be doubted.

Almost all cases of tuberculosis of the lung in adults, apart from the rare cases of the infantile type, show clearly that the process began near the apex. There are exceptional cases of quite different distribution, but so great a majority show the oldest lesion in the upper part of the upper lobe that it must depend upon some mechanical principle. The most familiar condition is that seen so very frequently at autopsy in which

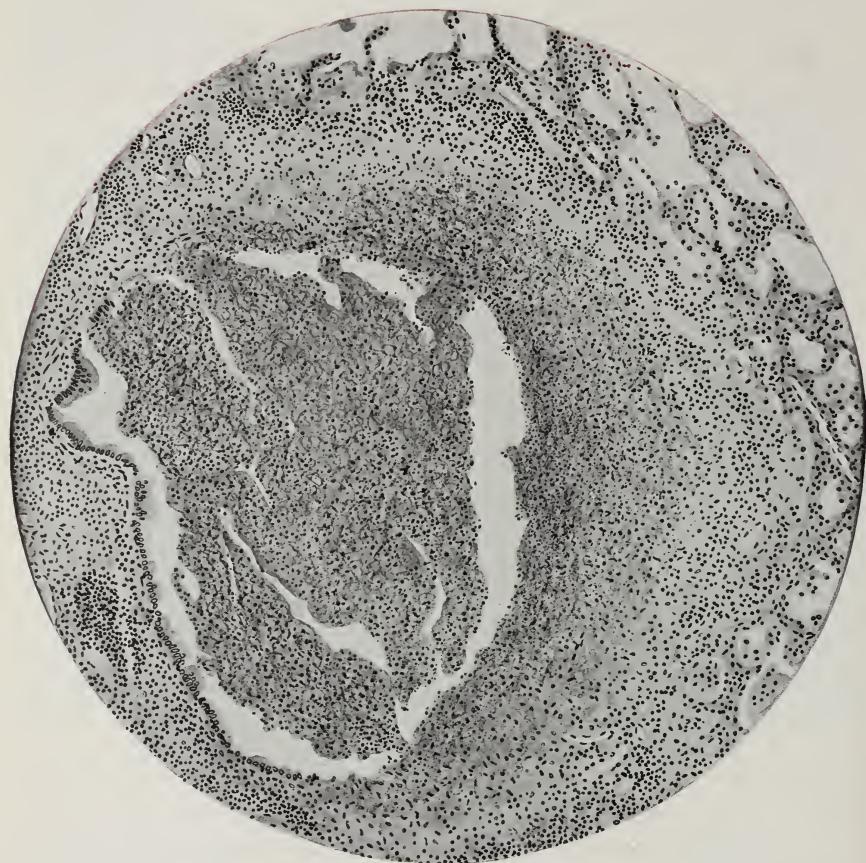


Fig. 353.—Caseous tuberculous bronchitis and peribronchitis. The mucosa on one side is still well preserved.

there is a cavity in the upper lobe widely open into one or more bronchi with wide-spread tuberculous lesions throughout the rest of the lung or also in the opposite lung (Figs. 354, 356, 358, 361, 362, etc.). These may be areas of caseous pneumonia or they may be masses of tubercles with more or less scarring, not only in the form of encapsulation, but throughout the injured lung tissue. The bacilli are obviously transported by the bronchi, but they may grow directly through the tissue or be carried by lymphatics or blood-vessels. It is plain that under these circumstances

with varying rate of distribution and changing immune reactions the end-result will be complicated.



Fig. 354.—Chronic pulmonary tuberculosis with cavity formation and aspiration of tubercle bacilli by way of the bronchus, which opens into a cavity. Conglomerate patches of caseous pneumonia in lower lobe. Pleurisy with many small tubercles.

—Why the process begins near the apex is still obscure. There are various theories about the mobility or immobility of the apex as it projects out of the thoracic cavity in adult life, which is unlike the con-

dition in children, and there are discussions of its blood-supply and of the directness of the course of the apical bronchi. Baemeister found that by immobilizing the apex of the thorax in animals he could produce localization of the tuberculous lesions there. Grober thought the bacilli advanced from infected cervical lymph-nodes to the dome of the pleura and crossed to the lung, but no one accepts this idea now. All the arguments are rather weak and seem inadequate to explain the extraordinary regularity of this localization.



Fig. 355.—Chronic pulmonary tuberculosis with several cavities. Scattered patches of caseous pneumonia.

The exact mode of formation of the apical scars remains uncertain. Birch-Hirschfeld thought that the progressive pulmonary tuberculosis must start in a tuberculous ulceration of the wall of a small bronchus going toward the apex, and, indeed, we have occasionally seen this. Its wall becomes caseous and the process extends to the adjacent lung tissue, so that a caseous area is formed usually 1 cm. or more below the actual apex. Since the bronchial wall is the first to be destroyed, the central part of this area, becoming liquefied, empties into it and a cavity is left with which the bronchus remains in open communication. Such a cavity extends by further caseation and destruction of the tissue round

about. The bacilli appear to grow into the tissue and the tuberculous lesions develop and undergo necrosis so that the cavity grows apace. According to the resistance there is a more or less vigorous effort toward checking this advance aided by the formation of a bulwark of granulation tissue, but this, in its turn, becomes necrotic. Sometimes it is effective and the cavity is held to the size it had reached and is cleaned out, and the wall of granulation tissue even relined with epithelium, but



Fig. 356.—Chronic pulmonary tuberculous cavities filled with glutinous fluid opening into bronchi. Scattered tuberculous foci. Lymph-nodes but little involved.

this, of course, is rather rare except in very small apical cavities which may later become obliterated.

A small cavity in the upper lobe, then, is the usual point of origin of the more extensive tuberculosis of the adult lung. It is interesting that the lymph-nodes at the hilum are not conspicuously affected in the cases which run a slow course, and even in those in which an extensive pneumonia is rapidly produced they seldom show the extreme enlargement and complete caseation that is so commonly seen in children. This is

evidently due to the local fixation of the bacilli resulting from the immunity by this time well developed.

A slight haemorrhage may occur in the very early stage and give warning of the nature of the disease, but extensive fatal haemorrhages come about only in those cases in which the excavation of the lung proceeds with great rapidity and an artery is eroded, often with the formation of a little aneurysmal sac in the weakened wall, which then bursts.



Fig. 357.—Rapidly advancing pulmonary tuberculosis with large cavity in the upper lobe and extensive caseous and gelatinous pneumonia throughout the lower lobe. There is caseous bronchitis with excavation. The tissue was loaded with bacilli.

The secondary lesions are of two main types. Bacilli may be poured into the rest of the lungs and with the influence of the allergic hypersensitiveness acute pneumonic processes result (Fig. 357). Or, if the discharge is not so abundant and resistance is high, there are formed tubercles with encapsulation and subsequent caseation, but with progressive wide scarring. The tissue of the lung is rendered useless, it is true, but it does not become necrotic so rapidly as in the other case and the lung is not riddled with excavations.

In the first case, which is that of a florid or rapidly progressive phthisis, the cavity formed as described remains without much evidence

of healing in the tissues about it, the liquefied necrotic material loaded with bacilli is poured into the bronchus and in paroxysms of coughing is aspirated back into the other bronchi going to the lower lobe of the

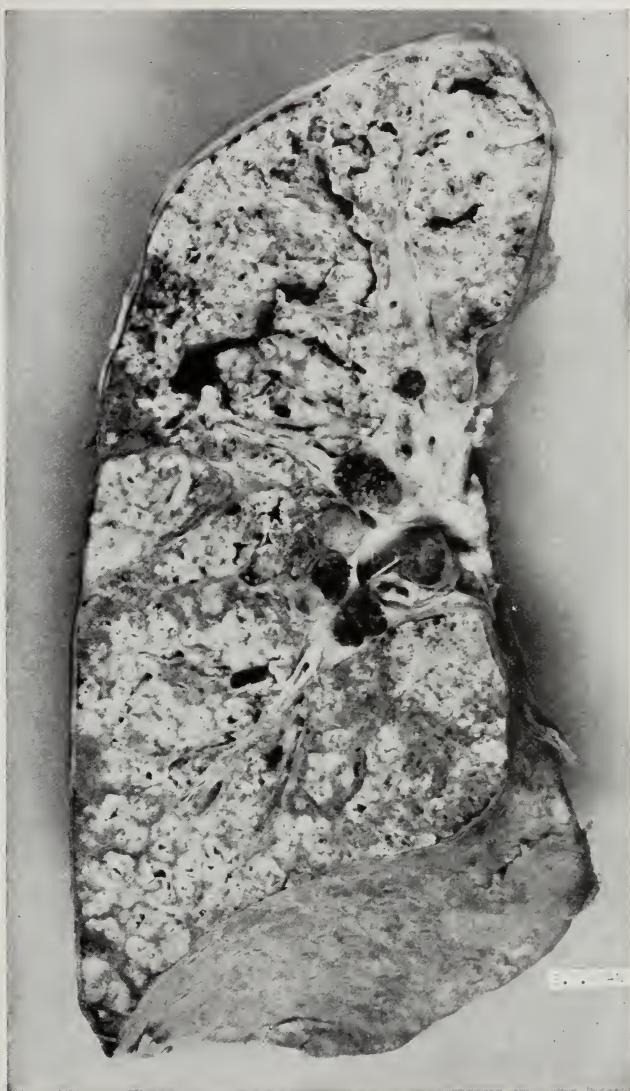


Fig. 358.—Pulmonary tuberculosis with cavities in upper lobe. Profuse confluent lobular areas of caseous pneumonia. Lymph-nodes at hilum little involved.

lung (Fig. 357). The walls of these become necrotic; indeed, even in the smallest bronchioles, the necrosis and hyaline change in the walls are very characteristic. Patches of pneumonia, sometimes very small, often larger and confluent, and very rarely lobar in extent, are produced

and tend to rapid caseation. In some cases, but not in all, the areas of pneumonia are surrounded by a dense oedema from which the glutinous viscid fluid can be drawn upon the knife in long strings. It is this which has given the name caseous and gelatinous pneumonia, applicable to some cases after fixation. The exudate in the fresh pneumonic patches is composed of mononuclear phagocytes of large size, exactly as seen in the soft tubercles, together with lymphoid cells and often with many red corpuscles and polymorphonuclear leucocytes, although in many if not most cases these are lacking, a fibrin network is present, and there are great numbers of tubercle bacilli. The alveolar walls are infiltrated too



Fig. 359.—Margin of area of caseous pneumonia which has lasted for some time. Beginning formation of tubercle nodules composed of epithelioid cells in margin.

with the same cells. The exudate becomes less compact as the margins of the area are reached and in the surrounding alveoli only a few large mononuclear cells are found in the fluid content of the alveoli (Fig. 341). It is characteristic that these cells become loaded with fat, so that yellow opaque flecks are seen in the gelatinous areas. Necrosis of the whole central portion occurs rapidly, leaving only a margin of alveoli with living cells and reducing the rest to a more or less homogeneous pink-staining area in which, however, the outlines of the alveoli can be seen for a long time, probably because of the resistance of the elastic tissue. Large areas quickly become liquefied and discharge through the bronchus, and when the caseous consolidation is very extensive the excavation of the lung may be very rapid. Such a wide-spread pneumonia

may simulate the lobar pneumonia of pneumococcal origin in all its manifestations clinically, but instead of a crisis with disappearance of the symptoms there come the expectoration of a greenish sputum with shreds of elastic tissue and, on auscultation, the signs of cavity formation. This was first described by Fränkel and Troje. Even in such a pneumonic process, however, it is usual to find evidences of resistance—tubercles with giant-cells appear along the margin of the caseating area and fibroblasts spring up and form a wall which attempts to stay the advance, but generally with limited success (Fig. 359).

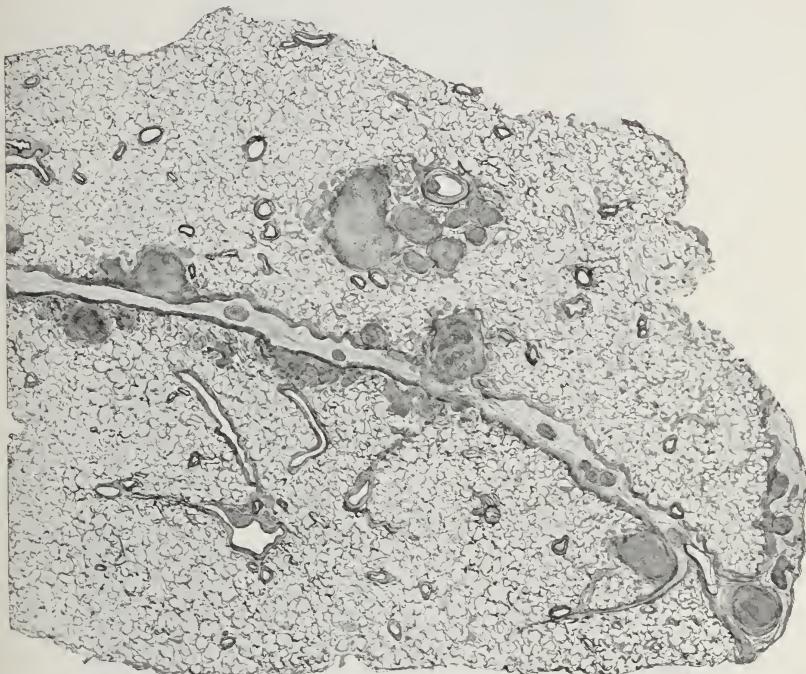


Fig. 360.—Distribution of tubercle bacilli by lymphatics, with development of tubercles in the interlobular septa.

In the other type of case, in which there is greater resistance from the beginning, the bacilli are not distributed in such massive doses or else they find the tissues much better able to withstand them, not responding with such a violent inflammatory reaction. At any rate, one finds groups and masses of tubercles with epithelioid and giant-cells, often coalescent and surrounded by a great deal of connective tissue. These areas undergo central caseation too, but more slowly, and the scarring seems to be maintained. Much of the lung tissue, especially the whole neighborhood of the original cavity, becomes extensively scarred, although tubercles and areas of caseation are still recognizable throughout it (Fig. 362). Occasionally it seems as though the bacilli spread directly through the tissues so that areas of gray scar tissue show where

they have passed and produced lesions which heal, while the advancing margin shows fresh and caseating tubercles (Fig. 361). Indeed, we en-



Fig. 361.—Pulmonary phthisis with cavity formation. There are extensive masses of pigmented scarred tuberculous tissue the advancing margin of which is made up of fresh tubercles.

countered one lung recently in which this process seemed to have spread uniformly from apex toward the base—the whole upper part of the lung was left as a spongy network of scar tissue which looked almost like nor-

mal lung, while the advancing margin showed as a row of yellow tubercles stretching all the way across.

Persons with such resistance live long enough to allow the formation of huge cavities, often occupying the whole of the upper lobe, the lower lobe being also excavated and scarred. Dense pleural adhesions bind



Fig. 362.—Chronic phthisis with several cavities in the much scarred upper lobe.  
Caseous lobular pneumonia throughout the lower lobes.

such a lung to the thoracic wall and the cavity is held open to become infected with all sorts of bacteria, yeasts, moulds, and even insect larvæ. The bronchi, of course, stop short at the wall, but blood-vessels often stretch across the cavity or stand up in high ridges on the wall, or appear from both sides as long, tapering stumps, finally corroded through. Such blood-vessels would hardly give rise to an extensive haemorrhage.

When cut across it is possible to squeeze a small drop of blood from the cut end, and section shows that they are reduced to almost solid cords, often by thrombosis, with subsequent organization and recanalization, sometimes by obliterative endarteritis.

Even with all this the lymph-nodes at the hilum are usually not greatly enlarged and are not caseous, although they generally contain tubercles. But such extensive open tuberculosis is, of course, usually accompanied by tuberculous infection elsewhere in the body. There may be intestinal ulcers with corresponding infection of mesenteric lymph-



Fig. 363.—Chronic pulmonary tuberculosis, cavities with extensive scarring and scattered tuberculous lesions.

nodes, and scattered tubercles through the rest of the organs. The opposite lung may show very limited infection, sometimes only scattered tubercles, although, of course, it is usually more extensive. Tuberculous laryngitis and tracheitis are very common results of the constant expectoration of infected sputum, and the dangers to other persons who come into frequent contact with such a patient are obvious.

The destruction of so much of the tissue of the lung brings about a great diminution of the respiratory surface, and would, of course, cause great dyspnoea if such patients were to make any considerable muscular effort. The bed of the blood-stream through the lung is largely ob-

literated and the remaining lung substance is overdistended, so that one might expect to find hypertrophy of the right side of the heart, but this is seldom the case except in those in whom the disease has lasted for years.

Although pleural adhesions are usual over areas of tuberculous involvement approaching the surface of the lung, and especially over cavities, it may happen that the extension of the cavity comes to perforate into a pleura which is not yet obliterated, so that its contents, including air, are drawn into the pleura, allowing the lung to collapse and setting up an empyema with pneumothorax or pyopneumothorax. This complication, serious in itself, still further obstructs both respiration and pulmonary circulation.

Fever, which may be very irregular, is common in phthisis and is probably in large part due to secondary bacterial invaders. The consumptive wastes away and becomes anemic, the metabolism of fat is disturbed so that it accumulates in the liver, and there are general evidences of poisoning to which the ancient term "cachexia" applies.

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**Tuberculosis of the Pleura and Pericardium.**—Tuberculosis of the pleura in adults is not infrequently the first lesion that gives rise to disabling symptoms. It begins with fever, with some accumulation of fluid in the pleural cavity, and with the production of a fibrinous exudate with tubercles on the pleural surfaces. With rest and open air treatment this generally subsides, doubtless with the formation of adhesions, but if it progresses a thick layer of granulation tissue in which caseous patches make their appearance is accompanied by a fibrinous and fluid exudate. Tuberculosis of the pericardium follows almost exactly this course and in the end the visceral and parietal pericardium may become enormously thickened and caseous, adhering where they are not kept separate by fluid.

The appearance of these changes is seen in Figs. 364, 365. In both cases it is clear that infection is produced by the rupture or extension of caseous lymph-nodes into the serous cavity with the liberation of caseous material with abundant bacilli, but in the case of the pleura the infection may come from the lung.

**Tuberculosis of Heart and Arteries.**—The occurrence of caseous tubercles presenting on the endocardial surface is not very uncommon and has been carefully described by Baker. (Arch. of Path., 1935, xix, 611.) In the myocardium itself miliary tubercles may be found but more extensive nodules with caseation are rare. So, too, it is very unusual to find vegetations on the valves caused by lodgment of the tubercle bacilli. Caseous or smaller and fresher tubercle nodules have been found on the intima of the aorta but these, too, are very rare.



Fig. 364.—Tuberculous pleurisy.

**Tuberculosis of the Digestive Organs.**—From what was said above, it is evident that while tubercle bacilli may be taken into the digestive tract with the food, it is still questionable whether their entrance into the body by that path is of great importance in the production of pulmonary and general tuberculosis. Isolated primary tuberculosis of the intestine can rarely be demonstrated in adults, although commoner in children. Indeed, as a consequence of the study of the results of a great many investigators, Beitzke concludes that in tuberculous children about

25 per cent. of the cases show primary intestinal infection. The result is infection of the mesenteric lymph-nodes, or even of the ductus thoracicus, or, on the other hand, the transportation of the bacilli by the portal blood to the liver, where tubercles may be formed. Miliary tuberculosis is apparently rarely or never the direct outcome of primary intestinal tuberculosis, but if a partial immunity be set up or if the bacteria be relatively non-virulent, pulmonary tuberculosis may follow. Thus while it is thought by some that pulmonary tuberculosis may follow an intestinal absorption or intestinal tuberculosis, the readiness with which it is

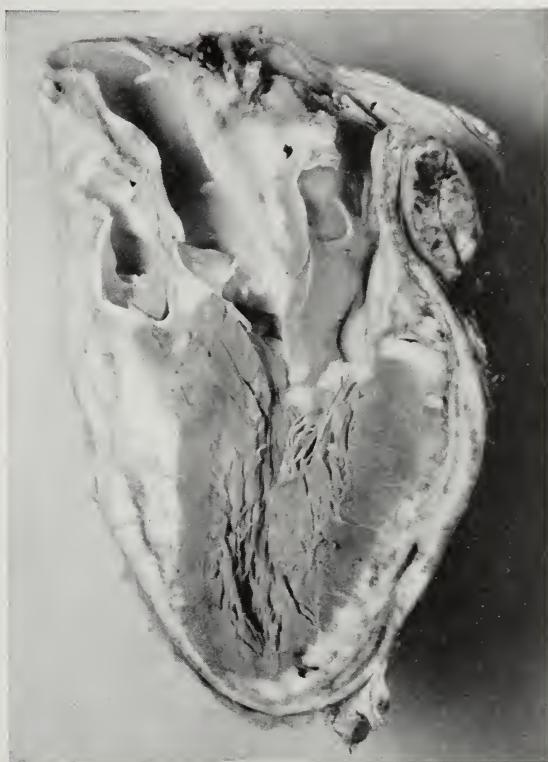


Fig. 365.—Tuberculous pericarditis.

produced by aspiration leaves this method of infection in a place of secondary importance, which in adults, at least, is probably very slight.

Tuberculous lesions of the mouth, pharynx, oesophagus, and stomach occur, but are quite rare. They arise by direct infection of the mucosa, or sometimes, as in the case of the oesophagus, from invasion by caseous glands or other tissues from without. In the stomach the lesions are miliary and conglomerate tubercles in the mucosa, or ragged and precipitous ulcers.

The liver regularly presents very minute miliary tubercles when there is a general distribution of the bacilli by the blood-stream. In

some cases these become conglomerate, and even quite large and centrally caseous. The most interesting form is that in which caseous nodules appear near the bile-ducts, and after the discharge of their con-

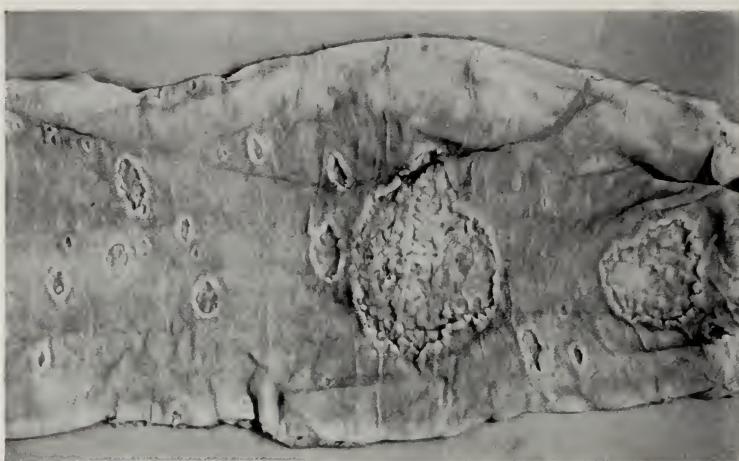


Fig. 365A.—Tuberculous ulcers of intestine.

tents into the ducts become deeply bile stained. Tuberculosis of the pancreas is not often observed, and usually consists in the presence of miliary tubercles.



Fig. 365B.—Tuberculous ulcer of intestine.

It is in the intestine, however, that the bacilli cause their greatest ravages, and the lesions there are of interest not only in themselves, but because they may lead to other extensions of the disease. Aside from the rare instance of isolated primary tuberculosis in adults and those

in children, in which the bacilli are probably swallowed in quantities in the milk, the intestinal lesions are usually caused by the swallowing of sputum from tuberculous cavities in the lungs. The mucus of the sputum protects the bacilli in their passage through the acid gastric juice, so that they reach the intestine alive.

*Intestinal Tuberculosis.*—The lesions in the intestine are predominantly ulcerative, and are found in their greatest intensity in the small intestine above the ileo-cæcal valve. Often enough, however, they both extend far up in the small intestine, and are found in numbers in the colon. They have, therefore, broadly, the same general distribution as the ulcers in typhoid fever, but they are not nearly so sharply limited to the Peyer's patches and solitary nodules. Even though the bacilli may lodge there, they soon produce an ulceration which extends wide of those structures and involves indifferently the surrounding mucosa. Indeed, the ulcers have a rather strong tendency to encircle the whole gut, whence they are



Fig. 365C.—Tuberculous ulcers of intestine seen from outside and showing distended lymphatics running toward the mesenteric lymph-nodes.

often called girdle ulcers. Their beginning can be seen as swollen, conglomerate nodules with central caseation, but the softening and discharge of this yellow, opaque central substance into the intestine leaves an ulcer which, when it has reached a larger size, is characteristic enough and very unlike the typhoid ulcer in its details. The margin is ragged, nodular and irregular, thickened, and undermined. The base is generally covered with yellow necrotic material, but this is sometimes cleaned off so as to reveal the tuberculous granulation tissue which really lines the ulcer, and which is generally studded with palpable nodules. The submucosa or musculature may be exposed, or the ulcer may perforate the whole wall.

Such ulcers can generally be located from the outside by the congestion of the vessels in that spot, and especially by the crop of minute gray tubercles which spring up in the subserous tissue and cluster along the lymphatic channels. Evidently from the mucosa the bacilli are carried into these lymph-channels, and the tubercles are actually formed inside them in such a way as to block the lumen. It is for that reason that these lymphatics become so conspicuous as they run over the surface of the intestine to the mesentery. Sometimes they are greatly distended with clear fluid, or even with opaque white chyle, and are beaded or like a string of

sausages, because they are obstructed at intervals. In such a case they can often be traced through the mesentery to the lymph-node, into which they empty and which usually shows tuberculous lesions too. (Fig. 365C.)

Microscopically (Fig. 367), the tuberculous granulation tissue is found not only lining the base of the ulcer, but formed in the submucosa wide of the actually undermined part, and through the crevices of the muscle layer even into the subserous tissue. It often shows patches of caseation and abortive tubercles, but the tubercles are usually rather indefinite in their structure.

There is one form of intestinal tuberculosis which is rather sharply localized about the ileocecal valve and there produces a great mass of hard, tuberculous scar tissue, which may constrict the intestinal lumen until only a large probe will pass. In one such case seen recently that whole stretch of the intestine was removed by



Fig. 366.—Tuberculous erosions of the lower ileum. Both sides of the intestine are shown at the same level.

the surgeon and the young man has been quite well ever since. More common is the localized ulcerative tuberculosis of the rectum, which, extending in the form of a sinus to the skin at the anus, gives rise to the so-called anal fistula. In nearly all these cases the granular lining of the sinus is found to be tuberculous.

**Tuberculous Peritonitis.**—Apparently the principles involved in the production of tuberculosis of the pleura and pericardium hold also for the peritoneum and we must ascribe it to the direct entrance of considerable quantities of organisms into the cavity aided by the allergic sensitization which would naturally exist if such a caseous focus as could supply the bacilli were already in existence. It is quite improbable that these bacilli could come from tuberculous ulcers in the intestinal wall. But actual tuberculous peritonitis results from the rupture of

a caseous lymph-node or the extension of a caseous lesion from some enclosed or adjacent tissue. It seems that caseous disease of the Fallo-



Fig. 367.—A tuberculous ulcer of the ileum, with undermined edges. The ulcer has penetrated the muscularis, and there are tubercles in the submucosa and in the thickened subserous tissue.

pian tubes may rather be secondary to the presence of bacilli in the peritoneum, although the reverse extension is also possible.

The bacilli are distributed by the prevalent streams in the abdominal cavity, and reach the vault of the diaphragm and the floor of the pelvis in great numbers. Sometimes their effects in the form of tubercles are seen in hernial sacs. In the earliest stages minute gray, translucent tubercles may be scattered everywhere over the surface of the peritonum and of the omentum, without disturbing the normal gloss.

In other cases the tubercles are quickly covered by an exudate of fibrin, sometimes nearly dry, sometimes with the effusion of a very great amount of clear or slightly turbid fluid, sufficient to float up the intestinal coils and prevent them from being glued together. A soft, friable, vascular granulation tissue springs up and replaces the fibrin, so as to form organized adhesions in the cases where there is no fluid, and in these adhesions the tubercles become larger and centrally caseous. The omentum is retracted and folded so as to form a solid, prismatic mass, which can readily be felt stretching across the abdomen. In its substance tubercles and caseous areas are embedded with the fat lobules in a tuberculous granulation tissue. With the lapse of time the adhesions become dense and tough, so as to bind the



Fig. 368.—Tuberculous peritonitis.

abdominal contents inextricably together into a matted mass (Fig. 368). Over the liver and spleen, and especially between the liver and the diaphragm, quite large caseous areas may form in these adhesions, and the tearing apart of the intestines may open cavities and canals filled with soft caseous material. Within the intestinal mucosa may be quite intact.

In those cases, however, in which the peritoneal infection is due to the exposure of caseous tubercles outside intestinal ulcers, the affected areas are usually bound together, so that finally perforation of the ulcer produces only localized faecal abscesses in the adhesions, or fistulous communications between adjacent coils. Where the resistance is high, the intestines may be found matted together by adhesions which are loose and fibrous and which show only here and there scattered encapsulated tubercles.

In other cases large encapsulated and sometimes pedunculated tubercles may occur in association with old adhesions, or even without much other change in the peritoneum. All these things indicate the possibility of healing, and, indeed, the idea has been widely entertained that those thick fibrous plates which are often found partly covering the liver and spleen (the so-called iced liver) may perhaps be due

to a healed tuberculosis, even though they show no distinct anatomical evidences of their origin. In the acute forms, where there is much fluid exudate, definite advances toward healing may sometimes be attained by opening the peritoneum and removing the exudate. This has been explained by Wright on the ground that the accumulated fluid has exhausted its bactericidal power, and that the advent of fresh fluid and cellular exudate brings with it new powers of destroying the organisms.

The distribution of the tubercle bacilli is particularly well followed in the study of the lesions of the lymph-nodes, for these organs act as sieves in the course of the lymph-channels along which the bacilli are so commonly carried. For this reason changes produced and registered in these nodes are of assistance as a clue to the portal of entry of the organisms.

**Tuberculosis of Lymph-nodes.**—The lesions are quite the same in character as elsewhere. The bacilli lodge in the sinuses of the node or are carried into the lymph-cords, and produce tubercles often with associated tuberculous granulation tissue and an inwarding of many large mononuclear phagocytic cells (Fig. 369). The tubercles are sometimes discrete and remain so, but more often they become conglomeration and suffer extensive caseation, so that almost the whole node may be reduced to a soft, cheesy mass. Healing occurs through hyaline changes and scarring, generally with the deposit of calcium in coarse grains, or in such a way as to convert the whole node into something like an irregular pebble tightly bound up in a fibrous capsule.

All these lesions are most common in the bronchial nodes, but are very frequent in the mesenteric nodes also, where, especially in children, very great enlargement may take place and is sometimes known as *tubes mesenterica*.

From tuberculous foci in the tonsils and upper air-passages the cervical chain of nodes may be infected and caseous. In such a case they become matted together by fibrous growth and present a great swelling along the side of the neck (Fig. 370). The caseous material may sometimes burrow out to the skin, so that a discharging sinus is established. More rarely a similar condition is met with in the axilla or groin, sometimes as the result of peripheral tuberculous infections. The thoracic duct, receiving bacilli from tuberculous abdominal nodes, may develop caseating tubercles along its lining and thus contribute to the formation of an acute miliary tuberculosis.

In the spleen there occur miliary and conglomerate tubercles, often rather loose and cellular in their structure, and without the coherent tissue formation seen elsewhere. In this organ, too, there arise very large caseous solitary tubercles with dense fibrous capsule (see Fig. 337).

**Tuberculosis of the Genito-urinary Tract.**—The development of the tuberculous lesions and their anatomical form, as well as their ultimate fate, are quite the same in these organs as elsewhere, but the mode of entrance of the bacilli and their further distribution have long been debatable.

As has been stated, direct introduction of bacilli by coitus is rarely shown to be productive of genital tuberculosis. Infection of the genito-urinary tract is practically limited to the deposition there of bacilli brought into the blood-stream, but even then there are favorable and unfavorable localizations. In general miliary tuberculosis tubercles can develop nearly everywhere. When fewer bacilli are in circulation, however, and the development of a tuberculous focus depends in some degree

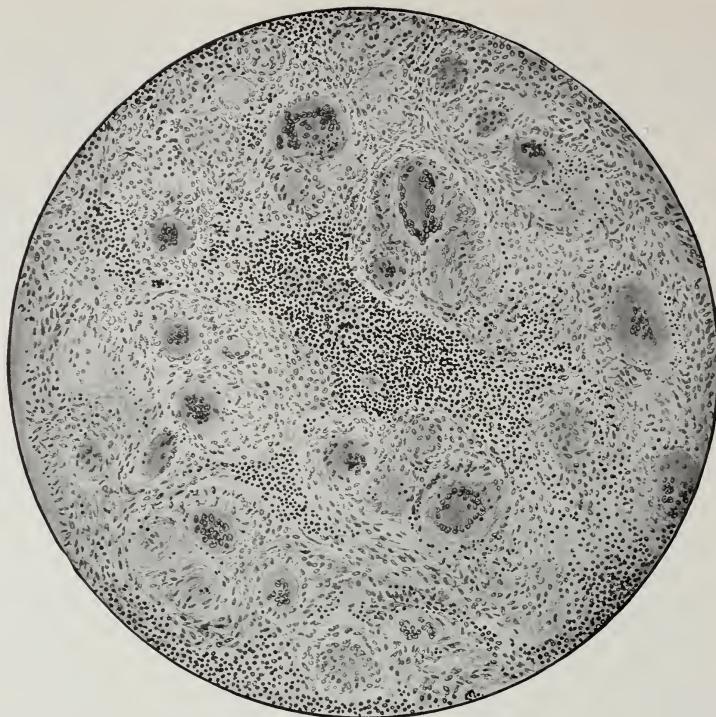


Fig. 369.—Scattered tubercles in a lymph-node.



Fig. 370.—Packet of caseous cervical lymph-nodes.

upon favorable conditions in an organ, we find that the kidney, the epididymis, and sometimes the Fallopian tubes are the most susceptible to the infection. It is in them that the oldest lesions are found, and it is from these foci of disease that bacilli spread to infect the rest of the genito-urinary tract. Walker and Sawamura find that the initial lesion which is of course itself secondary in character is practically never in the bladder or ureters, in the prostate, seminal vesicles, vasa deferentia, or testis, but that all these structures are rapidly enough infected later, when great quantities of bacilli are poured into them from a caseous kidney or epididymis. So, also, in the female the ovary and uterus are rarely affected primarily, while the tissue of the Fallopian tube seems specially susceptible and later distributes bacilli in quantity elsewhere.

With these results in mind there are relatively few difficulties in explaining the distribution of the disease. With regard to the genital glands in the male, it is not impossible that tuberculosis of prostate and seminal vesicles should arise by infection from the bladder, and that the disease should extend along the vas deferens to the epididymis, but the reverse direction is more common. More dispute has arisen as to the possibility of an ascending tuberculous infection of the kidney from tuberculous disease of the bladder, in a way analogous to that admittedly followed in the ascending suppurative pyelonephritis following cystitis. *A priori* this would seem the most plausible explanation when one finds, at autopsy, an old caseous focus in the epididymis, tuberculosis of the prostate and bladder and of the ureter, pelvis, and kidney on one or both sides. This is especially striking when, as is so frequently the case, the tuberculosis of the kidney is limited to the development of small patches of caseous tuberculous granulation tissue at the tips of the papillæ and along the walls of the calyces, without any sign of involvement of the cortex. This, in connection with the continuous affection of the ureteral mucosa from the ulcerated bladder, makes it hard to resist the idea that the bacilli have been floated up from the bladder in the lumen of the ureter. Still the mucosa of the ureter is not, as a rule, continuously tuberculous in these cases, and may show little change; on the other hand, when the renal tuberculosis is somewhat more advanced the whole wall of the ureter is usually thickened and rigid, suggesting the involvement of the lymphatics as well, and there are many who would explain the advance of the infection from the bladder to the kidney by this route. In spite of much investigation of this possibility, which has generally led to negative results it is not finally settled and should be studied further.

Experiments, especially those of Walker, show that while fluids may pass out of the bladder into the ureter when, through ulceration, the valve-like ureteral orifice is destroyed, or, when through obstruction, the bladder contracts against a quantity of urine which cannot readily escape, deliberate infection of the bladder rarely results in the production of an ascending infection. Although Walker had a few positive cases, he leans to the view that infection is haemogenous and primarily brought by the blood to the kidney and only secondarily to the pelvis and ureter.

The conditions found at autopsy leave me still with the belief, however, that tuberculosis of the kidney is often an ascending affection, and that the conditions of the experiments and the different anatomical arrangements of the animals explain the experimental results.

**Tuberculosis of the Kidney.**—In generalized miliary tuberculosis minute tubercles are found in the cortex of the kidney, beginning, as Benda states, in the glomerular capillaries, where masses of bacilli are lodged as emboli. Doubtless they may be formed also about the other capillaries, and in their growth and conglomeration they soon extend in a direction parallel with that of the conducting tubules, to form gray streaks, often with an opaque yellow centre, reaching from the cortex into the pyramid.

Probably tubercles are also formed by bacilli which lodge in the tubules in the course of excretion (Aschoff), and these may take part in the production of the more extensive caseous areas which arise in the margin between cortex and pyramid (Israel). Such caseous areas grow until they destroy much of the kidney substance and discharge their contents into the pelvis. In other cases the caseating area begins in the papillary part of the pyramid, usually up in an angle of the calyx, and from there the process of erosion extends deeply into the kidney. These are the cases



Fig. 371.—Renal tuberculosis. In one kidney the tuberculous process has practically destroyed the kidney. In the other, calyces are excavated and there are caseous tubercles in the cortex.

which specially suggest an origin from an ascending infection. In any event the late result is the great destruction of the kidney substance. What remains of the pelvis is ulcerated; the papillæ have disappeared, and the calyces are represented by irregular cavities lined by caseous granulation tissue and excavated deep into the kidney (Fig. 371). The organ may be enormously enlarged and finally appear as a lobulated sacculated mass, in the walls of which hardly any kidney substance remains. If the capsule is perforated, a perirenal tuberculous infection occurs, and the extension of the caseating process, preceded, as always, by the formation of tuberculous granulation tissue, can go on until a fistulous tract is opened into the peritoneum or out through the skin. Healing must be very rare, but one finds occasionally shrunken kidneys with encapsulated, mortar-like, or stony masses of probable tuberculous origin. In persons whose resistance is great the caseation is often limited by the enormous production of scar tissue, so that the kidney, while greatly enlarged, contains relatively small pyramidal cavities surrounded by thick walls of fibrous tissue.

It is perhaps unnecessary to describe in any detail the tuberculous lesions in the rest of the genito-urinary tract, since in each case they

are due to the development of tubercles in or under the mucosa, soon becoming associated with abundant granulation tissue which undergoes caseation, but causes great thickening of the walls of these organs.

The *ureter* becomes a wide but rigid tube, with ragged ulcerated lining, and is easily felt through the abdominal wall. In the bladder miliary and conglomerate tubercles occur in the mucosa, especially of the trigonum, followed later by shallow, ragged ulcerations with nodular base. The *seminal vesicles* show tubercles in the mucosa, or the wall is thickened and the lumen choked with the product of its caseation. Distinct tubercles are not usually seen in the *prostate*, but the gland becomes enlarged and riddled with caseous patches. The *vasa deferentia* are enlarged and filled with caseous material, so as to be impervious, and in quite the

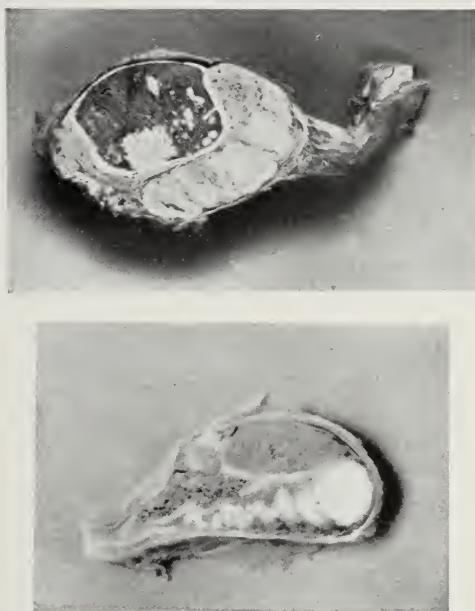


Fig. 372.—Tuberculosis of epididymis.

same way the tuberculous *epididymis* (Fig. 372) forms a great caseous mass which may discharge by fistulae through the skin of the scrotum. Invasion into the *testicle* may take the same form, or there are scattered tubercles.

In the *ovary* tubercles may be found in preformed cysts or in the tissue itself, the caseation and softening of which produce a cavity. The *Fallopian tubes* behave much like the seminal vesicles—their walls are sometimes thickened and studded with small tubercles, which, when on the outside, appear really as a form of localized tuberculous peritonitis. The tube may later become distended and obstructed with caseous substance. In the *uterus* caseation of the endometrium of the fundus is not very rare.

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**Tuberculosis of the Nervous System.**—The central nervous system does not escape tuberculous infection, which is usually carried to it by the blood-stream, although occasionally it may be due to direct extension from a caseous focus in neighboring bony structures, especially perhaps in the vertebrae.

It is rather striking that in generalized acute miliary tuberculosis we are not accustomed to see miliary tubercles in the substance of the brain or cord. But when bacilli scattered by the blood-stream produce lesions in other organs it is common enough to find a few caseous nodules in any part of the brain substance. These range in size from 1 or 2 mm. to great tumor-like masses several centimetres in diameter. The very fact that they can attain such a size that they behave like a tumor compressing and destroying nerve-tracts shows the slowness and localization of their development. In a case which we observed recently the red nucleus and the oculomotor nerve were involved, producing the curious Benedict syndrome with paralysis of the eye muscles and tremor of the opposite arm. Such "solitary" tubercles are found as caseous masses with a capsule of tuberculous tissue with abundant large mononuclear phagocytes. They may lie embedded in the cerebrum or cerebellum or may approach the ventricle or the meninges. The more common and obvious tuberculous affection of the central nervous system is *tuberculous meningitis*, sometimes known as basal meningitis, from the fact that the meningeal exudate is usually found to be very thick and abundant over the base of the brain where it surrounds the medulla and pons, the region of the hypophysis and optic chiasm, and extends laterally and upward over the cerebellum and into the Sylvian fissures, gradually fading away as it passes up over the convexity of the cerebral hemispheres. The ependymal lining of the ventricles is generally involved with the formation of many minute glistening nodules and the accumulation of much fluid. The choroid plexuses sometimes show caseous tubercles, but regularly take part in the ependymal involvement. Hydrocephalus of this type has long been recognized as a characteristic feature of tuberculous meningitis, and is thought to be due to the occlusion of the foramina of egress of the cerebrospinal fluid by the thick exudate.

Although we have always looked upon tuberculous meningitis as the simple result of the carrying of tubercle bacilli to the meninges by the blood-stream, Rich has pointed out that this does not accord with the facts. In an animal the intravenous injection of tubercle bacilli or even their injection into the carotid arteries never directly produces tuberculous meningitis. The distribution of the lesion, very intense in the large cisterna of the arachnoid over the base of the brain and decreasing upward over the convexity of the hemispheres, suggests that large quantities of bacilli are poured into the cerebrospinal fluid and are transported by that fluid along its normal course, producing lesions in lessening intensity as the bacilli are caught up in the meshes of the arachnoid. Further, the lesions themselves are evidently in the meshes of the arachnoid affecting the blood-vessels of the pia from the outside. Therefore, he has looked for an abundant source of tubercle bacilli in

the course of the cerebrospinal fluid, and found it at once in the caseous tubercles which empty their bacillus-laden contents into the cerebral ventricles from their position in the choroid plexus or in the substance of the brain, or else from more superficially placed caseous tubercles which empty bacilli directly into the meshes of the overlying pia arachnoid. In any case the massive infection of the cerebrospinal fluid whether in the lateral or third ventricles, aqueduct or fourth ventricle or in the cisterna at the base, will bring about a characteristic distribution of great numbers of bacilli and the typical basal meningitis. Even

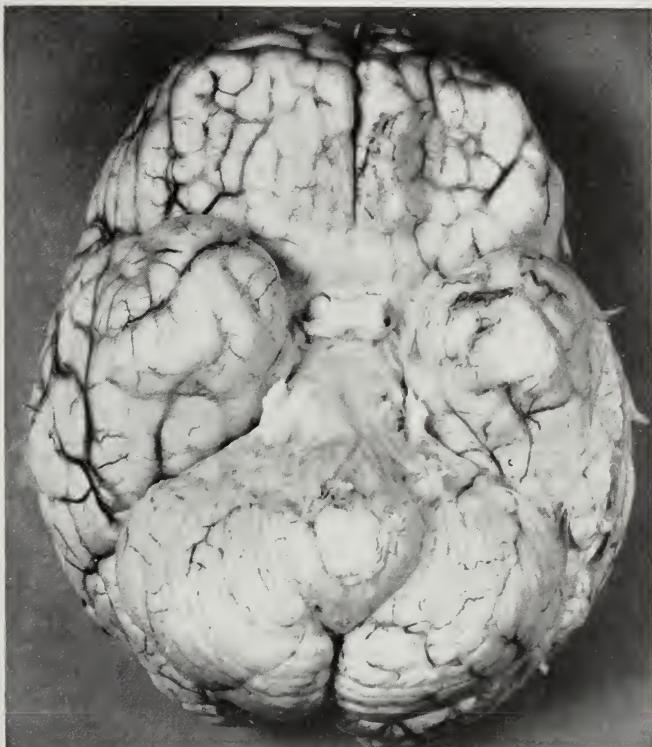


Fig. 373.—Tuberculous meningitis. Cranial nerves and whole base of brain covered and masked by infiltrated meninges. Swelling is shown by the forcing of part of the cerebellum into the foramen magnum.

the irruption into the meninges of the convexity may do this through some reflux in the usual current, although one generally sees then a local and typical distribution of the meningitis.

It seems to me that no one can fail to recognize the cogency of this reasoning, especially when it is stated that in every case of tuberculous meningitis studied by sectioning the brain carefully a caseous tubercle has been demonstrated extending into the ventricles or the meninges.

The meningitis thus produced is very characteristic in appearance and is more gelatinous and translucent than the purulent forms from

other infections. Over the floor of the third ventricle and about the optic chiasm, where it is thickest, it seems to form a translucent grayish tissue in which the blood-vessels are embedded (Fig. 373). On passing upward

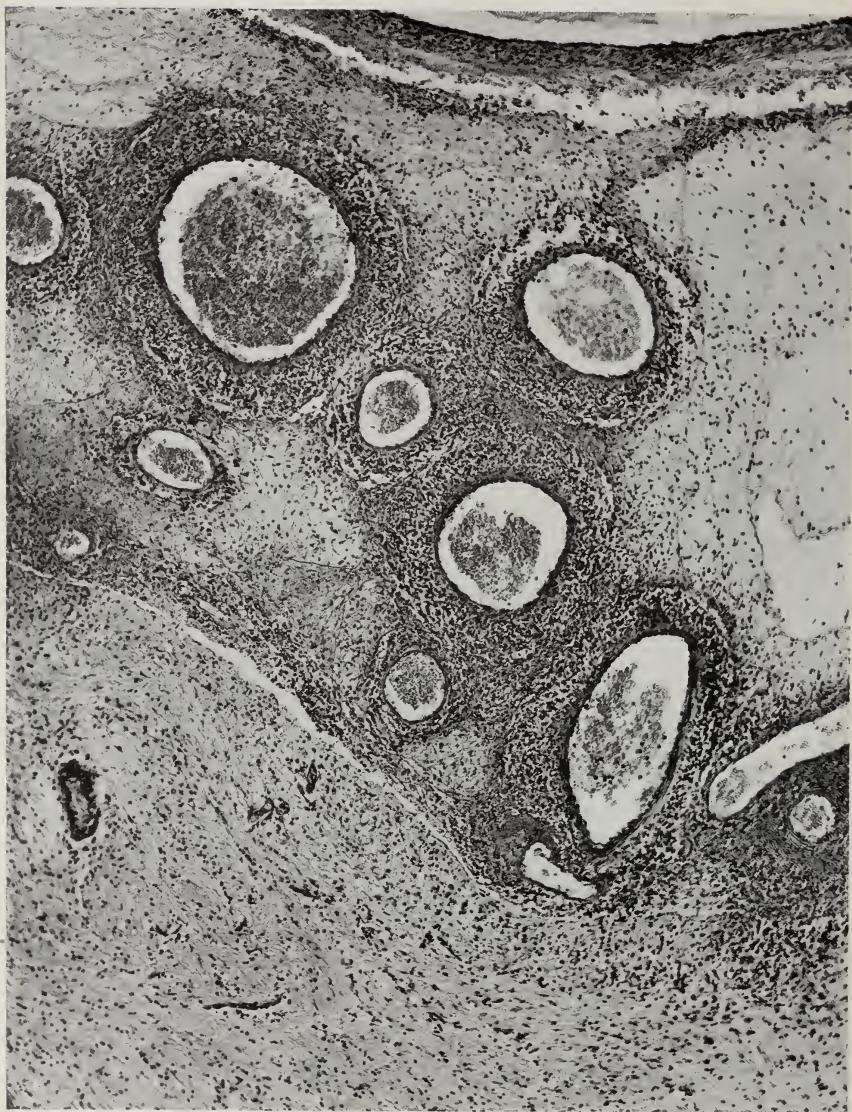


Fig. 374.—Tuberculous meningitis showing abundant exudate. Partly caseous and characteristic changes in the adventitia of the vessels.

into the sulci over the cerebrum this is less abundant and small opaque nodules stand out along the course of the vessels and can be recognized as little intermittent caseations of the adventitial walls, or as minute areas of caseation apparently unconnected with blood-vessels. In sec-

tions (Fig. 374) it is found that while there is an abundant diffuse exudate of fluid with a network of fibrin and great numbers of cells, largely mononuclear in character but with some polymorphonuclear leucocytes, the most striking changes develop in the vessel walls. They are eccentric thickenings affecting especially the adventitial coat, but causing also an obliterative thickening of the intima. The media is passively invaded and destroyed and the collection of epithelioid cells shows extensive caseation which generally reaches into the surrounding exudate. There must be a very considerable obstruction to the flow of blood in these narrowed vessels.

While the exudate in such cases has the character of being very quickly produced as an intense inflammatory process tending to casea-



Fig. 375.—Several caseous tubercles approaching ependyma in the fourth ventricle and the meninges in the cerebellum.

tion, evidently due to the presence of swarms of bacilli and active allergic sensitization, there are occasional cases in which the effects of resistance or small numbers of bacilli show themselves. In these one finds hard nodular tubercles along the adventitial walls of the vessels, with concentric epithelioid cells and giant-cells, and with these there is relatively little fluid or loose cellular exudate. Once more we have the contrast between the effect of great doses of bacilli in an individual with intense allergic reaction and that of a smaller dose in a person whose resistance is high in comparison with the allergic reaction. Whether this explanation will be final remains to be seen, but it represents an attitude which seems right at present.

The optic nerves are involved in this process and so too are the other cranial nerves with various disturbances of their functions.

The tuberculosis of the eye takes different forms and is not necessarily associated with tuberculous meningitis. Miliary tubercles may be seen in the choroid along the course of the arteries and massive caseous tuberculous lesions may fill the cavity of the eye, displacing the vitreous humor. Other tuberculous lesions affecting the conjunctiva, the iris, etc., are well known and for details concerning these works on ophthalmology must be consulted.

**Tuberculosis of the Ductless Glands.**—Among the organs of internal secretion the only instance in which we know that tuberculous disease is

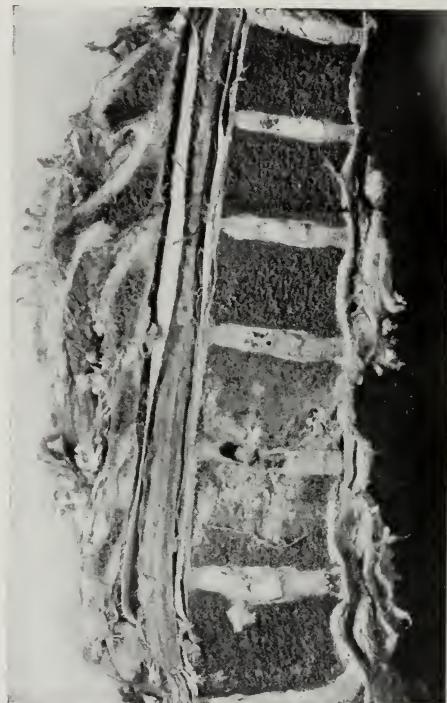


Fig. 376.—Caseous tuberculosis of vertebrae.

of practical importance is that of the adrenal glands. Miliary and conglomerate tubercles occur there, but more commonly extensive caseous areas develop which can involve the whole gland on both sides and destroy it completely. In such cases Addison's disease, of which we shall speak in another place, generally follows.

**Tuberculosis of the Skin.**—In the skin there are certain definitely tuberculous conditions, among which *lupus vulgaris* is the most common, in which the bacilli may be found producing tubercles and tuberculous granulation tissue. Recently in a case of generalized miliary tuberculosis I have seen numerous papules and vesicles scattered all over the

body and containing tubercle bacilli. There are other lesions of the skin, however, such as *lichen scrophulosorum*, which are known as tuberculides, and which, though always associated with tuberculosis, have yet been studied without avail in the search for bacilli or tuberculous tissue. They have been thought to be due to diffused toxins, or even to be the expression of an anaphylactic reaction.

**Tuberculosis of Bones and Joints.**—This subject is so far reaching in its details that no attempt can be made here to give more than the barest outline. For the rest, surgical works must be consulted.

The bacilli are brought to the bones and joints by the blood-stream or by extension from a neighboring lesion. It is especially in the bones that traumatism aids in the development of the infection by forming a point of lowered resistance where the bacteria can gain a foothold. Ac-

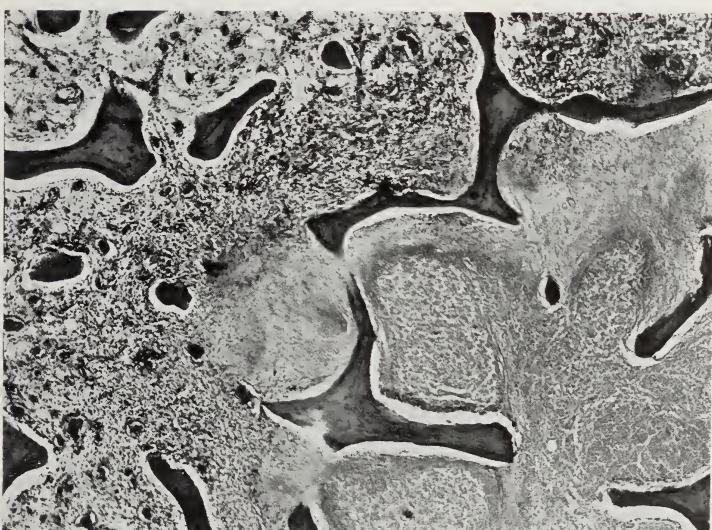


Fig. 377.—Caseous tuberculosis of vertebrae.

cordingly, it is not uncommon to find lesions formed in the bones in the apparent absence of tuberculosis elsewhere.

Tuberculous lesions usually begin, as Guillemain has maintained in opposition to König, in the bone rather than in the synovial cavities of the joints, and it is the cancellous bone which is usually first involved—practically never the shafts of long bones. Miliary tubercles may, of course, occur, but far more important is the tuberculous osteomyelitis, which is not part of a general miliary tuberculosis (Fig. 376). This begins frequently in a vertebra, doubtless from transfer of the bacilli by the blood-stream, and produces extensive caseation with destruction of the cancellous bone. This infection may extend so that the caseous material burrows under the sheath of the psoas muscle on one or both sides, extending downward under Poupart's ligament, the so-called psoas abscess.

When caseation has advanced far enough, the affected vertebral centrum is crushed together by the weight of the body and an angular deformity of the spine ensues (Fig. 379). It is seen in this instance that a great deal of scar tissue is formed about a small central space showing that the actual collapse has been long survived and, indeed, healing in such cases must be almost the rule if we may judge from the great number of hunchbacks one sees on the streets.



Fig. 378.—An old healed tuberculous lesion of the hip which has left the acetabulum greatly distorted and with numerous exostoses.

Tuberculosis beginning in the cancellous tissue near the ends of long bones may extend to the joint surface, whereupon the joint becomes infected also; the cartilage becomes necrotic, uplifted, and softened. At first, miliary tubercles may appear on the synovial membranes, with effusion and fluid. Later the joint is lined by a tuberculous granulation tissue, and the condition may last for a long time, with persistence of

the fluid, induration of the tissues around the joint, formation of polypoid clusters of fat tissue and of small hyaline bodies, like rice grains, in its cavity. Irregular erosions of the surfaces occur, and indeed there follow the most extensive excavations into the bone, with collapse and wide destruction of the mechanism of the joint. Fistulæ are burrowed out through the surrounding muscles and fasciæ to the skin, through which caseous débris and spicules of bone are discharged. Such destructive processes are very common in the hip-joint and especially in children. The whole head of the femur may be destroyed and the bone dislocated. To relieve the tenderness and pain the leg is drawn up and



Fig. 379.—Tuberculosis of vertebræ, destruction of centre, with scar and cavity formation. The spinal cord has accommodated itself to the kyphosis.

rotated inward, and through disuse atrophies. When the joint disease heals, there remains the condition so often seen in people in the street who walk with the affected leg held stiffly bent and with the aid of a crutch.

Tuberculosis of the bones of the face and of the ribs is generally in the beginning a periosteal affection which erodes the bone and produces accumulations of caseous material—the so-called “cold abscesses.” In the fingers there may be central caseation in the diaphysis of the phalanges, with secondary new growth of bone outside. The enlargement of the internal cavity and the repetition of the reparatory process result finally in a spindle-shaped enlargement of the bony shell (*spina ventosa*).

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## CHAPTER XXXV

### TYPES OF INJURY.—DISEASES DUE TO FUNGUS INFECTION

*General scope.* Yeast-like fungi. *Torula.* Meningeal infection. Thrush. *Blastomycosis or coccidioidal granuloma.* *Sporotrichosis.* *Actinomycosis.* General character; mode of infection. Ringworm. Favus.

THE great confusion which exists in the literature on fungus disease is largely due to the enormous field—Saccardo has recorded some 57,000 species—but more especially to the fact that many synonyms have been invented for each form and, still worse, that the same name has been given to quite different organisms. It is quite impossible for anyone who has not spent years in the special study of these parasites, to speak with any assurance and the student is referred to the works of

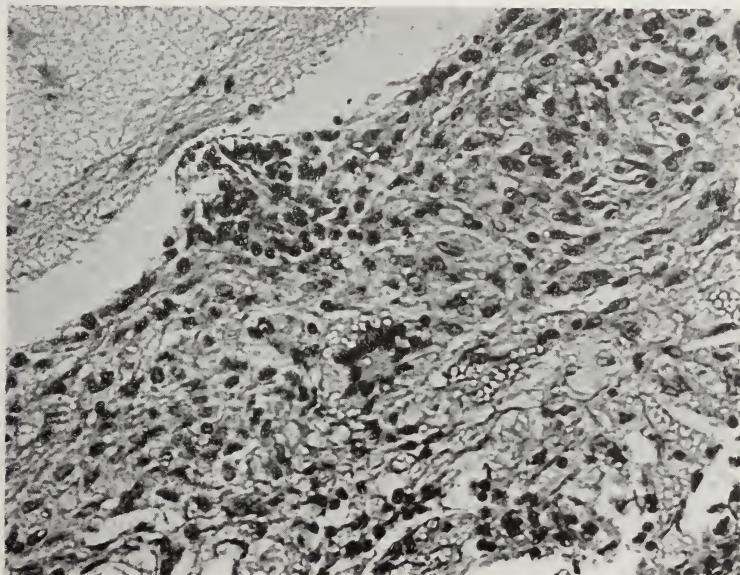


Fig. 380.—*Torula* meningitis. Numerous organisms widely scattered.

Castellani, Brumpt, de Beurmann and Gougerot, etc., for details of classification.

The simplest forms are the yeast-like fungi of which that commonly known as *Torula histolytica* (Stoddard and Cutler), or *Cryptococcus histolytica* (Vuillemin), the latter coming more and more into use, causes a severe and fatal meningitis resembling tuberculous meningitis, with areas of caseation, giant-cells and much connective tissue. The round refractive budding organisms are seen in numbers, especially engulfed in giant-cells.

In three of our four cases the meningeal reaction has been quite chronic, with a fibrous tissue formation in addition to the older caseous areas and tubercle-like reaction. In the fourth the reaction was largely of the mononuclear and epithelioid cell type, with myriads of small yeast-like forms of the fungus. Here, in the fresher, less resisted infection the budding forms are like the vegetative forms seen in cultures; in the more fibrous lesions many of the organisms are unstainable and show merely as shells, or as large doubly contoured organisms such as appear in culture in the least favorable media (chlamydospores). In our fourth case there were scattered visceral lesions in the liver, kidney and bone-marrow composed of mononuclear and epithelioid cells in which the organisms could be stained.

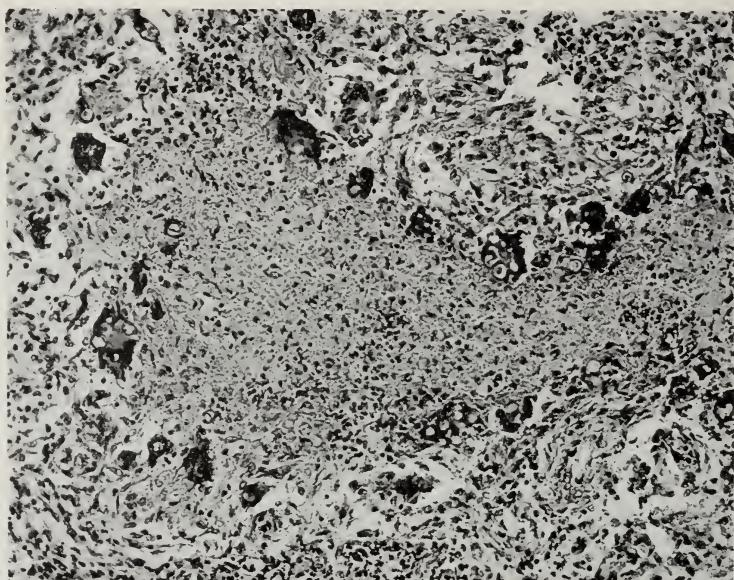


Fig. 381.—Blastomycotic meningitis. The organisms especially in phagocytic giant-cells.

From the meningitic lesions the fungi had invaded the superior longitudinal sinus of the dura and there were curious hyaline changes in the pleura, lymph-nodes and spleen, evidently resulting from former reactions to the fungus, which as in the case of Sheppe, probably gained entry by the lungs. Visceral involvement, however, is rare (Freeman, Fitchett and Weidman).

In the tissues the fungus occurs as round or oval forms reproducing only by budding and never even in culture forming ascospores such as characterize the related *Saccharomyces* or yeasts. None produce gas from sugars in culture, but they throw out a mucoid material both in culture and in experimental lesions in rats, although the gelatinous cysts reported in many cases were not conspicuous in ours.

This infection with predominant brain and meningeal involvement

seems to form a coherent group while other *Torulae* of doubtful relation appear in some skin diseases and bronchial affections.

**Thrush.**—*Oidium albicans* is the usual name for the most common form of thrush which is found in creamy patches in the mouth, pharynx, larynx and cesophagus, although it is maintained by Castellani that when cultivated, most of the organisms causing the lesions fall into the genus *Monilia*. The lesions are a very common finding at autopsy in cases of poorly nourished infants dying from any cause, and in an occasional debilitated adult. The soft patch consists of a mass of macerated desquamated epithelium with a feltwork of short mycelia. Sometimes the yeast-like forms are very abundant also. The mycelia penetrate the epithelial layers and can be found in the submucosa. Usually the inflammatory reaction is scant, at times polymorphonuclear leucocytes appear, but more commonly the mononuclear reaction is the more prominent.

Cases of generalized infection due to these organisms are very rare. In a recent case, that of a child of seven and one-half years of age, there was a preceding chronic skin infection of the face and scalp. At autopsy there were extensive lesions in the lungs, a generalized lymph-node involvement and focal lesions in the spleen and liver (Pels, Dresel and Salinger). These consisted of semi-caseous necrotic lesions surrounded by accumulations of mononuclear cells. The smaller lesions in the spleen and liver showed less necrosis but great numbers of phagocytic cells containing the yeast-like organism. These were very minute, round or oval, bodies with no production of mycelia. In the tissues reproduction took place by budding. In culture, in addition to the small forms, a long, tangled mycelium appeared.

**Blastomycosis.**—The term blastomycosis has been loosely used to cover a variety of skin infections. Gilchrist, Stokes and Rixford described *Blastomyces dermatitidis* and *Coecidioides immitis* as the parasites concerned. Stoddard and Cutler insist that the coccidioidal granuloma is a disease quite different from oidiomycosis and torula infection, and would give up completely the term blastomycosis, as already covered by the latter two names. But, at any rate, the term blastomycosis is well established and Gilchrist's description of the pustules on the skin of the face or body shows the papillary thickening of the epidermis beneath which are abscesses with giant-cells. Visceral lesions like abscesses, with giant-cells and thick surrounding connective tissue, are also found. The parasites are rounded, refractive, spore-like bodies which in culture can develop a mycelial growth. The coccidioidal granuloma, also described by Rixford and Gilchrist, is very similar but the organism, *Coccidioides immitis*, is different—it occurs as large round, doubly contoured bodies, never budding in the lesions but increasing by forming internal spores. It forms a coarse mycelium in cultures. Of the twenty-four cases of this infection collected by McNeal and Taylor, all but two were fatal.

**Sporotrichosis.**—Sporotrichosis, produced by another fungus which grows as a mycelium with clusters of spores, was first described by Schenck, in 1896, in this hospital. It infects the skin and produces

granulomatous tumors which spread along the lymphatics but sometimes also invade the internal organs, producing nodules like tubercles or abscesses.

Actinomycetes of many types are pathogenic and appear as mycelia of thread-like filaments with concentrated masses outlined by club-shaped terminals which form the so-called sulphur granules. Since this is so important an infection, it may be treated separately.

### ACTINOMYCOSIS

This disease, common in cattle, and recognized as an infectious process by Bollinger, was later described by J. Israel for man. The cattle present a tumor-like swelling, usually of the jaw, with sinuses and purulent discharge in which peculiar yellow granules or sulphur grains are found. In human beings the affection is quite commonly also a swelling of the jaw, but there are several other typical localizations, namely, in the thoracic organs, in the intestines, or in the skin. Ponfick recognized the identity of the disease in man and animals. Examination of the pus or of sections of the granulation tissue lining the sinuses shows the causative agent to be a branched organism which grows in tangled mycelia. Numerous broken portions resembling bacilli or cocci occur. The sulphur grains are knots of the mycelium with radially projecting tips, which form a layer covering the central tangle. Each of these tips is surrounded by a club-shaped or bulbous covering of homogeneous, refractive material. The microscopical section through such a granule, therefore, shows a curved or scalloped margin of such clubs, arranged parallel or at least radially. It was from this arrangement that the name actinomycetes or "Strahlenpilz" was derived.

There are many other closely allied organisms, which are commonly spoken of under the name streptothrix, and most writers make a point of applying the name actinomycetes to that organism which produces the disease in man and cattle, saying that the streptothrixes differ from it in not being able to produce the radiate, club-like growths. So often has this been repeated that the distinction will doubtless persist for a long time. The truth of the matter is, however, very different. Such club-bearing knots of mycelium are not formed by the organisms in culture, but only in the tissues of an animal (exceptionally in cultures in serum or animal tissue). So far from their being unable to form such clubs, those of the streptothrix group which can infect animals produce the most beautiful clubs under the proper conditions. One, commonly known as the Streptothrix asteroides, if injected into the peritoneum of a rabbit so that the infection meets with more resistance than if injected directly into the blood, will form everywhere in the organs graceful, plume-like masses of clubs in every respect similar to those of *Actinomyces bovis*.<sup>\*</sup> Indeed, there is no valid reason for separating these organisms into two groups, and since the name streptothrix has long been preempted for an alga, it is necessary, according to all rules of nomenclature, to call them all actinomycetes, that being the first name applied to any of the group.

It is perfectly true that not all this group have the same pathogenic powers. Some, indeed, are entirely saprophytic, while others, such as the *Actinomyces asteroides*, have been found in subacute abscesses in the brain, in generalized peritonitis, etc.

\* For that matter many bacilli—the diphtheria bacillus, Möller's grass bacillus, and others—can do the same thing under favorable circumstances.

The *Actinomyces bovis*, described by Wolff, Israel, Wright, and others, is an anaërobic organism, and is recognized as the cause of the disease in both cattle and man. It has not been found in the outside world in spite of the existence of so many allied forms, and probably lives on the mucosæ of the mouth and digestive tract. It has always been thought to be introduced into the tissues by straws or splinters, but it begins to seem more probable that it merely takes advantage of the



Fig. 382.—Actinomycosis. The peculiar lobulated masses of mycelium, edged with a row of clubs, are surrounded by leucocytes, outside which is a layer of gránu-lation tissue rich in large, fat-laden phagocytic cells. Outside this is dense fibrous tissue.

presence of such a foreign body to display its pathogenic properties. Details of the morphology of these remarkable organisms must be read in the papers cited.

Having reached the tissue, the presence of the mycelium is quickly responded to by necrosis of the cells and by the abundant accumulation of leucocytes. The process advances slowly though, and there is a most profuse formation of granulation tissue round about such an area after

weeks or months; while the central part of the lesion is made up of liquid pus full of the branching organisms, the outer zones are composed of such dense fibrous tissue as to form a tumor-like mass. Lining the cavity is still fresher granulation tissue, which is now loaded with large mononuclear wandering phagocytic cells, which are themselves so full of fat-granules as to give this layer an opaque yellow color. Frequently,



Fig. 383.—Actinomycotic abscess in liver. The figure shows the extraordinary scarring about the abscesses, which are merely loculi in a dense fibrous mass.

lying loose in the pus in the centre, there is one of the sulphur grains with its clubs (Fig. 382). No giant-cells are found, as a rule, nor any distinctly tubercle-like nodules. The mycelium grows and advances into the tissue, destroying and liquefying it slowly with the aid of the abundant leucocytic reaction, and is attended constantly by the most tremendous formation of encapsulating connective tissue. Given such a process,

it is not surprising that this becomes one of the most destructive of all diseases. The infection burrows through the tissues for great distances, completely distorting whatever it traverses, and it stops for nothing—bones are penetrated as easily as muscles, and from the lung such a mine-like advance may push through the pericardium and heart wall into the interior of the heart.

More than half of the infections are in connection with the mouth and pharynx, and seem to begin in the gums about the teeth, although sometimes the tongue or cheek is first affected. The abscess-like lesion, with its bulwark of connective tissue, usually appears in the parotid or submaxillary region, extending thence, with destruction of the jaw, into the neck. Another group begins in the thorax, probably in the bronchi or in the substance of the lung, and extends thence, sometimes to appear in a sinus or series of sinuses perforating the skin. Naturally, the pleura approached by this process becomes enormously thickened. A third site of predilection is in the intestines, and especially in the ileocecal region, where a submucous abscess soon forms a mass which progresses with adhesions to adjacent abdominal organs and to the abdominal wall, often forming long, burrowing sinuses between the muscles or reaching bones or joints. At times one finds great masses of dense fibrous tissue riddled everywhere with cavities full of pus, which represents the ramifying and anastomosing suppurating centres. Actinomycosis of the ovary and tubes has been observed in many cases. The fourth group of cases, which is much smaller, is thought to be due to infection through the skin. Here again the deeper tissues, including the fasciae, bone, and joints, may be penetrated and destroyed.

In the course of such a chronic infection metastases into the internal organs may occur, and we find abscesses in the spleen or liver (Fig. 383) or elsewhere which may become evacuated or may, in their turn, burrow and wall themselves off. Usually, however, if the disease has progressed to that point, life is cut short by an intercurrent affection. Amyloid is often found in the organs at autopsy.

Closely related to the actinomycoses are the maduromycoes which are caused by organisms very similar, but with separate filaments producing chlamydospores. There are various genera, such as Madurella, and the organisms produce in the pus yellow, red, or black granules. Entering through some cut or abrasion they set up, especially in the tropics but sometimes in this country, the so-called Madura foot, or mycetoma. The foot is greatly enlarged and pustules which lead down into deep anastomosing sinuses are scattered about the skin and in bursting open liberate a purulent fluid with the characteristic grains. Great disintegration of the tissues, even including the bones, is produced.

Madura  
foot

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Other fungi act as parasites especially on the surface of the body. Such are the cause of ringworm or tinea which in its various forms is produced by organisms related to the Trichophyton. These are familiar affections which, in the case of the scalp, produce circles of baldness with scaly margins and elsewhere as slightly elevated, roughened and inflamed rings. In the tropics, the so-called Tokelau, or tinea imbricata, caused by Endodermophyton tropicale, is a most common and astonishing pattern of concentric rings which cover the whole body. In this country the most frequent trichophyton infection is that of the feet which comes from walking barefoot in gymnasiums or swimming pools. It is frequently transferred to the groin or to the axillæ and persists with great discomfort unless properly treated. The Achorion schoenleinii, a closely related form, produces favus in the scalp, a disease which causes complete baldness, after producing hard masses of mycelium, with inflammation and destruction of the roots of the hairs.

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## CHAPTER XXXVI

### TYPES OF INJURY.—SPIROCHÆTAL INFECTIONS. SYPHILIS

*Syphilis. History. Aëtiology. Course of the diseases. Experimental syphilis in animals. Immunity. Congenital syphilis. General considerations. Acquired syphilis, primary, secondary and tertiary stages.*

THE history of syphilis is a long and interesting one, its beginnings shrouded in mystery, although its earliest recorded appearance in Europe in the Middle Ages is striking because it raged as a sort of epidemic of extreme violence, the affected persons suffering the most destructive inroads of the disease. Of its naming by Fracastorius, of the discovery of the curative effects of mercury and iodides, even of the great names of those especially concerned in its study in the early days, such as John Hunter, Jonathan Hutchinson, Fournier, Ricord, and others, the student must read elsewhere.

Edwin Klebs in 1878 was apparently the first to inoculate successfully syphilis into animals and even saw spirillar organisms in the lesions, but the time was not ripe for such a discovery and it roused little interest. But since Metchnikoff in 1903 succeeded in transmitting syphilis to a chimpanzee and Schaudinn and Hoffmann made the great discovery of the actual living cause of the disease, the Spirochæta pallida or Treponema pallidum, as it is now called, a new era has opened and everything in its comprehension, its prevention, and even in its cure should now become possible.

Already great advances have been made through experimental studies in animals, and various substances have been synthesized which are powerful to destroy the spirochætes, but we are still very ignorant as to many things. The life-story of the organism is not completely known. Many lesions caused by this organism are probably still unrecognized as syphilitic, and many others are doubtless falsely ascribed to syphilis. Whenever we attempt to apply our ordinary experience of immunity to the phenomena of this disease we meet with rather anomalous results difficult to interpret. There seems to be a reluctant tolerance established between host and organism which lasts with mutual injury for a very long time, but there is little to suggest the formation of such antibodies as we recognize in the case of bacterial infections and intoxications. We quite naturally attempted to apply the same terms to the phenomena of spirochætal infection, but it seems possible that we fail simply because quite different principles are involved. Thus, the allergic modification of the reaction of the tissues, so vivid in tuberculosis, may not exist at all in syphilis, although many people insist upon employing it as an explanation of the secondary lesions of the skin, while others regard it as the basis of the caseation of gummata. Fur-

ther, the sort of protection against all injury from syphilis that comes to women just because they are pregnant or have recently borne a child is quite unlike anything we know in bacterial infections, and the conditions that surround the transmission of the disease to the unborn child are not paralleled by any other infection.

We are accustomed to think rather rigidly of a regular progress in the acquired disease sharply divided at appropriate periods into primary, secondary, and tertiary stages, but everyone who has much clinical experience with syphilis knows that there are the greatest variations in the character of the lesions, the time of their appearance, and their severity. Much depends upon treatment, and it seems that the very type of anatomical change is profoundly influenced by this, so that while formerly a tumor-like nodule readily becoming caseous (gumma) was thought the most characteristic lesion, it is now a rare occurrence to find anything more than a diffuse inflammation or the scar of a healed gumma.

Noguchi announced the discovery of a method for the cultivation of the spirochæte in artificial media, but apparently it was not the *Treponema pallidum*, the actual cause of syphilis, that he and others cultivated, but some other organism, for while it is perfectly easy to produce syphilitic lesions in animals by direct transfer from human lesions, the cultivated organisms will not do this. This is confirmed by Zinsser's experiment mentioned later, in which it is shown that immunity against cultivated organisms gives no protection from the virulent forms.

More recent investigators feel confident that they are working with the true *Spirochæta pallida*, but that it rapidly loses its virulence in artificial culture. They say (Gammel and Ecker) that no culture medium is known which will preserve the virulence of the spirochæte although it remains motile.

But Kast and Kolmer have reviewed all the work and take the stand that while saprophytic spirochætes from smegma and saliva have been cultivated, they themselves found it impossible to cultivate the *Spirochæta pallida* from human or rabbit syphilitic tissues and feel that the cultivation of virulent spirochætes has not been generally accomplished and remains a problem of importance.

The development of stains for their demonstration in the tissues by Levaditi, Jahnel, and others, and the use of the dark field illumination for their study while alive have, however, greatly promoted our knowledge of the behavior of the organisms. But still we do not know with any certainty the whole of their life-cycle, and the recent experimental studies of Bergel seem to show that there may be extremely minute granular forms or even invisible stages which may under other conditions develop again into recognizable spirochætae.

It must be said that much remains to be done before we can feel sure that this is true, but if it were, it would help greatly to explain some of the difficult points in congenital infection.

**Course of the Disease.**—The infection is transferred from person to person and nothing is known of any life of this organism apart from its parasitic life. Ordinarily the disease is transmitted by coitus, but it is

also quite frequently traceable to extragenital infection, as through kissing, the use of infected utensils, towels, etc., or through shaving with a contaminated razor. The danger to surgeons and dentists of infecting their fingers through cuts or abrasions during an operation upon a syphilitic is considerable.

The spirochætae pass through an abrasion or directly through a mucous surface and appear to penetrate very rapidly into the tissue and into the lymphatic channels, so that they are in an incredibly short time distributed throughout the body. For this reason any attempt at prophylactic treatment must be very prompt to be of the slightest avail.

Nevertheless, days pass before a local lesion makes its appearance at the point of entrance of the organisms. This, the so-called chancre, is a very peculiar and characteristic hard nodule and is accompanied by evidences of the infection of the regional lymph-nodes.

After a second incubation period of varying length, often eight to ten weeks after the first infection, there appear in the skin and mucous surfaces new manifestations caused by a distribution of the spirochætae by the blood and their multiplication in certain places. These are the lesions of the secondary stage, and here the greatest variety of form is shown. Lymph-glands in general are enlarged, and some other tissues, such as the iris, cerebral vessels, testes, etc., may be involved. The secondary lesions usually heal without leaving any great destruction behind them.

After another period which may stretch out over very many years during which the patient has supposed himself cured, the destructive lesions of the tertiary stage appear. These arise in any situation in the internal organs or the skin—no tissue seems exempt. Characteristic is the formation of tubercle-like nodules, often of large size and firm consistency (*gummata*), becoming caseous internally, and ending, after wide destruction of tissue, in healing, which leaves behind a most extensive scar. Or a less characteristic, wide-spread, cellular granulation tissue may in the same way lead to destruction of the tissue and distortion from scar formation. Warthin especially emphasizes this in what he calls the new pathology of syphilis, and describes in detail focal accumulations of plasma and lymphoid cells about the small vessels and in the interstices of almost all the organs in cases of late and often unsuspected or latent syphilis. In many of these, especially in the heart, blood-vessels, and central nervous system, and also in the pancreas, adrenals, and testes, he has sometimes demonstrated the spirochætae, while others are recognized as syphilitic by their histological identity with those of assured origin. These lesions are so much more frequent and therefore of so much greater significance than definite gummata that Warthin objects to the usual statement that the gumma is the characteristic lesion of tertiary syphilis. In autopsies upon untreated Chinese coolies at the Tan Tock Seng Hospital in Singapore I found gummata so regularly and in a form so suitable for the illustration of a text-book that I am inclined to the surmise that, were it not for a certain inherited immunity in our race and the effects of treatment, the gumma would still easily hold its place as the most characteristic feature of tertiary syphilis. Nevertheless, as the disease exists, Warthin is doubtless right.

in stating that the less conspicuous but wide-spread and destructive focal lesions are much more important, since they disable the vital organs.

Following the tertiary stage there may appear still other lesions involving especially injury and scarring in the central nervous system (tabes and progressive paralysis), which have long been suspected of being syphilitic and spoken of as parasyphilitic affections. Recently the spirochætae have been demonstrated in these tissues (Noguchi) and the matter set upon a firm basis. Even successful treatment by specific medication has been carried out. Such lesions are often said to constitute a quaternary stage of the disease.

Thus, syphilis is seen to be a generalized infection of extraordinary chronicity and tenacity in which, at some periods, the whole blood and tissues of the host are infected with the spirochætae, while during years they seem to disappear or remain hidden somewhere only to multiply again at some point and produce new changes. There is a certain regularity in the progression of the different stages, although the length of time required for the appearance of each varies extremely.

**Experimental Syphilis in Animals.**—Since the original inoculation of a chimpanzee by Metchnikoff a very great deal of work has been carried on in the attempt to elucidate the problems of syphilis by its experimental production in animals. The names of Neisser, Uhlenhuth, Brown and Pearce, and Chesney and his associates are especially familiar in this connection, and it has been found possible to infect the anthropoid apes and most of the monkey tribe as well as several other animals. Of all, the rabbit seems most useful because it has been found to be quite susceptible. Neisser has made extensive studies in apes in Java, and the others have throughout many years studied the effects in rabbits. The lesions produced are not quite identical with those in man, as might be expected, and the results of these studies have so far been rather disappointing. It has been shown that certain tissues, such as the testes and perhaps the ovaries, are especially susceptible to the localization of the spirochætae. Chesney has shown that granulation tissue offers an especially ready entrance to the spirochætae, although so resistant to invasion by bacteria. Various aspects of immunity and resistance to reinfection have been studied, however, and the outlook for further enlightenment from this source seems good.

**Immunity.**—It was at one time thought (Ricord) that a person who had once had syphilis was quite immune from further infection, and also that while materials from the primary lesion or initial sclerosis as well as those from secondary lesions were highly infective, the tertiary lesions were non-infective. All of this has proved untrue. Finger and Landsteiner showed that a gumma contains living spirochætae which can, when inoculated, produce an initial lesion followed by secondary rashes, and they and others have also shown that while a certain increased resistance may appear after the first infection, a new inoculation may be successful in any stage of the disease (superinfection). It is stated by them that the inoculation when it causes new lesions to develop in a person already syphilitic, produces, not always chancre, but lesions which belong to the

stage of the disease in which he is, but it seems that this rests on very few observations and must be confirmed. There are, however, several instances in which a whole series of chancres or primary lesions has appeared as the result of successive exposures to infection.

The study of immunity in syphilis is complicated, as it is in tuberculosis and possibly in many other diseases in which it is far more definite, by our inability to tell whether the person still harbors the living infectious agent. We are accustomed to think of immunity after complete recovery from such diseases as small-pox, poliomyelitis, typhoid fever, etc., as lasting throughout the rest of life after the infection has been completely overcome and the body purified of the last traces of such a living parasite. But have we any evidence that this really so, or is it possible that in all such cases organisms persist in some focus, perhaps in a form not easily recognized, as long as the immunity lasts? Neisser thought that in syphilis resistance to reinfection existed only so long as the animal was still infected and attempted to prove this experimentally in monkeys, but in rabbits, which are the only other readily susceptible animals besides man, it becomes evident that an immunity gradually develops and increases with the lapse of time so that it is much more effective in the late stages of the infection. Treponemicidal drugs may destroy the infection at an early stage, though only with great difficulty or not at all in later stages, and this cuts short the further development of immunity, although it leaves whatever resistance has been developed up to that time. Since sterilization of the syphilitic infection in man or animal seems possible only in the very early days of the disease, it may be expected that the degree of resistance developed by that time will be very slight, and reinfection of such cured cases seems relatively easily possible, although actually it is very rare.

Efforts to produce active immunity by injecting dead treponemas or materials derived from them in cultures have been fruitless, and no one has succeeded in transferring a passive immunity by injecting blood or serum from an immune person. Zinsser and his associates have produced agglutinins, precipitins, and even treponemicidal substances by immunizing animals with cultures of the treponema, but these seem to act only upon culture forms and not against the virulent organisms. There seem to be developed in the body no powerful antibodies, and it is suggested that the persistence of the infection is due to the mutual adaptation of tissues and organism so that they live together with difficulty and mutual injury, but at least for a very long time. The student is referred to Chesney's able reviews of this whole subject.

With regard to the relation of syphilis to yaws, I have myself seen in the Fiji Islands the universal prevalence of yaws and the almost absolute absence of syphilis among the native Fijians, although the Hindu population recently introduced into those islands is thoroughly infected with syphilis. One has the impression that yaws, which is caused by an almost identical treponema, confers protection against syphilis. St. Johnstone examined carefully a labor battalion of Fijians which was sent to France during the war. They had all had yaws, but no syphilis. On their return there were many cases of gonorrhœa, but none of syphilis.

An interesting phenomenon is the so-called Herxheimer reaction which consists in an exacerbation of syphilitic lesions with inflammatory changes when drugs such as arsphenamine, which presumably kill the spirochaetæ, are given. It is most striking in the secondary lesions of skin and mucous membranes, but it apparently affects also the lesions of internal organs, and swelling of lymph-nodes, joints, and periosteal lesions with pain and the intensification of the symptoms of syphilitic disease of the nervous system and meninges, the vascular system, liver, etc., are evidence of this. Various explanations are offered, but perhaps the most acceptable is that there is a liberation of specific toxic substances from the disintegrating spirochaetæ which acts upon tissues already in a state of allergic hypersensitivity.

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**Congenital Syphilis.**—In connection with the efforts to learn something of the defences of the body against the inroads of syphilis it seems that the extraordinary circumstances that surround the transmission of this disease to the foetus should afford most valuable clues. Two old observations have been handed down in the form of laws. Of these, the so-called Colles' law states that a woman who bears a syphilitic child is herself immune and may suckle the child with impunity, although another nurse would be infected. Profeta's law states that a healthy child may be born of a syphilitic mother and is then immune "at least until there is a complete exchange of its primary cells." Both of these laws require essential modification, although they contain much truth.

Two chief questions arise, one as to the mechanism of the infection of the foetus, the other as to the nature and extent of the immunity of the mother and of the healthy offspring.

Various possibilities present themselves in the case of the mother. She may be infected before conception, at the time of fertilization, or during the later stages of pregnancy, or possibly not at all, although the

fœtus is born with all the lesions of syphilis. When the mother is definitely infected the process is merely identical with acquired syphilis in general, although it is perhaps conceivable that an infection appearing late in pregnancy, if not evidently due to a new contact with an infected man, might be thought of as derived from the infected fœtus. This, like the last possibility in which the mother remains apparently well and even suckles her syphilitic child, seems to point to an infection from the father's fertilizing sperm cell, the whole brunt of the infection being felt by the developing fœtus. This idea is directly opposed to that which maintains that the mother is infected at all of these times, and that the fœtus is infected through the placenta from her. There are grave difficulties in both explanations—not so much theoretical as arising from actual observations. It is, of course, quite possible for infection to reach the fœtus from the mother by way of the placenta, and this has been shown experimentally in animals by Uhlenhuth. But is it possible for the spermatozoon to carry a spirochæte into the ovum which it fertilizes? The possibility that the ovum may itself bring the infection would be hard to maintain, since it implies that the mother is syphilitic, so that placental transmission could not be excluded. It is generally agreed that a spirochæte is too large to be introduced into the ovum in the act of fertilization, but Hochsinger, in his interesting paper in which he warmly defends the idea of paternal infection, leans on the possibility that certain granular or still more minute forms observed by Bergel may, indeed, be small enough to be thus brought into the interior of the fertilized ovum and persist throughout the development of the embryo as an infection of the fœtus from the beginning. It has not been possible so far to produce this condition experimentally in animals and the proof of its occurrence remains circumstantial. Dr. Williams has reported the case of a woman whose seventh pregnancy resulted in double ovum twins, of which one was syphilitic, and died, the other normal and still living. She admitted intercourse with a syphilitic man as well as with her normal husband, and it is explained that one ovum was fertilized by the normal, the other by the syphilitic, man. She had later eleven normal children, and she, her husband, and children showed negative Wassermann reactions. There are a number of other instances in which in the middle of a series of normal children one is born syphilitic because the mother in the conception of that child was fertilized by another man who was syphilitic. Such cases are very impressive, but no one, as Trinchese shows, has been able to demonstrate spirochætae in the tissues of the embryo until after the fourth or fifth month of development. If this is true, is it necessary to assume that the virus remains there in its hypothetical invisible form until that time, undergoing evolution when conditions become suitable, into the recognizable spirochætae?

Most observers seem to believe that in the ordinary cases in which several children in succession are born with the lesions of syphilis, it is more probable that the infection takes place from the mother, who is infected before or at the time of the first conception, even though she may show no symptoms of syphilis other than a positive Wassermann

reaction, and this, as Hochsinger points out, may be only temporary during the time closely following the pregnancy and lactation, changing later to a negative result.

No explanation is available for this remarkable protective effect of pregnancy. The careful study of Moore should be consulted. From this it will be learned that while the Wassermann reaction is variable during pregnancy, it is generally positive, and it has even been possible to demonstrate the spirochæta in the tissues or secretions of such women (Buschke, Uhlenhuth, and Mulzer). The later course, physical examination, Wassermann reaction, and development of actual lesions, all go to show that the women who bear syphilitic children are themselves actually syphilitic, although the severity of the disease is greatly decreased, in many instances to such a point that never, throughout their lives, is it possible to demonstrate in any way that they are abnormal. Moore states that it is fair to assume that pregnancy is the factor which suppresses the lesions of the disease. The protection may persist over a long period of years and possibly for a lifetime. Spontaneous cure seems in a few instances to have been the ultimate result.

It seems necessary to believe that some substance produced in the course of pregnancy and non-existent in the tissues and body fluids of males and non-pregnant women is antagonistic to the spirochætae, but whether this is derived from corpus luteum, or other organ of internal secretion, or from the placenta or foetus, is merely a subject for speculation.

In spite of the limitations, therefore, which were suggested by Jonathan Hutchinson in 1876, and worked out in detail by Moore and other writers, there is more than a grain of truth in Colles' law.

The difficulties encountered in attempting to explain Profeta's law are of the same character. It is evident that a child may be born apparently well, although from a syphilitic mother, and remain uninfected through the period of suckling, but some time later it becomes susceptible to an acquired infection. It is difficult to understand exactly how the child can escape infection *in utero* unless the suppression of symptoms and lesions is part of the process described in Colles' law, the immunity of the mother being directly conferred on the child. Later infection might be regarded as due to gradual disappearance of this immunity or as the effect of a large dose of a foreign strain of spirochæte. Such children should be studied as minutely as the Colles mothers if we are to understand this important clue to immunity in syphilis.

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- Profeta: Lo Sperimentale, 1865.
- Trinchese: Beitr. z. Geburtsh. u. Gynäk., 1913, xviii, 201.
- Williams: Amer. Gynæc. Assoc., 1924.

**Primary Stage.**—The initial lesion or chancre arises, as mentioned above, at the point of infection one to four or more weeks after exposure. It is nearly always dependent upon an abrasion, although in the case of the mucous surfaces it appears that infection can occur directly. The abrasion in the skin or mucosa usually heals after a few days without leaving any trace, and it is only later that the specific lesion appears in the same place. Nevertheless, even though such an area be excised and cauterized a few hours after the exposure, it is frequently, if not always, found that transportation of the spirochaetæ has already occurred, so



Fig. 384.—Primary syphilitic lesion of corona. Early stage (Fordyce\*).

that general infection later makes itself evident. The delay in the appearance of the first sign of the initial lesion is thought to be due to the fact that in the process of accommodating themselves to the new host many of the spirochaetæ are destroyed, so that it requires time for those which survive to develop the lesion. This begins sometimes as a tiny vesicle, usually as a delicate thickening or induration of the surface tissue, over which, as time passes, the epithelium becomes necrotic and

\* Professor Fordyce has kindly allowed me to use photographs from his clinic for Figs. 384, 386, 387, and Dr. Keidel has given the Figs. 388, 389, 401, and others from the Department of Syphilis in the Johns Hopkins Hospital.

converted into a brownish crust which comes off, leaving a shallow ulcer. The induration extends and becomes a flattened hard mass, easily rendered bloodless by bending or by pressure, and easily movable in the surrounding tissue (Fig. 384). There is a characteristic, bacon-like translucence about this mass. The ulceration may extend and become

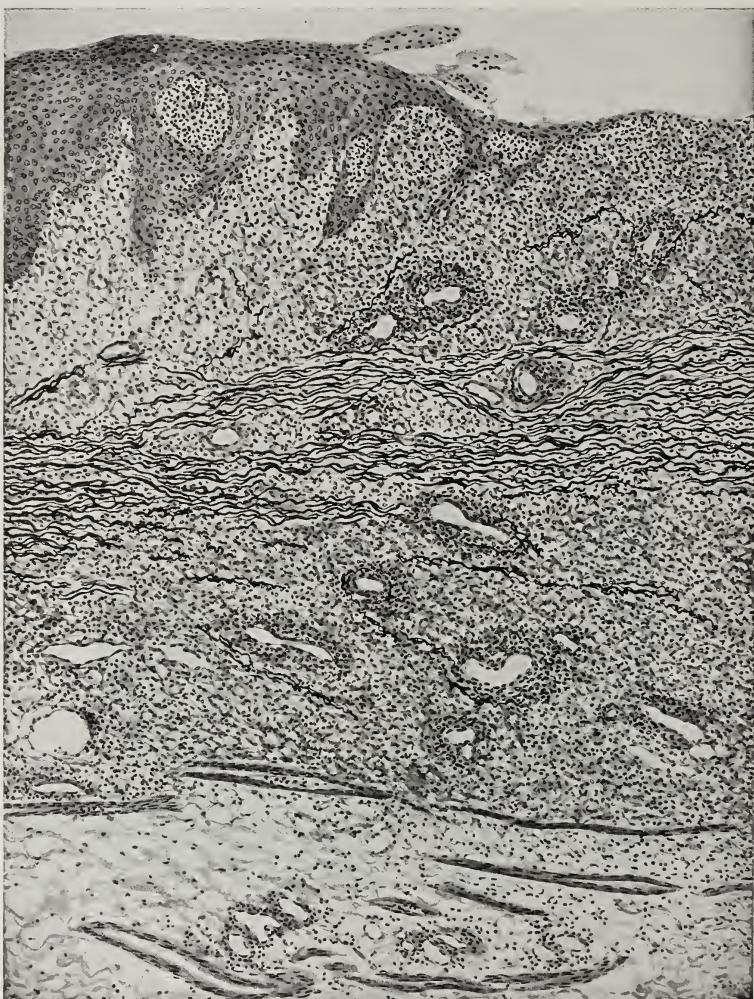


Fig. 385.—Edge of chancre, showing ulceration through the epidermis and great accumulation of mononuclear cells, especially about the vessels and lymphatics.

quite deep, a considerable area may be involved, and the chancre may persist for quite a time; but in the end it heals up, the induration disappearing, and the ulcer leaving a scar. Occasionally, but not often, considerable distortion and loss of tissue may be produced.

Histologically (Fig. 385), it is found that the induration is produced by a great accumulation of cells in the skin and subcutaneous tissue.

Ehrmann has shown by injections that great numbers of new blood-vessels are formed and that there is stasis in these venules from the pressure of the cells, often with haemorrhages and the formation of blood-pigment. The accumulated cells are in part polymorphonuclear leucocytes, which are found especially in the base of the ulcer, but predominantly they are mononuclear cells of the type of lymphocytes, plasma cells, and larger mononuclears. They are assembled in great numbers about the blood-vessels whose internal layer is enormously thickened, and extend from the main mass of the induration in the form of thick mantles in and about the adventitia of such vessels. Ehrmann described the induration as largely dependent upon the alterations in the lymphatic channels, which are often choked with mononuclear cells or



Fig. 386.—Chancre (Fordyce).

with proliferated masses of their own endothelial cells. In our preparations it is difficult to see any such proliferation of the endothelium of lymphatics or blood-vessels, although many of them are packed with wandering cells, but there are masses of tissue composed of large pale cells of irregular and indefinite outline with large vesicular nuclei. These are seen to be proliferated fibroblasts, and they, together with the abundant wandering cells, doubtless give the firmness and translucence to the tissue.

Leading away from the chancre are lymph-channels along the course of which little nodular accumulations of cells may be found.

The chancre may develop on the prepuce, in the coronal sulcus, on the glans penis or the frenulum, or about the orifice of the urethra, in about this order of frequency, or it may appear on the skin of the penis

or of the scrotum. In the female the labia majora or minora, the orifice of the vagina, the clitoris, the vault of the vagina, or the vaginal portion of the cervix are the commonest sites. But the lip, tonsil, or the cheeks, eyelids, breast, fingers, etc., may also be infected through the various processes of exposure mentioned above.

A short time after the appearance of the chancre the regional lymph-glands swell and become hard. The inguinal glands are most commonly affected, of course. In them the spirochaëtae are found just as they are in the chancre. The lymph-sinuses are filled with wandering cells, chiefly of the mononuclear type, and later there is a proliferation of the



Fig. 387.—Secondary syphilitic lesion of skin. Papular syphilide (Fordyce).

connective-tissue elements. There is little tendency to great swelling or to suppuration in such syphilitic buboes in contrast to the condition following infection with Ducrey's bacillus (soft chancre or chancroid) and that in gonorrhœa.

Chancres can be experimentally produced in animals by the inoculation of spirochaete-containing material, and recently Chesney has found that when the spirochaëtae are smeared on the surface of granulation tissue, which has been produced by making an open wound in the skin of a rabbit, they develop there and rapidly produce an enormous lesion far larger than is commonly seen in human beings.

**Chancroid or Soft Chancre.**—This is a type of ulceration of the genitalia transmitted by coitus or other contact and caused by a small Gram-negative streptobacillus which was described by Ducrey. The bacillus is easily cultivated and often grows in short chains. It is capable of producing a similar ulceration on inoculation in the skin of a person already infected or an uninfected one. The ulcer spreads rapidly and has a ragged outline with undermined edges (Fig. 386). There is no induration about it, but the base is rough and covered with necrotic material and bleeds easily. While the penis and labia are most commonly affected, the ulceration may extend to the skin elsewhere. Red, tender lines which are palpable run from the ulcers toward the inguinal region and are often beaded with little firm nodules. These are the inflamed lymph-channels, and the nodules or *bubonuli* are swollen collections of lymphoid tissue which may become abscesses. The inguinal lymph-glands become greatly swollen and tender (*buboës*); on incision a quantity of



Fig. 388.—Secondary syphilis: pustular syphilide (Keidel).

purulent material is evacuated and the glands are found to be matted together and excavated by the destructive process which extends from one gland to another. This lesion, like the ulcers, finally heals, with an extensive scar. There are no general symptoms and no lesions in other organs.

**Secondary Stage.**—In rare cases after the healing of the chancre no other symptoms appear, and this may be true if vigorous medication be instituted in the primary stage. But usually six or ten weeks after the infection, that is, after a second incubation period, the secondary lesions of the skin and mucosæ make their appearance with fever, loss of appetite, muscular pains, etc. No brief description can even outline satisfactorily the extraordinary variety of these phenomena. They simulate every kind of skin disease and may be mistaken for the rashes of exanthematic diseases (measles, chickenpox, etc.), as well as those produced

by various drugs (Figs. 387, 388, 389). They have a tendency to heal up and then to recur, but although they may produce the most extensive outbreak all over the body, they are seldom destructive and leave little trace of their presence.

The simplest rash is the *macular syphilide*, which begins on the trunk and may quickly appear over the whole body. It is quite like the rash of measles in some cases, and histologically presents chiefly a widening of the blood-vessels with slight accumulation of cells. Further accumulation of leucocytes and oedema is characteristic of the *papular syphilide*, in which the eruption is somewhat raised. With the fading of these



Fig. 389.—Secondary syphilis: follicular syphilide (Keidel).

rashes discoloration of the skin may remain for a time. Some often develop superficial crusts due to epithelial necrosis and exudation, while others are definitely *pustular*, little abscesses forming in each lesion. Many of these syphilides have a tendency to heal in their central part, while spreading and producing new lesions at the periphery. Ring-formed macular, papular, or pustular eruptions arise in this way. Scaly patches resembling psoriasis appear on the palms and soles at a later stage, and still later there may be found the rounded, terraced, elevated patches with necrotic crusts—the so-called *rupial* eruption, which is more correctly regarded as a tertiary lesion. Many other forms and

combinations occur, descriptions of which may be found in text-books of dermatology. Not infrequent are pigmentary changes, in some of which there is a deepening of the color of the skin, in others a complete fading away of pigment in certain areas, which leaves them white in contrast with the surroundings (leucoderma). Patchy falling out of the hair (syphilitic alopecia) is also characteristic of this stage of the disease.

Soreness of the throat, with evident though slight inflammation, is common. Most characteristic, however, is the appearance of the so-called mucous patches in the mouth and throat. These are white areas in the mucosa, slightly elevated or superficially ulcerated and infiltrated with fluid and cells over which the epithelium is proliferated. They discharge the spirochaete and are a ready source of infection. Similar patches may occur in the vagina.

Besides these lesions of the skin and mucosæ in the secondary stage, certain others are very prominent. These are the condylomata and moist papules, which as inflammatory elevations loaded with spirochaetæ appear chiefly about the genitals or on the inner sides of the thighs or anal folds, or elsewhere where skin surfaces touch one another, so that sweat or other secretions and dirt are retained. They, too, form a common source of infection. The flat condyloma (to be distinguished from the pointed condyloma, which is not of syphilitic origin) is a broad, lobulated elevation covered with greatly thickened and somewhat macerated epithelium, infiltrated with leucocytes. The papillæ of the skin are enlarged by the widening of the blood-vessels and especially by the great accumulation of wandering cells.

We have recently made an attempt to study the development of the secondary skin lesions by excising minute pieces of skin and neighboring lymph-nodes from persons showing various forms of the eruption. In all the changes consist essentially in perivascular lymphatic accumulations of mononuclear cells with a few neutrophile and eosinophile leucocytes. The cells are relatively few in the macular forms, but become so numerous as to form masses in the papillæ and deeper layers of the corium in the papular forms. In some rather later lesions there were about the vessels numerous sharply outlined nodules composed of elongated cells and resembling tubercles. These are associated with an infiltration of the tissues with mononuclear cells. The adjacent lymph-nodes show a characteristic change which consists in the appearance of compact masses of large rather pale-staining cells in the lymph cords and the presence of abundant mononuclear cells in the sinuses.

Doubtless spirochaetæ are present in all these lesions, but they are hard to demonstrate.

**The Tertiary Stage.**—The most characteristic, though not the most common, manifestation of the effects of the spirochaetæ in this stage of the disease is the gumma, which received its name from its elastic, rubber-like consistency ("Gummigeschwulst"). Most commonly such nodules are found embedded in the tissue and surrounded on all sides by radiating fibrous tissue, which in itself is not especially peculiar. But the central portion is firm, elastic, opaque, and yellowish white, like hard cheese. This is the necrotic caseous part, analogous to that found in

tubercles, but different in its elastic, firm consistency and in the slighter tendency to liquefy. In it one may sometimes discern faint outlines of pre-existent tissue now necrotic. The margin or capsule is often not specially characteristic (Fig. 390), being made up of a rather dense tissue rich in epithelioid cells, such as are found in tubercles, and closely infiltrated with mononuclear wandering cells. Giant-cells with multiple nuclei such as are found in tubercles occur, but are rarer here. Baumgarten denies their existence in gummata, claiming that they are char-



Fig. 390.—Gumma of testicle, showing caseous centre. Atrophy of adjacent tubules.

acteristic of tubercles, and that if they do occur it is because of a coincident tuberculous infection. Such nodules may be of almost any size from minute points as small as the smallest tubercle to huge, tumor-like masses easily felt through the abdominal walls as they project from the liver, where they seem to reach their greatest size. In the miliary gummata there may be no caseation or coagulative necrosis and the nodule is seen as a more or less concentrically arranged group of epithelioid cells richly mingled with mononuclear wandering cells and ocea-

sionally with giant-cells. The arrangement is usually indefinite and irregular, lacking the sharpness and precision of the architecture of the miliary tubercle.

Spirochete have been demonstrated by animal inoculation in larger gummata by Finger and Landsteiner, but they are not easily found in sections. How, then, is one to tell a gumma from a tubercle when it is found at the autopsy? Histologically it seems almost impossible to make an absolute differentiation between them. A section through a gumma in the lung tissue might have exactly the appearance of one from a large caseous encapsulated tubercle. A miliary gumma in the liver might correspond exactly with some types of tubercles seen there. Demonstration of the presence of tubercle bacilli or of spirochaetes would settle the matter, but these searches are notoriously uncertain. Better would be the inoculation of a guinea-pig with the material. The Wassermann reaction might afford decisive evidence. But, as a rule, the gross appearance and distribution of the lesions are found to be typical enough in each disease to allow one to discriminate—not always from the situation of any one lesion, but from its relation to other lesions throughout the body. Thus gummata are commonly found in the periosteum invading the bone; in the skull they are frequently found involving the meninges and extending into the substance of the brain. Such a matting together of periosteum, skull, meninges, and brain into a solid caseous mass by a tuberculous process would be rare. In the brain substance they occur and have a different consistence from that of the very similar large solitary tubercles which are found there too, but the tubercles would in all probability be associated with readily recognizable tuberculosis of the lungs, etc. This is most often the really effective aid to diagnosis, for it is not difficult to recognize well-developed and widespread tuberculosis. In the liver small tubercles and small gummata are similar; the condition of the other organs will generally decide their nature. Large tubercles are rare; large, partly healed gummata are common. Nevertheless we have recently had a case in which a caseous tubercle 7-8 cm. in diameter occurred in the liver. Its abundant content of tubercle bacilli and the wide distribution of tuberculous lesions elsewhere made the diagnosis clear. In the testicle gummata are common, while tuberculous infection practically always begins in the epididymis, and only later may extend to involve the testicle.

Gummata have a strong tendency to heal, so that they are commonly found as disappearing centres of caseous material in great radiating scars. This is far less often true of tubercles. Many other instances might be mentioned in which the attendant circumstances give the main clue to the diagnosis. The history of the case, the Wassermann reaction, the bacterial findings, the distribution of the lesions and their relation to lesions elsewhere, their size, consistence and gross appearance, their tendency to heal or to break down, and, least of all, their histological structure—these are the things upon which the diagnosis of syphilis in the tertiary stage may be based.

Not all tertiary lesions are distinctly gummatous, however, for there frequently arises a diffuse infiltration of tissues with wandering cells and

a proliferation and new formation of connective tissue, which results in the formation of a *syphilitic granulation tissue* analogous to the tuberculous granulation tissue which plays so great a part in old tuberculous lesions. In places this tissue may have a gummatous character and undergo the same retrogressive changes (coagulative necrosis) as are seen there, but here again the tendency is toward healing, often with much distortion. Here, as elsewhere, in syphilitic processes the smaller blood-vessels generally show thickening of the intima and changes in the endothelium, which may result in their practical obstruction. About these vessels there accumulate mononuclear wandering cells in great abundance.

It will be observed in considering the development of the tertiary syphilitic lesions that they often arise in places where there were secondary lesions which had healed, and it has been suggested that they are the effect of the further growth of spirochætae which had been left behind in the healing of the secondary syphilis. The evidence is not entirely convincing in regard to this, although there are many well-attested cases in which gummata appeared on the site of old secondary lesions. It is difficult to say whether this holds good for the gummata of internal organs.

## CHAPTER XXXVII

### TYPES OF INJURY.—SPIROCHÆTAL INFECTIONS.—SYPHILIS (Continued)

*Syphilitic lesions of the circulatory system, arteries, heart, aneurysms. Syphilitic lesions of lymph-nodes, blood-forming organs, alimentary tract, respiratory tract, bones and joints, genital organs.*

**Syphilitic Lesions of the Circulatory System.**—It seems fair to say that the most important of all the changes produced by syphilis are those which affect the heart and arteries.

In our experience the most frequent serious and destructive lesion caused by syphilis is syphilitic aortitis with or without aortic insufficiency or aneurysm formation, and for that reason we shall devote much space to its detailed consideration and to illustrations. Our older records, of course, never refer to it, although it is easy to recognize it in the descriptions. It was impressive, and a revelation, to listen in 1903, at the meeting of the German Pathological Society in Cassel, to the discussion by Chiari, Benda and Marchand, of the discovery of Doeble and Heller of the syphilitic nature of these changes, and particularly to realize the perfectly characteristic and peculiar appearance of the aorta so affected. Since then every one has recognized it at a glance except perhaps when it is very old and combined with arteriosclerosis. It seems to be one of those simple triumphs of observation that make one ashamed of having been so blind. Still worse is it to recall that this condition had been fairly clearly described in this laboratory by Penrose years before. (Johns Hopkins Hospital Bulletin, 1898, ix, 140.)

Syphilitic aortitis comes rather late in the course of the disease and may be unsuspected, although, as LongCOPE has pointed out, there are frequently distinctive symptoms of pain and reflex respiratory disturbance.

It is especially the aorta which is affected, so that we rather naturally speak of syphilitic aortitis. The proximal parts of the innominate, carotid, and subclavian may sometimes be involved, and even the roots of the other large branches, such as the celiac axis, but in a rather large material we have found very little evidence of change in the walls of these vessels even a short distance away from the aorta. The mouths of such vessels, however, and especially the mouths of the coronary arteries and the intercostals, may be greatly narrowed or distorted, displaced, or even obliterated by these changes. All of this is perhaps consistent with the fact that the lesion is usually sharply localized to a limited area of the aortic wall, although sometimes it is much more diffuse.

It seems that the patches of recognizable syphilitic alteration are most common in the sinuses of Valsalva and in the arch of the aorta, although we have seen isolated and sharply outlined patches in the mid-

dorsal or in the lower dorsal region in aortas otherwise perfectly smooth and elastic and thin walled.

When the sinuses of Valsalva are thus affected the aortic valves are likely to be involved and to undergo analogous changes, but every combination of aortic and valve involvement may occur, and sometimes the valves may remain perfectly delicate and competent when the nearby wall of the aorta is profoundly affected.

It seems possible to recognize fairly well the age of the lesion by its gross appearance. A relatively fresh patch of syphilitic aortitis is sharply outlined from the adjacent smooth intima, elevated and thickened and distinctly translucent, with a pearly sheen which is made somewhat more striking by the irregular wrinkling of the intimal surface. In contrast with this an arteriosclerotic plaque would probably be found associated with flat areas of yellow opacity in the neighboring intima, its surface smooth, and on section, a lenticular mass of opaque yellow material containing fat and cholesterol crystals in its depths. On section the syphilitic patch shows no such fat accumulation, but beneath it the media can be seen to be broken or interrupted and flecked with yellowish opacity along its course. The adventitia shows no noticeable change in arteriosclerosis, but outside the syphilitic patch it is thickened and indurated.

An older area of syphilitic aortitis is generally more extensive, but at any rate its intimal covering is much more irregularly pitted, drawn, and scarred into a most distorted surface. Usually there are areas which seem greatly thinned out, so that the whole wall is bulged outward and the intervening portions stand out in relief. When looked at against the light these stretched portions are seen to be much thinner than the intervening parts. Over such an old syphilitic patch the adventitia is greatly thickened, dense and scar-like, at its edges suddenly passing into the loose, soft, normal adventitia. This feature, which is so conspicuous that the distribution of the syphilitic lesions of the aorta can be easily recognized from the outside, is practically never mentioned, although so constant.

On cutting through such a patch, particularly if the cut edge shows normal aorta and the marginal portion of the patch, the nature of the change can be easily seen with hand-lens or even without. The thin normal intima suddenly becomes thick, irregular and translucent or hyaline, the normal smooth uniformly thick media which is gray and translucent on account of its parallel strands of muscle and elastic tissue, suddenly becomes thin, irregularly beaded and interrupted, with minute flecks of opacity, the normal loose web of adventitia suddenly becomes a dense thick layer of scar-like consistency which is prominent externally as the intima is internally. In one of the thinned areas which tend to be ballooned out by the blood-pressure the media may be entirely lost or reduced to a few thin fragments. Very old syphilitic areas may be smoothed out and converted into scar-like tissue and are often hard to recognize with certainty, although it is evident that the media has been especially injured. In all this it seems that the brunt of the injury is

borne by the media, even though the infection is brought through the adventitia by the vasa vasorum or possibly, as Klotz thinks, by lymphatics, while the intima and adventitia become thickened as a compensatory process in the attempt to strengthen the wall.

It is difficult to convey in words an idea of the perfectly characteristic appearance of the intimal thickening (Fig. 391). Longcope describes it well as follows: The pale gray, translucent, elevated, succu-



Fig. 391.—Syphilitic aortitis, showing a peculiar irregular scarring of the wall of the aorta with sharp demarcation.

lent-looking patches alternate or are irregularly intermingled with yellowish, scarred, pitted and seared areas or with grayish patches that look like thin crinkled silk. Sternberg speaks of branching creases and furrows which give the intima something of the appearance of the bark of a tree. Contracted, radiating scars and sunken dells form a transition to actual sacculations of the aorta. While the wall becomes very thin in these places, it is thick and scar-like between them, often bluish white, almost like cartilage.

Microscopical study of such an aorta shows that it is essentially a destructive and inflammatory process affecting the media more seriously than the other coats, although it seems that the spirochaëtae must arrive

by way of the vascular supply of the adventitia. In the early stages they have been found especially in the adventitia, and gummatous nodules have been described. Generally, however, the adventitia presents a rather conspicuous infiltration of mononuclear wandering cells about the *vasa vasorum* accompanying them into the media (Fig. 392). In the media there are patches of necrosis in which the parallel arrangement of the muscle and elastic tissue can still be traced, and about such areas there are wandering cells. Later these are absorbed and scars are left with prolongations of the *vasa vasorum* and still the clustering mononuclear cells. An elastic stain shows extensive interruption of the elastic lamellæ at these places. The intima is thickened into a wavy mass of hyaline lamellæ without fat or cholesterine deposits and without

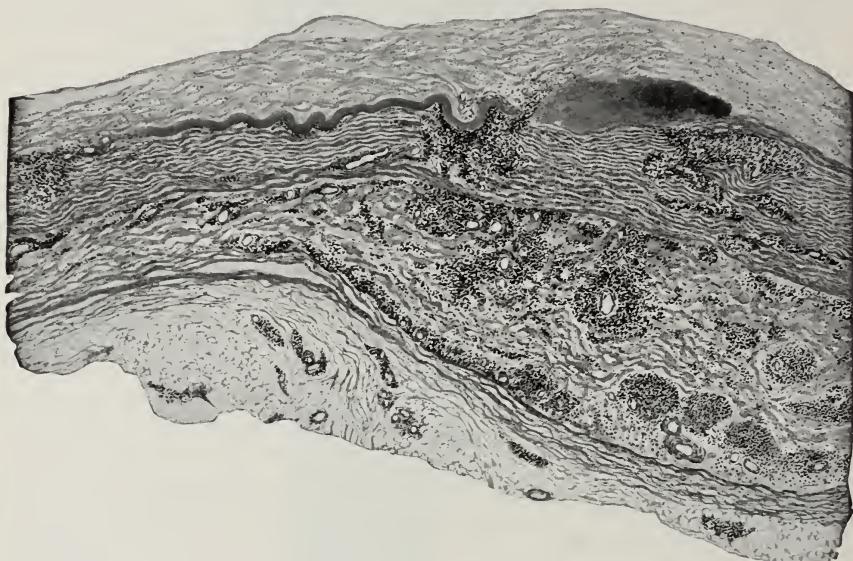


Fig. 392.—Syphilitic aortitis. Gummatous foci about *vasa vasorum* in the adventitia and media. Frequent breaks in the media.

disintegration or calcification. In still later stages the adventitia is found dense and scar-like, very much thickened, and at the margin of the lesion suddenly giving place to the loose meshwork of the normal adventitia. The media is merely a débris of patches of disordered muscle and elastic tissue separated by scars and generally very narrow when compared with the adjacent normal media. The intima becomes denser and more scar-like, but only in very protracted cases does it show any tendency to calcification (Figs. 393, 394). That this is a very different process from that seen in arteriosclerosis must be evident, and in spite of the effort at compensatory strengthening of the wall by the intima and adventitia it is clear that such an area is a weak place and may be stretched out into a sac by the pressure of the blood.

**Syphilitic Aortic Insufficiency.**—Next to the arch of the aorta the

sinuses of Valsalva seem especially liable to the localization of this affection, and are sometimes distended into sacculations which press into the base of the heart. The aortic valves are involved, especially at their

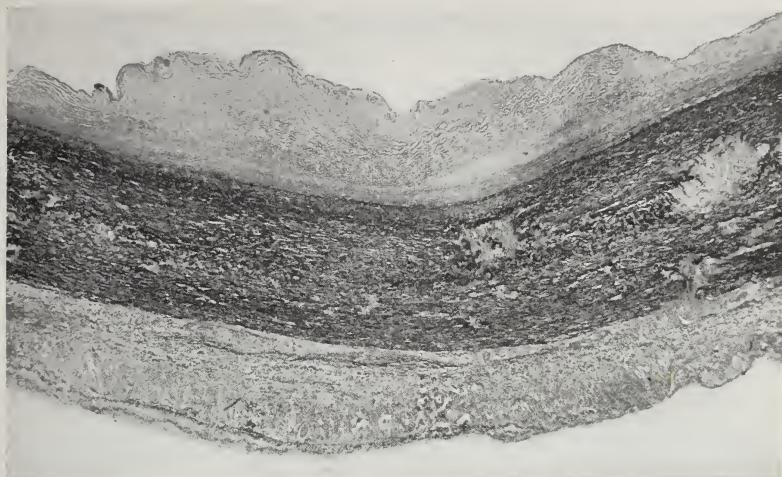


Fig. 393.—Syphilitic aortitis. Elastic stain. Great density of adventitia with many breaks in elastic tissue of media and irregular thickening of intima.

adjacent angles of attachment, and instead of meeting there as delicate films they often become fused into the wall of the aorta so that a wide space is left between them (Fig. 395). This in itself constitutes an ir-



Fig. 394.—Syphilitic aortitis with dense thickening of adventitia, irregular interruption and scarring of media and thickened intima.

remediable insufficiency because the valves can do nothing to close the space. This seems in some cases to be due to transverse contractions of the valves, which pulls apart the points of attachment and leaves the

valves tightly stretched across the sinuses of Valsalva. But the edges of the leaflets are thickened into round cords and the rest of the valve thickened and shortened or otherwise irregularly distorted, so that their inability to close the orifice is very evident (Fig. 397). Besides this, even when the valves remain delicate, the aorta and the aortic ring may be so dilated that the valves are no longer adequate to close the orifice.

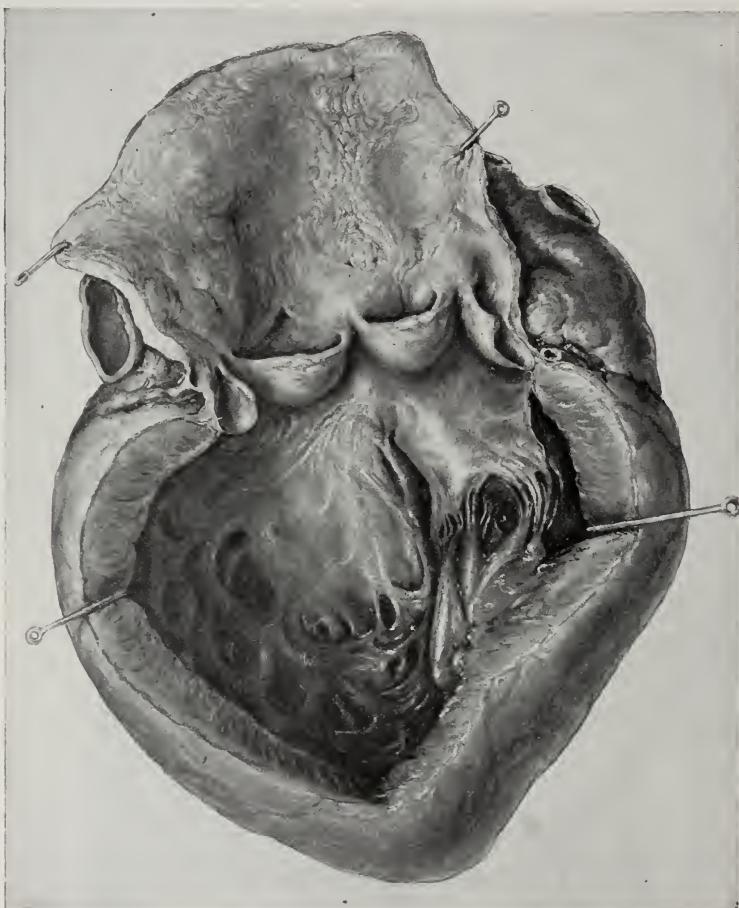


Fig. 395.—Syphilitic aortitis and aortic insufficiency. The aortic valves are thickened and rolled at their margins and widely separated at the angles.

Thickening of the endocardium of the interventricular septum below the aortic orifice is often very striking and appears in irregular white bands which run over the surface like white cords. Whether this is a continuation of the syphilitic process or a mechanical result of the insufficiency it is hard to say, especially since these thickenings sometimes take the form of valve cusps with the concavity always turned toward the aortic orifice through which a jet of blood regurgitates. Sometimes

there are several of such valve cusps plastered on the septum like swallows' nests on the face of a cliff.

Section through the aortic valves shows them thickened throughout without new formation of blood-vessels and edged or ending in a whorled mass of hyaline fibrous tissue into which the elastic tissue layer which runs up from beneath the endocardium of the ventricle frays out and is recurved. It is noteworthy that such valves, although so distorted, are extremely rarely the seat of secondary lodgment of bacteria, contrasting in this respect with the valves scarred by old rheumatic infection, which are so prone to a secondary bacterial endocarditis.

**Syphilitic Myocarditis.**—There is a tendency to ascribe the final failure or decompensation in cases of syphilitic disease of the aorta and



Fig. 396.—Syphilitic aortic insufficiency. The valves show the thickened, cord-like edges with corresponding shortening.

aortic valves to a corresponding disease of the myocardium, and Warthin especially emphasizes this, stating that syphilitic myocarditis is relatively frequent and often overlooked since the lesions are essentially microscopic. He finds accumulations of wandering cells about blood-vessels often with demonstrable spirochætae, and in later stages, scars in similar positions. We have seen very few cases in which active syphilitic myocarditis was suggested, and have been unable to feel that scars found in the myocardium were really syphilitic. (See also Clawson and Bell.) Nevertheless, that syphilitic disease of the myocardium could occur in the form described by Warthin is fairly self-evident, and that it would heal with the traces indicated by such scars is equally clear. If

the individual had survived long enough to establish these scars it seems doubtful however, that the actual decompensation was due to them. It would be perhaps better explained as due to the fatigue of heart-muscle long overburdened by the aortic insufficiency. Cases of this sort have been described by Magill and by Hamman and Rich, all in patients with recognized syphilis, all showing the same histological picture although in none of them were spirochaetes demonstrated. The symptoms of muscular insufficiency with attempted compensatory hypertrophy were found in all and it seems only reasonable to accept the diagnosis of syphilis.

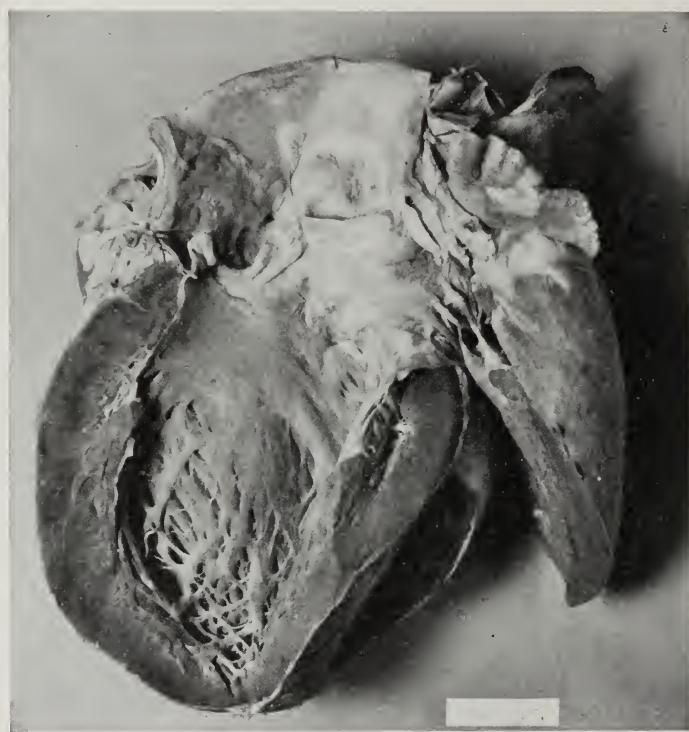


Fig. 397.—Localized syphilitic aortitis and aortic insufficiency.

Actual gummata may occur in the myocardium, and sometimes interrupt the conduction bundle of His.

**Aneurysms.**—The wall of the aorta, weakened by the process described above, is peculiarly liable to stretching and tearing, so that it frequently becomes distended into a saccular dilatation known as an aneurysm. The name is also loosely applied to various other conditions, dissecting aneurysms, false aneurysms, mycotic aneurysms, arterio-venous aneurysms, etc., which are described in other places, but true aneurysms are the result of syphilitic disease of the wall of the vessel. This relation to syphilis was suspected long ago, although accessory aetiological factors were also adduced, but since the recognition of the

definite syphilitic nature of the neighboring arterial change it has been realized that the association is a constant one, and we have no doubt now, nor any difficulty in recognizing syphilitic aneurysms.

The general character of an aneurysm may be made clear by the description of one of the commoner forms—the saccular aneurysm of the aorta. In such a case (Fig. 399) it is found that the sac most commonly springs from the convexity of the arch, and that intense sclerotic alterations of the aorta surround its mouth. The orifice is round or irregular in outline, and the edge is rolled over into it somewhat, so as almost to overhang its cavity. The cavity itself may reach a very great size, the sac thus formed pushing aside the surrounding organs or embedding itself in them in the most remarkable way. Mechanical effects pro-



Fig. 398.—Syphilitic myocarditis with extensive scarring.

duced in this way are of great variety, depending largely upon the point of origin and size of the sac. Pressure on the recurrent laryngeal nerve produces an alteration of the voice from spasm or paralysis of the vocal cord, coughing, dyspnoea, etc. Pressure on the trachea flattens it and causes dyspnoea. Later the aneurysm may rupture into it after eroding its wall. The lungs yield and collapse before the aneurysm. Pressure on a bronchus narrows it, and behind the obstruction bronchiectasis arises. When the sac reaches the bony structures of the thorax, which do not yield, it hammers its way through them, appearing under the skin through a hole in the ribs or sternum. If it extends backward to the spine, it destroys the centra of the vertebrae even down to the spinal canal (*cf.* Fig. 35), leaving the yielding intervertebral discs standing

almost unaltered; in the same way it may break through the ribs in the back and appear under the skin there. Then it is not long before the skin becomes thinned out and bluish, and finally the sac ruptures, so that death follows at once. Often it ruptures, long before reaching the skin, into the pleura or pericardium, trachea, or oesophagus, or even into the superior or inferior vena cava.

The character of such a sac which can produce a huge and destructive tumor, which destroys itself as soon as it completes its advance, must be



Fig. 399.—Syphilitic aortitis with aneurysm of arch of aorta partly filled by thrombus.

interesting. It is not really composed of the stretched-out walls of the vessel, for microscopic examination with suitable stains shows that practically all those elements stop sharply at the edge of the orifice. The elastic tissue and the muscle are suddenly interrupted. Endothelium may persist and attempt to line the sac, but it is evident that it soon fails in this and is lost. Indeed, nothing but connective tissue, and that essentially new formed, goes to make up the sac. It grows largely by new breaks in the wall which seem to be made good by further formation of fibrous tissue. The current of blood eddies about in the cavity, and its

pulsation gives the sac its power of breaking down the resistance of the tissues. But the endothelial lining is imperfect, and thrombosis occurs, and, if time be allowed, as it so often is, layer after layer of compact thrombus material may be hammered down on the wall of the sac until it is in large part filled up (Fig. 400). Occasionally the aneurysm may be completely obliterated in this way. The character of the fibrous wall is such that little upgrowth of organizing granulation tissue into the

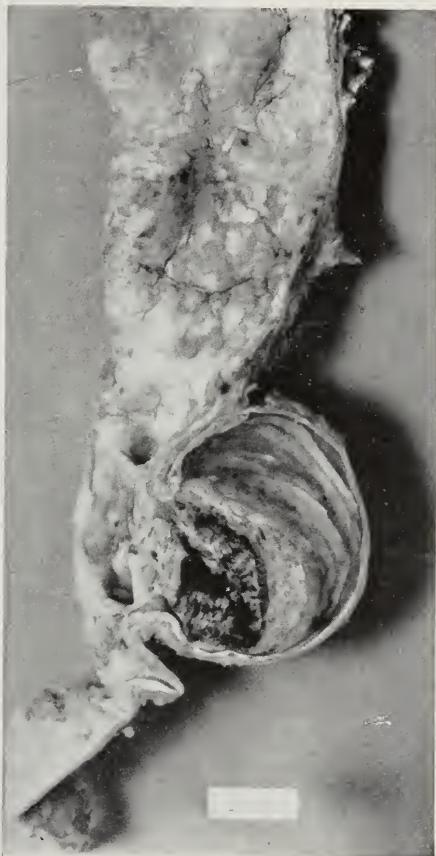


Fig. 400.—Old syphilitic aortitis aneurysm of abdominal aorta with laminated clot almost completely filling it.

thrombus appears, and the lower layers become even more compact, until, on a smoothly cut section, they look like onyx. The wall itself becomes hyaline, and it is often impossible to say, in a microscopic section, where the wall ends and the thrombus begins. In the smaller and fresher aneurysmal sacs the wall, wrinkled and irregular, is generally shining, thick, and rather translucent, and quite uncovered with thrombi or covered with only the merest film.

Quite the same characters are found in aneurysms in the abdominal aorta or its branches, in the arteries of the extremity or the head. Sometimes several small ones occur side by side, even in the aorta; sometimes, when one in a peripheral artery has been cured by operation, a new one will appear in another vessel. There was a syphilitic negro cook on a steamboat who returned to the hospital three times, each time with a new aneurysm. But usually one is enough if it affects the aorta, and all the vaunted methods of cure are rather unsatisfactory except in rare cases.

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**Lymph-nodes.**—The regional lymph-nodes, as has been said, become infected and swell slightly a few days after the appearance of the initial chancre. This swelling is never great, nor does suppuration take place unless there is combined with the syphilitic infection some other, such as that characteristic of the soft chancre. Instead, the nodes remain small and firm and recede after a time to their former size. In the secondary stage, that is, at the end of the second incubation period, the lymph-nodes become enlarged and palpable throughout the whole body. This is so characteristic that it becomes a valuable diagnostic aid in this stage of the disease. Microscopically in both these stages the change is seen to be essentially an increase in the number of lymphocytes, and especially of larger mononuclear cells, which fill the sinuses and are often phagocytic.

These large cells are also found with the lymphocytes in the lymph cords and are looked upon by most writers as endothelial or reticulum cells. Their nature is questionable in this case, as in many others in which they appear in the same way. The connective-tissue framework of the nodes seems to be increased after a time.

In the tertiary stage a similar enlargement of the nodes in certain localities may occur, but the most characteristic change is in the development of gummata in their substance. This is not common and is usually found in association with gummatous lesions in the neighboring organ. Thus large gummatous masses in the bronchial nodes were found in a case of syphilitic disease of the lungs, while gummata of the portal and retroperitoneal nodes accompanied a fresh gummatous cirrhosis of

the liver with involvement of the vena cava (Johns Hopkins Hosp. Bull., 1903, xiv, 88).

The spirochæte are found abundantly in the swollen nodes accompanying the primary and secondary stages.

**Blood changes** in syphilis are indefinite and not thoroughly studied; there has been much confusion as to the part played in producing them by mercurial treatment, but it seems that the infection by itself can produce a rather severe anaemia in the secondary stage. This is sometimes spoken of as syphilitic chlorosis. A moderate lymphocytosis is also found.

**Alimentary Tract.—The Mouth.**—It has already been mentioned that primary and secondary lesions occur in the mouth, chancres upon the tonsils, lips (Fig. 401), and tongue being relatively common among the forms of extragenital infection. Histologically and in their gross appearance they resemble those found elsewhere, and the glands which drain these regions become enlarged and very hard during the existence of the chancre.

The diagnosis is sometimes difficult, especially in the case of the chancre of the tonsil, which is often anything but characteristic.

The tertiary lesions are common and important. Gummata sometimes appear on the *lips*, but more often the whole lip becomes indurated by the formation of a diffuse infiltration throughout it of the character of the syphilitic granulation tissue. Ulceration may be most extensive, and with scarring the mouth is extremely distorted, so that, for example, the whole upper lip is destroyed, the gap extending into the nostrils and exposing the teeth and gums. With healing, the orifice of the mouth is drawn into a stiff, triangular opening. On the *tongue* actual gumma formation is more common, diffuse infiltration less so. The gummata, often multiple, arise beneath the surface and extend to the upper surface of the tongue, where they break through, forming a deep ulcer with steep walls and stiff, translucent base. Healing leaves a distorting scar.

It is important to distinguish such ulcerating gummata from epithelioma of the tongue and from tuberculous ulcers. The epithelioma starts from the surface, usually at the margin, and extends to the floor of the mouth, growing more slowly than the gumma. Histologically it is, of course, easy to make the distinction.

The diffuse infiltration of the tongue is more serious, because it causes great enlargement and rigidity of the organ, later, in healing, leaving the surface deeply fissured but otherwise smooth. This smooth atrophy of the villi of the tongue has long been recognized as syphilitic. Particularly harmful is the rigidity of the tongue which exposes it, especially where it is enlarged, to all kinds of injuries.

Gummata are rare in the tonsils, but are more common in the hard and soft palate. Beginning usually from the nasal side from the periosteum the gummatous nodule projects both into the nose and mouth, and, soon ulcerating and discharging its contents, it produces great destruction of the bones of the nose and an open perforation from the nose into the mouth. This allows of a nasal speech (*rhinolalia*) and also

of the passage of food and fluids through the nose. It is even worse when the soft palate is in the same way partly destroyed, for the necessary opening and closing off of the posterior nares is impossible. Gummatous ulcerations of the pharynx usually heal with less distortion, but the



Fig. 401.—Various examples of chancre of the lip (Keidel).

healing of the lesions of the soft palate and fauces is likely to produce a sort of stenosis or great narrowing of the buccopharyngeal and nasopharyngeal passages.

*Œsophagus and Stomach.*—Primary and secondary lesions of the œsophagus are practically unknown. Tertiary or gummatous changes

have been described—gummata arising in the submucosa and rupturing to produce ulcers which in healing give rise to stricture of the canal.

In the stomach there have been found diffuse infiltrative processes in the submucosa and mucosa and also gummatous formations which on breaking down produce extensive ulcers, easily distinguished from the ordinary round ulcer of the stomach. Such lesions may sometimes extend into the duodenum. Harris and Morgan describe the finding of spirochætes there.\*

*Intestine*.—Tertiary lesions of the small intestine are usually localized in the jejunum, or the upper ileum, where they appear as flat elevations of the character of a syphilitic granulation tissue involving submucosa and mucosa. Multiple ulcers are found which extend in the

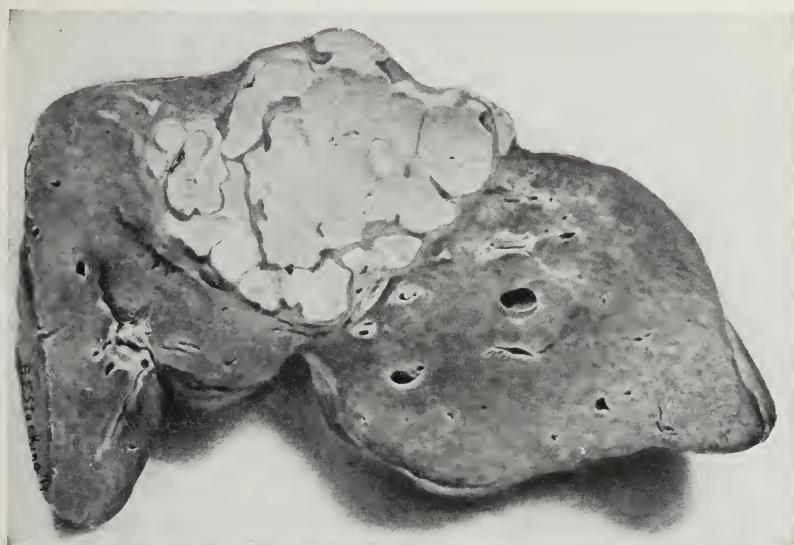


Fig. 402.—Large gumma of liver.

form of rings round the gut, and which in healing may produce strictures. There is a remarkable example of this in the Pathological Museum of Columbia University; but the condition must be very rare. Indeed, the only syphilitic lesions of the intestinal tract which are common are those found in the *rectum*. There, especially about the anus, chancres may appear, and secondary lesions in the form of moist papules and flat condylomata are extremely common. Various other secondary lesions involving cellular infiltration of the mucosa, abscess formation, and even fistula production occur at this stage.

**The Liver.**—Little is known of any secondary syphilitic lesions in the liver. The recognized changes are essentially characteristic of the tertiary stage and consist in the formation of gummata, often with extensive inflammatory infiltration of the liver substance, and scarring. It is not usual to find fresh gummata at autopsy, but in one case we

\* Harris and Morgan: Jour. Amer. Med. Assoc., 1932, xcix, 1405.

found numerous groups of miliary and submiliary gummata which, in some places, were beginning to be caseous and in others were surrounded by scars. The formation of these lesions involves the destruction of the liver substance and to a less extent the pushing aside of the tissue. They are usually numerous, but sometimes they coalesce into a great tumor-like mass (Fig. 402). In one instance which I saw there was a great nodular tumor projecting from under the edge of the liver so as to be palpated through the abdominal wall. It melted away rapidly under energetic antisyphilitic treatment, which, after all, with the history, was the chief proof of its gummatous nature.



Fig. 403.—Gummata in the liver with extensive scarring. There is one large gumma in the wall of the vena cava, as it passes behind the liver, with thrombosis of the vein.

Iodides as well as mercury were given in this case, as has been done for many years. Jobling and Petersen have recently explained the action of iodides as follows. The softening and removal of caseous necrotic material from a gumma is due to a tryptic ferment. The gumma, however, persists and remains firm because it contains large quantities of antitryptic substances which are of lipid nature, being combinations of unsaturated fatty acids. Their power of antagonizing the ferment depends upon their unsaturation, which in turn can, as is well known, be satisfied by iodine, this forming the basis of the well-known index used in estimating unsaturated fatty acids. Administration of iodine by saturating the antitryptic substances destroys their power over the tryptic ferments, which then dissolve the caseous material.

Probably the most common condition is that in which numerous distinct gummata of the consistence of Swiss cheese are formed throughout the liver, and are found as the centres of extensive radiating scars. In one such liver (Fig. 403), in a case which presented evidences of syphilis

elsewhere, the organ was decreased in size and roughly and very coarsely nodular. On cutting through it, it was found to be permeated by a network of coarse bands of gray fibrous tissue which separated large masses of relatively normal-looking liver tissue, into which, however, finer bands extended. At three or four places on the cut surface there were at the nodal points of the scars firm, yellowish-white masses of caseous material up to 1 cm. in diameter. Further, as it penetrated the diaphragm, the inferior vena cava was surrounded by a large gumma

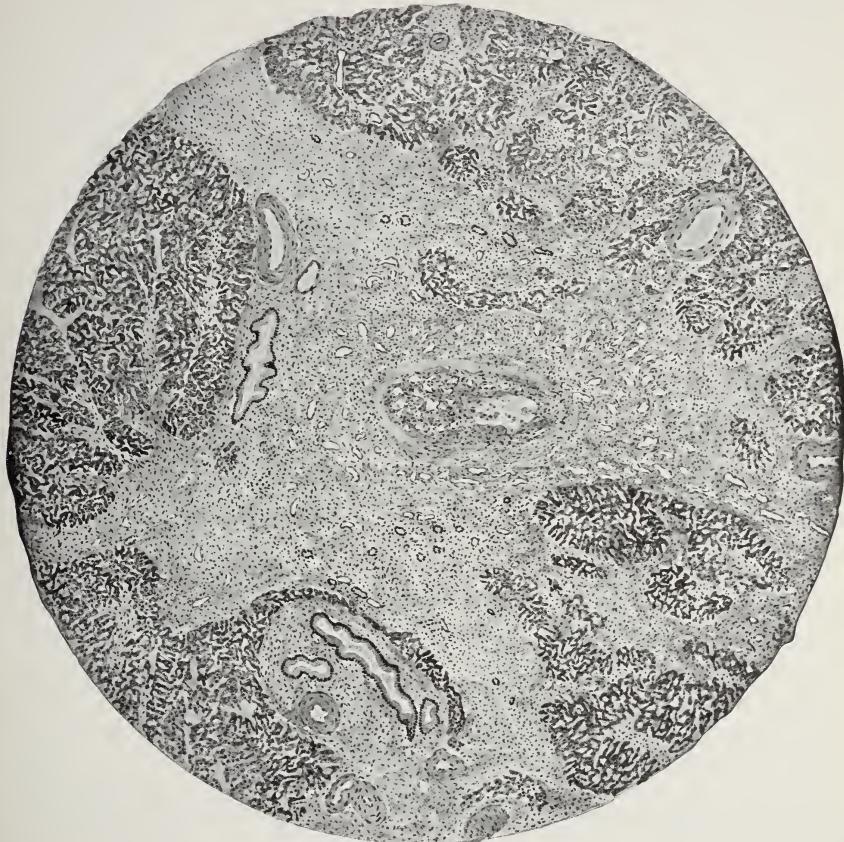


Fig. 404.—Old scar in a syphilitic liver. In the centre is a large vein which has become partly recanalized after obliteration.

originating in the liver and projecting through the diaphragm. It involved the wall of the vein and almost occluded its lumen, the closure being completed below by a great thrombus which extended down into the renal veins.

Such are the relatively fresh conditions, but generally only the broad scars remain (Fig. 404), and one finds the liver greatly distorted by the replacement of whole areas of liver substance by these scars, which have retracted into the organ as though cords had been tightly tied about it,

cutting deep into its substance. The rest of the liver is normal or, more usually, enlarged by a compensatory hypertrophy. Many of the features characteristic of cirrhosis of the liver, the regenerative processes, and the distortion of the circulation as well as of the liver tissue, may be found in these cases. Ascites, portal stagnation, splenic enlargement, and jaundice may occur, but they vary with the varying mechanical conditions, and the presence of large gummata and scars about the portal region and bile-ducts naturally plays an important part in this regard.



Fig. 405.—Old syphilitic cirrhosis with deep constrictions where there are scars.

Such a deeply lobed, distorted liver (Fig. 405) is almost always the result of syphilitic infection. It is not, however, the only effect which can be produced by that disease, since in other instances one may find a much finer scarring, evidently due to a more diffuse affection.

In the *salivary glands*, particularly the parotid, and in the *pancreas* gummatoous and diffuse syphilitic lesions have been described in a few cases.

Warthin has studied the pancreas in old cases of syphilis, and found that it often shows scarring, and that the scars are frequently the site of definite infiltrations of plasma and lymphoid cells, such as he has

found to be characteristic effects of syphilis in other organs. This chronic interstitial pancreatitis, so-called, is often accompanied by diabetes, and, indeed, in two cases he found the spirochætae in the areas of cellular infiltration. Warthin will not say that diabetes is dependent upon syphilis as its common cause; this demonstration is rather part of his general thesis that syphilis produces wide-spread injury and cellular infiltration of many organs, which is generally overlooked.

In the *kidney* gummata are sometimes met with and changes leading to diffuse scarring and contraction of the kidneys due to syphilis have been said to occur. Probably they depend upon intimal lesions in the renal arteries.

**The Respiratory Tract.**—Syphilitic lesions are found in the upper air-passages, larynx, and trachea, and rather less commonly in the bronchi and lungs.

In the *nose* chancres are not uncommon, appearing at the orifices of the nostrils, or the alæ nasi, or even in the interior, on the septum. They are caused, as a rule, by infection from the fingers or from handkerchiefs.

In the secondary stage the most common manifestation is a syphilitic erythema, or reddening, which appears in flecks, sometimes later covered by a necrotic layer of epithelium and occasionally giving rise to nose-bleed. This is the basis of the coryza which is a common accompaniment of this stage of the disease. Papules and actual condylomata sometimes arise in the nose. Far more important and quite common are the lesions of the tertiary stage, which, as elsewhere, are diffuse syphilitic infiltrations or gummata. The former may produce thickening of the mucosa over the septum or turbinates, generally with ulceration, which may penetrate the cartilage or bone, and, often through the aid of secondary infections, leads to destructive perichondritis and periostitis. Naturally this process involves the risk of extension upward to the ethmoid and sphenoid bones, and meningeal infection may follow. Sometimes great tumor-like masses are formed at the base of the septum or elsewhere. Similarly, definite gummatous lesions appear in the mucosa or in the perichondrium or periosteum of the bones which constitute the interior of the nose. Extensive deep ulcerations follow, and whole bones become necrotic sequestra. The septum may be completely destroyed, as well as the turbinates, and large portions of the vomer and the nasal bones. The nose is in this way hollowed out into a great cavity, the lining of which is a scarred and atrophic mucosa. The process is accompanied, so long as necrotic bone is present, by the most nauseating foetor. At times, as has been mentioned above, perforation of the hard palate or destruction of the soft palate occurs. In the course of healing the most extensive adhesions and strictures of the air-passages develop, so that sometimes the nasal cavity may be quite shut off from the pharynx. Great deformities of the face result, since, with the collapse of the nasal bones, the nose sinks into the opening produced. The mildest form of this is perhaps the saddle-nose so often seen in the streets and so common in late cases of congenital syphilis, in which the bridge of the nose is

sunken and the tip turns upward, exposing the nostrils in front (Fig. 406). But in countries like Morocco, where the disease is neglected, one sees the most extreme deformities, produced by ulceration through the skin, so that the whole nasal cavity is open to the outside and into the mouth, and all semblance of a face has disappeared.

In the nasopharynx the same series of lesions may appear, and there are instances of chancre of the Eustachian tube having been caused by the use of an infected Eustachian catheter.

**Larynx.**—The lesions of the larynx might be inferred from what has been said of the nose. Although secondary changes occur there, the tertiary phenomena are most important. Gummatous lesions involve the arytenoid cartilages and epiglottis most commonly, but may affect any

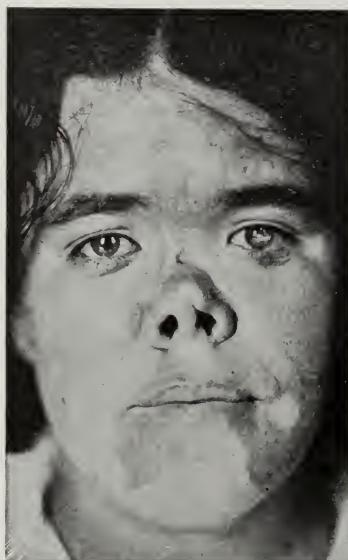


Fig. 406.—Late congenital syphilis showing "saddle-nose," interstitial keratitis, and leucoderma.

other part. The deep precipitous ulcers with abundant yellow secretion are capable of destroying the vocal cords and of leading to necrosis of the cartilages. They must be distinguished from tuberculous and cancerous ulcers in the same places. Healing leads to great deformity and stricture formation in the larynx, for which tracheotomy is sometimes necessary.

We have observed at autopsy one case in which the obstruction of the larynx was extreme, the vocal cords being converted into great scarred masses which could not be much separated. One effect was the dilatation of the trachea and bronchi and an extensive secondary infection of the lung with the formation of huge abscesses.

**Trachea, Bronchi, and Lungs.**—Tertiary lesions in the trachea and bronchi are usually in the form of syphilitic granulation tissue, although

sometimes definite gummata may arise in the wall or extend from outside. The process causes much thickening of the wall with ulceration which lays bare and softens or destroys the cartilage rings.

In such a case the trachea and bronchus may collapse at an angle or be compressed. Usually healing takes place with the formation of a scar which causes a stenosis of the canal. Almost any part of the trachea may be involved, but it seems that the region of the bifurcation is most commonly affected, the stricture narrowing one main bronchus. This was the condition found in a case studied in Baltimore, and the effect upon the lung, as might have been foretold, was to produce most extensive bronchiectasis. The reasons for this are discussed elsewhere.

The clinical signs in such a case are rather definite, since the harsh stridor of the air passing the obstruction, and the prolonged expiratory sound on that side, indicate clearly the existence of a stenosis. When the stenosis appears in a branch of the main bronchus there are localized changes in the breath sounds, and the bronchial dilatation and emphysematous alterations in the lung are limited to the area which is supplied with air by that bronchus.

In the lung itself, aside from the congenital changes, the lesions due to syphilis are not very clearly nor surely recognized. Gummata of various sizes up to tumor-like masses occur anywhere in the lung. They are grayish or reddish-gray nodules, sharply outlined, and radiating fibrous strands into the rest of the lung. One occasionally sees these masses, which in the absence of obvious tuberculosis and when other signs of syphilis exist it seems proper to diagnose as gummata; but doubtless many of those described may have been localized encapsulated tubercles. About the large vessels at the hilum of the lung and the large bronchi gummatoindurative processes occur, with great thickening of the adventitial walls of the vessels and some constriction of the bronchi. Great scars extend out into the remainder of the lung and bronchiectasis follows the obstruction. This has been called the indurative bronchiectatic type of pulmonary syphilis. Whether pneumonic or ulcerative forms of syphilis with cavity formation really exist is uncertain. The confusion with tuberculosis, and especially the fact that syphilitics are very prone to tuberculosis, makes this point difficult to settle (Flockemann: Centrbl. f. allg. Path., 1899, x, 469).

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Bones and Joints.—It is said that periosteal inflammation may form a part of the secondary stage of syphilis, but there is as yet very little anatomical evidence with regard to this. Secondary lesions of the joints are also mentioned. But the later lesions of both bones and joints are far more frequently met with and far more serious.

Tertiary lesions of the *bones* seem to affect most commonly the skull, the tibia, the fingers, and other bones which are very superficially situ-



Fig. 407.—Tertiary syphilis: ulcerated gumma of leg (Keidel).

ated, while less is known of those which occur in the more protected bones. Possibly this is due to the influence of trauma in determining the site of gummatous affections. Part of the anatomical changes due to syphilis are distinctly and characteristically gummatous, while there are others which are quite like the results of chronic inflammation of the bone produced by other causes, except perhaps in their history and in their association with other syphilitic lesions. Probably, however, the study of these chronic inflammations for spirochaetae will show more clearly their syphilitic character. Although the bone is soon involved, these are at first essentially affections of the periosteum, which is torn from the bone by an inflammatory infiltration composed chiefly of mononuclear wandering cells. With rupture of the periosteum the overlying skin may be broken through, after which the place is exposed to

further infections. Such an ulceration often exposes the underlying bone, parts of which become necrotic and separate from the rest as a sequestrum which may be discharged. Syphilitic ulcers of this type are long in healing (Fig. 408). By no means all such inflammations end in ulceration; instead, they produce a great new growth of spongy bone on the surface of the old cortex, forming in this way a convex layer



Fig. 408.—Tertiary syphilis: syphilitic ulcers over shins (Keidel).



Fig. 409.—Syphilitic periostitis and osteophyte formation.

which, when the bone is macerated and dried, has something of the appearance of rough pumice stone. Sometimes it is much denser and may even be very hard and solid (Fig. 409). Such osteophytes often rise in a sort of wall about the area of most intense inflammation where necrosis has actually occurred. It is this process which gives origin to many of the thickenings with rough, irregular surface which one finds so commonly on the shafts of long bones in any collection, but it must

be recognized that these are not all syphilitic—other non-specific forms of periostitis can produce the same thing. In another form the new production of bone is more extensive still, and no longer limited to the activity of the periosteum; it is laid down in each Haversian system and through the cancellous bone in the interior, so that the shaft of the bone becomes dense and ivory-like and the whole bone is much heavier than normal. There is no special localization for these processes, although it is true that thickenings of the long bones, the clavicles, the sternum, etc., are particularly common.

Somewhat more easily recognized and characteristic of syphilis are the gummatous lesions which may arise in connection with the peri-



Fig. 410.—Old syphilitic erosion of the skull. The margins in this case are smoothed off by a healing process.

osteum or in the interior of the bone. In the first case the gummatous tissue extends along the blood-vessels into the bone, enlarging their canals and eroding the bone to a peculiar worm-eaten appearance. Sometimes, as in the skull, the periosteum can be torn off, pulling out of their canals a lot of these great cellular extensions and leaving a coarsely corroded surface. Complete destruction of the bone is easily produced by their confluence, and it is common in these cases to find the skull penetrated by a ragged hole filled by the gummatous mass which generally extends to involve the dura mater and often enough the underlying brain. But there are many cases in which the dura limits the process and the necrotic débris is discharged externally. Osteophytes from the periosteum surround such an area and make the defect seem

deeper. The same gummatous nodes are often found on the shins, extending into the cortex and marrow cavity, and often circumscribing and causing the necrosis of fragments of the bone. The most extensive destruction may occur in the skull (Fig. 410), and especially in old specimens derived from long untreated cases, one sees great gaps in the cranium with ragged margin and surrounded by rough osteophytes. In all these processes the simultaneous existence of rarefaction and condensation or sclerosis of the bone is to be observed. In this respect the syphilitic changes stand in contrast to the tuberculous, where rarefaction of the bone is accompanied by very little new formation.

Gummata formed in the marrow cavity are of sufficiently frequent occurrence, although they were practically overlooked until Chiari demonstrated their existence. They are gelatinous patches, often bright yellow from their content of fat, which may occur singly or in such numbers and continuity as to involve the whole marrow cavity. Generally there is no outward evidence of their existence, but the cortex may be attacked and eroded and the periosteum outside produce a new layer of bone to correspond. In this way there may be a spindle-shaped dilatation of the bone; canals or fistulae are formed through the cortex, and, except for the absence of sequestra, the bone comes to look like the end-results of an ordinary osteomyelitis.

Gummatous osteoperiostitis with enlargement and rarefaction and internal destruction of the bone in the phalanges, is found in the so-called syphilitic dactylitis. The finger swells and sometimes there is fracture of the weakened bone or the gummatous material is discharged through a fistula.

These, then, are the usual syphilitic affections of the bone: (a) periosteal gumma formation with necrosis of the underlying bone, followed by ulceration and exposure through the skin or by the extensive osteophyte growth, and (b) gummatous osteitis or osteomyelitis with necrosis and erosion of the directly affected part and rarefaction or sclerosis of the surrounding bone.

All these things may make their appearance fairly early in the disease or only after long years of apparent health.

As in the case of the bones, the joints, bursæ, and tendon-sheaths often reveal a susceptibility to syphilis only after many years of the disease. There may be an accumulation of watery exudate only, or the formation in the synovial membrane of a syphilitic granulation tissue with ulceration, and great proliferation of the adjacent unaffected membrane and synovial villi. Probably in many cases the joint affection is secondary to the appearance of gummatous infiltration of the epiphysis.

This lifts up and destroys the cartilage, and healing takes place after much loss of time through the obliteration of the cavity by fibrous tissue. In the bursæ and tendon-sheaths painless swellings due to the appearance of a lining of gummatous granulation tissue persist for a long time but yield, as do the joint affections, to specific treatment.

The accurate recognition of syphilitic lesions of the bones has acquired a special importance for those who have been attempting, by

studying mummies and long buried skeletons, to determine the origin of the so-called pre-Columbian syphilis. This is to investigate the widely accepted idea that syphilis was introduced into Europe by Columbus' returning sailors who became infected in Haiti or some one of the neighboring islands.

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#### SYPHILIS OF THE GENITAL ORGANS

Of the syphilitic lesions of the male and female genitalia, aside from the primary chancres and the condylomatous and other affections of the secondary stage which have already been mentioned, the gummatous and interstitial changes in the testicle are the most common and important.



Fig. 411.—Gummata of the testis. Firm caseous nodules stand out in relief on the cut surface.

Gummatous and other lesions have been described in the vagina, uterus, tubes, and ovaries, and also in the vas deferens, seminal vesicles, etc., but there are such rare occurrences, and so imperfectly studied that we may turn at once to the testicular affections.

It has been pointed out by Chesney and others that in rabbits inocu-

lation of the testicle permits a more active growth of spirochaetæ than inoculation elsewhere and is accompanied by an extensive reaction. Indeed, it appears that syphilitic orchitis may be the prominent lesion in animals inoculated subcutaneously, so that it seems that the testicle constitutes a favorable medium for the growth of these organisms.

Gummata are relatively frequent there, probably more frequent than in any other situation except, perhaps, the liver and periosteum. In the series of untreated cases already referred to as studied in Singapore, 7 instances were found in performing 40 autopsies (Fig. 411), but in a second series at the same hospital eight years later, when treatment had been resumed, no cases were found.

Such gummata appear as firm, dry, opaque, yellowish masses pushing aside the tissue of the testis (Fig. 390) and later becoming encapsulated.



Fig. 412.—Pearly scars through the substance of the testis, the so-called chronic fibrous orchitis.

In other cases in this country we have seen the whole testis involved in the caseating process, sometimes producing great masses which might be mistaken for tumors.

In that this is primarily an affection of the testis it differs from tuberculosis, which begins, as a rule, in the epididymis, only secondarily, if at all, invading the testis.

Aside from the gummatous process Warthin states that in many cases the lesion is to be found in the form of loose granulation tissue with accumulations of plasma cells and lymphocytes among which spirochætæ are sometimes found.

Whatever the original form, healing results in the production of scars which show on section as shining, translucent, pearly bands against the dull brown of the remaining testicular substance, and are commonly re-

ferred to as chronic fibrous orchitis (Fig. 412). About the actual scars where all the original tissue has been destroyed there are usually areas in which the tubules have become atrophic with great thickening of the basement membrane. The spermatogenic elements disappear in the reverse order of their formation until only spermatogonia and Sertoli cells remain, and later these too disappear, leaving only the hyaline membrane of each tubule still recognizable for a long time. Leydig's cells may persist among these for a very long time.

The idea that such orchitis fibrosa is pathognomonic of syphilis is certainly mistaken, as pointed out long ago by Chiari and others. It may follow trauma, gonorrhœa, mumps, and other things. Mills, in studying the testes from the cases of pneumonia following epidemic measles and influenza, was able to show an atrophy of the spermatogenic cells very frequently. Still, the presence of extensive atrophy and scarring of the testicle may well form confirmatory evidence of syphilis when found in conjunction with other lesions, such as an aneurysm.

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## CHAPTER XXXVIII

### TYPES OF INJURY.—SPIROCHÆTAL INFECTION (Continued)

*Syphilis:* *Syphilitic lesions of nervous system.* *Syphilitic meningitis.* *Tabes dorsalis.* *General symptoms.* *Lesions of the nervous system, theories concerning it.* *Dementia paralytica, its relation to tabes; symptoms.* *Anatomical changes in brain and cord.* *Congenital syphilis.* *General relations.* *Lesions in respiratory organs, liver, pancreas, bones, etc.* *Late forms of congenital syphilis.* *Other spirochetal infections:* *Yaws.* *Spirochatosis icterohaemorrhagica.* *Vincent's angina or Trench mouth.*

#### SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

BECAUSE of their frequent occurrence and their gravity, syphilitic lesions of the central nervous system are second only in importance to those of the circulatory system. The commonest and, therefore, the most important are those forms of meningitis or meningo-encephalitis which



Fig. 413.—Gumma of brain distorting cerebral convolutions and adherent to the meninges.

are usually spoken of as neurosyphilis, although this term may also include other forms. Less common are large gummata in the brain, often extending from the dura and skull (Fig. 413). There are also to be classed here, since the actual demonstration of the spirochætæ in the tissues, dementia paralytica and tabes dorsalis.

**Syphilitic Meningo-encephalitis.**—There is a suggestion that certain persons or families are predisposed to a cerebral localization of the infection (Keidel) or even that certain strains of the organism are particularly likely to invade the central nervous system, but both of these ideas require further proof. At least it seems clear that when the nervous system is invaded, this occurs at a relatively early period in the disease sometimes only a few days after the primary infection.

The symptoms are variable and it seems that clinically there might be distinguished three groups (Merritt and Moore): (1) Acute syphilitic hydrocephalus, from meningitis obstructing the cerebrospinal fluid, with headache, nausea and vomiting, choked disc and stiff neck; (2) meningitis affecting the cerebral surfaces with headache, nausea, convulsions and mental disturbances, and (3) basilar meningitis with cranial nerve palsies. In these the cerebrospinal fluid obtained by lumbar puncture is under tension. It shows no bacteria, but a lymphocytic reaction with few polymorphonuclears, usually a positive Wassermann reaction, although that of the blood may be negative, and sometimes spirochaetæ, as in the cases of Kemp and Chesney, Leitch and others.



Fig. 414.—Gumma in the brain showing the indefinite outline.

There are not many careful studies of the pathological changes but the student may be referred to the articles of Nonne, Krause, Gennerich, and for the clinical description to those of J. E. Moore and Keidel, and the recent review of Merritt and Moore. Strasman describes the meningeal changes as areas of clouding of the pia which microscopically show the blood-vessels in the pia and entering the brain surrounded by lymphocytes with numbers of spirochaetæ. The vessels entering the cord were similarly thickened and nearly obliterated with swarms of spirochaetæ in their walls and extensive changes in the substance of the cord, apparently resulting from this disturbance in the blood-supply. Leitch found practically the same condition in a child of one year and Nonne describes a similar case with abundant spirochaetes in the pia and adventitia of the pial vessels.

Actual gumma formation in the brain, such as to produce a gross caseous nodule, is not very commonly observed, at least since the treatment of syphilis has become so energetic and so universal. The most common are those cases in which a gummatous mass is found in the cortex of the brain connected through the pia-arachnoid with the dura and even penetrating through the skull (Fig. 413). Such a gumma may be several centimeters in diameter or there may be a conglomeration of caseous masses occupying a much greater space. The central yellow, opaque, firm, necrotic material is surrounded by grayish-red tissue, which radiates into the surrounding brain substance, and extends with much grayish granulation tissue to the dura (Fig. 414). The brain substance is not merely pushed away—it is invaded and infiltrated in this process, and along the vessels there is a great accumulation of mono-

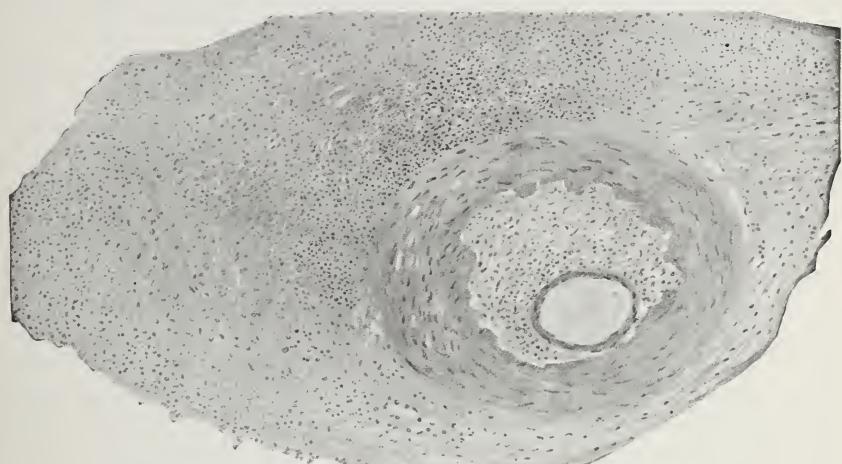


Fig. 415.—Gumma of pial blood-vessel. Syphilitic meningitis.

nuclear cells. The gumma may be lodged in the medulla or in the spinal cord, but it must be said that most common are those which are superficial and connected with the meninges.

Gummata involving cranial or spinal nerves, often at their roots, surround and enclose the nerve-fibers and often bring about their destruction with consequent degeneration of the peripheral part and paralysis. One case which we observed at autopsy with paralysis of the arm muscles revealed a caseous gumma, matting together the nerves of the upper arm (Remsen).

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### LOCOMOTOR ATAXIA, OR TABES DORSALIS

We may consider this disease here, together with the general paralysis of the insane. Statistical study has given figures which point in an unmistakable manner to syphilis as its cause. Erb found syphilis in 89.5 per cent. of the cases, and others have found a similar percentage. Recently Noguchi found the spirochaeta in the cord in 1 case out of 12 and others have found them not infrequently.

The disease is in large part an affection of the lower sensory neurons, although we shall find that these are unequally altered in different parts, and that while many of the phenomena are to be explained as the result of this lesion, there are others which are not.

The clinical aspect of the disease is extremely variegated, though most of the symptoms are the result of disturbances of the sensory apparatus, partly irritative, partly paralytic. Reflexes and movements depending on muscle sense, and, consequently, coördination, are much disturbed.

Violent stabbing pains in the limbs or elsewhere (lightning pains) occur especially at night; sudden attacks of cramp-like pain in some internal organ—stomach, larynx, bladder, etc.—are known as gastric or laryngeal or vesical crises. A period of sexual excitement is followed by impotence. The tendon reflexes are abolished; the pupils become inactive and fixed. Sensation is dulled or perverted; the patient no longer feels the floor he walks on, or feels it like so much wool. He loses his sense of the position of his extremities and must watch his feet in order to set them in the right place; inattention may result in a fall. The gait becomes peculiar and slapping. This ataxia, which has given rise to one of the names, may affect any or all of the muscles.

So-called trophic changes arise in various places. Half of the tongue atrophies; an ulcer appears in the foot and proceeds to grow deeper, painlessly, until it perforates the foot. The bones become fragile and break, and fail to heal again. Joints loosen and become disorganized; the cartilage softens and the bone is eroded, or great dislocation may occur. Disturbed nutrition of the tissues in general seems to arise and the patient dies of an intercurrent infection, although seizures, simulating apoplexy and epileptiform convulsions, may have been survived. The details of these symptoms must be read elsewhere, most clearly perhaps in Marie's "Leçons sur les maladies de la Moelle."

**Lesions.**—At the autopsy the lesions depend upon the stage of the disease. If the patient dies at an early period, it may be necessary to search with the microscope for any change, but if it has lasted a long time the spinal cord with its posterior nerve-roots shows a characteristic appearance. The meninges (pia arachnoid) may be thickened and cloudy in part or quite normal looking, but the posterior columns are sunken

and the dorsal roots look gray and smaller than normal. On section, the dorsal columns are gray and translucent in contrast to the remaining pinkish, opaque, white matter. It is rarely possible to distinguish with



Fig. 416.—Tabes dorsalis. Dorsal region of cord. Moderate sclerosis of posterior columns (Fordyce).

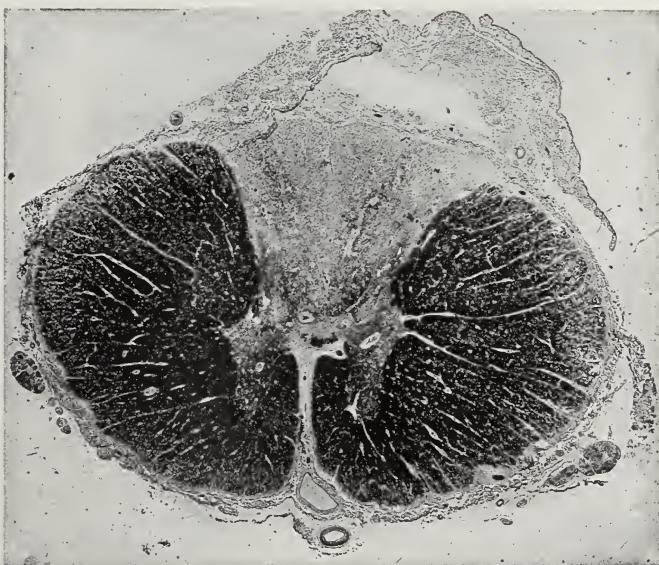


Fig. 417.—Tabes dorsalis. Dorsal region of cord with extreme sclerosis of the posterior columns (Fordyce).

the naked eye the exact distribution of this gray material in the dorsal columns, but with certain stains the microscope shows it well. The grayness and translucence are due to the disappearance of the lipoid myeline

sheaths, as well as the axis-cylinders of the nerve-fibers and their replacement by an overgrowth of neuroglia. If the process were fresh enough, the myeline might not have disappeared entirely, but its remnants could be made visible as black globules by the use of osmic acid, which does not blacken the normal myeline sheath. After a week or two, however, these fat-globules disappear, and then the injured area can best be made apparent by the Weigert stain, which colors bluish-black all the normal myeline sheaths and leaves the wasted and scarred area unstained. It is usually this unstained area which one can demonstrate in tabes (Figs. 416, 417).

It will be recalled that the posterior roots are largely made up of central processes of the dorsal root ganglion-cells, which were at one era of development bipolar and still are in certain cranial ganglia, but which now have one T-shaped process,

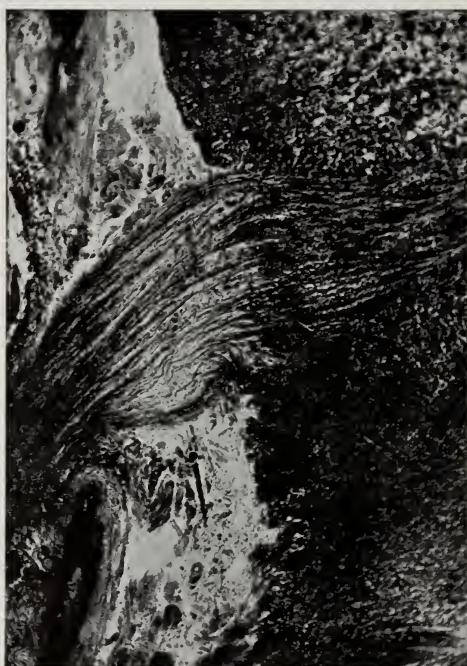


Fig. 418.—*Tabes dorsalis.* Degenerative changes in the posterior nerve-root (Fordyce).

one branch of the T coming from the periphery, while the other enters the cord. On entering the cord in the posterior root the fibres swerve a little to the median side of the end of the posterior horn of the gray matter, which does not quite reach the surface. They pass through the zone of Lissauer, which is made up of fine fibres which also come in as part of the nerve, and turning upward a short way, sweep along with the other fibres into the posterior column and into the posterior horn. The fibres entering by the posterior root bifurcate, sending a short branch downward, a longer branch upward. Three main groups are generally distinguished in the distribution of these upward branches: a short group which quickly turns into the gray matter of the posterior horn, a median group which runs up in the column

of Burdach—sometimes all the way, but often leaving it to turn into the gray matter and end about a cell there—and a long group which passes into the column of Goll and runs up to the nucleus of that column in the medulla or even further. It is the column of Goll which brings fibres even from the lower lumbar region.

The fibres of the dorsal root, which enter the gray matter, end in arborizations about ganglion-cells of that side, a great many of them constituting the fibre reticulum of the column of Clarke; or they pass forward to terminate about a ganglion-cell of the anterior horn, or cross by the posterior commissure to end similarly in the gray matter of the opposite side. Each fibre gives off many fine branches or collaterals which terminate in quite similar ways about the ganglion-cells of the gray matter, and thus forms abundant incidental connections at every stage in its progress upward in the cord, which are doubtless of fundamental importance in the establishment of reflex arcs.

Flechsig, Trepinski, and others have shown that, according to this distribution of the fibres, and according to the varying time at which they are matured by receiving their medullary sheaths, one may distinguish various subdivisions or tracts in the column of Burdach—a posterior, a middle, and an anterior root zone as well as a median zone which lies within the column of Goll against the median line.

In the middle root zone two types of fibres can be distinguished by their different time of myelinization, etc. Naturally these fields seen in any cross-section are only the expression of the currents of fibres at that particular level, and so must change as one ascends the cord, except inasmuch as the incoming fibres deport themselves in the same way at successive levels. But if a group of fibres entering the cord becomes recognizable by any degenerative change it need not be expected that those fibres will occupy the same position in the field higher up; on the contrary, they assume a new position or disappear because they have turned into the gray matter to end.

Consequently, it could only be through an exact repetition of the same degenerative change in each successive root that anything like the same distribution of degenerated fibres would be found at different levels, and even then in the higher levels the scarred remains of those entering far down and continued upward to that point would be added to those newly entering from a higher root.

The statement is generally made that in tabes dorsalis the beginning of the sclerosis or scarring is first seen in the “bandelettes externes,” or parts of Burdach’s column lying against the posterior horn; that the middle root zone is early involved and also the zone of Lissauer and the column of Goll, but that the anterior or ventral root zone is found intact until very late in the disease. While this is true, it must be true in any given case in different degree in different parts of the cord. The complete escape of a whole entering root, or of a series of them, from the effects of the disease at a point higher in the cord, allows intact fibres to appear in these situations, so that at those levels the areas of sclerosis are reduced to the upward prolongations which still continue from those below. And it is true that such escape of the roots may occur, just as it is true that the lesion need not be symmetrical on the two sides. But all this merely emphasizes the fact that the degenerative lesion in tabes is not like that produced by the cutting of a single dorsal root between its ganglion and the cord. The result of that would fade away into the gray matter, except in so far as a few degenerated fibres might be recognized continuing up the column of Burdach or in the column of Goll all the way to the medulla. Instead, in tabes there is a nearly constant and nearly symmetrical addition of the results of degeneration with the advent of each succeeding

dorsal root. And, nevertheless, the irregularities show that the process is not to be regarded as the complete degeneration of a column or system, but as a succession of segmental degenerations accumulating their results in the cord as one passes upward. It would be most instructive to have a reconstruction of this lesion from an early case of tabes, before the whole posterior tracts had become fused in the sclerotic band, to show the topography of these repeated additions of sclerotic tissue in the cord and their relation to the changes in the roots.

It is with regard to the nature of the changes in the roots that the most persistent dispute has raged. It is agreed that while the roots are pathologically altered, the changes in the portion between the dorsal root ganglion and the cord is more extreme than that in the peripheral nerves or in the ganglion-cells themselves, and consequently nearer to that seen in the cord itself. The following views have been expressed, most of which will doubtless disappear in the light of the simple explanation which must finally come some day.

The whole lesion is due to vascular obstruction (Adamkiewicz, Pandy); it is the effect of injury or destruction of peripheral ganglionic elements, which may also be responsible for ascending degenerations after amputations (Marie); it is a systemic degeneration of tracts in the cord itself corresponding with their developmental characters (Flechsig, Trepinski); it is the effect of destruction of the cells of the spinal root ganglia; it is the effect of meningeal inflammation about the entering roots which causes their compression and destruction (Nageotte); it is the effect of direct or indirect action of the syphilitic poison on the nerve roots, affecting less the ganglia, but producing the degenerative changes described (Redlich, Obersteiner). This is partly based on analogy with similar affections found in ergot poisoning and pellagra.

Of these, the last seems most likely to prevail, since the disease is clearly shown to be syphilitic and spirochætae have been demonstrated in the pia arachnoid and in the granulation tissue found in the interstices of these degenerating roots. Really it appears that except for the demonstration of the spirochete nothing has been contributed to the pathogenesis of the condition in the last twenty years, although a great amount has been written.

In the end one finds practically all of the posterior columns in the lumbar and dorsal regions reduced to a scar-like mass of neuroglia, the only exceptions, up to an advanced stage, being the ventral root zone and the medial zone. Lissauer's zone, the column of Clarke in the gray matter, and the column of Goll, with most if not all of the column of Burdach, are thus degenerated. In the cervical region the lesion is less extensive and reduces itself toward the column of Goll. Since these tracts are so intimately concerned with muscle sense and with the reflex arcs it is not surprising that ataxia, the loss of the sense of position, failure in the discrimination of weights, etc., should be prominent features of the disease.

Tactile sensation, temperature sense, etc., which are so largely concerned in the short relayed tracts in the cord and in the other ascending tracts not involved in this process, are less affected. The cells of Clarke's column connecting with the cerebellospinal tract must, however, lose some of their relations, since the fibres entering with the dorsal roots which arborize round them are destroyed.

It is difficult to explain the various "trophic" disturbances which are found in the tissues, such as the bone and joint changes mentioned above

and the alterations in nails, skin, etc., which are so frequent. With regard to the so-called Charcot's joints or tabetic arthropathy (Fig. 419) there has been much speculation. This is an extraordinary condition in which a joint is completely disorganized and the end of one bone, as in the knee, may greatly override the others, producing the so-called bayonet joint. Although Charcot ascribed the whole to atrophic disturbances, Kienbock and others find that it really follows fractures which result from the complete analgesia and the rarefaction of the bone, so that even a slight strain may break off part of the end of a bone. Kienbock distinguished hypertrophic forms, which extend with further tears



Fig. 419.—Charcot joint. Syphilitic arthropathy involving knee, with erosion and new formation of a lower articular surface. Extensive destructive changes in surrounding tissues with fistulæ.

and fractures with haemorrhage into the stretched joint cavity, and atrophic forms in which there is complete fracture and separation of the bones with no attempt at healing, but atrophy of the ends of the bones.

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**DEMENTIA PARALYTICA (GENERAL PARESIS, PROGRESSIVE PARALYSIS OF THE INSANE)**

Another affection long known to be in some way associated with syphilis and, like tabes, spoken of as parasyphilitic, is now shown by the aid of the Wassermann reaction and by the demonstration of the spirochaetae in the brain to be definitely a syphilitic disease. It has been suggested by Möbius and others that this is a disease practically identical with tabes dorsalis except that it is localized in the brain; and it seems that in a sense this is true, although the difference in localization makes a great difference in the disease as far as the manifestations are concerned; indeed, the lesions of the spinal cord in this condition are rather different from those found in tabes, and the symptoms resulting from them are also different.

Clinically, dementia paralytica is a most dramatic illness whose mental symptoms vary somewhat with the character of the individual. It is remarkable, however, to observe how, under this infection, all minds are planed down to the same low level. It usually begins insidiously, with drowsiness, lapses of attention, peculiarities of conduct, and accentuation of predominant personal characteristics, and proceeds to graver departures from civilized custom which are often shown in their true light in the police court.

Confusion of ideas and failure of memory, together with loss of self-restraint, are soon accompanied by delusions of grandeur in which the patient becomes most extravagant in his belief in his own powers and possessions.

Even at the beginning of this stage his condition may not have been recognized, and he is at the risk of committing mistakes in business or otherwise which may cost him dear.

In later stages memory is lost to an astounding degree; the patient lives only in the moment, totally forgetful of what happened an hour ago; writing becomes characteristically disturbed and finally impossible; speech is slow, blurred, and full of mistakes, the delusions take the place of everything else and are occasionally interrupted by violent maniacal outbreaks or by apoplectiform or epileptoid convulsions, from which the patient usually recovers without any after-effects. With all this, and to the end of life in the most miserable bodily and mental disruption, he is in a state of glowing content. This euphoria, or sense of well-being, is enough to compensate for most of the horror of the disease, but in other cases there is deep depression or complete mental dulling.

Aside from the mental derangement there are bodily evidences of the ailment—the pupils are irregular in form or size and usually rigid, as in locomotor ataxia. Paresis of many muscles may appear, and after the disease is well advanced contractures in these muscles hold the extremities in a helpless rigidity, so that the patient is permanently bed-ridden. Bed-sores of great extent are likely to appear in such cases. Loss of tactile and pain sense is common and readily results through inattention, in injuries such as burns and lacerations. The so-called trophic disturbances are found here as in tabes—perforating ulcers of the

foot, great haemorrhages in the outer ear following a slight injury, disorganization of the joints, great porosity and fragility of the bones, with fractures after trifling blows. Extreme emaciation alternates with periods of obesity, but in the end the weight usually goes down until, at death, the patient seems almost a skeleton.

Death occurs after one to three years, though sometimes there are remissions during which mental and bodily health seems pretty good and death comes only six or eight years after the onset. It may be the result of great emaciation and gradual exhaustion, but most commonly it is brought about by an intercurrent infection, especially bronchopneumonia, to which these demented people, with their dulled sensation and disturbed reflexes, are particularly exposed from the aspiration of saliva or food into the bronchi. In any case they are more than usually susceptible to infection in their state of disturbed nutrition.

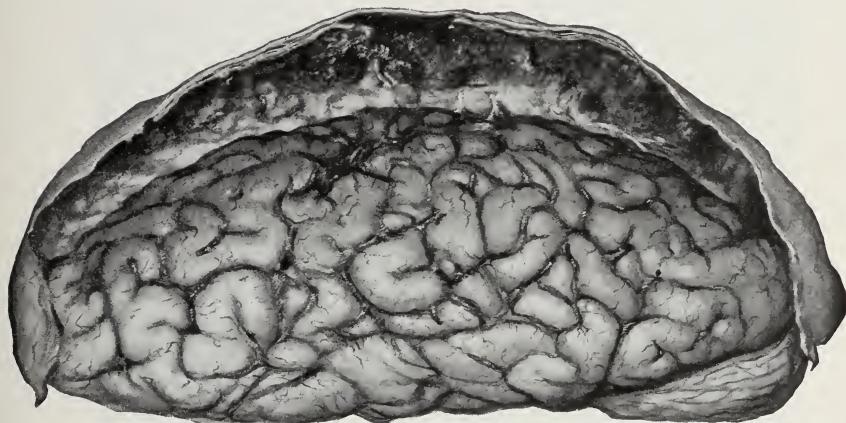


Fig. 420.—Chronic haemorrhagic internal pachymeningitis.

At autopsy the most striking changes are in the brain and meninges. The dura is often lined over one or both halves of the brain with a thick, blood-stained layer of new tissue, which it is often possible to separate into several sheets, the deeper of which are stained a dull rusty brown by the pigment formed from the extravasated blood (Fig. 420). This haemorrhagic pachymeningitis is not peculiar to general paresis, but is found in many other conditions.

The pia arachnoid is usually opaque and grayish white or very oedematous. Not infrequently it stretches across quite wide sulci, which are then partly filled with fluid, and sometimes the surface of the brain presents a great depression full of yellowish fluid, through and over which the arachnoid stretches. All these things are the result of the atrophy and shrinkage of the cerebral substance, the decrease in the bulk of the convolutions throwing wide the sulci (Fig. 421). The whole brain is a good deal decreased in size—on an average by 150 grams, but the two sides may be asymmetrical. The cerebral ventricles are often widened and contain an excess of fluid. Their lining is roughened by the

appearance of minute gray, sand-like nodules which are outgrowths of neuroglia which push the ependyma before them. This "ependymitis granularis" also occurs in other conditions.

Microscopically, alterations are found especially in the more anterior portions of the cerebral cortex. The meninges are found to be thickened and infiltrated with mononuclear wandering cells, among which plasma cells are prominent. They are often intimately adherent to the brain substance. The vascular prolongations are accompanied by mantles of the same plasma cells and other smaller mononuclears, and even about the smallest vessels, which seem dilated and increased in number, the spaces are filled with these cells.

The nerve-cells of the cortex are in all stages of degeneration, shrinkage, and disintegration, and great numbers of them have disappeared. Those which remain have lost their protoplasmic processes in many cases

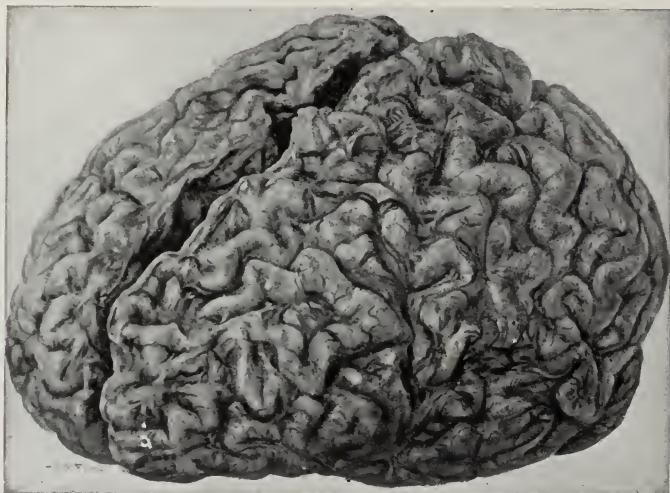


Fig. 421.—General paresis. Surface of the brain showing atrophy of the convolutions (from Weygandt).

and often their axone fibre. They are also greatly disarranged, so that the normal layers and vertical rows are no longer to be made out, but the cells lie confused and sparsely scattered in the cortex. Naturally the fibres, and especially the tangential association fibres and collaterals, are greatly reduced in number. The radial fibres seem more resistant, but even they are markedly diminished. In consequence of these losses the cerebral convolutions shrink and fall apart. But in the place of the lost cells and fibres a great new growth of neuroglia springs up. Abundant neuroglia cells, including the so-called spider cells, appear, together with a relatively dense network of neuroglia fibres. This is especially concentrated on the exposed surface and in those places where the brain substance is invaginated by the nutrient vessels. Every vessel is thus surrounded by a network of fibres. Sometimes there are even projecting brush-like masses on the outer surface, which aid in causing

the adhesion of the meninges. The superficial layer, normally rather indistinct, here becomes a dense felt-work of neuroglia fibres extending a little way into the cortex and devoid of nerve-cells.

The spirochætae found by Noguchi and Moore in paretic brains were scattered in the cerebral substance, not particularly in association with the vessels and not in this external neuroglial layer. Jahnel and others have since found the spirochætae in great numbers throughout the brain. The cerebrospinal fluid is rich in lymphocytes and contains also plasma cells. It is rich in globulins and gives the Wassermann reaction in extreme dilution.

In the remainder of the brain the lesions are very similar, with widespread loss of nerve-cells and fibres. This is well seen in the basal ganglia, the pons and medulla, as well as in the cerebellum, whose peculiar cortical cells may be greatly reduced.

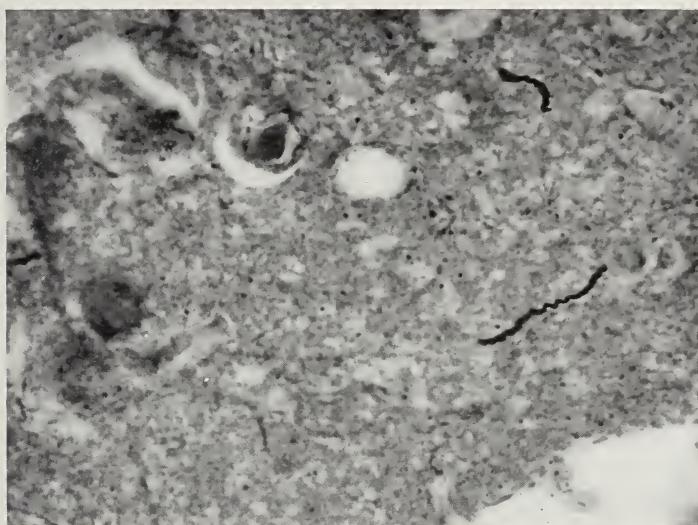


Fig. 422.—Spirochætae in the brain in general paresis.

In the spinal cord, tract degenerations are found in limited areas of the posterior column, generally together with descending degenerations of the pyramidal tracts. Doubtless, while the posterior tract degeneration depends upon the same ætiological factor as the changes in the brain, the descending degenerations may be due to lesions in the motor cortex. These are the changes in the so-called tabo-paresis, which, as has been said, does not correspond precisely with tabes in symptoms or anatomical basis.

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### CONGENITAL SYPHILIS

The term congenital syphilis is to be preferred to hereditary syphilis inasmuch as it appears that the disease is not transmitted as hereditary characteristics (dependent upon the chromosomes of the uniting germ cells), but rather as an infection transmitted to the foetus in the course of its development, either by spirochaetæ which accompany the sperm cell and probably infect the mother, or by spirochaetæ from the tissues of the mother, herself previously infected. In all these cases, except perhaps in late postconceptional syphilis, in which both placenta and child may possibly escape, the placenta is the seat of syphilitic alterations. There are found diffuse infiltrations with wandering cells, vascular changes both in the placenta and in the umbilical cord, distinguished, as elsewhere, by thickening of adventitia and intima, and curious modifications of the villi, consisting of new formation of loose connective tissue about the central blood-vessels, such as to cause a great bulbous swelling of each villus. Hence there is a marked enlargement of the placenta, which, because of the striking disproportion between the size of the placenta and that of the child, is always suggestive of syphilis.

Evidently the spirochaetæ can enter the foetal blood readily enough from such diseased placentæ, and finding in the foetal tissues a specially suitable medium for growth, proceed to multiply to an extent never approached in the tissues of the adult in acquired syphilis. They are to be demonstrated in perfectly astounding numbers by the Levaditi method of silver staining in most of the tissues of the syphilitic new born, where they lie scattered everywhere among the cells, generally without producing any very evident change about them. It is probable, however, that when the organisms are present in such great numbers it is because the death of the infant occurred *in utero*, so that until its birth its tissues formed a non-resistant culture-medium for the spirochaetæ. Except for the lack of warmth, the same thing would apply to the cases in which the autopsy is performed a long time after death. This is emphasized because the babies which show the most extreme lesions are not particularly those in whose tissues abundant spirochaetæ are found. Vigorous treatment with arsphenamine may also have destroyed the spirochaetæ.

Another consideration must be mentioned here in discussing the intensity of lesions, and that is the age of the baby. It has been found impossible to demonstrate the spirochaetæ or lesions of any sort in foetuses earlier than the fifth month (Trinchese), and although this seems open to question it is at least obvious that the tissues of very premature infants, at sixth, seventh, or eighth months, will probably show less advanced lesions than those which go on to term or live some time after birth.

It is not very profitable to attempt to assign the lesions to the stages ordinarily recognized in acquired syphilis. Certainly there is nothing that resembles the local primary lesion, but probably there would be no such local lesion if spirochaetæ were introduced into the blood-stream

of adults. Whether any of the phenomena can be properly compared with secondary lesions is questionable. There is in general wide-spread inflammatory reaction with destruction of tissue and scarring. Rarely there are actual gummata, but, as a rule, there is retardation and distortion of the normal growth and development of the organ. This is especially well seen in the retarded growth of the bones, in the persistence of myeloid tissue in extramedullary situations, and in the delayed development of the kidney.

The effects of syphilitic infection in the parents upon the children seem to become somewhat weakened with the advance of time and with successive pregnancies. The first pregnancies after infection end as a rule in early miscarriages; often the foetus is found in an extreme state of maceration, as though it had been dead a long time. In the later pregnancies the child may be born alive with lesions of syphilis, and die soon. Still later it may survive and even show no sign of disease at first, but pretty surely in childhood or adolescence or even in later life the stigmata or characteristic and destructive marks of the disease appear somewhere, either in the form of a finished process, or as a progressive disease which may lead to the deformity or death of the patient. It is evident that this so-called "syphilis tardive" forms an interminable subject with quite as many variegated possibilities as in the acquired form.

Indeed, practically all of the effects of acquired syphilis appear in the congenital retarded form, even including tabes and general paresis, and none of them shall be discussed again here. The following concerns those which are peculiar to the congenital form.

The new-born syphilitic child or dead foetus commonly shows some affections of the skin, such as the plantar and palmar pemphigus, in which the skin of the palms and soles is lifted up in bullæ or blisters filled with fluid; another type shows extensive scaling off of the epidermis, sometimes over great areas (specific ichthyosis).

There may be ulcerative lesions over the buttocks and thighs which later heal to form inconspicuous scars. Papules and areas of infiltration on the lips, especially at the angles of the mouth, burst later and ulcerate, healing afterward to form radiating scars—the so-called *rhagades*. The same thing happens in the peri-anal region.

Coryza or "snuffles" is a practically constant accompaniment and is extremely serious to the nursing child, since it cannot breathe through its nose while it suckles. On this account it may practically starve to death. In still-born infants, or in those which die shortly after birth, the lungs show in many cases a peculiar change, generally spoken of loosely as white pneumonia or *pneumonia alba*. There has been much dispute about the nature of this, and while some have tried to separate a desquamative from an interstitial form, others have found these two processes combined.

The lungs are enlarged and heavy, the consolidation, usually patchy, is smooth, pale, and elastic. Microscopically (Fig. 423) in all the cases I have seen, there has been a combination of great thickening of the

alveolar septa with some desquamation of the epithelium, and in places an infiltration with leucocytes and mononuclear wandering cells. The epithelial lining cells are cubical in form from the lack of distention, and while many are desquamated into the air-cells, there seems to be no very great multiplication on their part. On the other hand, the connective tissue of the lung is enormously increased in bulk about vessels and bronchi and in the alveolar walls themselves. These are so thick



Fig. 423.—Congenital syphilis of the lung: pneumonia alba. There is great interstitial growth of connective tissue with infiltration of wandering cells and thickening of the alveolar epithelium.

that the alveoli look like glandular spaces in a solid tissue; the capillaries are wide and the thickening of the septum shows that they form two separate layers, one closely underlying each epithelial lined surface. The connective tissue forms a loose network, evidently rather edematous, in which the connective-tissue cells are scattered, sparsely mingled with a good number of mononuclear wandering cells. In rather rare cases distinct gummata have been seen in the lungs.

In the *liver* there occurs a variety of lesions. The organ is generally enlarged and firm, sometimes it has a normal dark red appearance on section, sometimes it is pale grayish brown or much jaundiced and rather translucent, with numerous scattered foci of opaque yellow. Perhaps the commonest change is a general retardation of its development, so that at birth it still appears as an organ actively engaged in blood formation. Bullard thinks of this as a compensatory myeloid activity on account of the general fibrosis of the bone-marrow. The capillaries are wide and in places distended with groups of blood-cells of all sorts, myelocytes, lymphocytes, eosinophiles, and particularly nucleated red corpuscles. In other places the liver-cell columns are widened into bulbous masses of protoplasm in which are grouped numerous large

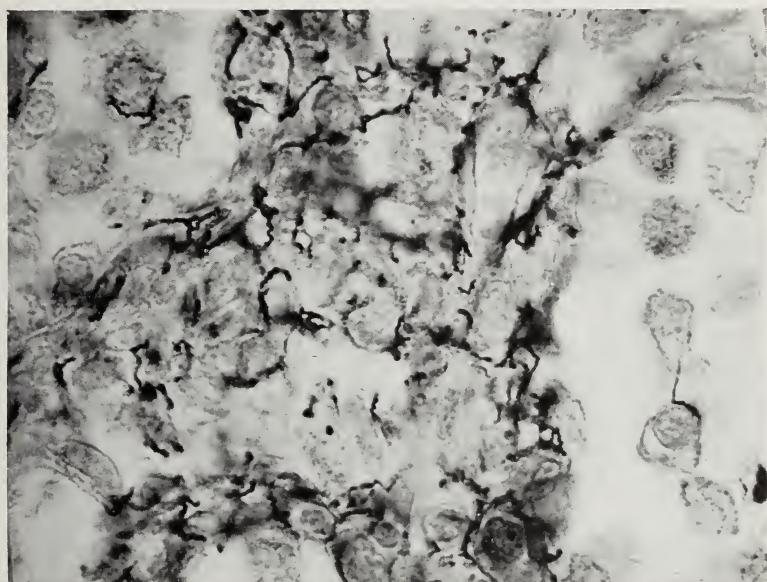


Fig. 424.—Abundant spirochaetæ in the lung in congenital syphilis.

nuclei, evidently indicating a continued new formation of liver-cells. There is nothing clearly specific about such an anatomical picture—the same thing may be found in a normal foetus of a rather earlier stage of development, but the abundant distribution of spirochaetæ through the tissue determines its syphilitic nature.

More distinctive are the cases in which the whole lobular arrangement of the liver-cells is rendered indefinite by the diffuse new growth of fibrous tissue everywhere through the organ. The liver-cell strands are reduced to small distorted bands of protoplasm containing many nuclei, sometimes clustered almost as in a giant-cell, and separated everywhere by a loose fibrous tissue in which run the isolated capillaries. In the case illustrated (Fig. 425) there are numerous foci of necrosis in which there are crowded abundant leucocytes and fragmented nuclei. These

evidently form one type at least of what are called miliary gummata, although there is nothing very specific in their appearance. They, like the rest of the liver, contain quantities of spirochætae. Occasionally one finds more definite concentrically arranged miliary gummata, like small tubercles in the liver, and these have been well described by Hecker. More rarely there are larger caseous gummatous nodules surrounded by scar tissue and ending in a lobulated cirrhotic deformity of the liver.

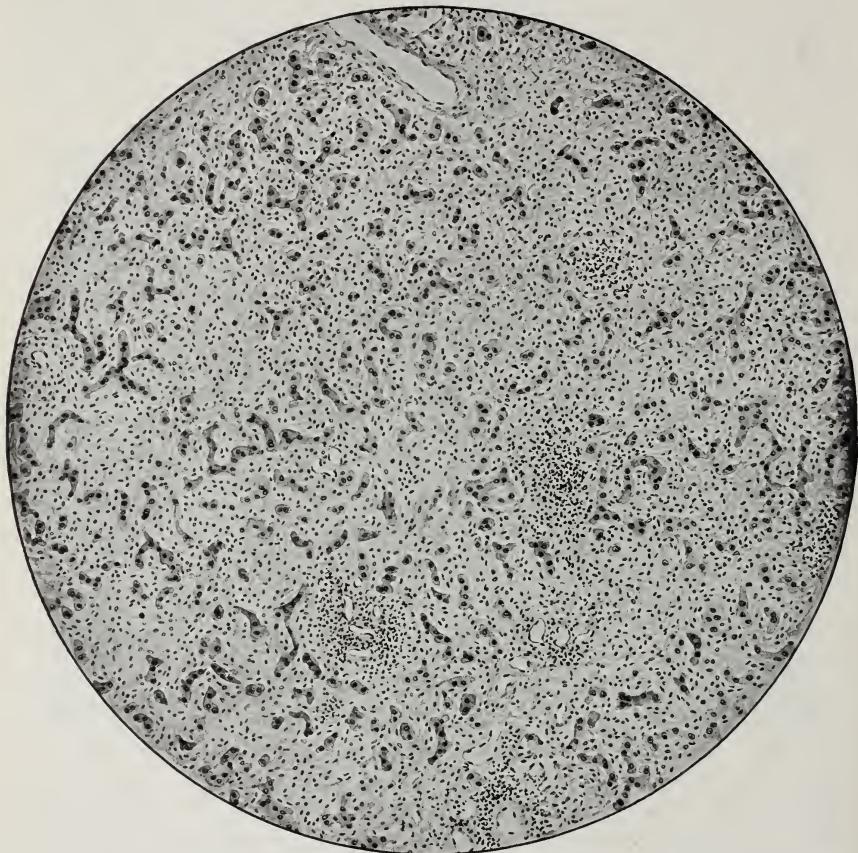


Fig. 425.—Congenital syphilis of the liver. The liver-cell strands are separated by fibrous tissue, and there are accumulations of wandering cells in places. Such foci may later become caseous.

The *pancreas*, so rarely involved in acquired syphilis, is commonly affected by the congenital form. Again, there are rarely gummata of definite form, but very commonly diffuse granulation tissue growth and retardation of development (Fig. 426). One finds the pancreas slightly enlarged and gray and firm. On section the acini are spread apart and apparently incompletely differentiated, the islands of Langerhans often appearing, as in the foetus, in persistent connection with the branches of

the pancreatic duct. Focal necrosis of a more or less suggestive gummatous character is often found in the interstitial tissue. Changes in



Fig. 426.—Congenital syphilis. Pancreas of child with excessive interstitial connective tissue separating acini. The island of Langerhans is still in connection with a duct.

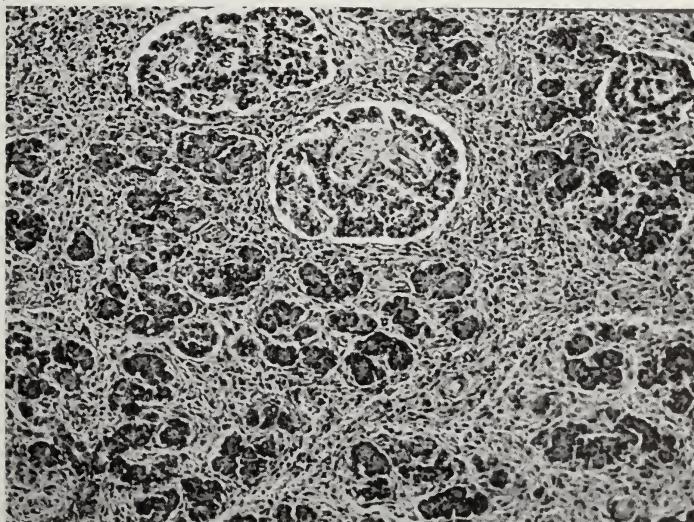


Fig. 427.—Congenital syphilitic lesions of pancreas.

the submucosa of the small intestine and especially in the duodenum have impressed us recently. They have been observed by many authors,

and consist in a dense infiltration of the submucosa with wandering cells, probably with some new formation of connective tissue. Ulcerations and even abscess-like areas of necrosis extending into the submucosa have been found.

Various authors have recognized congenital syphilitic lesions of the stomach, with thickening of the submucosa and infiltration with lym-



Fig. 428.—Bones in congenital syphilis showing the irregularity of the line of ossification, with rarefaction and necrosis.

phoid cells. Spirochætæ have been demonstrated there, and the condition attracts the attention of clinicians especially by the irregular contractions of the stomach.

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Congenital syphilitic disease in the *kidneys* produces rarely definite gummatæ, but often patches of atrophy and destruction of tubules and glomeruli with scarring. The same peculiarity is true of the *testicle*, in which the gumma, common in the acquired form, is replaced by atrophy or maldevelopment of the tubules, often with interstitial connective-tissue formation, which leaves the organ distorted, small, and hard.

Campos has studied a long series of cases of congenital syphilis in our laboratory with regard to the changes in the kidney, and finds regularly a retardation in development, so that there is still at birth and later a neogenic zone at the margin of the cortex. The blood-vessels are almost always surrounded by a mantle of cells which prove to be myeloid elements, so that blood formation is going on here as well as in the liver.

Syphilitic osteochondritis, first described by Wegner, is a characteristic lesion found in varying degrees of intensity in the bones of the

syphilitic newborn, although it does not affect equally all the bones, being most distinctly developed in the epiphyseal region at the knee.

The line of ossification, which ordinarily forms a perfectly even thin pearly gray line between cartilage and bone, loses this delicate aspect and becomes wider, irregular and indefinite, sometimes with yellowish opacity (Fig. 428). This is due, as shown in Fig. 429, to the incomplete ossification with extremely thin laminæ approaching this region, and to the appearance of a rather dense cellular infiltration there. It is shown by Schneider that it is in this band and in the periosteal tissue that the



Fig. 429.—Congenital syphilis. Lesions in a bone, especially near the line of ossification.

spirochætæ are most abundant, and it is evident that the granulation tissue there is in response to their presence. It may even become necrotic with fragments of calcified cartilage and with disintegration and separation of the epiphysis from the shaft. This stops the process of bone formation because of the necrosis and collapse of the active layer.

The readjustment of such a fragmented bone, if the child survives, must, if it ever really occurs, be very difficult, and greatly retard the development of the bone. But there are, of course many cases in which,

at most, there is rarefaction and lengthening of the lamellæ of bone and strands of cartilage matrix so that the formation of bone is delayed.

Bullard finds by actual measurement of large numbers of syphilitic infants and children that growth of the bones in length is distinctly retarded as compared with that of normal controls. The blood-forming functions of the bone-marrow are almost annihilated by the conversion of the tissue into a sort of granulation tissue with few remains of myeloid elements.

There are many other lesions to be found in such newborn syphilitic children, but they all proceed on the same principles, and these may suffice to illustrate.

**Late Forms of Congenital Syphilis.**—Very important and difficult to comprehend are the syphilitic lesions which appear after the lapse of months or years in children born of syphilitic parents, which at birth may not have shown any signs of disease.

Fournier, in his book on "L'heredosyphilis Tardive," includes practically every ailment that flesh is heir to under this heading, so that at



Fig. 430.—Hutchinson's teeth.

first it must seem fanciful; but while one remains skeptical about some of the phenomena referred to syphilis, good proof is brought for most of them.

The scars and deformities or stigmata of syphilis are recognizable, as well as the active progressive disease, and often serve to indicate the character of some other more obscure process which is still going on. Various deformities due to retardation of development leading even to dwarfism are regarded as syphilitic. These, as they affect the skull, produce irregularities of form and asymmetries, or a hydrocephalic dilatation which might seem due to other possible causes.

Perfectly distinct, however, are the malformations of the nose, gummato destruction of the nasal bones producing saddle-nose, while even greater deformity is caused by collapse of the cartilaginous part of the septum, which allows the tip of the nose to telescope into the rest, so that there is a fold of skin on each side.

Various changes in ears and eyes occur with deafness and impairment of vision. Of these, the commonest and most easily recognized is the interstitial keratitis, which gives a steamy opacity to the cornea and

which may obstruct vision very completely, or finally clear away entirely (Fig. 406).

Changes in the teeth may be quite characteristic of congenital syphilis, especially perhaps the so-called Hutchinson teeth which are rather bulbous and tapered, with a gap or notch in the centre of the biting edge, but no cross striations (Fig. 430). The so-called mulberry molar, which is the first permanent molar, has enamel cusps crowded together on a narrow crown, and this, too, is syphilitic. A good discussion of the development of such changes is given by Karnosh.

In the skeleton the lesions of late congenital syphilis are practically those of the tertiary stage of the acquired form, including chronic forms of periostitis, arthritis, etc. But the atrophy or, rather, maldevelopment of bones which produces the extreme delicacy and small size of the skeleton in some of these cases is rather different, as is also the extraordinary local or partial gigantism, which is of similar origin and follows the great local overgrowth of bone.

Lesions of the nervous system and of the various other organs of the body are like those of acquired syphilis, except that they seem to be intensified in these patients, inasmuch as the infection has begun with the beginning of their lives and affected their resistance throughout.

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#### OTHER SPIROCHÄTAL INFECTIONS

Space will allow only the briefest mention of certain other diseases known or thought to be caused by various spirochaetæ, which are of very great importance in the tropics, but unfamiliar here.

**Yaws** or **framboesia** is a disease resembling syphilis in some respects, which is caused by the *Spirochaeta* or *Treponema pertenue* as shown by Castellani. It is not a venereal disease, but is apparently transmitted by contact, for the primary lesion may be found in positions which suggest this. It is extremely common in the tropics, and most of the children in the islands of the Pacific, in the East and West Indies, and elsewhere seem to acquire the infection. It is less common in adults. It is thought to give rise to primary, secondary, and tertiary lesions, as in the case of syphilis, but the primary lesions are not very different from the secondary, and the connection of the distorting, destructive processes which are said to be tertiary lesions with the others is not entirely convincing, although pretty generally accepted. The primary lesion, gen-

erally shown as such, is usually a vesicle or pustule, developed on the hand or on the hip of a mother, where the skin came into contact with the infected child she was carrying, or on the breast. The secondary lesions appear as a great crop of large flattened vesicles, which quickly become changed into honey yellow pustular elevations (Figs. 431, 432). These, on section, show a great thickening of the epithelium and a dense infiltration of plasma-cells beneath (Fig. 433). The spirochaetæ are most readily found in the early stages, before the breaking of the crust allows of secondary infection of the pustule. The tertiary lesions are found in



Fig. 431.—Yaws. Secondary eruption in florid stage (Fiji Islands).



Fig. 432.—Yaws. Showing extensive spread of crusted lesions (Tonga Islands).

the bones and other tissues of the extremities or of the face and upper respiratory passages, and there they produce the most extensive losses of tissue, with scarring and extraordinary distortions. The secondary lesions disappear in a magical way under salvarsan treatment.

**Spirochætosis Icterohaemorrhagica (Weil's Disease).**—This disease, long known as Weil's disease, occurs in endemic and sometimes epidemic form in Japan, and affected large numbers of soldiers in the trenches in France, Belgium, and elsewhere in Europe. It is an affection which begins suddenly with fever, headache, general aching pains, and nose-

bleed, and is often marked by the vomiting and coughing up of blood, and by the passage of blood with the stools. After about five days the fever passes off and jaundice appears. After five or six days more the fever reappears and lasts for about a week. It has been shown by Inada and his co-workers that the cause is a spirochæte which also infects rats, the *Spirochæta icterohæmorrhagica*, and that it is probably transferred through the skin of human beings from the infected urine of the rats. This does not seem altogether convincing, and it has

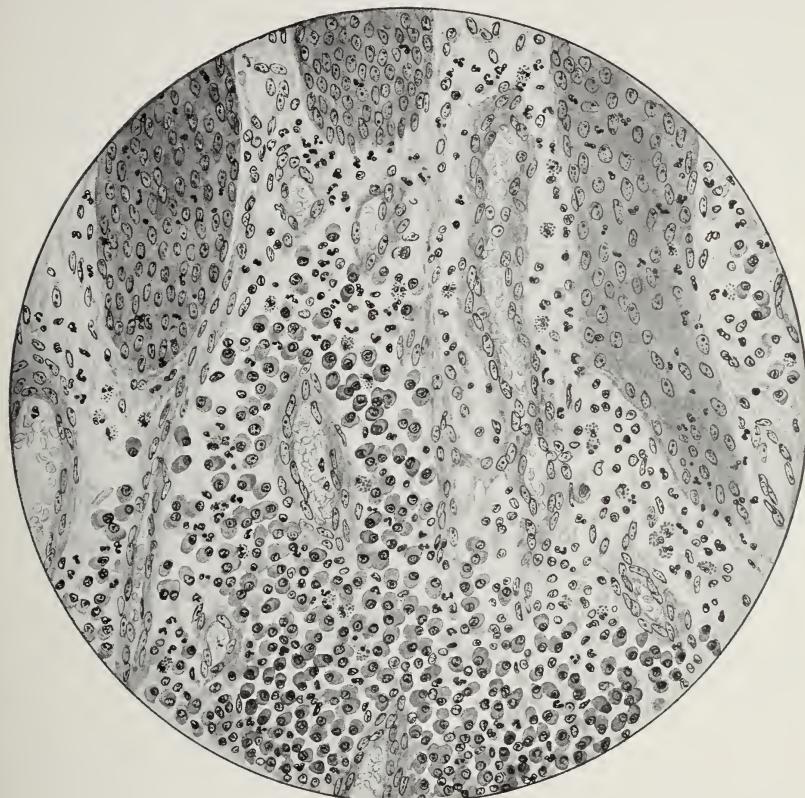


Fig. 433.—Yaws. Deeper layers of skin in a secondary lesion showing the great accumulations of plasma-cells.

been suggested that it may possibly be transmitted by some biting insect. During the first days of the illness it is found in the circulating blood, after the fifteenth day in the urine. It seems that a certain amount of immunity is developed and may be produced artificially in animals. Relapsing fever and rat-bite fever are other diseases of a very similar character, concerning which references are given below.

**Vincent's Angina.**—This condition, also known as trench mouth, since it was prevalent among soldiers in the trenches during the World War, is an infection usually of the gums and fauces caused by a spiro-

chæte, *Treponema Vincenti*, together with a fusiform bacillus. It is contracted through the use of unclean table utensils which have been used by those already infected, or by contact with infected persons, and is favored by lack of proper care of the teeth. It is thought by some that a deficiency of Vitamin B<sub>2</sub> in the diet plays a rôle. The infection invades the gums and produces ulceration and separation from the teeth. It may also extend to the pharynx and even into the bronchi. This is the basis of the name Vincent's angina which is often associated with diminution in the number of leucocytes (leucopenia). The lungs may even be involved and we have recently observed an instance of the most extensive haemorrhagic necrosis of the whole interior of one lung with putrid inflammation of the bronchi in all of which the combination of spirochaetæ with fusiform bacilli was found. Some authors recommend orange juice in the treatment of the slighter infections but the cleansing of the mouth with antiseptics seems more effective.

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## CHAPTER XXXIX

### TYPES OF INJURY.—RICKETTSIA INFECTIONS

*Typhus. History. Interrelation of various diseases caused by Rickettsia. Character of typhus fever. Lesions; experimental studies of transmission.*

#### TYPHUS FEVER

A CONDITION formerly confused with typhoid fever has long been recognized as occurring in great epidemics with high mortality. In 1819 and 1846 it raged with especial violence in England and Ireland, although extensive epidemics had been more common in Russia and the Balkan countries. It is a disease which associates itself with the crowding and unsanitary conditions of war and famine. It was common in prisons. We are even now hearing daily of its ravages in the Balkan States, where all the favoring conditions exist.

In spite of the unfortunate choice of name (*Typhus exanthematicus*), it has nothing whatever to do with typhoid fever (*Typhus abdominalis*). The distinction between the two diseases was clearly made by W. W. Gerhard in a vivid description which is to be found in the American Journal of Medical Sciences, 1836, after Louis had described the lesions of typhoid.

Extensive studies of this and related diseases have been made in recent years and it has become evident that in many parts of the world infections which commonly go by different names are practically identical or at least so nearly so that it is thought that they may have had a common origin, though perhaps long ago, so that they have been slightly modified. Thus, Zinsser feels that Brill's disease, in New York, is essentially typhus fever transplanted by immigrants, chiefly Jewish, from Russia and southeastern countries of Europe where typhus is endemic. In these cases the spread of the disease occurs only in louse-infested neighborhoods. So, too, the Tabardillo of Mexico, the type described by Maxey in the southeastern states of this country, the Rocky Mountain spotted fever, and even the Tsutsugamushi disease of Japan are closely related, if not quite identical.

They have in common the fact that they are caused by infection with peculiar organisms named by da Rocha Lima *Rickettsia* after H. T. Ricketts who first described organisms of this sort in connection with typhus fever. That now recognized as the cause of typhus is *Rickettsia prowazekii*, while other names such as *Dermacentroxyxenus rickettsii* and *Rickettsia nipponica*, have been given for the causative agents of Rocky Mountain spotted fever and Tsutsugamushi disease. They are small bacteria-like bodies, Gram-negative, but stainable with methylene-blue with which they are seen in clusters or pairs often with deeper polar staining in the intestinal cells of the louse and in various cells in man,

chiefly in endothelial cells of small arterioles and in perivascular cells. They are not small enough to pass through a Berkefeld filter. They may be cultivated or at any rate kept alive in tissue cultures.

Curiously enough, the serum of typhus fever patients will agglutinate a certain bacillus, *Proteus X 19* which was described by Weil and Felix as the probable cause of the disease. This, as shown by Castaneda and Zia, is because there is a common specific antigenic factor. Absorption of typhus serum with *Proteus X 19* removes only *proteus* agglutinins, leaving *Rickettsia* agglutinins intact, while absorption with *Rickettsia* removes both. This is still spoken of as the Weil-Felix reaction.

The lice concerned in the transmission of the disease typhus are the common *Pediculus humanus*; for Rocky Mountain spotted fever it is a tick, *Dermacentor andersoni* which lives on rabbits, ground squirrels, goats, sheep, etc.; for the Japanese type it is a mite, *Leptus akamushi*.

These diseases are similar in that they are characterized by high fever, intense illness and weakness. An outbreak of macular or papular eruption, often haemorrhagic, epistaxis and vomiting may occur and there is often delirium. The rash, sometimes called "mulberry rash," is most striking and is especially related to the anatomical changes. A terminal pneumonia or coma with evidences of general intoxication lead to death sometimes in a high percentage of cases.

**Lesions.**—At autopsy in typhus there was recognized formerly only the general condition found in nearly all acute infectious diseases, namely, an acute splenic tumor and some cloudiness of the organs. But many investigators have taken advantage of the opportunities for the study of the disease which occurred during the war when typhus was so prevalent, and new pathological lesions have been found. They consist in vascular changes in the brain, affecting especially the minuter vessels of the medulla, but also those of other parts of the brain, of the skin, and of the heart muscle. The lesion is an arteriolitis and periarteriolitis, with circumscribed proliferation and accumulation of wandering cells and leucocytes about the arteriole, but beginning with proliferation and necrosis of the endothelium.

The *Rickettsia* which is present in the circulating blood and can be inoculated into monkeys and guinea pigs, is found also in the altered endothelial cells of the small vessels and sometimes in phagocytic cells outside them. This is particularly well shown in the paper of Wolbach on Rocky Mountain spotted fever and in the studies of Wolbach, Todd and Palfrey upon typhus fever in which they emphasize the aetiological relation of *Rickettsia prowazeki* to the disease. The lesions are thus essentially vascular and perivascular in brain, skin, kidneys, muscles, etc., and in each situation the endothelial cells are swollen and contain the minute parasites in great numbers. Harris and Lillie describe thrombosis of arterioles in the brain in Rocky Mountain spotted fever with perivascular lesions and degenerative changes in brain cells and axones. Similar perivascular lesions with thrombosed arterioles occur in the subcutaneous tissues and various organs.

All these diseases confer a durable immunity upon those who recover

from an attack and animals inoculated experimentally with blood of patients or with ground-up material from infected lice, or by allowing them to be bitten by infected lice or ticks, develop a similar immunity, if they recover. Their blood agglutinates the Rickettsia. Zinsser shows that the serum of a horse treated with Mexican Rickettsia acquires a Weil-Felix reaction, agglutinates the European louse vaccine, and protects against the European virus.

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## CHAPTER XL

### TYPES OF INJURY.—VIRUS DISEASES

*General conception of viruses. Specific relations. Immunity production. Herpes simplex, herpes zoster. Poliomyelitis. Infectious nature, transmission. Lesions of nervous system. Epidemic encephalitis, various types, lesions and general effects. Parkinson's disease. Multiple sclerosis; Schilder's disease.*

It is realized that a considerable number of infectious diseases, transmissible from one person to another, and resulting in profound destruction of tissues and death, must be caused by some agents which can multiply in contact with living tissues. But great difficulty arises in the study of these diseases because nothing that can be recognized as the cause can be seen or cultivated except in living tissues. Still, it is possible to transmit such a disease by inoculating the affected tissue into a susceptible animal and in a few instances the causative factor has been kept active and even made to multiply in tissue cultures. So minute are these invisible elements that they will in most instances pass unchanged through fine filters which would retain any bacteria or particles visible with the highest powers of the microscope.

There is, therefore, much doubt as to their nature and while nearly everyone thinks of them as living beings capable of reproducing themselves and multiplying when they can invade living cells, there are others who feel that they must be inanimate, ferment-like, substances which perhaps set up a modification of the vital activities of the tissue cells. Indeed, quite recently Stanley has succeeded in crystallizing the virus which causes the mosaic disease of tobacco. What may result from this remains to be seen. Further, it may perhaps be said that the protein nature of such viruses is indicated by the fact that their contact with the tissues, if it is survived, leads to immunity. Indeed, the immunity which follows an attack of one of these diseases is of life-long duration and far more complete and final than any protection that follows recovery from a bacterial infection. This is important in the recognition of the virus nature of such diseases as scarlet fever, influenza, etc., even though it is so widely believed that they are due to the secondary bacterial invaders.

A great number of diseases of man, animals and plants belong in this group, so many indeed that the student must be referred to the various reviews for a survey of the whole list. They are among the most serious of epidemic diseases since it is in many cases difficult to determine how the transmission from person to person occurs, so that effective preventive measures can hardly be devised. Nevertheless, sometimes, as in the case of yellow fever, it has been possible through learning that a mosquito is the agent of transmission, to protect people so that the

disease has disappeared from countries like Cuba where such care has been taken.

It is difficult to draw a sharp outline for this group because in some cases it seems possible to see infinitesimal granules which appear to be the causative agent and which will pass a filter with difficulty if at all, as in the case of vaccinia and smallpox. In the case of Rickettsia infections, typhus fever, etc., it is still more questionable since these Rickettsia bodies which are transmitted by the bite of ticks are easily seen both in the human tissues and those of the tick. Still, while perhaps these should be put in a separate group, the mere filtrability of the organism is not the most fundamental character and indeed the widespread use of the term filtrable virus is being abandoned.

The highly specific relation of these viruses to certain animals or plants and even to certain tissues, is striking. While, for example, from a given human disease inoculations may perhaps be made in a monkey, all other animals are completely non-receptive, and in such a case it is quite impossible to produce an immune reaction with a protective serum in any other animal. So, too, dermotropic and neurotropic viruses are described which thrive only in the skin in one case, in the central nervous system in the other. But other viruses are not so selective and will grow in various tissues, although they seem sharply limited to certain animals, or they may become adapted to other tissues although ordinarily localized in only one.

In the tissues the viruses cannot be seen on histological examination although there are in many instances the so-called inclusion bodies which appear in some cases in the cytoplasm, in others within the nucleus. These are thought by Ledingham and others to be closely packed masses of the virus "elementary bodies."

Of the virus diseases which affect man, perhaps the most widespread are those known often as children's diseases, such as measles and mumps and chickenpox, from which most persons have recovered with lasting immunity. Scarlet fever, rabies or hydrophobia, infantile paralysis or poliomyelitis, encephalitis and smallpox are the main serious and largely fatal epidemic diseases, unless we include here typhus fever, Rocky Mountain spotted fever, and related types as they occur in various countries.

It seems probable that the intensive study which is being devoted in all countries to these infections, must soon lead to a clearer understanding of their nature.

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Two afflictions long known in human beings, have recently roused interest because of their recognized virus origin and possible relations to other virus diseases. These are the familiar herpes simplex ("fever

blisters"), and the less common herpes zoster, the cause of "shingles." From the vesicles produced by these infections, viruses have been isolated and kept alive in tissue cultures.

In the case of herpes simplex, or febrilis, Goodpasture has shown that while the virus may remain latent somewhere in the body, it appears under certain conditions, as for example in connection with some febrile disease such as pneumonia, and produces vesicles about the lips or elsewhere. It may also do this if freshly inoculated, although the ordinary means of transmission is not clear. Experimentally inoculated it travels along axis-cylinders to the nervous system and may produce destructive lesions there. Indeed, Gay and his associates hold that it may be the cause of epidemic encephalitis and in certain recent cases of peculiar character in which the so-called Virus B has been isolated, the resemblance to herpes is marked. Intranuclear inclusions are formed in the ganglion-cells.

Herpes zoster is an infection which produces a group of vesicles generally in a band-like arrangement halfway round the chest, although sometimes it affects the face, and may invade the conjunctiva. There is fever and pain but after a time the vesicles heal and disappear. It is remarkable, however, that for years after apparent recovery such persons may have attacks of agonizing pain referred to the region of distribution of the vesicles. Such attacks last only a short time but recur, sometimes only after intervals of weeks or months.

The virus is transmitted by the nerves to the posterior root ganglia and as Lhermitte has recently shown, the destructive lesions extend into the gray matter of the posterior horns with degeneration of the myelinated fibres and an inflammatory reaction later with neuroglial proliferation. This lesion may even be extended to the anterior horns and may spread in the dorsal part of the cord beyond what corresponds with the affected skin.

An attack of herpes zoster is supposed to confer immunity but there are instances of recurrence. Most interesting, although not finally proven, is the impression which is supported by many writers, that contact with a case of herpes zoster may result in the development of varicella or chickenpox. Netter describes 240 of such cases and states that the reaction of fixation with varicella antigen is positive for zoster. Bokay who was one of the first to observe this relation, describes the result in children exposed to herpes zoster as typical varicella.

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**ACUTE POLIOMYELITIS (HEINE-MEDIN'S DISEASE; INFANTILE PARALYSIS)**

Recently it has been shown that this disease which affects especially young people and children, is an acute infection transmitted from person to person, occurring therefore in epidemic form and capable of reproduction by inoculation into monkeys (Popper and Landsteiner, Flexner). The causative agent is too small to be visible even with the highest powers of the microscope, and will readily pass through a porcelain filter. It can, thus, be isolated from the infected spinal cord and is found in the nasal mucosa of inoculated monkeys and persons ill of the disease. Although no one has succeeded in cultivating this virus on cell-free medium, it has been found possible to maintain it in tissue cultures, as is true in the case of several other viruses.

The disease begins, usually in children, with vomiting, fever, leucocytosis, and general malaise. Pain in the back, neck, and extremities is nearly always present and is sometimes extreme, so that the child winces and cries out on being moved. When the symptoms begin there is a marked drop in the proportion of lymphocytes in the blood. After several days' illness, paralyses suddenly appear and extend to involve one or both legs or a leg and arm or even all the extremities, together with the trunk muscles. Paralyses of the muscles supplied by the cranial nerves are not frequent. When the respiratory muscles are thus involved, death ensues.

The paralysis is most commonly of the flaccid type but in some cases it is spastic. The mortality is fairly high but many cases recover with permanent paralysis. Atrophy of the muscles with subsequent contractures lead to the most crippling deformities. On the other hand, there are many so-called abortive cases in which, after the initial febrile symptoms are over, recovery takes place without paralysis. Survival of the disease leaves an immunity, and the serum of such immune individuals has a protective effect in animals inoculated with the disease-producing agent. It is through the discovery of the existence of such an immunity that one may recognize those persons who have passed through an abortive attack.

**Transmission.**—Doubtless they, as well as those more seriously affected, can act as carriers and transmitters of the disease, and it was partly through the recognition of this fact that the chain of events could be made complete in the explanation of the epidemic occurrence of this affection. It appears that the chief, if not the only portal of entry of the virus is the nasal mucosa from which entry is gained to the olfactory lobes through their end organs and thence, by way of the axis-cylinders, to the substance of the central nervous system (Flexner). This has recently received proof through experiments by Brodie and Elvige, in which the olfactory lobes were removed and after complete healing, instillation of the virus into the nose had no result. It seems that the brain itself is rarely involved but that the virus reaches especially the anterior horn cells of the cord. Toomey has recently shown that if the virus is injected into the vagus nerve it reaches the medulla and so, too, Fairbrother and Hurst and Jungeblut and Spring have demonstrated

that it is carried by way of axis-cylinders rather than by the blood-stream, lymphatics, or cerebrospinal fluid.

**Lesions.**—The chief lesions are found in the central nervous system, and commonly predominant changes are found in the anterior part of the spinal cord. There are such variations, however, that Müller has proposed a division into cerebral, bulbar and spinal forms. Peabody, Draper and Dochez suggest what seems a better division, into affections



Fig. 434.—Acute poliomyelitis. Spinal cord, showing a portion of the gray matter infiltrated with leucocytes accumulated about the vessels. Ganglion-cells of the anterior horn have become indistinct or lost.

of the upper and of the lower neurone, but this too is open to objections. It is useful in separating the spastic cases which are affections of the upper motor neurone from those with flaccid paralysis in which the anterior horn ganglion-cells are especially attacked. The primary changes are evidently due to the destructive action of the virus upon the nerve cells of the anterior horn with their axis-cylinders and cytoplasmic

processes and these are immediately followed by evidence of an inflammatory reaction, hyperæmia perhaps especially of the blood-vessels which pass into the cord through the anterior fissure with accumulation of lymphocytes and polymorphonuclear leucocytes about them (Fig. 434). This soon extends throughout much of the cord. Destructive changes become apparent in the ganglion-cells, perhaps especially in those of the anterior horn, and they are soon found to be in the process of disintegration or shrinkage. There is distintegration and fusion of the tigroid bodies and later the nucleus in each cell shrinks and becomes deeply stained or fades away and disappears. Direct invasion of phagocytic cells into the bodies of such ganglion-cells is often observed and the remains are surrounded by a cluster of them.

It is evident from the experimental studies of the path of the virus along axis-cylinders, that the primary lesion is in the affected ganglion-cells, and not as some writers have attempted to show, in the production of an inflammatory oedema which mechanically injures the cells.

With recovery, the injured ganglion-cells disappear completely, and after the fading of the inflammatory reaction the place is occupied by a dense neuroglia scar. Quite analogous lesions are found in the medulla oblongata, where the nuclei of cranial nerves become affected, and in the higher parts of the brain as well. This is referred to as polioencephalitis (Strümpell).

In the other organs less characteristic changes are found, but reference may be made to minute focal necroses of liver-cells with lymphocyte accumulation, and to similar changes in the lymph-glands which have been described by Peabody, Draper, and Dochez. In such lymph-glands the sinuses are filled with large phagocytic cells, as in typhoid fever. Cloudy swelling of liver and kidneys is usual.

Efforts directed toward immunization by the injection of serum of persons convalescent from poliomyelitis have been made by some while others prefer to undertake a more active immunization by the introduction of the virus treated with formalin or with sodium ricinoleate. While these methods seem capable of preventing the destructive invasion of the virus, they are useless if the virus has already reached the nerve-cells.

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**EPIDEMIC ENCEPHALITIS**

During 1917 there was an epidemic in Austria described by von Economo as a new disease, encephalitis lethargica. This appeared in other European countries in 1918 and in America in 1919, and still persists in sporadic form. It is an acute and chronic infectious disease with a high mortality in the early stages and particularly dreaded because even with recovery it leaves such disabling and disfiguring sequelæ which may change the whole character of the victim. The acute febrile illness is soon accompanied by disturbances of sensation, of reflexes, of motility, and of the mental state. There may be somnolence or delirium with insomnia, curious rigidities of the muscles and prolongations of their contractions, choreiform movements or myoclonic spasms, tremor, neu-

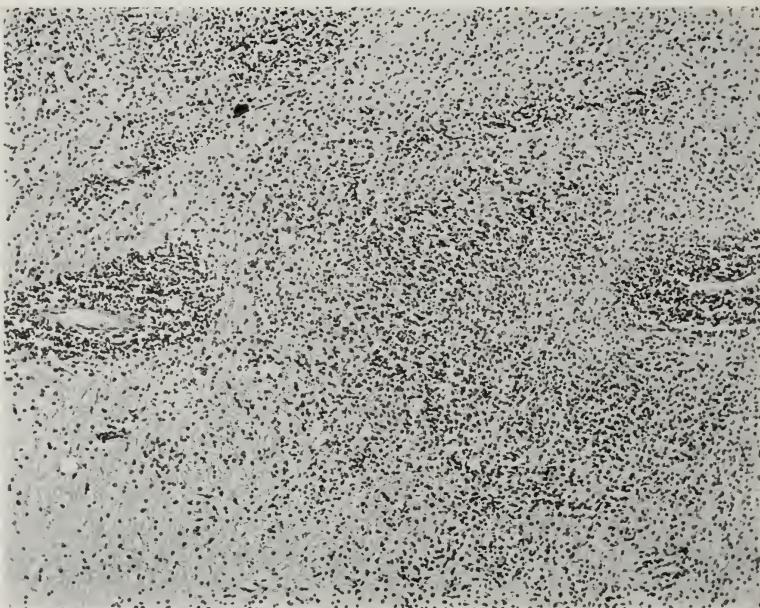


Fig. 435.—Encephalitis with perivascular cell accumulations and disintegration of tissue.

ralgia, paresis of the ocular and facial muscles, and, indeed, a great variety of symptoms which may simulate all sorts of quite different diseases recognized by the neurologist and psychiatrist. Later, the febrile stage being over, the residual disturbances appear more clearly and are often of the nature of pareses or rigidities of muscles. Something closely resembling Parkinson's disease or "shaking palsy" may develop rather rapidly and persist. The patient acquires a peculiar mask-like face and awkward pose with a rigidity and often with a constant movement of the fingers.

It seems that even now, although intense effort has been directed toward the discovery of the causative agent of this disease, we are still

uninformed. Everything seems to indicate that it is a virus analogous to that of poliomyelitis but it has not been isolated with absolute certainty. Gay and Holden feel sure that the virus of herpes simplex which they have found in the brain in several cases is the real etiological factor and with it have produced encephalitis in rabbits, but this virus has been found so rarely in recognized cases of encephalitis lethargica and is otherwise so widespread that further proof of its relation seems necessary.

Recently there has occurred a great epidemic of encephalitis in St. Louis and some nearby places with many fatal cases. The symptoms were much like those of the so-called von Economo encephalitis or encephalitis lethargica but the careful studies of Muckenfuss, Armstrong, McCordock, Webster and Fite have shown clearly that this was a disease caused by a specific virus to which mice and monkeys are susceptible but not rabbits, guinea-pigs, rats or other animals. It is filtrable, the virus particles being of a diameter somewhere between 22 and 33 millimicrons, while the virus of poliomyelitis measures 8-12 millimicrons. It is neutralized by the serum of persons convalescent from encephalitis of this epidemic or by the serum of recovered monkeys or mice, but not by serum from persons recovered from lethargic encephalitis, poliomyelitis, the Japanese encephalitis, nor the Austrian X disease. It is therefore a new and previously unrecognized cause of epidemic encephalitis and is the only one which has been studied in such a way as to present a clear and convincing picture of its identity. According to McCordock the cases of the St. Louis type differ anatomically from the lethargic type in showing a more intense infiltration of the meninges, more extensive degeneration of nerve-cells with neuronophagia or phagocytosis of the débris of these cells. The inflammatory foci are more widespread and even involve the spinal cord.

Still another type of encephalomyelitis has been described by Sabin and Wright following the bite of an apparently normal monkey and in this the virus has been isolated and is called Virus B. It will infect rabbits but has no effect on monkeys or dogs. Another case in our laboratory, studied by Kindell and Brown, similarly shows a virus which will infect rabbits. Its possible relation to herpes is being studied.

At autopsy, in cases of epidemic encephalitis, the lesions are found especially in the gray matter of the optic thalamus, the corpus striatum, the substantia nigra, the red nucleus, the hypothalamic region, and in the rest of the midbrain and medulla, without much involvement of the cerebral cortex or of the spinal cord. The lesions are very inconspicuous to the naked eye, but are sometimes visible in the form of minute haemorrhages. Microscopically they are found to consist of prominent perivascular accumulations of mononuclear cells with some haemorrhage and some disintegration of the tissue, involving nerve-cells. But the actual changes in the nerve-cells and fibres, apart from their displacement by oedema and cell infiltration, are really rather inconspicuous as at present described. There is nothing to correspond precisely with the destruction of the motor cells of the anterior horns of the spinal cord which is so

definite in poliomyelitis and which leaves such a distinct scar and such permanent paralysis, and the transience of the pareses seen in encephalitis seems to agree with this. Meninges and ependyma seem to be but little affected, although some authors mention a congestion of the pia, and there is no striking alteration in the character or quantity of cerebrospinal fluid. Cranial nerves sometimes show an inflammatory process as described by Burrows.

Encephalitis, perhaps not identical in its anatomical lesions with the epidemic form, has been observed as a sequel of measles, influenza, pertussis, chickenpox and smallpox. That following measles is characterised by an extensive demyelinization of nerve fibres about the perivascular accumulations of cells while after whooping cough the type is different as shown by Husler and Spatz, Rogerson and others. There the cells of the gray matter degenerate and disappear and there is much proliferation of neuroglia. There is much discussion of the probable nature of the injurious agency. In the case of varicella or chickenpox, the relation to the virus of herpes zoster mentioned above at once suggests itself but is not clearly proven. Interest has been especially aroused in recent years by the recognition of a similar encephalitis following vaccination against smallpox. This has been commoner in Holland, Sweden, and England than in other countries, and great effort has been made to reach an explanation. The anatomical changes in the brain are like those that occur in measles and smallpox but according to most observers (with the exception of McIntosh) not like those produced in animals by intracerebral injection of vaccine—nor is the vaccine virus always found in the brain in fatal human cases. Vaccine purposely cultivated in the brain of rabbits has been used in Spain and has never produced encephalitis. Perdrau found it impossible to recover the vaccine virus from encephalitis following vaccination and thought it probably not due to the vaccine but, as it often occurs in epidemics, rather to some other widespread virus affecting those whose resistance is lowered by vaccination.

The whole question is well reviewed by Thompson but seems still full of uncertainties. The recovery from encephalitis may seem to be complete but later there may appear the distressing symptoms of Parkinson's disease, or paralysis agitans. The face assumes a mask-like rigidity while the arms and fingers twitch. The gait is characteristic as the person stumbles along with bended knees with fingers twisting and arms moving aimlessly.

There is much difference of opinion as to the anatomical basis for this and while some, Hohmann, Hallervorden, Pushkin and others ascribe it to injury to the substantia nigra and putamen, others, Byrnes, Petri, think it due to changes in peripheral nerves and muscles and Byrnes lays especial stress on changes in the muscle spindles.

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### MULTIPLE SCLEROSIS

There are certain affections of the nervous system which while not of very frequent occurrence are of such serious import that they must be briefly mentioned, although we must, for this, depart from the general plan of discussing lesions on an aetiological basis since the causes are as yet unknown.

Of these, one of the most commonly observed is multiple sclerosis, with the related condition known as Schilder's disease.

Multiple, or disseminated, sclerosis, is a slowly developing affection which is characterized clinically by tremor which makes any intentional movement almost impracticable. If, for example, the patient takes up a glass to drink, the trembling begins and increases in violence, the shaking glass is knocked against the teeth and the contents spilt. Handwriting is almost impossible and ends in typical shaken lines. The eyes move from side to side (nystagmus), and there is peculiar scanning and explosive speech. Motor paresis and contractures occur later and there are sensory disturbances including those of vision. In the brain and cord in practically every possible position there are found small areas of glial overgrowth in which the nerve fibres are still preserved, at least to the extent that the axis-cylinders pass through but are deprived of their myelin sheaths. Such foci are thought by some to correspond with the distribution of the branches of a small artery. There is perivascular infiltration with small round cells and sometimes there are areas in the neighborhood where the glia is much rarefied and axis-cylinders still course through it. No definite secondary degenerations are usually obvious but they may occur. Naturally the effects depend upon the position and extent of such lesions. As to the causative factor nothing is known. Experimental studies with lipolytic ferments, anoxemia, etc., have given no trustworthy results.

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**Schilder's disease or Encephalitis periaxialis diffusa** is a very closely related disease in which again the cause is completely obscure and in which demyelinization occurs in much larger areas, especially in the brain. The symptoms are more intense than in multiple sclerosis and consist rather in spastic states of the body muscles and of the face and eyes with some pareses, or even complete paralysis of extremities. Great slowing of mental activity and abnormalities of vision and other senses may occur.



Fig. 436.—Schilder's disease. Areas of demyelinization in white matter of the cerebral hemisphere.

The brain shows, as we have seen in a recent case and as is well illustrated by Schaltenbrand, extensive areas of ragged softening with opacity and occasional petechial hemorrhages in the white matter of the hemispheres, extending to but not involving the arcuate fibres which run just beneath the gray matter of the cortex. Other areas involve various positions in the more central part of the brain, in the cerebellum, pons and medulla. These on section show extensive demyelinization and partial destruction of axis-cylinders. There is described especially a swelling of the oligodendroglia with mucoid degeneration in the marginal portions and, in the areas of complete degeneration, hypertrophy of the neuroglia which forms a network. We have been especially impressed

by the accumulations of cells about the blood-vessels. This suggests to some extent a similarity in origin with a number of other diseases in which a filtrable virus has been recognized as the cause.

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## CHAPTER XLI

### TYPES OF INJURY.—INFECTIONS CAUSED BY FILTRABLE VIRUSES

*Influenza.* History, mode of occurrence, symptoms, complications and sequelæ. Demonstration and cultivation of the virus. Common colds, cultivation of the virus. Stimulation of associated pathogenic bacteria. Rheumatism. General character, course and symptoms. Cardiac involvement. Specific lesions. Search for aetiological agent.

#### INFLUENZA

FROM remote antiquity the disease which is now called influenza or *la grippe* has been known on account of its extraordinary power of spreading with great rapidity over whole countries, or even over the whole world. The history of the disease, which may be read in Hirsch's Geographical and Historical Pathology, or in the monographs of Ripperger and of Leichtenstern, and in the summary of D. and R. Thomson, is truly remarkable, since the records of the epidemics go back to the tenth century and show that in some way not yet understood the peoples of all countries have been visited periodically. There is no definite regularity about the appearance of the great epidemics, although it has been thought that they come about every thirty years. Then the disease sweeps round the whole world, progressing westward in a general way, although this, too, is questioned. The last pandemic outbreak was in 1889, after which vague local epidemics occurred without attracting special attention until 1918, when the more familiar recent world visitation occurred.

The name *influenza*, which merely means "influence" in Italian, is derived from the mistake of someone, who, in attempting to read an Italian treatise, thought it the name proposed for the disease. It has long been recognized as a specific infectious disease, and from the general uniformity of the symptoms when occurring in epidemic distribution it has been easy to identify it in each new outbreak. Isolated cases at other times are, however, not so certainly diagnosed.

This affection suggests very strongly the existence of some form of invisible living virus which is very easily transported and has some of the characters of other diseases which we think of as virus infections, such as measles. Indeed, Bloomfield and Harrop have described a rash and an eruption in the mouth as quite characteristic.

The symptoms are much like those of a cold, with fever, catarrhal inflammation of the mucosæ of the nose and throat, general aching, and prostration. There is no leucocytosis, but a marked decrease in the number of leucocytes (leucopenia), and in association with this the resistance to bacterial invasion is greatly lowered—more, indeed, than in

any other disease. No one as far as we know has died of influenza, and we are practically entirely uninformed as to the nature of any changes in the internal organs which may result from it. It passes off after a few days and apparently confers an immunity, although it is difficult to make this statement with any assurance. It seemed nevertheless that those who had lived through the epidemic of 1889-1891 were seldom affected in the recent epidemic, while young, strong persons were attacked. In remote islands of the Pacific and elsewhere this did not come out clearly, and it seemed to be the old and weak who suffered. Experiments conducted by Prof. M. J. Rosenau for the purpose of inoculating volunteer non-immunes failed completely. Every conceivable mode of transmitting the disease from patients in every stage of the illness was tried, but in no way could he provoke the appearance of influenza in his volunteers. Similar experiments were carried out in California with young volunteers who had never been exposed to the disease, and these also gave negative results. Sputum, blood, and other fluids were inoculated, without the slightest effect. Nevertheless the disease spreads with the most astounding rapidity, and appears, as it seems, explosively in all quarters of a city or of a country at once. It seems incredible that anything but human intercourse could be responsible, but all sorts of other explanations have been proposed without much solid foundation. Much has been made of the fact that in several instances epidemics of influenza have appeared on ships while coasting along the shore of a country where the disease raged, although the ship never touched land.

Although no one has died of influenza directly, the predisposition of those affected to secondary infection with all sorts of bacteria is such that hundreds of thousands and even millions of persons died in the course of the last epidemic from the pneumonia produced by the secondary invaders. Almost all the bacteriologists and pathologists in the world have seized the opportunity to investigate the disease, and the results up to the present have been most confusing. After the pandemic appearance of the influenza in 1889, R. Pfeiffer studied the bacteria in the bronchial secretion of sporadic cases of bronchitis and pneumonia, and discovered a minute bacillus which was Gram-negative and required haemoglobin for its growth. Although the epidemic had been over for two years, he announced without any proof whatever that this bacillus was the cause of influenza, and it took the name *Bacillus influenzae*. Nothing could have been the source of more confusion, for this organism or one of its varieties is extremely widely distributed and common at all times and can be found in the throats of many healthy people, as well as in the bronchi of those with tuberculous and other pulmonary diseases. Rivers has found that there are pathogenic and non-pathogenic forms readily separable by cultural and agglutination characters. The pathogenic group is a serious cause of disease and is prominent among the secondary bacterial invaders in producing pneumonia after influenza.

There are still some investigators who think this bacillus of Pfeiffer is the cause of the epidemic disease influenza, and Blake and Cecil think they have reproduced the epidemic disease in monkeys by intratracheal

inoculations of the bacillus of Pfeiffer. I myself do not think the epidemic disease influenza is caused by this bacillus, because the forms of pneumonia which follow influenza are not all alike, and there is one perfectly characteristic group which is caused by the Pfeiffer bacillus in pure culture. Further, there are many cases in which I have been unable to find the bacillus at all, although other organisms, such as the pneumococcus or streptococcus, were present and produced pneumonia. It is, of course, possible that some bacterium might cause the epidemic disease and then be overgrown and obliterated by another, which produces the secondary pneumonia. But it is especially because of the phenomenal rapidity of the spread of the infection, which is so unlike that of any bacterial disease, that it seems improbable that it should be due to the bacillus mentioned. In Camp Meade, where the advent of the epidemic was awaited, since it had progressed from the north to New Jersey, 3 cases appeared in one day and 3000 next day.

Recently Long and his coworkers have by intranasal inoculation of bacteria free filtrates from rhinopharyngeal washings from patients with influenza, produced in chimpanzees a disorder characterized by fever, prostration and leucopenia. Smith, Andrewes and Laidlaw have inoculated ferrets in the same way and are able to transmit the disease from one ferret to another. More recently they have been able to transmit this virus to mice, producing lesions in the lungs after inoculation into nasal passages. Inoculation by any other route does not produce infection or immunity. Dochez, Mills and Kneeland have cultivated a virus filtered from nasal discharges in influenza, in a medium containing chick embryo tissue, and have inoculated intranasally human volunteers with the 18th generation of such cultures, producing what seemed to be typical influenza.

Francis and Magill have been able to cultivate the virus from cases of human influenza in Puerto Rico in a medium of Tyrode's solution with minced chick embryo and have with these cultures produced characteristic lesions in the lungs of mice and ferrets. The cultures, transferred after Berkefeld V filtration, have been carried through many serial transfers and are still capable, in great dilution, of infecting mice. Its true identity with the influenza virus is shown by the protective action of the serum of ferrets which have recovered from infection with the strains previously studied.

The virus isolated by Shope from swine influenza caused in ferrets a condition not to be distinguished from that produced by the virus of human origin. It is interesting that Shope found that while the pig virus is the essential factor in swine influenza, it alone produces a very mild affection but combined with a bacterium resembling the Pfeiffer bacillus, the *Haemophilus influenzae suis*, it produces the severe epizootic disease. These results seem to support the idea that epidemic influenza in man is caused primarily by a virus infection which facilitates the invasion of bacteria giving rise to pneumonia and other complications.

**Sequelæ of Influenza.**—In many cases pneumonia follows quickly upon influenza and is accompanied if untreated, by an intense inflammation of the larynx and trachea. The pneumonia is caused by pneumo-

cocci of all types—by a haemolytic streptococcus, by the *Staphylococcus aureus*, Friedländer's bacillus, the bacillus of Pfeiffer, or by a mixture of two or more of these and various other organisms. The anatomical character of the pneumonia varies with the resistance offered, as in the case of the post-measles pneumonias described under the heading Streptococcal Infections, but for some of the organisms there are more or less typical forms, since in all the patients the resistance is greatly lowered.

The pneumococci produce a confluent lobular consolidation (Fig. 437) which begins in very sharply outlined blocks of elastic oedematous

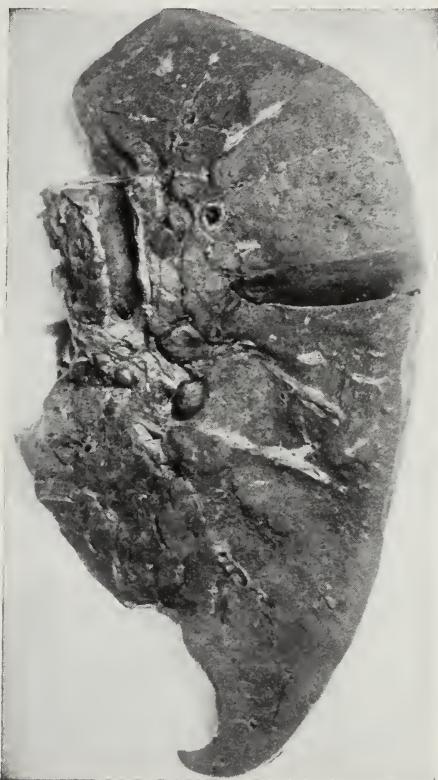


Fig. 437.—Pneumonia caused by the pneumococcus during the epidemic of influenza in a person still suffering from that disease.

haemorrhagic tissue in which the ductuli alveolares are lined with a hyaline membrane and are filled with fluid, while the alveoli contain a fresh red clot of exudate made up of a loose fibrinous exudate with well-preserved red corpuscles and leucocytes and myriads of organisms (Fig. 438). This hyaline lining membrane runs from the bronchioles down into the alveoli, but keeps the form of a thin layer. It does not give the reactions for fibrin. It is a substance which we have not seen in other cases of pneumonia than those following influenza, although it is said to appear in the lungs of those who have been killed by war gases. Good-

pasture has published a paper stating that this membrane is one at least of the specific lesions due to the influenza itself, while Wolbach has discovered that it contains fatty substances which stain brightly with Sudan. Staphylococci may be associated with a similar consolidation, but tend to produce discrete abscesses. Friedländer's bacillus causes an analogous consolidation, but with a viscid glutinous exudate. The haemolytic streptococci bring about a wide-spread and extreme cedema



Fig. 438.—Pneumococcal pneumonia in influenza. The ductuli alveolares are distended with fluid and lined with a peculiar hyaline material. The alveoli contain an extremely fresh exudate.

with extensive confluent consolidation. The tissue is loaded with organisms, and necrotic where they are most abundant. We found no cases in which the patient's tissues were resistant enough to produce the interstitial form seen after measles.

The influenza bacillus of Pfeiffer when present in pure culture causes in those persons who appear to be least resistant an intensely haemorrhagic consolidation in which the lobular areas run together. The leucocytic exudate is not very conspicuous, but is especially dense about the

bronchioles. In other cases which appear to be more resistant the Pfeiffer bacillus alone produces numbers of yellowish-white, firm, nodular areas of consolidation about terminal bronchioles (Fig. 439). These project from the cut surface almost like tubercles, but are found on microscopical examination to be due to the great thickening of the wall of the bronchiole and of the walls of the neighboring alveoli, partly by a new growth of connective tissue and partly by infiltration with wandering cells. The alveoli and the bronchiole are filled with leucocytes. This is a form of interstitial broncho-pneumonia somewhat different from that caused by the haemolytic streptococcus. The bacilli are not strictly

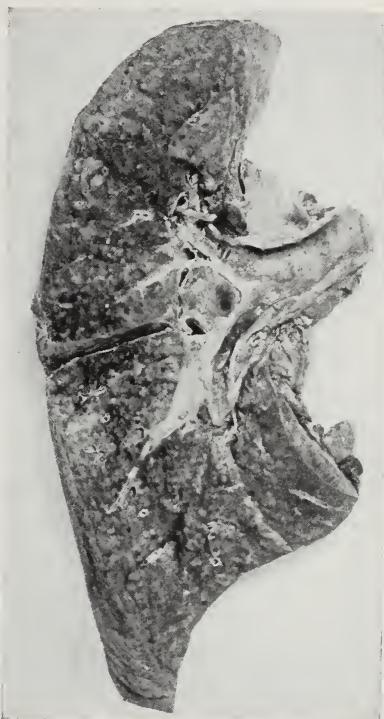


Fig. 439.—Interstitial bronchopneumonia caused by the bacillus of Pfeiffer in a person who began with influenza.

limited to the bronchiole, the exudate is composed of polynuclear leucocytes with little or no haemorrhage, the lymphatics of the interlobular spaces and vessel walls are not specially involved, and there is no great pleural effusion. Usually these lungs are dry and pale and adherent to the parietal pleura. This sort of nodular interstitial bronchopneumonia caused by Pfeiffer's bacillus is quite common in children as a sequel of whooping-cough, measles, etc., and is sometimes almost indistinguishable from tuberculosis when viewed only with the naked eye.

Healing processes end in extensive organization of exudate, bronchiectasis, and a most remarkable hyperplasia of epithelium in the

alveoli which produces epithelial masses which sometimes look like giant-cells, sometimes like an invading tumor.

The anatomical picture in each type of Pfeiffer bacillus pneumonia, fresh and late, is so frequently repeated that it seems to be characteristic enough to afford a very good indication of the bacterium concerned.

The bacillus of Pfeiffer has been found several times as the cause of acute endocarditis. It is also found not infrequently and especially in children as the cause of acute fibrinopurulent meningitis in the exudate of which it is abundant. Dr. Howland had 21 cases of this affection

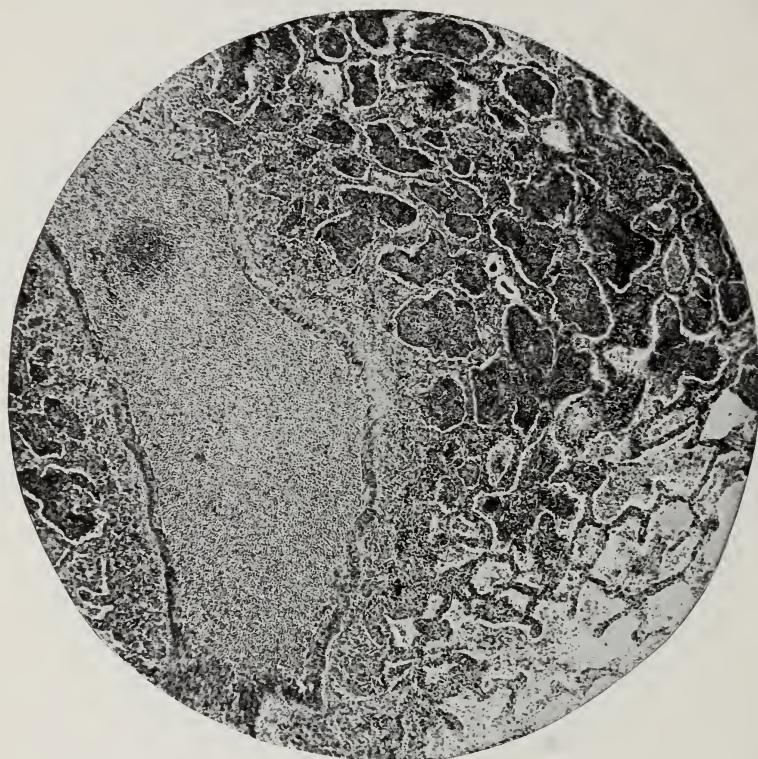


Fig. 440.—Interstitial bronchopneumonia caused by the bacillus of Pfeiffer.

and they appeared to be wholly independent of any epidemic. In one of these cases I found at autopsy not only the acute meningitis, but an acute peritonitis in which the same organism was present alone in the exudate.

It is probably in the upper air passages that it is most frequently to be found. Crowe and Neville found it often infecting the antrum of the upper maxilla. In the lung it appears to accentuate the development of tuberculosis, and in the cavities and in bronchiectatic spaces it persists for a very long time.

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## COMMON COLD

The general character of the common cold is familiar to everyone but until recently we had no clear idea of the causative factor. Dochez and his coworkers made a study of the bacteria in the nose and throat of numbers of normal persons throughout months, and found that the normal basic flora of the nose includes *Staphylococcus albus*, diphtheroid bacilli and sometimes *Staphylococcus aureus* and *citreus*, with Gram-negative cocci and non-hæmolytic streptococci occasionally present for short periods. In the throat they found Gram-negative cocci, non-hæmolytic streptococci and, in some cases, large Gram-positive cocci, *Hæmophilus influenzae*, etc. None of these seemed directly responsible for common colds but from persons at the height of a cold, nasal washings were filtered through Berkefeld or Seitz filters and inoculated into the nares of monkeys and later of human volunteers and produced typical colds. This virus could be cultivated on media containing chick embryo tissue and propagated for many generations. Even in the fifteenth generation, when the original inoculum had been enormously diluted, injection into the noses of human volunteers produced severe colds. Especially interesting is the evident stimulation of pathogenic bacteria to grow and infect the respiratory tract, and increase the injury produced by the primary agent. It seems that in the presence of the virus the character of such an organism as the influenza bacillus is changed in culture so that it is serologically different and grows in colonies of different appearance. This is somewhat suggestive of the alterations in the character of pneumococci described by Avery upon the transfer of specific carbohydrates, but the mechanism requires further study. It is quite parallel with the stimulation of the *H. influenzae suis* by the Shope swine influenza virus and the necessity for such cooperation to produce a severe disease.

Attempts to immunize against the bacteria concerned in colds, as secondary invaders rather than against the virus itself, have been made by Dochez and more recently by Rockwell and associates.

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#### RHEUMATISM

A disease which has long been somewhat confused with various other affections, in which joints are painfully involved, has gradually become clearer in our minds and is now recognized with perfect clarity by its peculiar and quite specific anatomical characters, although we have as yet no knowledge of its cause. It has been known by many names, acute articular rheumatism, rheumatic fever, etc., but it seems best to confine the name "rheumatism" to this sharply outlined disease, because none of the other "rheumatoid" affections have anything whatever in common with it.

Although for years many investigators have attempted to show that it is caused by one sort of bacterium or other—generally some type of streptococcus—there is no convincing evidence that any of the different bacteria occasionally found in the blood or respiratory passages have any importance as its cause. Indeed, in the most typical cases we and many others have found no bacteria at all, even after the most careful search by culture methods and the inoculation of animals. Although there are those who persistently maintain that the disease is due to streptococcal infection, we believe that it is not, but that its unique gross microscopical alterations show that it must be caused by some equally peculiar infectious agent.

Rheumatism is most commonly observed as a disease of children and young people. It is obviously an infectious disease of some sort and is not a local process, but a general infection producing lesions in various parts of the body. Of these, the most important is the involvement of all parts of the heart—the other lesions are of quite secondary interest. Those of the joints, which have generally been thought most characteristic, although painful in adults, are transient and produce no serious changes in the tissues. They may be absent in children.

One of the most distinctive features of rheumatism is its tendency to amelioration after severe symptoms, only to recur with the same severity after a period of well being. It is for this reason that healed lesions of the heart valves are so often found and serve as a favorable basis for secondary infection with streptococci or other bacteria producing a fatal superimposed endocarditis. The traces of the preceding rheumatism can generally be recognized in these cases.

It seems probable that rheumatism is caused by one of those elusive

'filtrable infective agents which we cannot see or cultivate and to which none of our laboratory animals is susceptible. It is evident that the problem of isolating and studying such a living being is very difficult, but under such circumstances, since its presence seems to favor the invasion of bacteria of various sorts, it is not surprising that many of these bacteria have been thought to be the actual cause of the disease.

Rheumatism is an extremely important disease not only because it is common and not very easily recognized, but because it seems to be the cause of most of the heart disease of children and young people, and

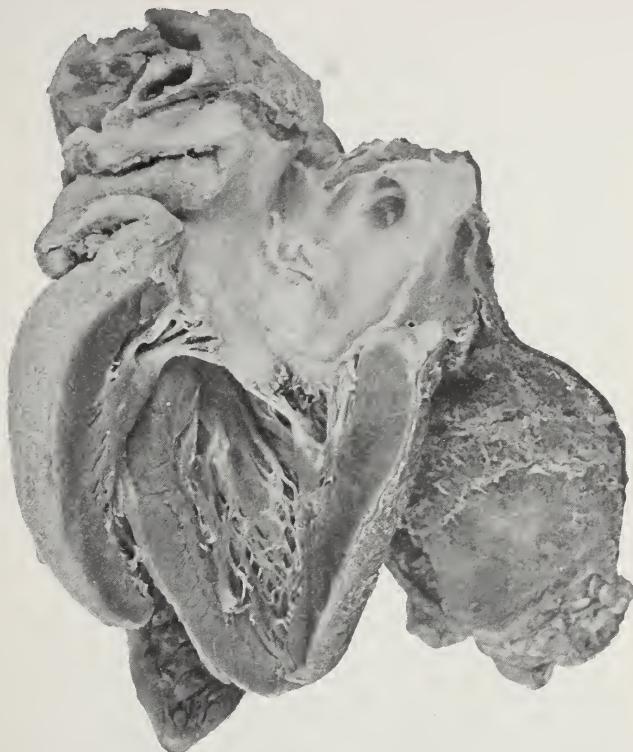


Fig. 441.—Rheumatic endocarditis; verrucose vegetations on mitral valve. Aschoff bodies in myocardium of left ventricle and subacute pericarditis.

therefore the cause of invalidism for the rest of their lives, and a constant underlying menace of secondary infection with the destructive bacteria that produce the fatal forms of ulcerative endocarditis.

It begins usually with a sore throat or tonsillitis, but this is not always serious enough to be noted. Chorea with irregular involuntary movements may come on early in the disease, often with some fever. This is definitely a part of rheumatism, although as yet we know little or nothing of anatomical changes in the brain which are associated with it. The awkward symptoms generally pass off after a time. Joint affections, as stated above, are rather trifling in childhood. In adults they are

extremely painful and disabling for a time, but do not, as a rule, persist long in one joint, but pass on to involve another. Even so this is essentially an affection of the tissues about the joint, and the actual wall of the joint cavity, synovial membrane, and cartilage is relatively little affected. High fever with excessive sweating is a very usual accompaniment. In some cases there develop firm nodules beneath the skin, usually about the elbows, knees, and ankle-joints, although they occur anywhere else, often along the spine and beneath the scalp. These are the subcutaneous fibroid nodules so well described by Cheadle. As will



Fig. 442.—Verrucose rheumatic vegetations on the mitral valve. Subacute and chronic pericarditis with adhesions.

be seen, they too have the anatomical peculiarities that are characteristic of the lesions elsewhere.

Except when some intercurrent disease causes death, these patients die with evidences of cardiac failure, or else they live for a long time, to be exposed to the chance of bacterial endocarditis or to suffer the long disability of chronic valvular disease.

The heart is found enlarged, generally with subacute pericarditis with serofibrinous exudate or with pericardial adhesions (Fig. 441). The

valves, except in the very fresh cases, are thickened along their line of closure from the effects of previous attacks and show minute, firm, rather translucent vegetations (Fig. 442). These are most commonly found on mitral and aortic valves, but in about half the cases the tricuspid valves are also involved. The left auricular wall shows, as we have observed, in a large proportion of the cases a rough thickened patch, 2 or 3 cm. in diameter, on the posterior wall, just above the mitral valve. (Seen in section in Fig. 441.) This seems to be a particularly characteristic phenomenon, and later, when this patch is scarred, it seems to form a

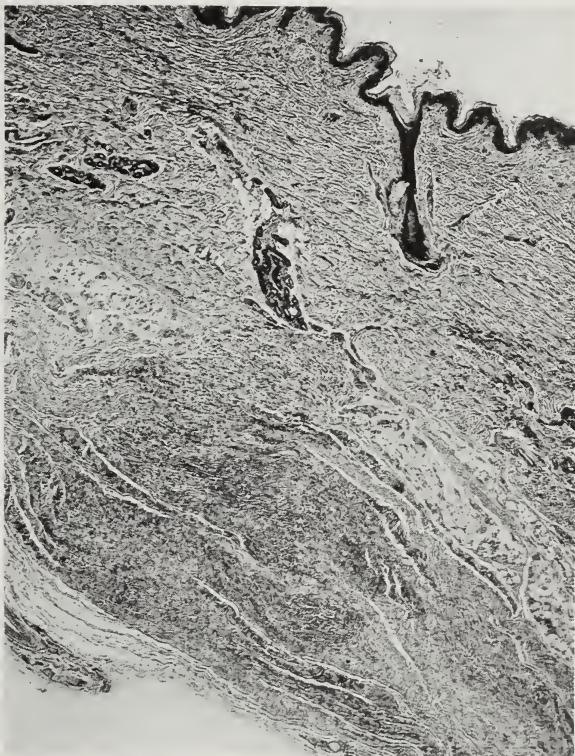


Fig. 443.—Rheumatism: Subcutaneous fibroid nodule.

favorable place for the deposit of the *Streptococcus viridans* when that occurs as a secondary invader producing endocarditis. Even when the patch is covered with myriads of streptococci the peculiar structure of the rheumatic nodules which compose it can be seen beneath.

The muscle of the heart-wall is studded with minute nodules which are grayish white and sometimes large enough to be seen with the naked eye, although often invisible except in a microscopical preparation. These are the so-called Aschoff bodies which were described by Aschoff in 1904 (Fig. 445). Some modification of these, associated with a more diffuse inflammatory process, seems to mark out as peculiar all the rheu-

matic lesions. They are accumulations of large mononuclear cells which are much like plasma-cells in form and staining properties. Their protoplasm stains red with pyronin. A few small cells accompany them, and they are usually found making up a nodule about the walls of a small twig of the coronary artery where they spread out the fibrils of the



Fig. 444.—Rheumatic lesion on the mitral valve. Vascularization, thickening and hyaline vegetation.

tissue into a spindle-shaped arrangement. But they are also found in clusters ranged along under the endocardium of the ventricle, and in the reticulum of the lining layer of the left auricle they appear in groups held in line by the rectangular arrangement of the fibres of that tissue.

There and in the loose connective tissue of the auricle wall and in that about the coronary vessels in the auriculoventricular sinus there is a dense inflammatory exudate of small mononuclear cells with fluid and fibrin. The original connective-tissue fibres often appear as hyaline strands closely surrounded by the large cells characteristic of the Aschoff bodies, ranged radially about them. The valves show a very advanced vascularization with much infiltration of mononuclear wandering cells among which are many clusters of the large cells described, and these are especially likely to appear just beneath the hyaline vegetations in which no bacteria are found (Fig. 444). Pappenheimer and Von Glahn have described such cell accumulations in the walls of the aorta, also various

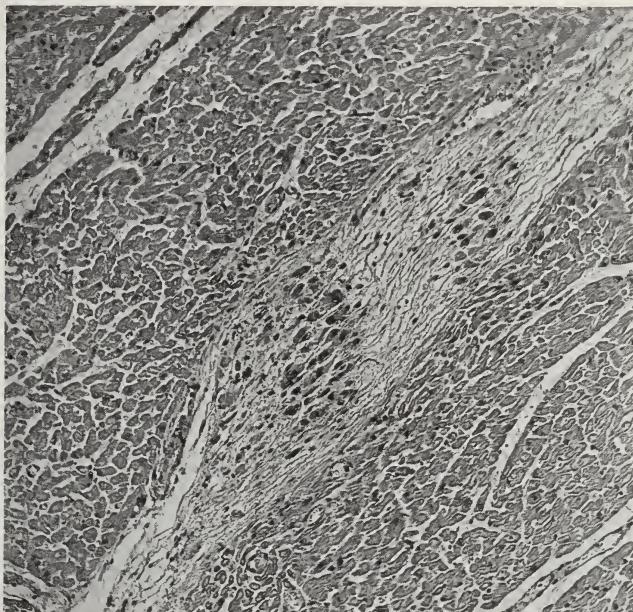


Fig. 445.—Aschoff body in the heart.

peculiar inflammatory changes in the walls of small arteries in the lungs, kidneys, and other tissues. The subcutaneous fibroid nodules are composed of a similar tissue, difficult to describe, but in which the essential feature is a convoluted mass of reticular formation everywhere necrotic in the central portion, but composed very largely of radiately arranged large cells of the type under discussion. Further out there is a more commonplace vascular granulation tissue with many eosinophiles and other leucocytes. Very similar lesions are found in the tendinous insertions and in the joint capsules, and, although we have had no opportunity to examine any joints when acutely inflamed in rheumatism, it seems that in that lesion too there is something of this peculiar type.

All this is described at such length to indicate its unique character, which marks out rheumatism as a disease quite different from any other that we know.

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Recent work is summarized by Swift, Gräff, Herz and others and especially well by Craciun. It appears that the lesions in rheumatism are developed to a different degree in different latitudes and, indeed, the disease is hardly to be found in the tropics. The search for specific lesions in other organs than the heart has gone on and there have been found especially interesting changes in the adventitia of the aorta by Chiari, Barnard, Bernard Shaw and others. In these cases thickened

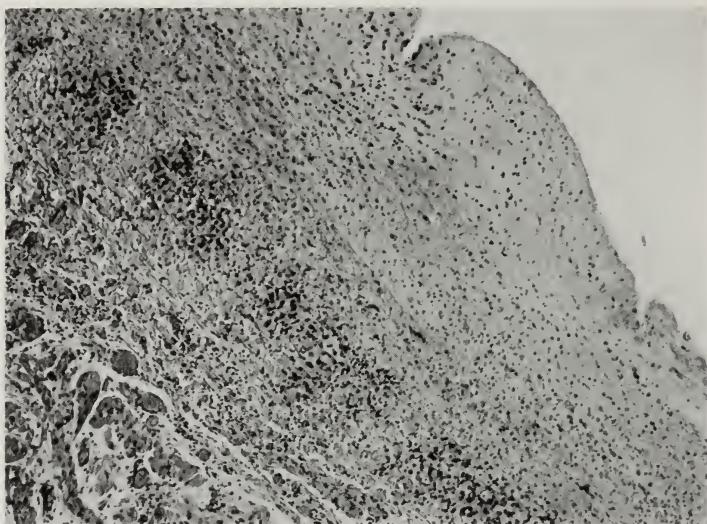


Fig. 446.—Section of the characteristic rheumatic thickening of the wall of the left auricle, showing the arrangement of cells like those of the Aschoff bodies in the lower levels.

rings of hyaline substance with cell infiltration in the marginal portions resembling that of the Aschoff bodies gives the aorta almost the appearance of the trachea in some instances. Media and intima are but little affected. The smaller arteries participate to some extent. Such changes have not been seen in our cases although carefully looked for. Renal changes have been described but since they are merely forms of glomerulonephritis without peculiar characteristics, it seems possible that they may have been due to associated bacterial infections. Little has been learned as to the pathological conditions responsible for the chorea although one or two authors have described focal perivascular cell infiltrations in the brain. Gräff emphasizes the occurrence of Aschoff bodies in the peritonsillar tissues and suggests that the tonsil is the

portal of entry, and shows perhaps the primary lesion in rheumatism. We have observed this in several cases. Coombs, Swift and others think of the small translucent vegetations upon the heart valves as arising from primary interstitial lesions in the substance of the valve over which the endothelium is finally destroyed. Since the changes seen in the valve substance, with their increased vascularization, resemble closely those seen in the myocardial framework, this seems a very plausible idea.

We have recently observed one case in which well defined Aschoff bodies were scattered not only throughout the parietal pericardium but through the more tendinous portion of the diaphragm and everywhere reddened by haemorrhage.

No convincing studies have appeared as to the nature of the aetiological agent although there are still those who ascribe the disease to one or other form of streptococcus.

But Schlesinger, Signy and Amies by centrifugalizing at high speed pericardial fluid from cases of acute rheumatism separated minute refractile granules measuring about 80–100 m $\mu$ . These are agglutinated by the serum of recovering cases but not by other sera. This at least seems to promise the recognition of a virus as the actual cause of rheumatism. They feel that a streptococcal infection aids the invasion of the virus or helps it to assume active character.

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## CHAPTER XLII

### TYPES OF INJURY.—INFECTIONS CAUSED BY FILTRABLE VIRUSES

*Yellow fever: Course, transmission by mosquitoes, aetiology, anatomical lesions.*

*Dengue: Symptoms, transmission.*

*Psittacosis: Distribution, transmission, aetiological studies.*

#### YELLOW FEVER

THIS was one of the most dreaded plagues of mankind a few years ago, but now, since the epoch-making studies of Reed and his colleagues, and the very effective application of these principles by General Gorgas, it has been almost completely exterminated from the American continents. It still exists in remote districts in sporadic cases or small epidemics. In Africa, especially in the Gold Coast, it has been recognized recently as a disease that is mild among the natives, but very fatal to foreigners.

It is a very grave febrile disease, with vomiting of blood, jaundice, haemorrhages in the skin and elsewhere, and extensive necrosis of the liver and kidneys with disturbance of their function.

Reed showed that it is transmitted by the bite of an infected mosquito, *Stegomyia fasciata* (*Aëdes calopus* or *aegypti*), but only after the lapse of twelve days after the mosquito has bitten a person ill of the fever and become infected. Evidently it requires twelve days for the development in the body of the mosquito of enough virus to infect a man, or else the virus must go through a twelve-day cycle of development in the mosquito. This is a mosquito very domestic in its habits, living about houses and laying its eggs in water found in receptacles there. Gorgas has shown that it is possible, by care in emptying frequently such receptacles so that larvae may not hatch, to reduce the number of mosquitos to a point below that at which their presence has a reasonable chance of spreading infection. But most effective is the careful screening of infected persons from the approach of mosquitos, so that shortly there are no more infected mosquitos in a neighborhood. This was the method used with success in ridding Cuba and other countries of the disease.

With regard to the aetiological factor there has been long and arduous search and the outpouring of a flood of literature. The work of Noguchi, on a spirochæte which he named *Leptospira icteroides*, held the interest for a time until it became clear that this was really *Leptospira icterohaemorrhagica* and derived from cases of infectious jaundice or Weil's disease which had been mistaken clinically for yellow fever. At least this seems the most plausible explanation. Sellards showed that the serum from patients convalescent from typical yellow fever gives nega-

tive Pfeiffer reactions to *Leptospira icteroides* and *Leptospira ictero-hæmorrhagica* which two organisms are immunologically identical and produce identical lesions in guinea-pigs. No spirochaetes are found in the typical yellow fever in Africa where Weil's disease is not prevalent.

On the other hand, Adrian Stokes, with his co-workers, was able to transmit yellow fever to monkeys by inoculation of blood from yellow fever patients or by allowing mosquitos to bite those patients, and after sixteen days to bite the monkeys. The lesions produced in these monkeys are identical with those of human yellow fever which is not true of the *Leptospira* infections of guinea-pigs.

The infective agent has been shown to be a virus which will pass through a Berkefeld filter and will grow in culture media which contain living tissue. It can be frozen and dried and can then be kept in a potent state for many months. Further, it is shown that the virus from African yellow fever is identical with that from the American disease.

Such virus, obtained by drying the blood serum, is enormously virulent and will produce the disease, yellow fever, not only in many kinds of monkeys of which the most frequently used is the *Macacus rhesus*, but also in mice and guinea-pigs. But in these latter animals, the mice and guinea-pigs, the virus has been inoculated by Theiler into the brain or into the peritoneum after some injury has been produced in the brain, upon which it localizes itself there and extends far and wide in the nervous system. It thus assumes a neurotropic character. Such a virus in small doses has been used for purposes of immunization and can be used alone if the dose is small enough but a safer procedure is that introduced by Sawyer, Kitchen and Lloyd in which the virus is injected just after the injection of immune serum from a person who had recently recovered from yellow fever.

The immunity following an attack of yellow fever lasts for many years and is probably permanent for the life of that person. It can be tested by its protective action in mice or monkeys.

Great interest attaches to the geographic distribution of the disease, often indicated by the immunity of the older members of a population, and by the distribution of the various mosquitos which act as vectors, of which, as stated, the *Aëdes aegypti* is the most important. With the advent of air transport the possibility of transmission of the disease to hitherto uninfected nations stirs interest, especially since Hewer has reported its unsuspected occurrence in the Anglo-Egyptian Sudan, which is in the path of airplanes to Asia.

The characteristic lesions are found in the midzonal necrosis of the lobules of the liver, the necrosis of the renal epithelium, often with calcification of desquamated cells, the ecchymoses in various tissues, especially in the gastro-intestinal mucosæ, and the jaundice.

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### DENGUE

Dengue is an acute febrile disease transmitted by the bite of a mosquito, *Aëdes aegypti*, but the aetiological agent of which is unknown. I may as well describe my own experience of this disease, because I had a typical severe attack in Calcutta. It began with fever, aching in the bones and joints which was less severe than it usually is (breakbone fever) and a punctate rash over the body which disappeared after two days with apparent drop in temperature, although the sense of illness persisted. Then with a new rise in temperature there came a great outbreak of a red macular rash over the face, hands, and feet with intense itching and sensation of tension in hands and feet. Illness and weakness became much more marked with a sort of delirium which went on for several days, ending suddenly with a sense of relative well-being. The rash faded and for two weeks or more the skin peeled off where it had been. The acute symptoms lasted about ten days, but I was left with the most extraordinary weakness, fatigued by the slightest effort, and a distressing sense of terror, all of which suddenly disappeared about ten days after the acute symptoms had gone.

The disease confers no effective immunity but after several attacks which are likely to come on each year a resistance is acquired which seems to be lasting.

There has been much dispute about the type of mosquito concerned in its transmission, but the matter has been finally settled by the work of Cleland and Bradley, Scott, Chandler and Rice, Siler, and others.

Nothing appears to be known of the pathological anatomy in this disease. Duval and Harris find that the aetiological agent is filtrable and appears as minute globoid bodies.

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## PSITTACOSIS

Psittacosis is a disease of parrots caused by a filtrable virus which can infect man, and not as was formerly thought by the bacillus of Nocard. During 1929-30 it produced a wide-spread epidemic in America and in European countries among those who came in contact with infected parrots. It causes fever and general illness, sometimes with delirium, and always with pneumonia in severe cases. Of 169 cases in this country during the epidemic 33 ended fatally, but there are few careful studies of the pathological changes. The pneumonia is said to resemble that found after influenza, a rather diffuse or confluent lobular pneumonia with moist purulent exudate and thickening of the alveolar and bronchiolar walls. No other constant or characteristic lesions are mentioned although there is usually an acute splenic tumor.

Rivers and his associates were able to infect with the virus parrots, mice, rabbits, guinea-pigs, and monkeys and their studies revealed focal necroses in spleen and liver with accumulation of leucocytes and mononuclear cells. In monkeys areas of pneumonia developed with infiltration especially of mononuclear cells and thickening of the alveolar walls, but only upon intranasal or intratracheal inoculation. They could also produce a form of meningo-encephalitis by intracerebral inoculation.

Neutralizing antibodies are formed in the serum upon intramuscular injection of the virus but it is not clear that this is an adequate protection against respiratory infection although vaccinated monkeys have an increased resistance to the active agent.

The exact nature of this aetiological factor is not known. Levinthal thinks it a bacterium, Lillie that it belongs to the Rickettsia group, Bedson that it is a protozoan or fungus. At least it passes filters and can be cultivated only in the presence of living cells.

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## CHAPTER XLIII

### TYPES OF INJURY.—INFECTIONS APPARENTLY CAUSED BY FILTRABLE VIRUSES

*Rabies or Hydrophobia: Aetiology, symptoms. Pasteur's virus for preventive inoculation, lesions. Landry's paralysis. Mumps: Symptoms and lesions; aetiology. Lymphogranuloma inguinale: Distribution, lesions, virus origin, Frei test. Periarteritis nodosa: Vascular changes and aetiology.*

#### RABIES OR HYDROPHOBIA

THIS condition is so widespread throughout the world that it demands especial attention, if only on account of its terrible character when human beings become infected, and of the great effort expended in preventing the development of the disease in persons who have been bitten by mad dogs.

It is generally agreed to be a virus disease since no bacteria are concerned and the active agent is filtrable and can be kept alive in tissue cultures, as well as in inoculated animals. From the wound which acts as the portal of entry the virus spreads evidently along the axis-cylinders of the nerves to the central nervous system where it is found in increasing quantity as days pass. The incubation period occupies as a rule more than two weeks, symptoms appearing most quickly when the wound is on the face or head. It begins with depression and irritability, followed then by a stage of excitement with muscular spasms which are most painful, in the muscles of the throat. It is this which makes any attempt at swallowing difficult and gave rise to the name hydrophobia. There is fever and often maniacal attacks, after which paralysis and coma lead to the death in collapse.

Pasteur devised the method of inoculating rabbits one from another until their brain and cords contained a "fixed virus" as contrasted with the "street virus." The cords of rabbits inoculated with the fixed virus and dried for varying numbers of days, afford the material for preventive inoculation of those persons who have been bitten but who have not yet shown any sign of the disease. When the symptoms are actually developed it is too late to hope for any good result from the attenuated virus.

In the brains of those who have died of this disease peculiar bodies are found in the ganglion cells. These, first recognized and described by Negri, are of diagnostic significance since they do not occur in that form in other diseases. They are bodies of irregular size and shape in the cytoplasm of the cells staining with acid dyes such as eosin but containing usually smaller bodies which are basophilic and stain blue with methylene blue. Many authors have regarded them as protozoan parasites, the cause of the disease, but the virus passes through a Berkefeld filter leaving them behind and even though the material remaining on

the filter is still capable of producing the disease, it seems by no means certain that the Negri bodies are actually one form of the virus. Goodpasture, in careful studies, concludes that they are the result of degenerative changes in the neurofibrils which enter the cytoplasm of the ganglion cell and that remnants of mitochondria are fused with them and give the basophilic particles. Nicolau and Kopciowska think them due to flocculation of Nissl bodies.

They do not occur in other organs, although the virus is found elsewhere. Evidently the virus escapes from the salivary glands and study devoted to them has shown Negri bodies in sympathetic ganglion cells there.

Many animals beside dogs and wolves are susceptible to rabies but it seems that the transmission of the disease to man is especially through them, since when all dogs are muzzled, as in Germany and England, hydrophobia disappears. Recently an outbreak in Trinidad was traced to infection of cattle, transmitted to man by the bites of vampire bats which had bitten the cattle.

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#### LANDRY'S PARALYSIS

Perhaps closely related to rabies is the acute ascending paralysis generally known as Landry's paralysis which seems to be of cytotoxic origin according to some authors. Milark describes the cord as vascular and soft, the changes extending up to the medulla and affecting the anterior and posterior horns of the gray matter with perivascular lymphocytes. The etiology is unknown but its occurrence in Trinidad after the bite of vampire bats suggested its relation to rabies.

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#### MUMPS

Mumps, or epidemic parotitis, is a common affection of young people appearing with febrile symptoms and a painful swelling of the parotid salivary glands. Various extensions of the infection may occur, sometimes involving other salivary glands or affecting the testes, or more rarely the ovaries and mammary glands. Cases are reported in which the pancreas has been affected even with the production of diabetes.

Most serious are the symptoms resulting from invasion of the central nervous system and cranial nerves. Deafness or extreme tinnitus, ocular alterations of various types, meningitis with oedema and mononuclear invasion of the perivascular tissues, and encephalitis or myelitis, may follow. The anatomical alterations in all these conditions seem to be as yet insufficiently studied and very little can be found in the literature. Recovery from the disease is usual with a lasting immunity.

Various ideas have prevailed as to the aetiological factor. It is clear that the saliva is infective and important in the transmission of the disease. Spirochaetes and other visible organisms have been thought responsible but recent work, especially of Wollstein, Findlay and Clarke, and of Johnson and Goodpasture, has shown that it is due to a filtrable virus which is obtained from the saliva of patients and upon injection into monkeys produces changes in parotid and testes identical with the human affection. Such monkeys become immune on recovery. The criticism that this may be the widespread herpes virus is invalidated by the fact that rabbits, insusceptible to this virus, can easily be infected with herpes or vaccinia—and further that the mumps virus is not found in the saliva of normal people.

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#### LYMPHOGRANULOMA INGUINALE

It is most unfortunate that very similar terms have come into use to designate quite different diseases, so that there is confusion in the literature. Lymphogranulomatosis is used by the Germans for the condition which we speak of as Hodgkin's disease. Granuloma inguinale refers to a venereal infection with bacillus variously named Calymmatobacterium granulomatis, Bacillus venereogranulomatis, etc., which produces, especially in the tropics, extensive projecting granulating masses beginning in the external genitals and spreading to the neighboring tissues without affecting especially the neighboring lymph-nodes. It may result in great destruction of tissue with later scarring.

What is known as lymphogranuloma inguinale is also a venereal infection, first recognized by Durand, Nicolas and Favre, in 1913, and caused by a filtrable virus. It is evidently very widespread and has been studied especially by Levaditi and his coworkers, by Barthels and Biberstein, Lee and Staley, and by Frei, the last of whom has devised a diagnostic test by injecting into the skin material from the lesions in a known case which gives a positive reddening when the infection exists.

The most distressing and incommoding obstructions of the rectum are produced in persons of about forty years of age by strictures which have generally been regarded as syphilitic. There is, however, no good evidence that these are syphilitic, and it seems now clear that they are

lymphogranulomatous in origin. I have reviewed our records of 15 cases at autopsy and find that with one exception all the typical ones were in women, and in none was there any positive evidence of syphilis. The narrowing of the gut occurs a short way above the anus, and is brought about by ulceration, often deep, with burrowing sinuses, which is succeeded by dense scar formation about the healing and still progressive ulcers. There is pain and tenesmus and obstruction with alternate constipation and diarrhoea, and the intestine above the stricture is dilated and hypertrophied and ulcerated from the stagnation of faeces. In sections through the scarred and contracted part of the wall we have found an old granulation tissue with great quantities of wandering mononuclear



Fig. 447.—Stricture of the rectum; lymphogranuloma inguinale.

cells, especially about blood-vessels, but nothing especially suggesting syphilis.

The primary lesion is a minute erosion, or papule, on the penis or prepuce which is soon followed by swelling of the inguinal lymph-nodes which become very greatly enlarged and fluctuant, often breaking through the skin with the formation of sinuses. In women, owing to the different lymphatic connections of the labia and vagina, the infection is carried not to the inguinal glands but rather to the wall of the rectum so that there arises a great infiltration of the outer wall of that part of the colon pressing upon its lumen and causing an extreme narrowing and obstruction, later with ulceration and even perforation with fatal perit-

onitis. These peculiarities of the lymphatic drainage are well shown in the diagrams of Barthels and Biberstein and in the paper of Lee and Staley.

The tissue changes consist in a dense infiltration with mononuclear cells with nodular accumulations of epithelioid cells and occasional giant cells, but necrosis proceeds rapidly with wide destruction of this new tissue.

Levaditi and his coworkers and Hellerstrom and Wassen have shown that the aetiological factor is a virus which will pass through a Berkefeld filter and is virulent for monkeys if inoculated intracerebrally. After many passages in monkeys, it has been inoculated in man, producing the characteristic lesions just described. It can be inoculated in mice in the same way and as in monkeys produces an encephalomyelitis with proliferation and infiltration of mononuclear cells throughout the meninges and about the vessels entering the brain. The virus is not essentially neurotropic and if introduced by way of the blood-stream does not affect the brain. A certain immunity can be produced and the serum of human beings after long illness will neutralize the virus in vitro. The Frei reaction is evidently an allergic response to the introduction of sterilized pus from a known case. Gray has recently described a series of cases in women in which the swelling and ulceration affected especially the external genitalia, recognized as specifically related by the Frei test. Tamura feels that he can cultivate the virus in the tissue-Tyrode medium of Maitland and uses the filtered heated cultures in diagnosis or even as a cure.

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### PERIARTERITIS NODOSA

Since the recognition by Kussmaul and Maier, in 1866, of this affection of small arteries, an enormous literature has grown up but even yet the problem as to its aetiology is unanswered. It is essentially an infectious process which produces changes in the media and intima of small arteries with cell exudation and hyalinization followed by more extensive leucocytic infiltration of the adventitia and immediately adjacent tissue. This may result in thrombosis, and obstruction of the arteriole, often with infarct formation in such organs as the kidney, or at times the vessel may become distended into an aneurysmal saccule and even rup-

ture. Such lesions in and about arterioles may occur almost anywhere but in the cases which we have studied they were prominent in the kidneys, pancreas, adrenal, voluntary muscles, liver and spleen. We have not found them in heart, intestinal tract or brain, although they have been seen by others in some of these situations. Clinically it is difficult to make a diagnosis of this condition which is sometimes acute and febrile, in other cases more slowly developed, ending in multiple aneurysmal sacculations with final fatal rupture of one of them. There are even cases in which nervous disturbances are due to such vascular changes in peripheral nerves (Gerlach), and doubtless other peculiar symptoms according to the site of the lesions.

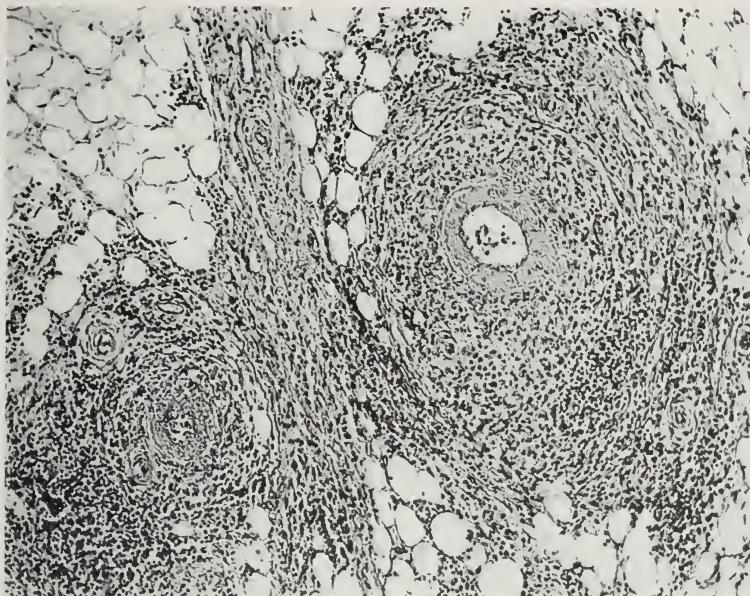


Fig. 448.—Periarteritis nodosa showing infiltration of walls of arterioles.

Harris and Friedrichs claim to have reproduced the disease in rabbits with an emulsion of nodules from the human case and later with a Berkefeld filtrate from the organs of the infected rabbit and conclude that the disease is caused by a filtrable virus. Others refuse this and suggest various other explanations but it seems hard to escape the idea that this is the result of a specific infection.

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## CHAPTER XLIV

### TYPES OF INJURY.—INFECTIONS CAUSED BY FILTRABLE VIRUSES

*Exanthematic diseases; General character. Measles: Occurrence, transmission, aetiology; secondary infections; pathological anatomy; neurological symptoms. Scarlet fever: Aetiology, course, pathological anatomy. Smallpox: Occurrence, relation to vaccinia, alastrim, chickenpox. Etiology, symptoms, pathological anatomy; relation of encephalitis following vaccination.*

#### EXANTHEMATIC DISEASES

THESE diseases have always been grouped together on the ground that they present skin rashes, which is, of course, not a safe basis for classification. But they are really much alike in that they are obviously caused by some sort of infection and are so easily transmitted from person to person that they occur in epidemic form. Further, they are peculiar in conferring, after one attack, a very lasting immunity with complete disappearance of the lesions, so that the question of continued infection does not arise. Until recently it has been felt that the nature of the infecting organisms is quite unknown, but of late years many supposed parasites have been described. It has been well said that if there is any doubt about a parasite it is usually not a parasite, and it has been common experience that when there is any doubt about the cause of a disease, the questionable parasites have been swept into oblivion at once when the true one appeared. A good example was seen in the case of syphilis.

There are many such diseases, including chickenpox, rubeola or German measles, Duke's fourth disease, erythema infectiosum, etc., but the most important are those which follow. Doubtless, before long the aetiology will be established in all and we may class them differently.

#### MEASLES

This is a disease of childhood because susceptibility is practically universal and the opportunity for infection so general that few children escape. There are few adults to infect, since nearly all have had the disease in childhood. In this is implied the fact that one attack confers immunity. The disease may be transferred *in utero* if the mother is ill with it when the child is about to be born. The child of a mother who has never had measles may contract it almost immediately after birth, while the child of an immune mother is born with an immunity which lasts one or two months. The mother's milk confers no protection. While such a situation prevails in most civilized countries, it is well known that in isolated lands, such as the South Sea Islands, where the disease was unknown, the advent of the infection with early explorers was followed by terrific epidemics which killed off many of the natives.

In the winter of 1917-18 the concentration of troops in training camps brought together great numbers of young men who had never had measles, and very great epidemics occurred. It was noted that the men from rural districts of the more sparsely inhabited states of the South were especially affected, while those from cities escaped.

Although under ordinary conditions measles is not considered a serious disease, the secondary pneumonia which follows when great numbers are crowded together is very fatal and the history of all great epidemics of measles reveals the prevalence of this type of pneumonia, apparently as the result of infection with a haemolytic streptococcus although this is not the usual organism concerned in secondary infection in more isolated cases. At least, I could demonstrate in old museum specimens from the epidemic which occurred during the Civil War, in 1864 and 1865, not only the peculiar character of the pneumonia but the streptococci in chains in the lungs. In the more sporadic cases we have usually found the influenza bacillus of Pfeiffer sometimes associated with other organisms, just as is usual in the pneumonia following whooping-cough, influenza and some other virus diseases. It seems, therefore, that the overwhelming spread of the haemolytic streptococcus in the measles epidemic in training camps in 1918 was due to the introduction of that organism under special conditions which one might expect again in another war.

The actual causative agent of measles appears to be a filtrable virus which prepares the way for secondary infections but which has not as yet been clearly recognized. Hektoen produced measles in two non-immune persons by injecting blood taken from a patient in the eruptive stage. Anderson and Goldberger similarly produced measles in monkeys by inoculating blood from early stages and were further able to filter the virus through a Berkefeld filter and with this carry on the disease from monkey to monkey. Sellards was unable to transfer measles to non-immune volunteers by inoculation but Duval and his associates have shown that a virus in the circulating blood during the febrile stage of measles can be filtered and will induce the symptom complex of human measles in monkeys, rabbits and guinea-pigs. So, too, Otero and McKinley have transmitted it to monkeys in the complete absence of streptococci or other bacteria from the inoculated blood and further demonstrate the development of immunity to a later injection of measles blood.

Transmission is ordinarily direct from person to person, probably by means of the respiratory tract, the infection presumably being carried in a spray from the coughing child.

The period of incubation is eight to nine days; the rash appears after about fourteen days. There are thus several days in which prodromal symptoms of headache, malaise, and nasal and bronchial catarrh prevail. Conjunctivitis, intense coryza with reddening of the pharynx and larynx, and, a little later, bronchitis, are characteristic and constant features. The so-called Koplik's spots in the mouth are minute white flecks surrounded by bluish and then red zones. They appear early and have a diagnostic importance.

The exanthem or rash appears first on the face and then spreads over the rest of the body. It is slightly elevated, grayish red, and distributed in flecks which are sometimes very small but usually conglomerated into larger patches which reach 1 cm. in diameter. It is common to observe a crescentic form in these patches. There are fever and leucocytosis and the catarrhal symptoms continue. With the lapse of a few days the rash fades and there may be desquamation of branny scales. The bronchitis clears up also unless there are further complications in the form of lobular pneumonia or other secondary infection.



Fig. 449.—Interstitial bronchopneumonia following measles in a child.

**Pathological Anatomy.**—Sections of the skin which pass through the macules show a moderate oedema and hyperæmia with some accumulation of lymphocytes about the blood-vessels. But there is no necrosis or intense inflammatory reaction. Postmortem, the pneumonia which is the usual cause of death is of the type which we have called *interstitial bronchopneumonia*. It seems to affect primarily the walls of the terminal bronchioles producing an infiltration with mononuclear cells which extends out later into the adjacent alveolar walls and, together with the polymorphonuclear leucocytes which fill the lumen of the bronchiole, produces small branched opaque white solid foci all through the lungs (Fig. 449). The surrounding alveoli become more and more involved

and filled with an exudate of fibrin and leucocytes while the alveolar walls become thickened by the accumulation of mononuclear cells. As stated above, this is usually caused by the influenza bacillus as a secondary invader but in the great epidemic we could not find any other organisms than the haemolytic streptococcus which was present in huge numbers in every case, usually producing also an intense pleural infection with great accumulation of turbid fluid which was practically a suspension of streptococci.

The other organs, besides the lungs and skin, are not characteristically affected in measles. There is usually a moderate acute splenic tumor and general enlargement of the lymphoid apparatus. The conjunctivitis, rhinitis, etc., are probably caused by the specific agent, but bacteria are so regularly associated that the affection is not peculiar. Otitis media is a not infrequent sequel.

Neurological symptoms occur in a small percentage of cases after measles and such forms of encephalitis have been studied especially by Ford, Greenfield and others. There may be muscular rigidity, spastic paralysis, ataxia, choreiform movements, aphasia, etc., and at autopsy there is found in the brain a perivascular demyelinization with some petechial haemorrhages and perivascular accumulation of cells. In this respect the encephalitic lesions are similar to the changes following smallpox or vaccination—and it is difficult to decide whether they are caused by the virus of the disease itself or by some other virus stirred to activity by the measles.

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#### SCARLET FEVER

This is generally looked upon as a more serious disease than measles, not only in itself, but because of the complications which accompany it, and the secondary affections which appear after recovery seems well established. It is curious, however, that at the present time scarlet fever seems to be a very mild affection, although occasional cases assume the maximum severity, and this recalls the fact that there have been several periods in history during which it prevailed for years as an almost negligible disease, each time followed, however, by other periods in which it raged with extreme violence. Sydenham lived to see such a change.

**Aetiology.**—Scarlet fever has always been thought to be a disease easily transmitted through contact with clothing and other objects con-

taminated long before by persons ill of the disease. This, like the idea of the extreme danger of contagion from the desquamated epidermis of the patient, is possibly only tradition. But scarlatinal infection has been acquired through cuts or scratches received during an autopsy on the body of a person dead or scarlet fever, as in the well-known case of Leube.

It is known that there is always an intense infection of the throat with virulent haemolytic streptococci. Sawtchenko and Moser succeeded long ago in producing immune sera with preventive and curative properties, from such streptococci. Dochez and Bliss found that the organism concerned is different from other streptococci, and with this specific haemolytic streptococcus Dochez has produced a serum, by active immunization of horses through the injection into their tissues of large quantities of agar containing the organisms, which will cause the disappearance of the symptoms in scarlet fever. Dick and Dick produced all the evidences of scarlet fever with the streptococcus which they isolated, and determined the presence of a toxin in the blood. This toxin they could isolate from cultures and with it produce an antitoxin specific for the disease which on injection into the skin of a person with scarlet fever causes a local blanching of the rash—Schulz-Charlton reaction. They also devised a test for immunity from scarlet fever, for in those who are susceptible the injection of the toxin into the skin produces a red reaction, while nothing happens in the skin of those who are immune (Dick test).

Dochez has been able to produce an infection in animals with rash and desquamation, although others have failed, and apparently it is in human beings that the infection is most characteristic. Blake and Trask show that the specific toxæmia lasts only as long as the rash, and that in the late septic cases, after the rash has faded, there is no toxin left, but an autogenous antitoxin. Persons with such an antitoxic immunity may harbor the Streptococcus scarlatinæ without any symptoms. Park shows that the antitoxin has no effect on complications that come after the rash has disappeared, and that for the best results the antitoxic serum must be administered early in the disease.

Stevens and Dochez emphasize the idea that an allergic reaction may go far to explain the acute symptoms of scarlet fever and the Dick reaction.

The student should consult the papers of Dochez, the Dicks, Park, and O'Brien. For all practical purposes the question of the cause of the disease is settled and scarlet fever is well under control, as far as individual cases are concerned. The specific Streptococcus scarlatinæ is always present; it produces a toxin which causes the general symptoms and the rash, although complications may be caused by the streptococcus itself in the tissues. The disease can be arrested and the toxic symptoms and rash made to disappear by the use of the antitoxic serum which does not affect erysipelas or puerperal fever or other known streptococcal infections which may coexist. It must be a calcified brain that would still harbor suspicion that there might be some other intangible organism really responsible for the peculiarities of the disease, but Frobisher in our

laboratory has shown that if a drop of the filtrate from the Dick strain of *Streptococcus scarlatinæ*, free from organisms, be added to a broth-culture of another streptococcus which is incapable of producing a toxin, such as one cultivated from cheese, the culture acquires the property of producing the specific toxin which gives the characteristic skin reaction—as though the filtrate contained a filtrable virus which can live symbiotically with a streptococcus and produce the toxin. O'Brien in his critical review accepts the *Streptococcus scarlatinæ* as the cause of the disease, but expresses this same suspicion by referring to the work of Dorset on hog-cholera, which was always thought to be due to infection with the *Bacillus suispestifer* until it was shown to be really caused by an invisible filtrable virus which alone gave its contagious character, although this is in nature always associated with the bacillus which produces the serious intestinal lesions.

Imamura and coworkers state that they have isolated a virus S from cases of scarlet fever, but feel that further research is necessary to prove that it is quite different from other viruses.

**Course of the Disease.**—The disease begins suddenly, after three or four days of incubation, with sore throat, fever, and swelling of the lymph-glands at the angle of the jaw and of the tonsils. With increase in the intensity of the angina and the appearance of whitish flecks of exudate on the red background there comes vomiting. Soon there appears on the face, and later over the whole body, the characteristic red rash which is made up of flecks much finer than in the case of measles and more closely set; the whole face and skin has a flushed red color. In all cases the angina represents a streptococcus infection, but there are some which proceed to recovery without much further evidence of bacterial infection, while in other cases there are phenomena of the most intense sort which appear to be largely due to the streptococci. Escherich, therefore, divides the cases into toxic and infectious types. In the more severe cases the angina becomes far more intense. The tonsils swell to the point of meeting in the midline and become partly necrotic. Considerable areas of mucosa of the fauces and the walls of the pharynx become covered with a false membrane of greenish color, the removal of which reveals deep ulcerations with foul base. The scarlatinal angina is thus an extremely destructive process. The neighboring lymph-glands in the neck are swollen to a great size and, if incised, sometimes exude a greenish pus, sometimes show their central parts as firm, necrotic masses which are later discharged. Such *scarlatinal buboes* may occur in this way in the early stages of the disease or appear much later after the acute symptoms have passed.

**Pathological Anatomy.**—Laryngeal and tracheal inflammation is found only in the severest cases, and then the occurrence of bronchopneumonia is likely. This lobular pneumonia commonly becomes confluent and leads to the production of abscesses in the lung. Extension into the pleural cavity results in empyema which may readily end fatally.

In the heart there may be no evident gross lesions even though the child die with signs directly indicating its involvement.

Stegemann shows that even in the early days of the disease there are changes in the heart ganglia, including degeneration and necrosis of the nerve-cells and infiltration with lymphocytes, and ascribes paralysis of the heart to these lesions. Later, in more protracted cases, there is similar infiltration of the heart-muscle and conduction bundle.

There are no specific changes in the nervous system, nor indeed can any be recognized in the other organs during the acute stage. It is true that necroses have been found in the liver, which is commonly the seat of cloudy swelling. The spleen is moderately swollen, markedly so only in cases where the streptococcus infection is predominant. There are

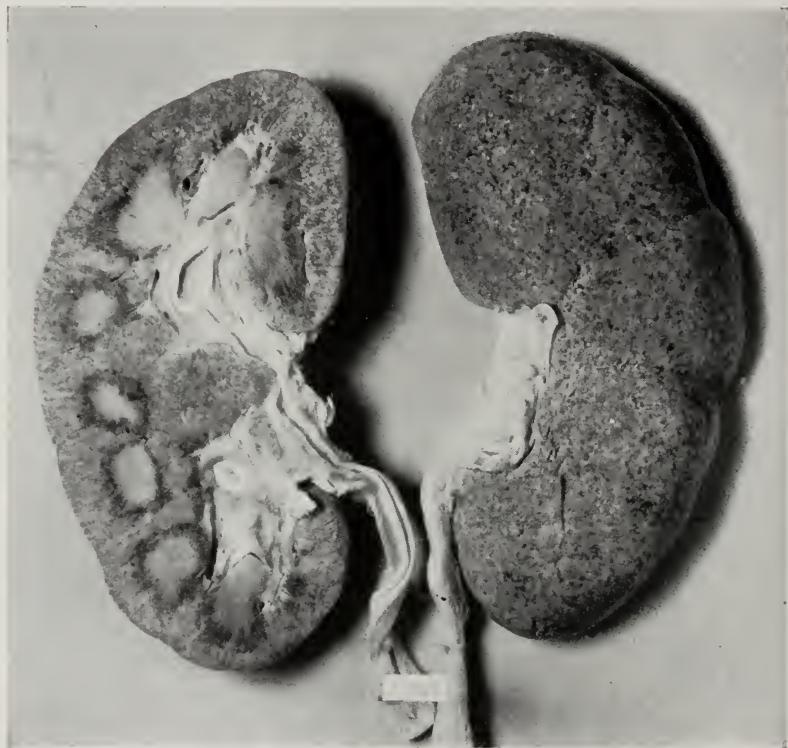


Fig. 450.—Acute interstitial nephritis in scarlatina. A section from this kidney shown in Fig. 451.

occasionally acute inflammations of the joints, with effusion of sterile fluid into the synovial cavities, but these disappear without leaving any disabilities.

Rach has studied the histology of the skin rash and has shown that in each flea there is a focus of acute inflammatory exudation, with outpouring of polynuclear leucocytes and red corpuscles into the substance of the skin about the blood-vessels. This extends into the epidermis, where there may appear small blebs filled with leucocytes. Later there occurs a thickening and dislocation of the epidermis which forms the well-known chaffy scales. A similar influence disturbing the growth of

the nails produces a transverse groove which, with the passage of time, gradually advances to the free edge of the nail.

There is a definite leucocytosis with a rather high percentage of eosinophile cells. The red corpuscles decrease for a time to about 3,000,000 per c.mm. Death may occur in the acute stage from general intoxication, with cardiac collapse, or from various lesions in the respiratory tract, or the patient may recover and progress to complete health. Recently we have studied a remarkable case in which arms, legs, and face became extensively gangrenous. The child was in the stage of

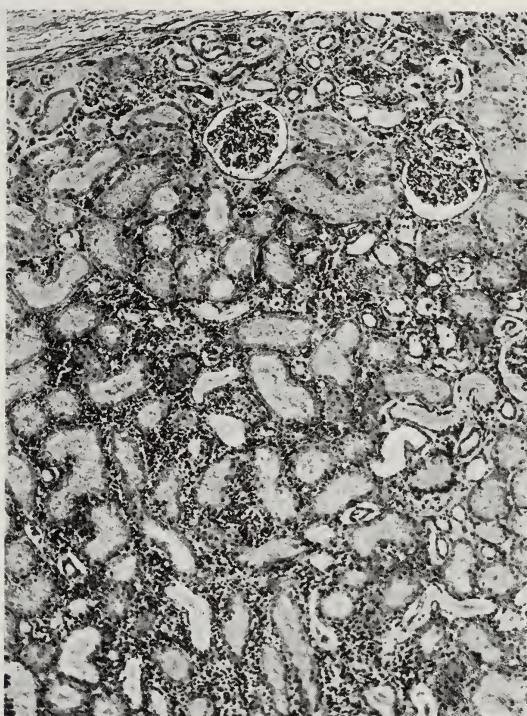


Fig. 451.—Acute interstitial nephritis in scarlatina. Section of kidney shown in Fig. 450.

desquamation. At autopsy some thrombi were found in the superficial veins, but no clear explanation of the process could be gained. This is apparently not an unusual occurrence in scarlet fever.

Nevertheless, in many cases in which the symptoms have passed away and recovery is apparently well-established, new symptoms appear in about the third week. Of these, a fresh swelling of the lymph-nodes and signs of acute nephritis are the most prominent. These are not due to a second complicating disease, but are late manifestations of the scarlatina itself. They appear to have about the same relation to the acute phenomena as the secondary lesions of syphilis bear to the primary lesion (Escherich), and evidently indicate the latent presence of

the organism in the body during the period of apparent recovery. The enlargement of the lymph-nodes seems independent of that which occurred in the primary stage and appears suddenly with pain. Usually it lasts only a short time and recedes after a few days, rarely ending in suppuration.

The *nephritis* is more serious. This has already been discussed in the chapter on Nephritis, but it may be pointed out again that there appear to be two forms—one in which the function of the kidney is not very greatly disturbed, except in the more severe cases, and in which the lesion consists essentially in the exudation of many wandering cells, chiefly of the character of lymphocytes and plasma cells, into the interstices between the tubules. This is the so-called acute interstitial nephritis which has been described by Councilman and others (Fig. 450). The second form is predominantly a glomerulonephritis in which the kidneys are found to be swollen and pale or mottled, often with opaque yellowish flecks. On section, the glomeruli project as grayish translucent dots. There may be ecchymoses in the substance of the kidney. Microscopically there are to be found all the changes previously described, which lead to obliteration of the glomerulus, by haemorrhage into the capsule with organization, proliferation of the capsular epithelium, and occlusion of the capillaries of the tuft by thrombi or by massed leucocytes. It is in the scarlatinal forms that the production of crescentic masses of capsular epithelium about the glomerular tuft is well seen, although, of course, this occurs in other types of nephritis. Degenerative changes in the tubular epithelium with destruction and desquamation of cells accompany the glomerular changes. Later, with the collapse of tubules, much loose connective tissue appears between the elements of the cortex, and in time the kidney may be extensively scarred. But in many cases complete recovery from all these injuries occurs, and if there is opportunity to examine the kidney of such a person much later in life, it is probable that only isolated scars may be found as the remains of the early injury. In other words, it is by no means inevitable that the occurrence of an acute scarlatinal nephritis should result in the production of a progressive chronic diffuse nephritis. The contrary is rather more probable. During such an acute and subacute scarlatinal nephritis the function of the kidney may be intensely disturbed. The secretion of chlorides and of water is diminished and there is generalized oedema. There is usually marked albuminuria and generally blood is passed in the urine. The blood-pressure is quickly heightened, and hypertrophy of the heart appears rapidly. Uræmic symptoms frequently occur, and may be severe enough to cause death.

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#### SMALL-POX

Small-pox is allied to measles and scarlet fever in the sense that it is a febrile disease strikingly characterized by the appearance of an exanthem or skin eruption. This, however, is scarcely a satisfactory basis for classification, and it may well be that when we learn the nature of the etiological factors in these diseases their relations will seem less intimate. Chicken-pox or varicella is a disease of milder character, but resembles small-pox much more closely than do the other exanthemata. A disease of cattle closely resembling small-pox, and known as cow-pox, is very rarely seen any longer, but is artificially preserved in the form of vaccinia. The relation of the diseases small-pox and vaccinia is not yet clear, since vaccinia inoculated in human beings produces only a local lesion which protects against small-pox, while human small-pox inoculated into cattle, rabbits, and other animals produces vaccinia and not small-pox. If small-pox be inoculated into human beings, as was done at the instance of Lady Mary Wortley Montague, before the discovery of vaccinia, a mild and localized affection is produced which protects against a severer attack of small-pox, but may sometimes be transmitted to other persons as true and severe small-pox.

The disease has occurred in extensive and very fatal epidemics, and when introduced into countries where it had not existed before, has in some cases exterminated the whole population. Even yet it rages at times with extreme violence. In 1798 Jenner published his observations on the disease of cows (cow-pox) which was often accidentally transmitted to milkmaids and others and which protected against the rather prevalent small-pox. He instituted vaccination, with the life-saving results which are so well known to day. Even yet, however, there are many persons of meagre intelligence who oppose the use of vaccination, and on account of their influence there are always unvaccinated individuals who are susceptible and thus make possible the occurrence of the disease.

**Ætiology.**—We are not definitely informed as to the cause of small-pox. Numerous writers have recognized in the epithelial cells of the pocks minute bodies which they have regarded as protozoan parasites. They were first seen by Weigert and then described by others. Guarneri named them *Cytorrhycetes variolæ*, and Councilman and his co-

workers have described them more fully, having found them in all their cases. Calkins has worked out a life-history by comparing the various stages, but tells me that he would now modify some of these conclusions. More interesting are the observations of Prowazek, Paschen and others who have found in the material from small-pox pustules and also in cowpox vaccine myriads of extremely minute dancing granules which they regard as the cause of the disease. These can also be demonstrated in the epithelial cells in the active lesion. We have studied these particles in vaccine and find them constantly. Indeed, the infectivity of the material seems to depend upon their presence. They are far smaller than the smallest bacterium, occur in pairs or short chains or singly, and move slightly. Lambert and Steinhardt, without seeing them, showed that the virus could be propagated in culture with pieces of growing skin and greatly increased in amount, as shown by inoculation. Noguchi has



Fig. 452.—Alastrim. Tenth day of eruption.

cultivated the virus in the testicles of animals so as to render it bacteria-free. We have separated the granules from the rest of the vaccine by bringing its specific gravity to a certain point and centrifugalizing, upon which they come to form a layer at the top. They can be washed and recentrifugalized repeatedly until they are bacteria-free and free of all adhering fluid from the original vaccine. Working with the washed granules Cracun and Oppenheimer have found that they multiply rapidly in tissue cultures as shown by inoculation of animals. This appears to settle finally the importance of these granules as the etiological factor.

In all cases of small-pox, except perhaps the very mild or abortive forms, there is an accompanying infection with streptococci. It will be remembered that this associated streptococcus infection is characteristic

of scarlet fever and of diphtheria also, so that it by no means excludes the idea of a separate and specific aetiological factor. Many of the lesions of small-pox, especially in the internal organs, are ascribed to the effects of the streptococci.

**Symptoms.**—The disease begins abruptly with a chill or with headache and malaise, and in a short time becomes recognizable by the appearance of shotty nodules in the skin which develop rapidly and reach their acme about the tenth day (Fig. 452). These at first feel like little firm points, but soon become vesicular, and from that quickly assume the yellowish opacity which reveals their pustular character. Practically all of them show a depression or dell, but occasionally this is obliterated, for reasons to be discussed. The pocks, or pustules, are usually about 3 mm. in diameter, but they may become confluent into

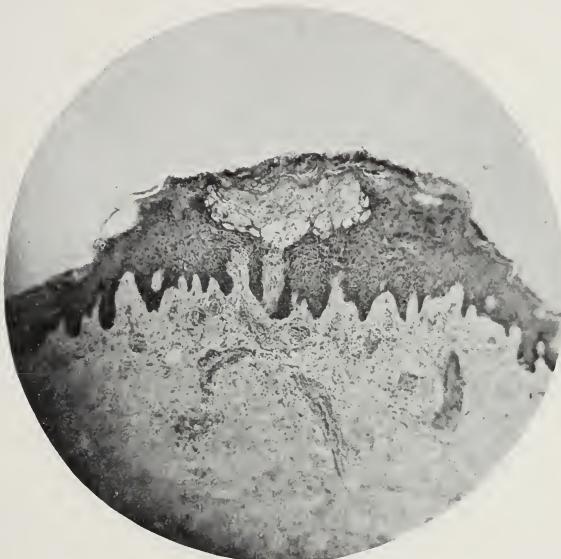


Fig. 453.—Early stage in development of alastrim pustule.

irregular patches. They develop in no particular relation to hairs or sweat-glands. After the height of their growth is reached they do not burst spontaneously, but dry up into crusts which adhere for a time and finally fall off.

Alastrim is a form of small-pox which we studied in a great epidemic in Jamaica in the summer of 1920. It differs from the classical small-pox only in its mildness and perhaps in its immunological relations, so that from the anatomical point of view it seems identical. During that summer only about 10 deaths occurred among 3000 cases. The patients, covered with a confluent eruption of pocks, were profoundly ill for only about one or two days at the height of the affection, but otherwise the general course was as in severe small-pox.

**Pathological Anatomy.**—Our study of the skin lesions in alastrim

showed that in the earliest stages the lesion consists of an infiltration of mononuclear cells and leucocytes about the vessels of the corium. The epithelial cells over this become vacuolated and separated and a vesicle is formed within the layer by the accumulation of fluid there—a fluid which is quickly filled with leucocytes (Fig. 453). There are sometimes bridges of epithelium left stretching between the roof and the floor of what is now a pustule. At first the Malpighian layer of the epidermis persists, and it may continue so, but usually later the papillæ of the corium are laid bare in the floor of the pustule, and they and the underlying corium become densely infiltrated with leucocytes (Fig. 454).

After the height of the process is over, new epithelium grows from the sides over the remaining Malpighian layer which usually forms the bottom of the pustule, or over the exposed corium if that layer has been de-



Fig. 454.—Margin of older pustule in alastrim. The epidermis is lost under the central part of the pustule.

stroyed, but also along the under side of the uplifted roof of the pock. Shortly it happens that the exudate, enclosed now between two layers of epidermis of which the upper becomes completely dried up, also dries up and is rubbed off as a crust with the adherent upper layer of epithelium. A depression is thus lined with epidermis. If the Malpighian layer has remained intact, no deep pitting results, but if the necrosis has extended into the corium, the healing of the pock leaves a pit.

Various modifications in the eruption occur and the disease is roughly divided accordingly into mild forms, in which there are hardly any skin lesions or symptoms; abortive forms, in which the lesions of the skin quickly recede and disappear; haemorrhagic pustular forms, in which haemorrhage occurs in and about the pustules; and purpuric forms, in

which more extensive haemorrhage into the skin forms a feature more conspicuous even than the pustules. The last is an extremely severe form in which death may occur before the eruption is well developed.

In the internal organs the changes are partly due to the specific cause of the disease, but are partly the effect of the accompanying streptococcus infection.

In the mucosae of the mouth and other body orifices and in that of the trachea and digestive tract there occur specific lesions of the character of those in the skin, and with the same degeneration and necrosis of the epithelium, but since there is no protective horny layer to allow of the development of definite pocks, they result in the separation of the epithelial cells, the infiltration of the tissue with leucocytes, and the production of indefinite small ulcers.

In the testes and bone-marrow more readily recognizable specific lesions occur. In the testes these are found as nodules in the substance, more numerous just under the tunica albuginea. They are formed by a focal infiltration of wandering cells among the tubules. After a time the tubules involved become necrotic and invaded by the mononuclear cells. Such nodules appear in section as opaque, yellowish spots with a halo of haemorrhage, and heal with the formation of small scars.

In the bone-marrow very similar lesions are found with central necrosis involving the blood-forming cells and marginal infiltration of mononuclear elements. The formation of polynuclear leucocytes is seen to be in abeyance in the bone-marrow and many degenerated forms are found. In the later stages of the disease the mononuclear types hold a predominant place among the emigrating cells on this account. Chiari has described this lesion as osteomyelitis variolosa, but it obviously does not resemble other forms of osteomyelitis.

In the liver there is intense cloudy swelling, and focal necroses are occasionally found. The organ is ordinarily much enlarged. In the kidneys there is no characteristic lesion, but degenerative changes appear in the epithelium of the tubules and occasionally there is acute glomerulonephritis. Interstitial accumulations of mononuclear cells are relatively common. Similar non-specific changes may be found in other organs, but it remains a question as to whether they are not produced by the streptococci. This is true also of the degenerative changes in the heart-muscle, which are like those seen in other acute infections, and perhaps also of the swelling of the lymph-nodes and spleen. In the lymph-nodes, the changes in the lymph sinuses include the appearance of many large phagocytic cells, together with abundant smaller mononuclear cells.

In most cases there is an acute bronchitis and in many there occurs a rather severe lobular pneumonia which may be confluent in character. This is often the actual cause of death and is probably to be ascribed to the bacterial infection.

Great interest has been stirred in recent years by the occurrence, in some countries especially, of encephalitis after vaccination and there has been much discussion as to whether this is a direct invasion of the vaccine, or some associated virus introduced with the vaccine. Prof. Led-

ingham reports that vaccine virus can be recovered from the blood, tonsils and nasopharynx after ordinary cutaneous vaccination but that there is no evidence that it can pass the blood-brain barrier. When directly inoculated into the brain it produces a meningitis. He takes the view that post-vaccinal encephalitis is more probably the result of activation of some latent virus already present in the vaccinated person.

Turnbull and McIntosh studied many cases and found a form of encephalitis affecting especially the pons and the lumbar cord in which the small vessels are surrounded by cells some of which are leucocytes while others are lymphocytes, plasma cells and more elongated cells. There is also demyelination and softening about the vessels. Wilson and Ford have described several cases of which we still have the sections. In one of these the disintegration of the tissue of the pons and medulla is advanced and the perivascular infiltration seems to be made up rather of glial elements than of the lymphoid cells which are found in the epidemic form. Turnbull and McIntosh were able to demonstrate the vaccine virus in emulsions of the brain from fatal cases by cutaneous inoculation but others have not been able to find it in the cerebrospinal fluid at any rate.

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## CHAPTER XLV

### TYPES OF INJURY.—DISEASES DUE TO ANIMAL PARASITES

*Introduction. General relation of parasites to host. Table of main zoölogical divisions. Amæbic infections: Types of parasites and life-history; intestinal infection; liver abscesses; abscess of lung. Pyorrhæa alveolaris. Malaria: Types and life-history of parasites; symptoms and pathological anatomy; Blackwater fever. Leishmaniasis; kala-azar. Trypanosome infections: biology; sleeping sickness.*

IT has been seen that, through the invasion of the lowliest forms of plant life and their adaptation to a parasitic existence in the animal body, many diseases arise. This is not less true of members of several of the great groups of the animal kingdom which have undergone biological alterations in the course of a parasitic mode of existence, involving in many cases anatomical changes which separate them from their closest relatives. The animals which have thus come to live as parasites belong to the protozoa, the worms, and to a less extent to the arthropods. The student must be referred for a discussion of their anatomy and their systematic relations with one another and with the related free living forms, to works on zoölogy and parasitology, perhaps particularly to the volumes of Brumpt and Braun. Only a few types can be mentioned here in their relation to common parasitic diseases of man.

**General Relation of Parasite to Host.**—Those parasites which live on the body surface are more nearly capable of maintaining their existence apart from their host than the obligate parasites which spend their lives in the interior of the body. The latter may go through their whole life-history in the body of one animal, or may pass a stage of it as free living creatures in the outer world; but most of them with or without such a period of freedom are compelled to pass through an important epoch of their development as parasites in a totally different animal. This alternation of generations is a most wide-spread phenomenon and leads to great complexities in the life-history of such parasites. So difficult to unravel are these metamorphoses and changes of host that the whole story of great numbers of parasites is still unknown, and that of even the most familiar has been revealed only recently. Thus the common tapeworm lives as a mature worm in man, while its larval form is found in the ox; the Bothriocephalus of man passes its larval stage in various fish; the filaria which invades the blood and lymphatics of man is larval in a mosquito, and so on. Naturally, in order that the transfer from one animal to the other should be made at the proper time, extraordinary adaptations have come about. In blood-sucking insects which act as intermediate host, the larvae, or spores, as though by an intelligent decision, lodge themselves in the salivary glands, and nowhere else in the body, and are consequently inoculated into the blood of the next

host. The effect of the specific adaptation is further seen in the complete dependence of the parasite upon one particular kind of intermediate host, as well as its particular kind of main host. Malarial organisms sucked into the stomach of a culex mosquito must die there although they develop in an anopheles, and after they have made the anopheles infective for man they perish if by mistake it bites a cow, and injects them into the cow's blood. Many nematodes, or round worms, bring forth active larvae from the eggs, and sometimes these are left to fend for themselves and attack their new host by their own activities. In this, some pursue a most devious course, as when the ankylostoma, necator, and strongyloides larvae penetrate into the skin of man and are swept by the blood into the lungs and bronchi whence they reach the intestine. Others, like ascaris, oxyuris, and trichocephalus, round-worm parasites of the intestines, lead a simpler life, their eggs being transferred with water or vegetables to another person's alimentary tract, or more directly to that of the patient himself, producing an intense infection. Of their life in these hosts, and the duration of their stay, some idea may be derived from the examples given.

Parasites act mechanically in several ways to injure the host. In the case of many of the worms which pass their larval stage in man (*Tænia echinococcus*, etc.), the great bulk of the cystic larva may occasion mechanical injury, especially in the brain, which lies in a confined space. The ordinary round worms (ascaris) produce many symptoms by mechanical irritation of the intestine and by wandering into such channels as the bile-ducts or the Eustachian tube or the appendix, where they cause obstruction. Strongyles, and the trematode, schistosomum, which live in the blood-vessels, may cause serious obstruction, disturbing the nutrition of the tissues. Toxic action is clearly associated with the uncinaria and bothriocephalus which produce profound anaemia, and Schaumann and Tallquist have isolated a haemolytic substance from the bothriocephalus. In other cases, as with malaria, the anaemia is produced in a more mechanical way by the destruction of the corpuscles in which the parasites live. The trichocephalus and the uncinaria actually suck the blood from the intestinal wall. Inflammatory reaction following upon tissue destruction is characteristic of infection with the trichina, amœbæ, and other organisms, and those which lodge in the tissues and remain there, commonly set up the new formation of much fibrous tissue in their neighborhood.

The following table will serve to indicate the relations of these organisms.

PROTOZOA:

SARCODINA:

*Rhizopoda*: Amœba, etc.

MASTIGOPHORA:

*Flagellata*:

Trypanosoma (Sleeping sickness).

Leishmania (Kala-azar).

Giardia (Lamblia) intestinalis.

Trichomonas, etc.

Spirochaetæ.

## SPOROZOA:

*Telosporidia:*  
 Gregarinida.  
 Coccidiidae.  
 Haemosporidia (Malarial parasites).

*Neosporidia:*  
 Myxosporidia (Parasites of fishes).  
 Microsporidia.  
 Sarcosporidia (Occasional parasites of man).

## INFUSORIA:

*Ciliata:*  
 Balantidium, etc.

## WORMS:

*Cestoda* (Tapeworms):

Taenia.  
 Bothriocephalus.

*Trematoda* (Fluke worms):

Distoma.  
 Opisthorchis.  
 Schistosomum, etc.

*Nematoda* (Round worms):

Filaria.  
 Trichocephalus.  
 Trichinella.  
 Ankylostomum (Hook worm).  
 Ascaris.  
 Oxyuris, etc.

## ARTHROPODS:

*Arachnoidea:*

Acarina: Ixodes (Tick).  
 Sarcoptes (Itch mite, etc.).

*Insecta:*

Rhyncoeta: Pediculi (Lice).  
 Cimex (Bedbug).

Diptera: Pulex (Flea).  
 Musca (Fly).  
 Culex }  
 Anopheles } Mosquitos.

## AMOEBOIC INFECTIONS

There are known to zoologists great numbers of amoebæ, most of which are free living; a few are parasitic in various animals, and among these are certain forms which infect man. Craig, in his paper of 1905, enumerates all the genera and species and points out that, although forms of Vahlkampfia and Trimastigamoeba may be of interest as occurring in such a way as to be confused with the parasitic forms, it is only in the genera Craigia and Entamoeba that true parasites of man are found. Chief interest is attached to the genus Entamoeba, which, together with about 40 other species, contains the forms *Entamoeba coli* and *E. histolytica*. Briefly, it may be said that *E. coli* is a harmless commensal in the intestine of man. It is found in a great proportion of healthy people who have never had dysentery, and is distinguished from *E. histolytica* as follows. It averages 30 microns in diameter, is grayish and dull-looking, without clearly defined ectoplasm, and possesses a large nucleus. Its movements are sluggish, and when it becomes encapsulated

it divides into eight young entamœbæ. The *Entamœba histolytica* is a distinct parasite in the intestine of man, and produces there and in other organs most intense destructive changes. It is recognizable by its larger size (20–60 microns) and by the striking contrast between its granular cytoplasm and its glassy, refractive, colorless ectoplasm. This latter is usually in active motion, throwing out and retracting pseudopods into which the remainder of the body streams. It multiplies also by fission, and when it undergoes encapsulation divides into four new amoebæ. The *Entamœba tetragena* is identical with this. Methods for their cultivation have recently been devised by Boeck and Drbohlav and by Craig and later by Meleney.

The pathogenic amoebæ are possibly introduced into the digestive system with uncooked vegetables or contaminated water, although, as Walker and Sellards have shown, it must be remembered that the amoeboid, or vegetative form, is very little resistant to exposure to external conditions. The more resistant encysted form is, however, found in the stools of many apparently healthy carriers, and transmission is probably more easily explained as the result of contamination of food by these people. Great public interest was aroused by the epidemic of amoebic infection with many fatalities which was traced to its source in two hotels in Chicago, which had a common water main, and in which there appeared to be connections between sewage pipes and those carrying the drinking water. Prolonged study of the conditions failed to reveal any other probable contamination of the food although possible carriers were sought among food handlers. The situation is discussed in detail in a symposium by McCoy and others.

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**Intestinal Infection.**—In the intestine the amoebæ find their way into the crypts of the mucosa of the colon and there produce small areas of necrosis from which further invasion into the submucosa occurs. In most cases the mucosa of the colon is the only area affected, the invasion taking place especially in the upper part of the large intestine. It is rare to find any lesions in the lowermost part of the ileum or in the appendix.

The earliest changes appear as elevations in the mucosa, with hyperæmia or haemorrhagic halo and a central plug of yellowish, necrotic material. Sometimes these elevations become quite large before the necrotic tissue is discharged, and I have seen cases in which the whole mucosa was covered with such patches without definite ulceration (Fig. 455). Usually, however, the softened substance falls away and reveals ulcers which show a great tendency to undermine the mucosa and to coalesce with one another, leaving bridges of mucosa between them. This is not always the case: numerous large or small discrete ragged

ulcers may be formed instead; but when it occurs extensively, as it does in some cases, the undermined mucosa dies and is found hanging in long shreds or sheets from the wall (Fig. 456). In one case observed recently at autopsy nearly the whole mucosa was thus destroyed, and great blackened, ragged films of mucosa were found hanging in the lumen. As a rule, the process is rather slow, and attempts at healing take place, so that the intestine tends to become greatly thickened by the formation of



Fig. 455.—Amoebic colitis. There are numerous confluent and discrete elevated necrotic patches and many small ragged ulcerations.

granulation tissue rather than to be perforated. Nevertheless, perforation does sometimes occur and is usually met by adhesions, so that only local abscesses are produced. Narrowing of the gut may follow such ulceration and healing.

Microscopically one may find in the earliest stages minute ulcers involving the mucosa alone, with amoebae in the margins of the tissue (Fig. 457), but more commonly the ulcer is found to extend in the submucosa and to be partly filled with disintegrated tissue with fragmented nuclei.

On account of the exposure to the intestinal contents many bacteria are present and there is some inflammatory reaction, but this is by no means

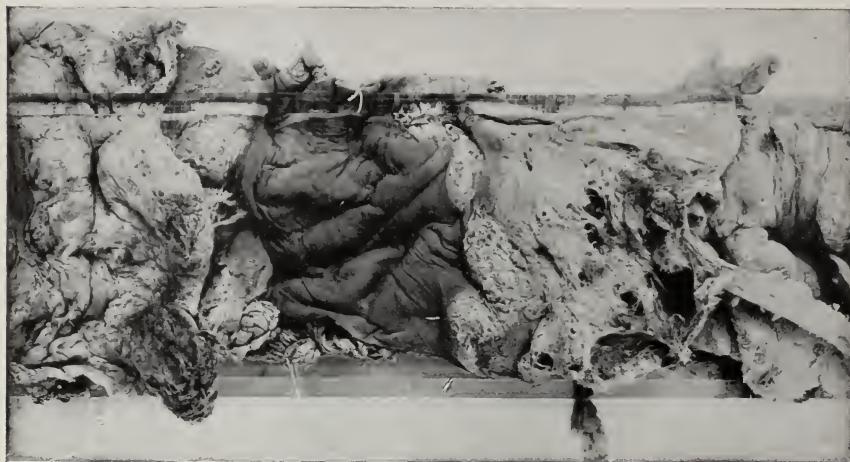


Fig. 456.—Amœbic colitis. Two large ulcerated areas over which the mucosa has been undermined and hangs in necrotic shreds.

so prominent as in the case of the bacterial forms of dysenteric ulceration. In the edges of the necrotic tissue the amœbæ are found lying in

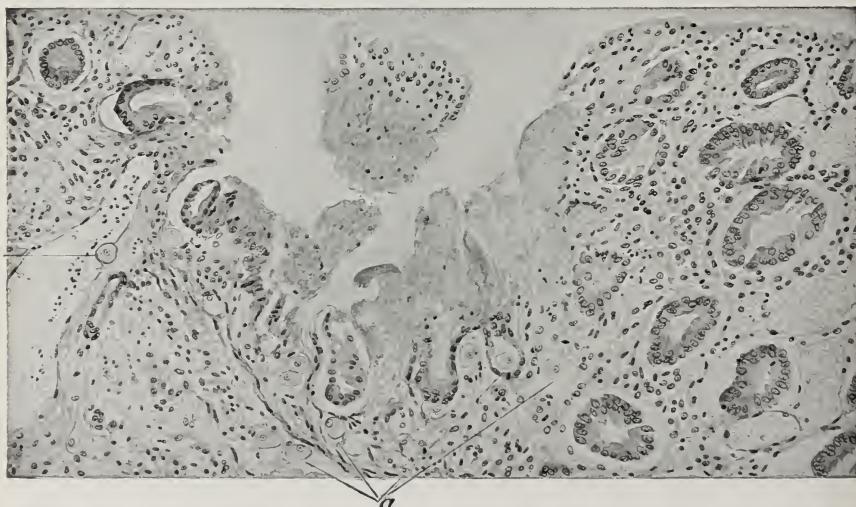


Fig. 457.—Beginning amœbic ulceration of the mucosa of the colon. Amœbæ (a) are seen in the crypts, in the stroma of the mucosa and submucosa, and in one case beneath the endothelium of a vein.

the crevices. Often they can be traced far into the submucosa or down into the interstices of the muscles or even into the subserous tissues, and when they are found, those in advance are usually not surrounded by

any reaction or by any evident changes in the tissues. At times they are observed underneath the endothelium of the branches of the portal vein, and in many cases I have found them lying free in the lumen of such venules together with the blood-cells. This is important, since it explains readily their transportation to the liver. The reparative changes are quite like those in any other ulcer, but it is evident that they are frustrated by a new necrosis of the tissue and must be repeated constantly.

There is practically no difficulty in recognizing the amoebæ which are found invading the tissue as the cause of the disease, although the clinician may run the risk, in the examination of the faeces, of mistaking the harmless and common *E. coli* for the pathogenic form.

Such ulcerative dysentery causes diarrhoea, with much tenesmus or painful straining, and the stools are made up of small amounts of mucus flecked with blood. The mucus may contain the amoebæ, but they are found more abundantly after a saline cathartic is given. The infection is extremely persistent and often drags on for months or even years.

**Liver Abscesses.**—Of the sequelæ of amoebic dysentery, the commonest is the development of abscesses of the liver. It is known that amoebæ enter the branches of the portal veins in the intestine, and are swept into the liver, where they lodge in the capillaries and produce effects similar in principle to those set up in the intestine. The amoebæ in the intestine take into their cytoplasm red corpuscles and bacteria as well as the débris of tissue-cells, and it is not surprising, therefore, that there are sometimes evidences of bacterial infection in the liver also. But usually it seems that these bacteria are digested, for the abscesses are likely to be sterile except for the presence of the amoebæ themselves. Although the lesions are commonly called abscesses, they are really not quite like the abscesses produced by pyogenic bacteria, inasmuch as the amoebæ cause the necrosis and liquefaction of tissue without any very pronounced inflammatory reaction. The contents of such abscesses, therefore, consist chiefly of the débris of liver tissue, with relatively slight admixture of leucocytes. Ordinarily only one such abscess is found, but in about one-third of the cases the abscesses are multiple, two or three rather large cavities being found in different parts of the organ (Fig. 458). Rarely there are hundreds of small foci. The drawing shows well the appearance of the rapidly forming fresh abscesses, of which there were several in this case, together with numerous very small ones. A description of the case may serve to present the fresher stages. The small abscesses (from which the contents can be squeezed out like paint) appear as opaque, yellowish-white areas occupying the space of one or two lobules. The large ones have a definite cavity lined with yellowish-white necrotic material resembling badly made custard. In the cavity one may find a similar substance or a turbid fluid with shreds of necrotic tissue hanging from the wall. In one abscess in this case there was a clear, straw-yellow fluid. The surrounding tissue ends abruptly in the necrotic lining of the abscess, but from the rapid extension of the cavity and the accumulation of fluid it becomes much compressed. The effect of this pressure is to stop the outflow of blood from regions drained by branches of the hepatic vein which pass by the ab-

scess, and thus to produce local areas of passive congestion. The same thing is to be observed in the neighborhood of metastatic tumor nodules in the liver. Other areas become anæmic from the compression of branches of the portal vein.

Far more commonly one finds the abscesses in a more advanced state in which it is no longer possible to recognize necrotic curdled liver tissue in the contents. Then they are filled with thick, creamy, gelatinous, purulent fluid or with a more pasty tenacious opaque material, which is often stained greenish from the admixture of bile from some duct which has been invaded. In these abscesses efforts at healing have been made in the adjacent liver tissue which result in the formation of a thick wall of granulation tissue. After that, the advance of the abscess

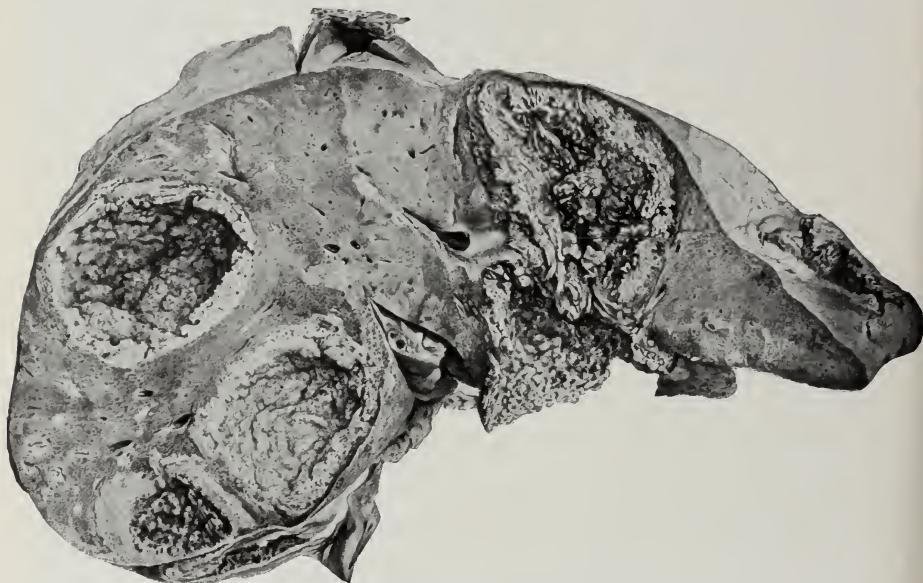


Fig. 458.—Multiple amœbic abscesses of liver (Mense's Handb. d. Tropenkrankheiten).

through the liver tissue is far slower. Even when a distinct wall is formed, shreds and long strands of necrotic liver tissue may be found hanging in the cavity. Later still, the amœbae may die out, most of the fluid be absorbed from the pus, and the wall contract down around the mortar-like material which remains. Usually this becomes pigmented with an orange-yellow pigment derived from extravasated blood. Finally the whole may be replaced by a pigmented scar. But although one occasionally sees this spontaneous healing, it occurs in my experience usually in those cases in which another abscess has formed elsewhere in the liver or in the lung, or in which rupture of the abscess has taken place either spontaneously or through surgical intervention.

The affection is a very serious one, and the mortality is high even with modern treatment. The growth and extension of the abscesses often

bring them to the surface of the liver, so that other tissues are invaded and rupture occurs in one or other direction. The commonest site is in the dome of the right lobe, whence extension can occur through the diaphragm into the substance of the adherent lung, with rupture and discharge of the pus (now stained brownish red, "anchovy sauce appearance") through the bronchus, so that it is coughed up and expectorated. This is the most frequent and favorable outcome. But extension and rupture may also occur into the free pleural cavity or the pericardium, into the peritoneal cavity or adherent colon or stomach or duodenum, or even through the outer skin. More rarely the portal vein or vena cava receives the content of the abscess.

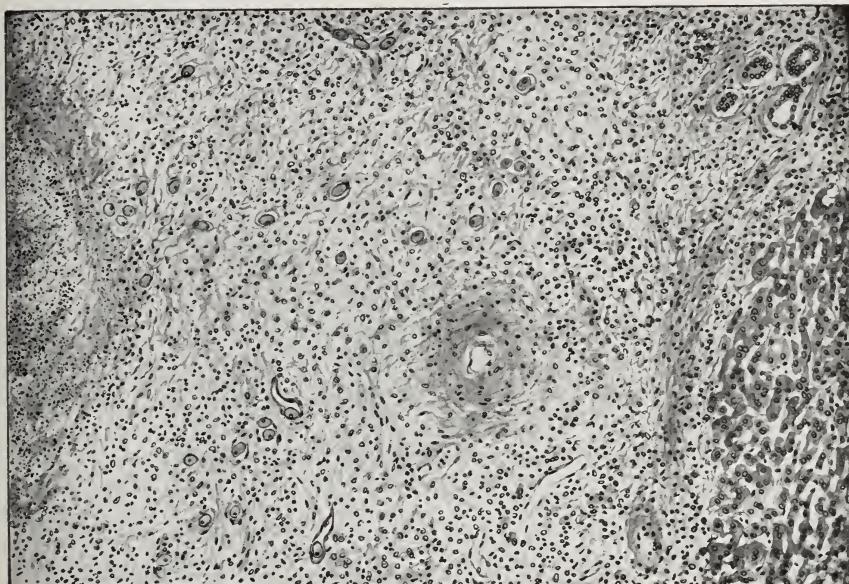


Fig. 459.—Subacute amoebic abscess of the liver. The amoebæ are seen in the crevices of the loose connective tissue which is forming round the abscess.

Histologically the appearances vary with the age of the abscess. In the very fresh ones the form of many liver-cells can still be seen, there is oedema of the surrounding tissue, the amoebæ are found in the edge of the living tissue, and there are a few mononuclear wandering cells whose nuclei are mingled with the fragmented nuclei of the tissue. Later the necrotic lining of the cavity loses its recognizable constituents and shows only a mass of nuclear fragments with a few leucocytes (Fig. 459). The amoebæ are still found only in the margin of the living tissue unless the abscess has been opened to the air. This is because of their need of oxygen, and it is observed by surgeons that when an amoebic abscess is opened no amoebæ are to be found in the pus which escapes, but only in scrapings of the wall. Next day, however, after the cavity has been exposed to the air, the pus which escapes is full of active amoebæ. When

the dense connective tissue with its lining of partly necrotic granulation tissue is formed the amœbæ wander in the crevices of that tissue.

These abscesses may reach a great size before rupture or evacuation takes place and may contain several litres of pus. They consequently destroy much of the liver tissue and occasionally one may find efforts at its regeneration.

**Abscesses of the lung** of quite the same character are produced by transportation of the amœbæ from the liver, apparently by way of the hepatic veins rather than by direct extension. Indeed, Bunting was able to trace in one of our cases emboli containing amœbæ from a thrombus in the hepatic vein which also contained them, and to show that this embolism of the pulmonary arteries had produced an amœbic abscess in the lung. By this time the original amœbic ulcers in the intestine were healed.

In the so-called **Rigg's disease** or **pyorrhea alveolaris**, the Entamœba buccalis has been thought to be the aetiological factor, and is found in great numbers in the pus which forms in the cavities between the loosened gums and the roots of the teeth. Such cavities extend down into the alveolar process of the jaw, which is eroded away. The good effects of emetine in curing the disease seemed to show that the amœbæ are responsible for its existence, but this has since been doubted.

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#### MALARIA

Since the discovery by Laveran in 1880 of the protozoan parasites which cause this disease, it has been possible to give a precise reason for the existence of three different types of malarial fever in man, since it is found that there are three different species of parasite. These can be recognized through differences in their morphology and by the differences in the time required for them to become mature, which decides the type of fever. Tertian malaria is that in which there is a chill every other day. In quartan malaria the chill comes on every third day, while in the aestivo-autumnal forms chills and the associated fever appear at irregular intervals.

The *tertian parasite* (*Plasmodium vivax*) is found in the red blood-corpuscles in the form of a pale, amœboid body growing rapidly to a rather large size and accumulating yellowish-brown pigment in fine granules which dance actively. It causes swelling and pallor of the red corpuscle which contains it, and on reaching maturity divides into 18 to

20 segments leaving the pigment in the centre of the rosette. Flagellated forms are seen. It requires forty-eight hours to develop from the earliest small hyaline form without pigment to the point of segmentation.

The *quartan parasite* (*Plasmodium malariae*) appears also as a small hyaline body in the red corpuscles; it grows more slowly, requiring seventy-two hours to complete its development up to the point of segmentation, and is throughout smaller and more dense and refractive than the tertian form. It produces blackish pigment in coarser granules and is more quiescent than the tertian form. Finally it breaks up into a small rosette of 6 to 12 segments, having at no time caused the corpuscle to swell or become pale, but leaving it rather shrunken and deeply colored.

The *aestivo-autumnal* parasite (*Plasmodium falciparum*) is often at first ring-formed, but later becomes an amoeboid body with brownish pigment. It develops in twenty-four to forty-eight hours and forms 8 to 10 segments, but these are rarely seen in the circulating blood, although they are to be found in the spleen and perhaps other internal organs. In its more mature form the organism is often found in the circulating blood in the shape of a rounded crescent, across the concavity of which the remainder of the corpuscle is seen to stretch. Such crescents may or may not give rise to the flagellated forms.

In studying the related forms, *Proteosoma* and *Halteridium*, in birds, and the aestivo-autumnal form in man, I was able to show that when these parasites were removed from the circulation the mature forms proceeded to enter upon a sexual cycle. During the existence of any of the types as parasites in the blood-corpuscles of the circulating blood, they merely continue the asexual cycle, wherein they grow in the corpuscle for a certain time, after which they divide by fission into many small segments which burst out of the corpuscle and enter others, starting the cycle afresh.

The sexual cycle has a different purpose. Under the microscope the mature forms are seen to break out of the blood-corpuscles into the plasma. Some remain quiescent; others, after violent convulsions of the protoplasm, throw out long, active flagella which beat about and soon become separate free-swimming threads, like spermatozoa. These make their way to the quiescent forms, and of the little swarm which hovers about each of these female forms, or macrogametes, it is seen that one and only one buries itself in the protoplasm, while the rest perish. The flagella, or microgametes, are really analogous to spermatozoa. A short time after the fertilization the zygote, or fertilized form, becomes very active and wanders about. At this point Ross, in India, discovered that there appeared pigmented cysts in the walls of the stomach of those mosquitoes which have bitten persons ill with malaria, and formed the idea that the process of fertilization and formation of the motile zygote described above must occur in the mosquito's stomach and that the development of cysts in the walls of that organ must be due to the fact that this new active zygote could push its way into that situation and there become encapsulated. After that, Ross found that minute transparent spores were produced in great numbers in such cysts and liberated into

the body cavity of the mosquito. Thence they wandered into the epithelial cells of the salivary gland of the mosquito, and were injected into the blood of the next person bitten, together with the salivary secretion. There the spores or sporozoites entered the red corpuscles exactly as did the hyaline segments from the rosette of the asexual stage. Hence, since an important part of the development occurs in the body of the mosquito, which is thus a host of the parasite, it seems certain that transmission to human beings must always occur in this way. Further, it is learned that while a form of culex transmits the proteosoma to birds, it is incapable of transmitting any human form of the parasite. For these another mosquito (anopheles) is the specific host and transmitting agent.



Fig. 460.—Malaria. Capillary in the brain filled with parasites of the aestivo-autumnal type.

To recapitulate briefly, the malarial parasite passes part of its existence in the blood-corpuscles of man, where it goes through a round of development ending in segmentation and the infection of other corpuscles by the segments which are set free. The other part of its existence is passed in the body of the mosquito. In the mosquito's stomach the elaboration of the sexual forms, conjugation, and the development of the actively motile zygote take place. There follows penetration of the stomach wall by the zygote, its encapsulation and the formation of tiny spores or sporozoites, which wandering through the body cavity into the salivary glands, are injected by the bite of the mosquito into the human body, infect the corpuscles, and start again the asexual cycle.

**Symptoms.**—The evil effects of infection in the human being are

therefore dependent upon the asexual cycle alone. The liberation of the segments involves the bursting and destruction of the red corpuscle, the spilling of the remaining haemoglobin and of the malarial pigment into the plasma, and the wandering of the motile segments to new corpuscles. This is accompanied by a sudden and extreme rise in temperature with a chill. According to the length of the cycle of development the chills are spaced twenty-four, forty-eight, or seventy-two hours apart. But this is only because large groups of parasites reach maturity at those moments. If, for example, in the tertian infection the parasites are not

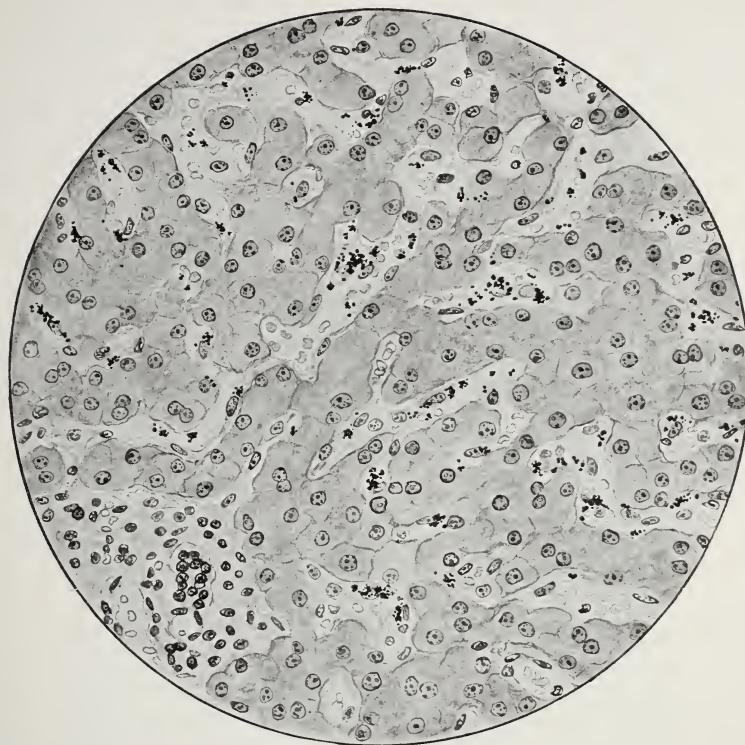


Fig. 461.—Malaria. Liver from a case of malaria of long standing. Kupffer cells and wandering cells in the capillaries are loaded with clumps of pigment.

all of the same age, but fall into two groups which mature at different times, there may be a chill every day. The liberation of haemoglobin and of malarial pigment, which is a kind of melanin, results in the pigmentation of the organs with haemosiderin and melanin, and the associated destruction of red corpuscles produces an anaemia which may reach a profound degree. There is, as a rule, a marked diminution in the number of leucocytes, although there may at times be a leucocytosis during the chills. The relative number of lymphocytes is increased.

The severer symptoms of the disease, aside from the anaemia and general evidences of poisoning which may constitute what is commonly

spoken of as cachexia, are dependent upon the great accumulation of the parasites in the brain or in the gastro-intestinal mucosa. There are, of course, other phenomena due to injuries to the liver and kidneys, but the symptoms of general intoxication are sometimes combined with coma when the brain is especially affected, or with cholericiform diarrhoea when the intestinal capillaries are loaded with parasites. In all cases the spleen becomes enlarged, and when the infection has lasted a long time, it may be enormous and very hard.

**Pathological Anatomy.**—At autopsy there is a distinct slaty or blackish pigmentation affecting especially the spleen, the liver, the brain, and



Fig. 462.—Malaria. Splenic pulp in aestivo-autumnal infection showing many pigmented parasites either free or enclosed in large phagocytic cells.

sometimes the intestinal mucosa. It is due not only to the parasites themselves, with their grains of pigment, but more especially to the quantities of pigment set free from other parasites and now held in innumerable phagocytic cells, both of the type of wandering macrophages and of the endothelial cells of the capillaries. This pigmentation is the most characteristic feature in the autopsies performed upon cases which have died after protracted infections.

In the *brain* the endothelial cells of the capillaries in the brain substance may show such pigment, but in intense infections one often finds that the capillaries are actually plugged with masses of corpuscles bear-

ing parasites, together with phagocytic cells and occasional free parasites (Fig. 460). Dürck found in the brains of persons dying of malaria in southeastern Europe during the Great War minute foci of necrosis surrounded by radially arranged neuroglial elements, thus producing small nodules which are sometimes accompanied by haemorrhage. In a beautifully illustrated paper he compares these subcortical foci with those which occur in typhus fever and in encephalitis lethargica. He is of the opinion that deaths in malaria are due to the involvement of the brain, not only because of these foci of necrosis and the cellular infiltration of the meninges and walls of the blood-vessels, but also because of the obstruction of capillaries by the parasite-laden corpuscles.

In the intestine the same condition may prevail, the capillaries of the mucosa being rendered impermeable by the mass of these cells.

In the liver Barker has described focal necroses. I have not found these in other cases, but there are always parasites in the capillaries and much pigment is present, especially in the stellate cells of Kupffer (Fig. 461).

The spleen is particularly rich in the parasites and, indeed, in the case of the aestivo-autumnal form, the segmenting forms are to be found only there. The phagocytic cells in and between the splenic sinuses are loaded with pigment and with fragments of cells and parasites (Fig. 462). These cells become so enlarged and so distended with this material that they finally burst, the débris being taken up by other phagocytic cells which are less engorged. Mononuclear wandering cells of other types take part in this process as well. Here, as in the liver, much of the pigment is the iron-containing haemosiderin derived from the haemoglobin set free in the destruction of the red corpuscles. In later stages there is found a great increase in the amount of connective tissue throughout the organ, doubtless caused to grow by the presence of so much pigment and the long-continued infection.

The bone-marrow is likewise pigmented, and while showing little new formation of polynuclear leucocytes, is rich in large phagocytic cells or macrophages.

Many other changes in the organs, such as cirrhosis of the liver, chronic nephritis, etc., have been ascribed to the action of the malarial parasite, but it seems that the evidence in these cases is not quite decisive.

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### HÆMOGLOBINURIC OR BLACKWATER FEVER

In persons who have had malaria or who are still infected with the parasites there may occur a violent and rapidly fatal disease in which the most striking symptom is the passage of red or almost black urine, the color being due to the presence of haemoglobin. Diminution of the urine to complete anuria may follow. There are general evidences of intoxication, with the most rapid and extreme blood destruction, which quickly leads to profound anaemia. The spleen is greatly swollen and tender, there is vomiting and intense icterus and fever. Recovery may occur without conferring any immunity, but rather predisposing to another attack, or the patient may die from suppression of urine or from exhaustion. Manson-Bahr finds that in persons returning from a tropical country, who have been infected with the estivo-autumnal (subtertian) parasite an attack of blackwater fever may come on in the reacclimatization period three or four months after reaching England. Either haemoglobin or methaemoglobin may be present in the urine, but no bile.

The condition has every appearance of being due to the action of some intense poison which produces haemolysis, but no such poison has been demonstrated. In some patients the administration of quinine will bring on an attack, but there are many cases in which it occurs although no quinine has been given. There are several hypotheses as to its nature: That it is an especially intense manifestation of malaria; that it is due to quinine, and, lastly, that it is caused by some specific infectious agent as yet undiscovered. Most writers, failing to prove any of these theories, conclude that malaria produces a condition which predisposes to black-water fever, which may at times be induced under the circumstances by quinine. In spite of the earnest endeavors of many investigators the matter is no more cleared up than this. The advocates of the theory that there is a specific infective agent have not proved their point.

At autopsy the spleen is found to be greatly swollen with many phagocytes and with extensive necroses. It is bright red and velvety on section, in contrast to the slaty or blackish spleen of chronic malaria. Necroses occur also in the lymphatic glands and in the liver. The kidneys are somewhat enlarged and flecked with red and black dots which are due to the haemoglobin in the tubules. The glomeruli are usually normal, the tubules filled with irregular clumps of haemoglobin, their epithelial cells slightly degenerated. Acute nephritis supervenes in some cases.

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### KALA-AZAR

Kala-azar is a most interesting disease prevalent in India, especially in Assam, in China, and some other tropical countries in which a protozoan parasite (*Leishmania donovani*) is found in great numbers in the reticulo-endothelial cells, especially, therefore, in the spleen and liver. The disease is transmitted as shown by Knowles, Napier, and Smith of the Calcutta School of Tropical Medicine by the bite of a fly, *Phlebotomus argentipes*. It can be transferred to the hamster, a small rodent

(Meleney), and apparently some such animals act also as a reservoir of the infection. The spleen becomes very greatly enlarged and microscopically the parasites are found in quantities in the Kupffer cells of the liver and in huge cells in and between the sinuses of the splenic pulp. They are also found in bone-marrow and in the lymph-nodes.

Other forms of Leishmaniasis, Oriental boil, Biskra button, Uta, etc., occur in other countries.

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#### TRYPANOSOME INFECTION

Various diseases of animals and at least one disease of man are caused by the invasion of the trypanosomes, which are large flagellated organisms of elongated form with an undulant membrane rising from the blepharoplast at the posterior end and terminating in the long flagellum at the anterior end. These multiply by fission in the circulating blood and invade all the tissues, being found especially in the lymph-glands and spleen and in the central nervous system and meninges. The intermediate host is some form of biting insect—in the case of *Trypanosoma lewisi* of the rat it is a louse, in the *tsetse-fly disease* of cattle (*nagaña*) caused by *T. brucei* it is a fly (*Glossina*). In the *sleeping sickness* of human beings, caused by *T. gambiense* and *T. rhodesiense*, it is also a *Glossina*, the *G. palpalis* being concerned in the first and *G. morsitans* in the second case.

The organisms conjugate in the intestine of the fly, and smaller flagellated forms are produced in great numbers which enter the salivary glands and are inoculated into the new host by the next bite.

The infection is extremely persistent and produces in man a disease which is fatal after a prolonged illness, or, at least, in spite of every effort at cure, drags on for a very long time. The sleeping sickness, a disease essentially of Africa, is characterized by swelling of the glands and fever, later followed by disinclination to work, rapid fatigue, and a soporific condition which may pass into almost continuous sleep. Occasionally there is agitation and delirium. The victims become greatly emaciated and lie helpless until they die, with or without the help of intercurrent infections.

The organisms are found widely scattered in the tissues, and in the brain produce hyperæmia and infiltration of the meninges and perivascular tissues, somewhat resembling that in *dementia paralytica*.

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## CHAPTER XLVI

### TYPES OF INJURY.—DISEASES DUE TO ANIMAL PARASITES (Continued)

*Cestode Infections:* *Tænia* and *bothriocephalus*; *T. echinococcus*; *echinococcus cysts in man*. *Trematode infections:* *Bilharziosis*; *Paragonimus* and *Clonorchis*. *Nematode infections:* *Trichiniasis*; *Biology of the parasite, symptomatology, pathological anatomy*. *Uncinariasis:* *Symptomatology; life-history of parasite; pathological anatomy*. *Infections with ascaris, onchocerca, oxyuris, trichocephalus, and filaria*. *Elephantiasis*.

#### CESTODE INFECTIONS

FOUR principal types of cestode worms are concerned in the infection of human beings, as follows:

- Tænia saginata*, or *mediocanellata*
- Tænia solium*
- Bothriocephalus latus*
- Tænia echinococcus*

Each of these worms requires an intermediate host for the development of its larval form, after which the ingestion of the tissues of that host allows the formation of the mature worm in the definite host.

**Tænia saginata** is found in its mature form in the small intestine of man, whence ripe segments, loaded with eggs, are discharged. The eggs pass into the digestive tract of the ox, and the embryo penetrates through the intestinal wall by the aid of six hooklets at its anterior end. It is then swept everywhere by the blood-stream, and lodging in muscles develops into the cystic larval form which, if the beef be eaten uncooked, becomes the mature form once more in the human intestine. The mature tapeworm has a head with four suckers but no hooks. Its segments are characterized by having a great many lateral uterine diverticula filled with eggs.

**Tænia Solium.**—The mature worm, which is provided with a circle of hooks as well as four suckers on its head, is rare in the human intestine in this country. It has segments which differ from those of *T. saginata* in showing relatively few lateral uterine pouches. The eggs get into the intestine of the pig, and exactly as in the case of the *T. saginata*, pass into the muscle and organs to produce cystic larvæ (*Cysticercus cellulosæ*) (Fig. 463). Occasionally by self-infection the eggs can reach the intestine of man, who then becomes also the intermediate host, allowing the development of the *Cysticercus cellulosæ* in his organs. There is a specimen in the Baltimore museum which shows a human brain studded everywhere with cystic larval forms of the *T. solium*. We have recently seen several cases of *T. solium* infection in man in which cysts of con-

siderable size were found in the meninges of the brain and spinal cord. A section through one of these (Fig. 464) shows the larval worm inverted throughout, so that it is interesting to speculate on the mechanism by which it is everted into its proper position. The epidermis covers the outside of the cyst-like structure, but, entering at a pore, lines the extremely tortuous canal of the inverted body of the worm. The tissue beneath the epidermis is quite like that of the mature worm, and already shows the canals of the water-vascular system. Accumulation of fluid rich in salt and albuminous materials has torn this mesenchyme so as to produce a large cavity. It seems probable that when such a cyst is swallowed, osmotic processes of some sort force fluid into this cavity so as to blow the head out through the pore and evert the worm into its per-



Fig. 463.—Cysticercus stage of *Taenia solium* in heart-muscle of a pig.

manent position. The two mesenchymal surfaces of the head and neck of the worm are thus brought together and fused, and the distended sac hangs for a time on the caudal end of the worm.

It has been suggested that since this occurs only when the cyst is swallowed, the entrance of fluid may be a result of the action of the acid of the gastric juice which causes the albuminous materials to swell.

**Bothriocephalus Latus.**—The larval form of this worm is found in the muscles of several fish, including the salmon, trout, perch, ling, etc., upon the ingestion of which the mature worm develops in the human intestine. It is a large, broad worm with elongated lateral suckers and with a different arrangement of the genitalia, the genital opening being on the face of each segment instead of at the edges, as in the *taenia*. Its

presence in the intestine causes an intense anaemia which has already been mentioned.

**Tænia Echinococcus.**—In the case of this worm, of which there are two varieties, man is the intermediate host, while the mature form is a parasite of the intestine of the dog. It is a very small worm, only 3 to 6 mm. in length in contrast to those tæniæ just described, which may reach the length of 30 to 40 feet. Many other animals can also act as the intermediate hosts. The adult is a worm with four suckers and two rows of hooks, which forms only three or four segments instead of many

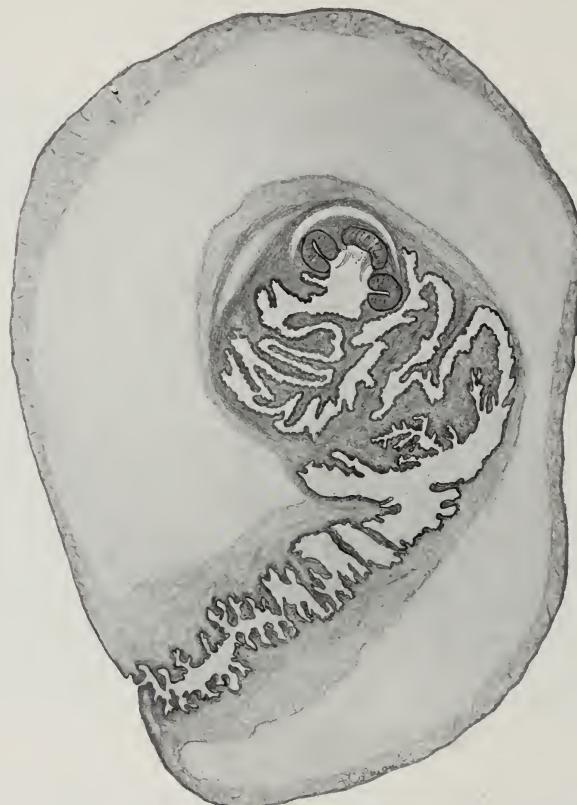


Fig. 464.—Cysticercus stage of *Tænia solium* from human meninges. Epidermis covers the cyst and lines the tortuous canal to the head of the worm.

hundreds. From dogs, especially in such countries as Iceland, where men and dogs live in the same rooms, the eggs are transmitted to the human digestive tract. The wandering of the embryos can take them to any organ of the body, and the development of the huge cystic larva is reported for every possible situation. In the case of *T. echinococcus*, single cysts form, but in infection with the allied form, *T. multilocularis*, the larval cysts are like a ramifying spongy tissue full of small cavities. The parasite produces injury by the space it occupies (as in the brain),

or by the toxic products or by the development of great numbers of secondary cysts through the rupture of the first and the liberation of the larvae.

When the eggs hatch in the human intestine, the embryo bores through the intestinal wall and is transported by the blood-stream to its lodging place. There it grows and surrounds itself with a thin, chitinous



Fig. 465.—*Echinococcus* cysts in the liver. Daughter-cysts with chitinous wall are dislocated from the outer wall.

membrane of pearly translucence which in turn is densely enclosed in a capsule produced by the reaction of the surrounding tissue. Inside the chitinous membrane the embryonic tissue grows and separates in its central part to allow for the accumulation there of a clear fluid rich in salt and albumin. It thus becomes the lining of a cyst (Fig. 465). From

this lining there spring up buds which may be extremely numerous as the cyst grows larger, and are finally recognizable as the heads of new worms. Some of the buds may, however, enlarge and themselves become hollow and constitute daughter-cysts in whose lining once more there may spring up little buds which give rise to new heads (Fig. 466). Such buds in the main cyst or in the daughter-cyst elevate themselves in bunches on little stalks and are now seen to be invaginated, so that what is to become the head of the adult worm is now turned inside out, so that in the dell at the tip of the bud one finds the crown of hooklets and four suckers facing inward (Fig. 467). With the liberation of such buds

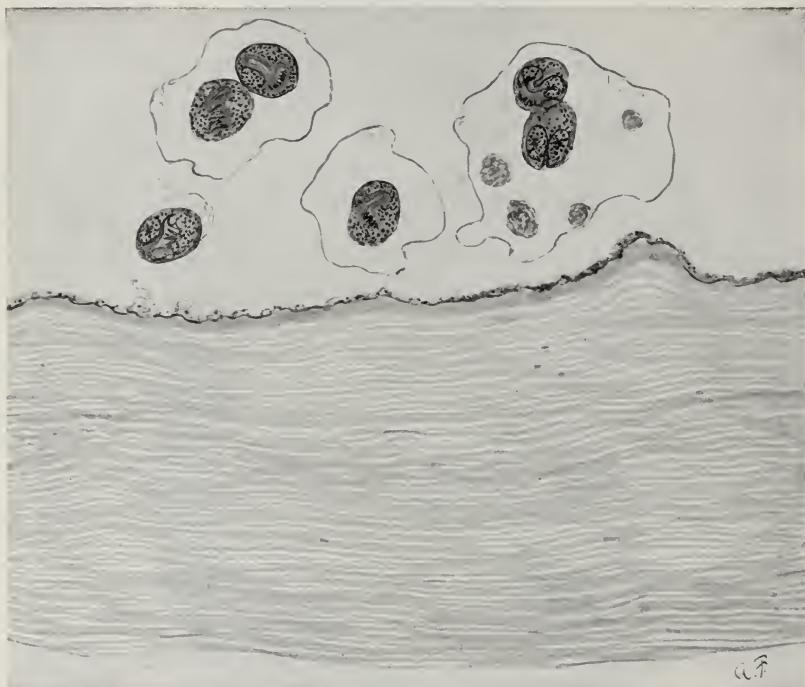


Fig. 466.—Chitinous wall of *echinococcus* cyst with lining membrane of the parenchyma of the worm and several daughter-cysts with scolices.

or scolices by the ingestion of the cyst material by a dog or other suitable host, the heads are quickly evaginated so that suckers and hooks present themselves in proper relations and fix themselves in the mucosa of the intestine, after which the worm proceeds to assume its mature form.

Such cysts are quite common in the liver of the pig, where they are multiple and cause huge enlargement of the organ. Later, in any organ which harbors such a cyst, if the opportunity for its ingestion by the definite host is postponed, the embryos may die and the fluid be absorbed. There remains what is easily recognizable as an obsolete *echinococcus* cyst, a rounded mass of mortar-like whitish material densely

encapsulated with fibrous tissue, underneath which can still be discerned the wavy, laminated, translucent chitinous membrane which is in itself



Fig. 467.—Single scolex or head from *echinococcus* cyst cut in median line, showing inverted suckers and rostellum of hooks. Two of the hooks are drawn separately.



Fig. 468.—Old *echinococcus* cyst of liver with mortar-like contents. The chitinous lining is loosened and thrown up in folds.

so peculiar as to be of diagnostic importance (Fig. 468). In the crumbly mass left after absorption of the fluid loose hooklets can be found scattered about, derived of course from the armament of the dead scolices.

The dissemination of some toxic material often gives rise to repeated attacks of urticaria and also to an alteration of the blood plasma, such that the presence of the echinococcus cyst can be recognized by complement deviation reactions.

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#### TREMATODE INFECTIONS

Fluke worms rarely cause disease in man in this country, but there are several wide-spread types of human disease due to their invasion in Africa and Asiatic countries.

Of these, the most important is the bilharziosis, caused by the various forms of *Schistosomum*. These are trematode worms in which the sexes are separate, the male being provided with a gynæcophoric canal in which the female is carried during conjugation. There are three known forms: *S. haematobium*, which is the common African form, producing eggs with a terminal spine; *S. mansoni*, found in the West Indies and South America and probably also found in Africa, with eggs with a lateral spine, and *S. japonicum*, the Asiatic form, whose eggs are elliptical and without any spine. It has been shown by Leiper that the eggs set free in the water motile miracidia, which invade various snails, *Bulinus*, *Planorbis*, *Blanfordia*, *Physopsis*, *Limnaeus*, etc., in which they develop into active cercariae, which escape into the water and can penetrate the skin of persons bathing. The cercariae wander in the body and become mature in the veins. The eggs are carried into various tissues and cause destruction and scarring. *S. haematobium* produces especially haematuria because of infection of the urinary tract with formation of polypoid granulation tissue in the bladder. There is prostatitis and intense cystitis, often with fistulous communications with surrounding tissues, renal infection, etc. Vesical calculi are frequently formed. *S. mansoni* causes chronic dysentery with tenesmus and the passage of blood. There is great thickening of the mucosa of the colon with the formation of polyps loaded with eggs. *S. japonicum* also produces dysentery, but no infection of the urinary tract. Later it gives rise to cirrhosis of the liver through the irritating deposit of its eggs in the tissues of that organ. In an autopsy which I saw recently the liver was hard and nodular, and in the depressions between the nodules there were ochre-yellow patches which proved, when portions of the capsule were torn off and examined with the microscope, to be full of eggs which gave the yellow color. On section, the same yellow discoloration was to be seen through many of the scarred areas. Similar patches of dull yellow were found in

the mucosa of the colon, and in these, too, there were found thousands of eggs.

*Paragonimus westermanii* is another trematode which causes in Formosa, Japan, and Korea frequent infection of human beings. It gives rise to cough with haemoptysis and later to emaciation and anaemia. In some chronic cases epileptic seizures of Jacksonian type form the final symptoms. The worm is found in its mature form encapsulated in the lungs, where it sets up an inflammatory reaction. The capsules are always connected by channels with the bronchi, and often with one another. Indeed, the worms may lodge and form their capsule within the lumen of the bronchus. In any case the eggs are abundantly discharged in the sputum. Occasionally, however, they are carried in the blood-stream to the brain, and there they, or even mature worms which can pass into the brain in the same way, give rise to the injury and irritation which produces the epileptic attacks. Other organs may also become the lodging place for the worms and their eggs.

The development has been worked out by Nakagawa and is essentially as follows: The eggs develop in water into free swimming miracidia, which penetrate into the body of snails, *Melania*, where they develop into cercariae and escape. The cercariae enter the tissues of freshwater crabs (*Potamon*, *Eriocheir*, etc.). These crabs when eaten raw or insufficiently cooked transmit the infection to man, in whom the encysted cercariae are set free when the cysts reach the intestine. They bore through the intestinal wall, pierce the diaphragm, and enter the lungs through the pleura. There they form capsules and develop into adult forms.

In the Chinese and sometimes in the Japanese there is another trematode, which in its mature form infests the gall-ducts and gall-bladder. This is the *Clonorchis* (*Opisthorchis*) *sinensis*. The worms do not necessarily produce much change in the liver, but in a case recently seen at autopsy in Panama the liver showed many areas of atrophy and scarring of the tissue with inflammatory reaction about the bile-ducts. Kobayashi has shown that several cyprinoid fishes act as the intermediate host, including *Pseudorasbora*, *Leucogobus*, and *Carassius*, some of which are eaten raw, and thus readily transmit the infection.

For descriptions of other trematodes which infect human beings, *Fasciolopsis*, *Heterophyes*, etc., works on parasitic diseases must be consulted.

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**TRICHINIASIS**

The trichina, or, as it is now called, *Trichinella spiralis*, was discovered by Owen in 1835 and has since been studied by Virchow, Zenker, Leuckart, and a host of others, the most compendious publication being that of Stäubli. It is a nematode, or round worm, the anatomical struc-



Fig. 469.—Pectoral muscle with encapsulated and calcified trichinæ.

ture of which will be found in any book on animal parasites. It carries out its whole life cycle in one animal, but it must then pass into the digestive tract of another animal to begin another cycle. The reason for this will be found in the following brief summary of its life-history. The worm is essentially a parasite of swine, but can live in rats, mice, guinea-

pigs, rabbits, dogs, cats, and many other animals as well as man. It is from eating insufficiently cooked pork that man is infected, but the pigs themselves are often infected through eating dead rats. The embryos, both male and female, are found in the muscle substance of the pig, and on being eaten by man quickly develop into mature forms when they reach the intestine. There the females penetrate into the substance of the villi and often actually enter the central lymphatic; the eggs hatch in the uterus of the worm, and the active embryos are set free from the



Fig. 470.—Larva of trichinæ encapsulated in muscle. There is abundant infiltration of leucocytes, most of which are eosinophiles, and many muscle-fibres are reduced to hyaline masses.

genital opening, after which they bore their way into the lymphatics, if they are not actually deposited there by the mother. Thence they are swept in great numbers through the mesenteric lymph-glands and the thoracic duct into the blood, and are to be found there by centrifuging, after treating the blood with 3 per cent. acetic acid, which dissolves away the red corpuscles. They are thus carried through the whole body but choose the voluntary muscles for their permanent abode. Doubtless they have to penetrate into them from the capillary by their

own activity. They lodge in every other tissue, but appear to find conditions unsuitable and never develop there; indeed, they are rarely found anywhere else than in the skeletal muscles. They are not found in the heart muscle, but are occasionally seen in the mesenteric lymph-glands and for a time are abundant in the peritoneal cavity.

Having entered the muscle, each one penetrates into a muscle-fibre, where it lies as a small, rod-like structure in the middle of the fibre. As the embryo grows the fibre loses its striations and becomes granular and swollen. The sarcolemma nuclei sink into the more or less homogeneous mass and surround the little worm. A little later the parasite, having developed until it shows the alimentary tract and a rudiment of the reproductive glands, coils itself up and becomes surrounded by a rather thick hyaline capsule which is usually elliptical (Fig. 470). There is a dispute as to the origin of this capsule, but it seems most probable that it is formed by the worm, as Leuckart thought, although there are many who think it produced by the host. But the host does not produce such a peculiar capsule for any other foreign body, and it seems specifically a part of this parasite. Fat may collect at its poles outside, and within it there are usually found a few cells at each pole. These may be included parts of the group of sarcolemma nuclei. Later, the capsule becomes partly or completely calcified, and then the worm is likely to die or has already died. Nevertheless, they live for years in the muscle, awaiting a chance to go through the development to maturity, in their turn, in the body of another animal.

The disease trichiniasis is a serious one, and often ends fatally when much of the infected meat is eaten. Death is probably due to the intense injury produced by the penetration of the intestinal wall, although more rarely it may occur after the embryo has entered the muscle. Much care is taken by the German government to prevent the sale of infected pork, and Stäubli's book is one long outcry against American pork. The frequency with which epidemics of trichiniasis occur in Germany is, however, probably the outcome of the German habit of eating raw pork and blood sausages.

The disease may simulate typhoid fever. There is fever and malaise, often with diarrhoea when the infection is intense, with oedema of the tissue below the eyes and sometimes of other parts of the body and often with profuse sweats. There is no Widal reaction, and there is a marked leucocytosis with an extraordinary increase in the eosinophile cells (Brown). Later the muscles become stiff and painful, and in the effort to relieve them there is dyspnœa, and general immobility. With the establishment of the worms in the muscle and their encapsulation, the symptoms gradually disappear.

If a person thus infected dies, the appearance of the organs varies with the stage of the disease. In the fresher stages the intestinal mucosa is said to be swollen and reddened but without definite haemorrhages. The lymph-glands are swollen in the mesentery and there is bronchitis, but there is usually no other organic change dependent upon the infection except, of course, the change in the skeletal muscles. The bone-marrow is hyperplastic and rich in eosinophile myelocytes.

The muscle parasites are not visible to the naked eye and there may be no sign of any change. It is only much later when, after years, they become calcified that they are visible (Fig. 469). Then they look like tiny opaque yellowish-white flecks in the muscle. Their distribution has guided the meat inspection in Germany and the diaphragm or neck muscles are chosen for study, since those places seem especially favorable for their growth.

O. R. McCoy has studied the evidence of immunity which is quite definite after the survival of one infection, but cannot be effectively produced by the injection of heat-killed or dried and powdered larvæ, although such animals develop some degree of immunity. Vitamin A deficiency seems to produce a lowered resistance to infection and interferes with the development of immunity to a second infection. In immune animals there is little resistance to the initial growth of adult worms in the intestine but they are more rapidly discharged and there is less muscle invasion by larvæ.

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#### UNCINARIASIS

Through the work of Stiles in this country and Ashford in Puerto Rico the enormous importance of this infection has been made clear and Stiles has shown that, in addition to the *Ankylostomum duodenale* or *Uncinaria duodenalis*, there is another form, called by him *Necator americanus*, which is the parasite especially concerned in America and the West Indies, but also widely distributed elsewhere.

All through the southern states and in tropical and sub-tropical countries around the world, the so-called "hookworm disease" is more or less prevalent. Ashford's description of it as it occurs in the "jibaro" or laborer in Puerto Rico is most vivid and gives a better idea of the ravages it causes than any other I have read. The people who work in damp coffee plantations are especially affected there. Elsewhere, those who work in the soil are the ones to suffer, chiefly when they get into mud, although Stiles suspected the influence of sandy soils. After having walked barefoot in the mud, they have a peculiar eruption on the skin which burns and itches. Some time after that such people find themselves weak and easily tired and unable to work. They grow pale and the skin assumes a yellowish clay color. The digestion is disordered, there is constipation or diarrhoea with occasional periods of abdominal pain. The nervous system is often much affected, and in some cases actual maniacal attacks interrupt the usual stupid condition. The extreme anaemia, often with eosinophilia, becomes more profound and there is often associated with it oedema of the face or of the whole body. The patient becomes unable to walk or to help himself in any way and may

die. The faeces contain numbers of the elliptical ova of the worm, but in Ashford's experience no blood. The whole affection can be cured with thymol, carbon tetrachloride, or other vermifuges.

Most interesting is the pathogenesis of this disease which has been worked out by Looss in Egypt. The eggs passed with faeces develop, if they find themselves in a moist place, into small active embryos. Whole areas of moist ground can be thus infected. Ashford mentions the damp ground in the shade of coffee bushes, Looss the mud in which the fell-



Fig. 471.—Head of ankylostome in section showing how the submucosa of the intestine is drawn up "into the mouth cavity.

been work after the Nile recedes. Looss' beautiful experiments showed that if water or mud containing larvæ at this stage were applied to the skin there arose almost at once a burning and itching sensation, and by the time the water had dried all the larvæ had bored their way into the skin, leaving their shed skins as empty shells on the outside. He repeated this with a leg about to be amputated and was able to trace the larvæ into the hair follicles and thus through the skin. They do not enter sweat-glands or sebaceous glands, but Schüffner found that they could pierce the skin anywhere. Further experiments with dogs

showed that they wander into the blood-vessels and are carried to the lungs, where they are too large to pass through the capillaries, but emerge into the air-cells. Thence, crawling up the bronchi, they get over into the oesophagus and reach the stomach and intestine, where after other moults they become mature worms.

Of course, the irritation felt by Looss (who thus produced a general infection in himself and long harbored the worms in his intestine) was identical with the ground itch or "*mazamorra*," which comes on after walking barefoot in infected mud or smearing the hands with it, and there seems no doubt that this is the ordinary mode of infection. Of course, the larvae may be swallowed if muddy water or mud-covered vegetables are taken into the stomach or if, as sometimes happens to these people, a craving for bulk in their food is satisfied by eating mud or clay. But although this infection by mouth has been regarded as the chief mode of entrance it seems now, in the light of Looss' work, to be less important and perhaps even uncommon.

The mature worms attach themselves to the walls of the intestine and draw into their capacious mouths some part of the mucosa (Fig. 471). They seem to be actual blood-suckers, although there is still difference of opinion about this. Sometimes haemorrhage can be found about the point at which they were applied, and it has been thought that much loss of blood might occur after they dropped off or changed to another place. But little blood is found in the stools, and it is not, as a rule, found in the intestine of the worm. The impression is, therefore, that they do not cause the profound anaemia by merely mechanically removing blood, and this is strengthened by the character of the anaemia, which is peculiar and marked by an outspoken eosinophilia. This, together with the nervous phenomena and the symptoms of general intoxication, point rather to a toxic substance produced by the worm as the cause of the anaemia. But Rhoads, Castle, Cruz and others and also Foster and Landsberg, find that it is a typical microcytic hypochromic anaemia such as is associated with long-continued haemorrhage. No toxic action of the hookworm need be postulated but only the removal of blood. It responds promptly to treatment with iron but is not much improved by liver extract or increased food.

The worms are found hanging to the wall of the small intestine and are pretty tightly attached. Hundreds of them occur in one case. Aside from the pallor, changes in the other organs are not especially characteristic. The spleen is not enlarged. The bone-marrow shows a response to the anaemia. The kidneys are found to present some exudate of blood and epithelial degeneration.

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### OTHER NEMATODE INFECTIONS

Brief mention may be made of certain other very common infections with nematode worms.

**Ascaris lumbricoides** is the common round worm found in the intestine of children, which, by its presence in numbers, exercises an irritating influence. It does not actually fix itself to the intestinal wall, but lies free or in convoluted masses in the lumen. The effects of its wanderings into other localities have been mentioned. Apparently it may secrete a toxic material, for there are general and nervous symptoms due to its presence.

The life-history of the Ascaris has been shown more clearly in the recent work of Stewart, and of Ransom and Foster. Stewart found that when eggs were fed to rats and mice the larvæ hatched in the intestine, reached the lung, and developed there, passing thence into the intestine, from which they were discharged. He thought that these animals must act as intermediate hosts, and that infection of the final host must arise from the ingestion of the partly developed worms thus excreted. Ransom and Foster show clearly, however, that these larvæ are discharged from the intestine of the rat or mouse only because they are unsuitable hosts. In pigs and children, if young enough, larvæ which are hatched in the intestine from ingested eggs wander into the lungs through the diaphragm and pleura. There they develop further, causing serious pneumonic phenomena, and later, passing up the trachea, they go down into the intestine, where they complete their development. The larvæ, as shown also by Yoshida, have a remarkable power of wandering through all the tissues and can penetrate the skin.

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**Onchocerciasis.**—There are various species of *Onchocerca* some of which affect cattle, others invade the tissues of men, in Africa and Central America. I have seen cattle in northern Australia with great rounded nodules as large as a baseball in the brisket or central fold of the neck. These were the tumor-like growths of loose connective tissue in which the mature worms are entangled and give rise to microfilariae which leave the spaces of the nodule and wander far and wide in the tissues. More interesting is the human parasite, *Onchocerca cæcutiens*, which produces such nodules in various parts of the body, perhaps especially on the head and shoulders. The adult male found there measures about 30 mm. while the female is 500 mm. in length by 0.4 mm. The microfilariae measure only 150–350  $\mu$  in length and from 6–8  $\mu$  in width. Their most serious effect is the production of blindness which is apparently due to the opacity of the cornea which they produce by invading it and stirring an inflammatory reaction. Whether they also affect the optic nerve where they have been found once or twice, is questionable.

The infection is transmitted by a biting fly, *Simulium*, and since the sexual reproduction occurs in the subcutaneous tumors, it appears that the fly effects merely a mechanical transfer of the microfilariae.

The whole subject is vividly described by R. P. Strong and his co-workers in their report from Guatemala.

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**Oxyuris vermicularis**, a small worm with pointed extremities, 3 to 5 mm. long, is a frequent inhabitant of the colon, where it attacks the mucosa, and by its bites produces haemorrhagic points, and an inflammatory reaction with intense itching of the anal region. Its eggs develop on vegetables, etc., or the embryos which quickly leave the shell may be transferred to the mouth and an extensive autoinfection produced. Invasion of the Oxyuris into the mucosa of the appendix has been shown to be responsible for a considerable number of cases of appendicitis (17 in a series of 129 cases, Cecil and Bulkley).



Fig. 472.—Elephantiasis affecting both legs (Singapore).

The *Trichocephalus trichiurus*, or *dispar*, is a similar worm with long, thread-like anterior end. It buries this anterior end in the mucosa of the cæcum and absorbs blood. No very marked symptoms are produced, but it can occasionally be the cause of appendicitis.

**Filaria Bancrofti**.—More important than these is the *Filaria Bancrofti*, whose embryos are found in the circulating blood in the form of delicate, actively motile threads which appear there only at night. They are transferred by the mosquitoes (*Culex*), in which they undergo a certain development, reaching the salivary glands or oesophagus, so that they are injected with another bite into another host. The mature worm, developing in the human body, invades and lodges itself in the lymphatic

channels, where it produces great distention, haemorrhage, and inflammation. Huge masses of lymphatic varicosities are the result and much obstruction to the flow of lymph. The effect of this is evident in nearly every tropical country in the occurrence of the so-called elephantiasis (Fig. 472) which affects the legs or the scrotum, causing huge enlargements due to lymph-stasis and new formation of tissue which are traceable to the presence of the worm. Chyluria, or milky urine, and chylous ascites are also characteristic features. In the Fiji Islands, where Bahr showed that the *Stegomyia* acts as intermediate host and carrier of the infection, I saw several cases of elephantiasis affecting the arms alone. The most frequently observed lesion in those islands is, however, a great swelling and induration of the lymph-nodes in the inguinal region or elsewhere, and in the disintegrated centre of each of these the filariae are to be found. Recently in Tahiti, where elephantiasis is common, I saw many cases with extremely advanced changes. Dr. Cassiau, who has had long and varied experience with the disease, expressed the idea that it is due rather to a chronic bacterial infection, and there are many who hold this view. It is in accord with the observations of Dr. Halsted on surgical elephantiasis, which show that in an extremity from which the return of blood has been somewhat obstructed repeated slight infection may produce a lasting swelling resembling elephantiasis. Even Manson, the discoverer of the mode of transmission of the filaria, now thinks that bacterial infection in addition to lymph stasis is necessary to produce elephantiasis. The student should read the paper of Halsted, Johns Hopkins Hospital Bulletin, 1921, xxxii, 309. But O'Connor, after long and careful study of the question in Polynesia and in Puerto Rico, is convinced that the obstructive lymphangitis produced by the filaria is the real origin of elephantiasis, and that while secondary infection with the bacteria may give it the character of a cellulitis, it is often possible to recognize the localization of the obstruction and, by removing the worm, cure the condition.

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## CHAPTER XLVII

### THE EFFECTS OF INJURIES UPON THE BLOOD AND BLOOD-FORMING ORGANS

*Importance of changes in blood-forming organs. The bone-marrow, its regenerative changes. The spleen. The lymphoid tissues. Injuries to the red corpuscles and erythrogenic tissues. Polycythaemia. Anæmia or oligocythaemia. Post-hæmorrhagic and other secondary anæmias. Hypochromic anæmia. Pernicious anæmia: Recent investigations. Sprue. Sickle-cell anæmia. Osteosclerotic anæmia. Splenic anæmia. Hæmophilia. Purpura hæmorrhagica. Hæmatoporphyrina. Hæmolytic icterus.*

THE fact that in the many disorders of the blood and of the blood-forming organs we are as yet in most cases ignorant of the cause, makes it seem preferable to discuss these conditions together and quite objectively. It is true, of course, that nearly all of the injuries which have already been considered cause changes in the blood and its sources, and sometimes we can trace these effects with the greatest accuracy, so as to derive enlightenment with regard to the principles which are probably concerned in the more obscure affections.

The blood, in virtue of its rapid circulation and of the powerful sifting and cleansing effect exerted upon it by the very blood-forming organs which are its source, does not show the direct effect of local injury except after very gross damage by haemorrhage or by chemical agents. Then it becomes impoverished by the loss of cells, or, in the second case, it shows the effect of the chemical (as in the formation of carbon monoxide haemoglobin, methaemoglobin, etc.). Instead, the changes which appear in the circulating blood are essentially those which depend upon the activity of the blood-forming organs, and may consist in an incomplete new formation of cells of the same type as those which were lost, or in the introduction of greatly increased numbers of some of the cells (leucocytes), or even in the appearance of cells which are not normally present in the blood (erythroblasts, myeloblasts, etc.). Thus it is clear that we shall have to deal but little with the direct effects of injurious agents upon the blood itself. On the other hand, the changes brought about in the blood-forming organs by direct injury or through the necessity of restoring to normal the injured blood, must interest us quite as much as the remarkable changes in the blood which then follow. It is as though an army during the battle should rapidly circle back into the mother country carrying the dead and wounded, returning to the battle with ever new reserves. In time there would come a change in the character of the army, depending upon the ability of the mother country to recruit.

#### BLOOD-FORMING ORGANS

Leaving aside the conditions found in embryonic life, it is clear that the bone-marrow constitutes the essential seat of the formation of most of the elements of the blood, although, as we have seen in the outline

given in Chapters IX and XII, the cells of the lymphoid series are furnished to the blood by the lymphoid tissues scattered everywhere throughout the body. Under stress of great need, tissue of the character of the bone-marrow appears in situations far removed from the bones, and cells swept into the general circulation may settle as colonies in the capillaries of various organs and there multiply to some extent (Tanaka). The part played by the spleen in blood formation is still disputed, and although some writers assign to it a most important rôle, others regard it

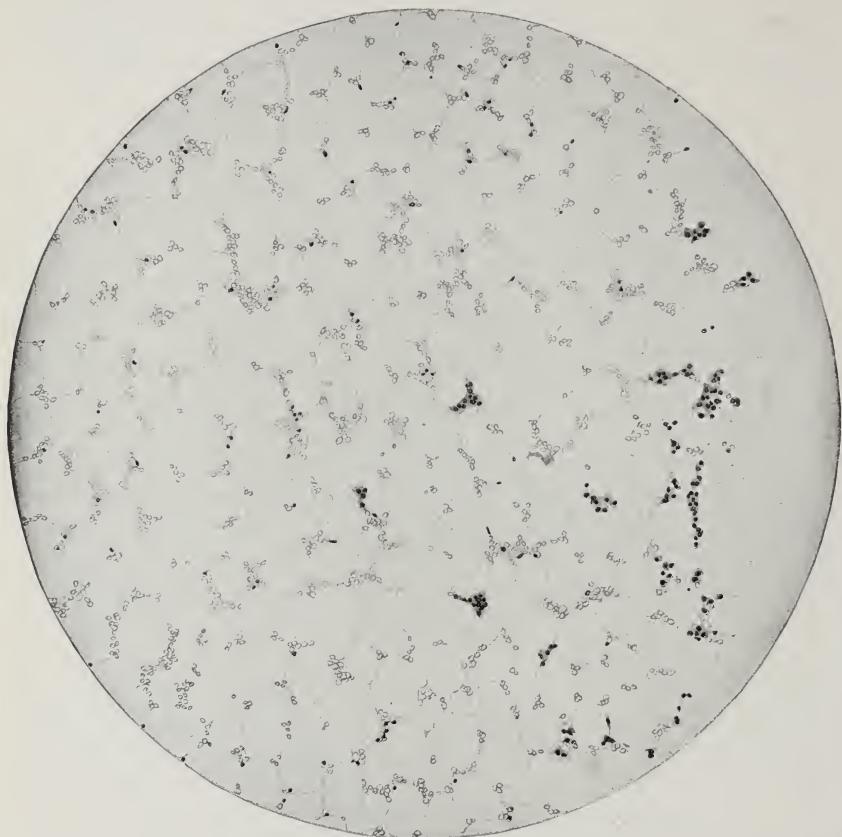


Fig. 473.—Bone-marrow from femur of normal adult, showing chiefly fat with very little myeloid tissue.

as chiefly concerned in the purification of the blood. This matter must for the present be left undecided.

**The Bone-marrow.**—Throughout life the marrow of the cancellous framework of the short and flat bones maintains its cellular character and is active in blood formation. In childhood this is true of the marrow of the long bones too, but with advancing age fat increases in amount there and replaces the marrow, often even in the cancellous regions of the ends of the bone. The microscopical study of such marrow shows

only a delicate framework with blood-vessels among the closely packed fat-holding cells. In the angles and crevices one may find a few cells of myelocyte or erythroblast type (Fig. 473). It seems that these are the cells which multiply at an astounding rate when special activity of the bone-marrow is demanded. In the marrow of the child's femur (Fig. 474) or in that of the short cancellous bones a very different condition exists. There is relatively little fat, and the delicate vascular reticulum is loaded with loose cells. Of course, as mentioned before, the osteoblasts and osteoclasts which are closely applied to the bone hold aloof and are

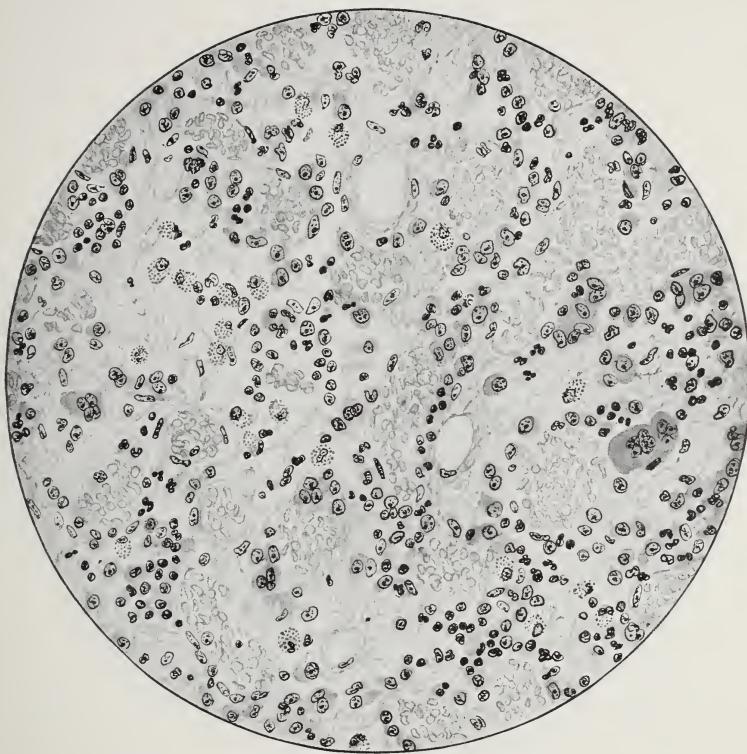


Fig. 474.—Bone-marrow from normal infant. It shows quite well-defined blood-channels, neutrophile and eosinophile myelocytes, megalocaryocytes, etc. There are numerous normoblasts which do not show well in this drawing.

concerned only in bone formation and destruction. The capillaries are wide and variable in diameter, and it is frequently difficult to trace their endothelial outlines. Indeed, one does not receive the impression that they are stout-walled tubes capable of carrying blood safely at a considerable pressure, but rather that their walls are extremely thin if not actually lacking in places. At times it seems as though the mass of cells in the reticulum were continuous with those within the capillaries, and one must suppose that some such relation may exist, to explain the phenomenally rapid delivery of cells into the blood-stream. For a discussion

of the histogenesis of the cells concerned the student is referred to the papers of Maximow, Jackson, Peabody, Doan, and others.

In such cellular marrow there are found, side by side, the following kinds of cells:

1. Those concerned in the production of red corpuscles: Megaloblasts, normoblasts, and the erythrocytes themselves.

2. Those concerned in the formation of the neutrophile, eosinophile, and basophile granular leucocytes: Myeloblasts without granules, myelocytes with neutrophile, eosinophile, and basophile granules, and the mature leucocytes themselves with these different types of granule.



Fig. 475.—Bone-marrow of rabbit after long treatment with benzol. Practically all the blood-forming elements are destroyed.

3. An indefinite but limited number of large and small lymphoid cells, situated usually about the blood-vessels and possibly capable of giving rise to lymphocytes and to their derivatives, including plasma cells.

4. Megalocaryocytes which, by constricting off portions of their granular cytoplasm, form blood-platelets, which they discharge into the blood.

In ordinary sections these cells are so intermingled that one cannot make out their relations to one another, but Bunting puts forward the

statement that they occur in definite groups or colonies at the margins of which the perfected cells are set free. This he has found especially striking in experimental anaemias in rabbits in which the bone-marrow had been injured by the injection of ricin or other substance used to produce the anaemia. So, too, Selling described the appearance of such colonies or pure cultures of the various cells in bone-marrow rendered practically cell free (Fig. 475) with injections of benzol and then allowed to regenerate. These preparations I have studied and the truth of the statement is very striking. There are isolated groups composed in one case entirely



Fig. 476.—Bone-marrow of rabbit. Beginning regeneration after benzol poisoning; islands of myelocytes and normoblasts.

of nucleated red cells (Fig. 476), in another entirely of myelocytes or of megalocaryocytes (Fig. 477), and in the later stages each of these comes to be accompanied by the mature cells which they produce. Bunting explains that with further development the groups become so interwoven that it is impossible to outline them clearly, but in the bone-marrow of his rabbits made anaemic with ricin he finds such islands with a central group of megaloblasts surrounded by normoblasts and these, in turn, by ordinary red corpuscles. It is on the basis of these observa-

tions that he regards the megaloblasts as normal constituents of the bone-marrow and the immediate ancestors of the normoblasts. It is well known that this is not the view of German haematologists (Naegeli), who hold to Ehrlich's statement that megaloblasts are embryonic cells occurring only under pathological conditions in adult bone-marrow, and that, therefore, pernicious anaemia, in which they become abundant in the marrow, represents a pathological return to embryonic conditions. It seems, however, that one may convince oneself of their common occurrence in normal and regenerating bone-marrow and of the prob-

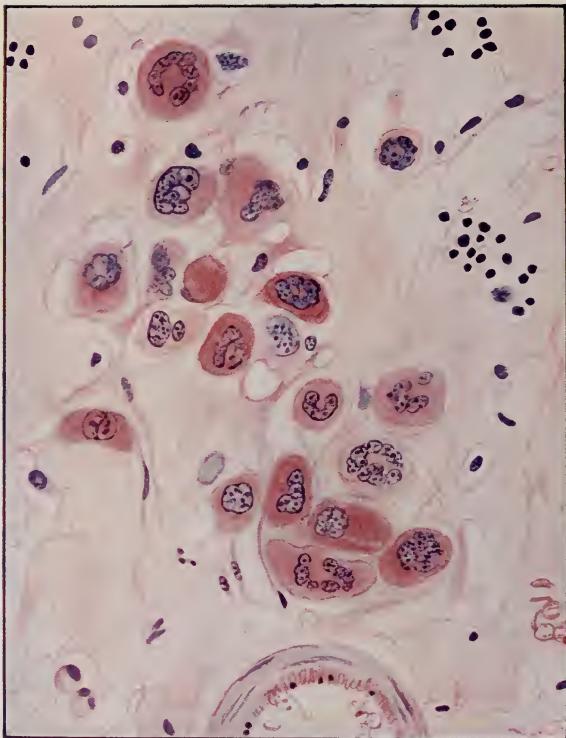


Fig. 477.—Bone-marrow of rabbit after benzol poisoning. Beginning regeneration; islands of megacaryocytes.

ability of Bunting's view that they represent the earlier stage in the formation of red corpuscles. The occasional sweeping of these nucleated cells into the blood will call for discussion below.

In quite the same way the myeloblasts and myelocytes of each kind grow in colonies and shed into the blood their polymorphonuclear descendants. These cells, when they have developed granulations, give an intense blue reaction with alpha-naphthol and dimethyl-para-phenylene-diamine which, in the presence of an oxidizing ferment, produce indophenol blue (*oxydase reaction*). This reaction is given by the granulated leucocytes of the blood but not by the mast-cells of the tissue

despite their basophilic granules. There is a conflict of opinion with regard to the monocytes—those, such as Naegeli, who find in them oxydase granules regard them as of myeloid origin, while others find no such positive granule stain and relate them rather to the histiocytes.

Ordinarily the lymphoid cells of the bone-marrow form an inconspicuous element of the cell mass and are sometimes collected in groups or lymph nodules. In those cases in which the injurious agent causes the isolated overproduction of lymphoid cells they may, however, increase to such an extent as to crowd aside all the other cells. Theirs is probably under ordinary circumstances the least prominent rôle among the bone-marrow cells.

The megalocaryocytes which maintain the platelet content of the blood are, like the other cells, vulnerable, and may be greatly reduced in number by toxic substances. They regenerate themselves in little colonies just as do the other cells (Fig. 477).

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**The Spleen.**—The studies of Weidenreich and Mollier have made clear the structure of the spleen as far as concerns its vascular arrangement, but there is still much to be learned with regard to the cellular structure of the splenic pulp.

The smaller branches of the splenic artery are surrounded for some distance by mantles of lymphoid tissue which constitute the Malpighian bodies. These are in every respect like nodules of lymphoid tissue found elsewhere and show the same reactions. Aside from them the tissue between the fibrous trabeculæ belongs entirely to the splenic pulp and into this the arteriole passes, to branch and empty into the wide venules,

which form a sort of feltwork making up most of the pulp. In the interstices between these venules is the reticulum of the pulp, in which are held great numbers of free cells. For our purposes the most interesting features are the structure of the walls of the venules and the nature of the cells in the pulp reticulum. The walls of the venules (Fig. 478) are very loose in texture, so that it seems extremely easy for cells to wander in and out. The lining endothelial cells are quite unlike those seen elsewhere, and instead of being flat and polygonal and uniformly adherent by their edges to the edges of the next cell, they are greatly elongated, thick, and pointed at each end, with a large and pointed nucleus which projects into the lumen of the venule. In many places the cells, which lie parallel to one another and lengthwise in the venule, have their nuclei side by side, so that between these rows of nuclei the wall is formed by the bodies only of the cells. A cross-section at that point shows only the unstained bodies of the cells, like little cogs on the inside of the venule, while at another level the venule may be lined all around with



Fig. 478.—Diagrammatic drawing of splenic venule showing the elongated endothelial cells, the structureless membrane, and the circular reticulum fibres (Mollier).

the prominent nuclei (Fig. 479). Outside the venule there is a delicate cylindrical basketwork of elastic fibrils; whether there is any other structureless membrane between is still disputed.

The reticulum between the venules shows a few elongated nuclei which belong to the cells of the connective-tissue framework. In chronic passive congestion and similar conditions these are very conspicuously increased in number and the fibrous reticulum is correspondingly denser. In the meshwork between the venous sinuses there are cells of various sorts. Red corpuscles are to be found there normally in moderate numbers, but in some pathological conditions in very great numbers. In the normal spleen neutrophile and eosinophile and basophile leucocytes are not more numerous than in most other tissues. Lymphocytes occur there, but in no great numbers, and the cells of the pulp stand out sharply against the Malpighian bodies in which the lymphoid cells are so numerous.

Two types of cell are prominent in the splenic pulp: one a large pale cell with branching pseudopods and very pale, large, vesicular nucleus. These cells apparently correspond with the larger forms of the highly phagocytic mononuclear wandering cells variously called clasmatoocytes, histiocytes, etc., and are found to contain particles and clumps of iron-holding pigment and débris of red corpuscles. Under certain conditions they become very conspicuous, especially if the section be stained to demonstrate iron. The other cell is morphologically much like the plasma cell with rounded or elliptical body, nucleus often eccentrically placed with deeply stained clumps of chromatin and a pale halo about it,

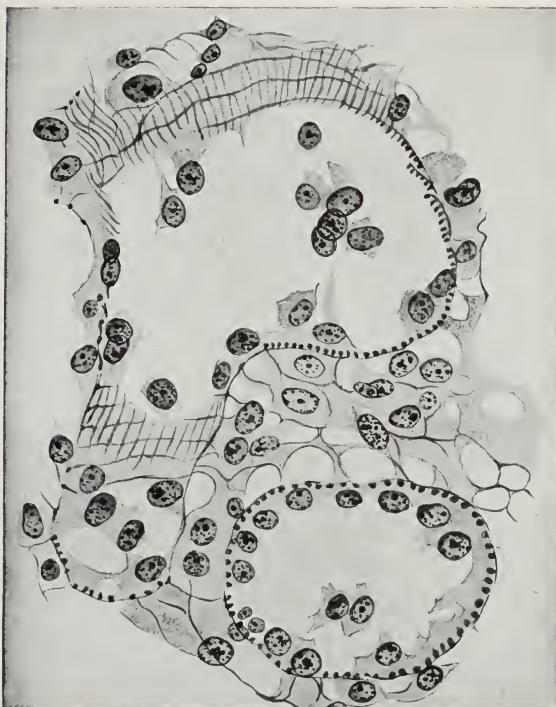


Fig. 479.—Section of spleen showing venules with endothelial cells and network of protoplasmic and reticulum strands (Mollier).

although the rest of the cytoplasm takes a bluish stain. Such cells are quite numerous and become especially conspicuous in many types of acute splenic tumor. This description perhaps fails to correspond exactly with that given by most authors for the cells of the splenic pulp, but such are the cells I have found in careful study of a great number of spleens made with the idea of discovering the precise nature of the reaction in acute splenic tumor. Of course in those conditions and in various other pathological states many other types of cells appear there in profusion.

The Malpighian bodies have a marginal zone of very abundant capil-

laries inside which zone is the mass of lymphoid cells. But in the central part large cells with pale vesicular nuclei, corresponding with the branching cells of the pulp, are found. In many cases these become very much increased in number and very conspicuous from their great phagocytic activity through which they load themselves with nuclear fragments and débris of cells. Such pale centres, generally spoken of as germinal centres, seem to us to have another significance.

As to the function of the spleen, it is even yet, after centuries of experiment and speculation (Malpighi attempted to discover this function by extirpating the spleen of a dog), impossible to say anything very definite. It is generally supposed to be an organ active in destroying injured blood-corpuscles and sifting out of the circulating blood the débris of such cells, the haemoglobin of which it prepares for use by the liver in the formation of bile-pigments. This idea depends chiefly upon the finding of pigment in the spleen, but there is little to show that all of this cannot be equally well accomplished after the spleen is removed. It is stated by many that the spleen is an active blood-forming agent, and Pearce and his co-workers have shown, among others, that there is a temporary anaemia after splenectomy, apparently compensated for by hyperplasia of bone-marrow and lymphoid tissues. Lymphocyte production is perhaps decreased for a time by splenectomy, but is soon reinstated (Murphy). Studies of the blood of the splenic vein as contrasted with that of the artery have been referred to, but they are open to criticism and give very contradictory results. Barcroft and his associates show that the spleen is essentially a reservoir for blood capable of expanding greatly during rest and contracting during exercise so as to drive a great store of blood out into the circulation (*Jour. Physiol.*, 1925-26, ix, 443).

Rich finds through injecting foreign protein into rabbits that the spleen develops the picture of an acute splenic tumor, evidently in the course of production of antibodies, and the abundant cells which appear in the splenic pulp are shown by tissue culture and study with the aid of motion pictures, to have the character of lymphocytes.

**The Lymphoid Tissue.**—The lymphoid tissue is almost universally distributed, since it occurs in conspicuous accumulations throughout the whole digestive tract, in the walls of the respiratory tract, in lymph-nodes in orderly arrangement everywhere throughout the body, in the Malpighian bodies of the spleen, and in inconspicuous nodules in the skin, bone-marrow, and other organs such as the thyroid, parathyroid, adrenal, kidney, liver, pancreas. The lymphatic channels lead its cells into the blood but are interrupted by others of its masses arranged as sieves to retain impurities. Everywhere the architecture of the lymphoid tissue is the same in principle although slightly more elaborate in those places where lymph-sinuses surround the more compact masses of lymphoid tissue. There is in this tissue a reticulum with many associated cells of large size and pale vesicular nucleus and, very commonly, in the follicles a central, palely staining mass of large cells related to if not identical with the reticulum cells. These have been looked upon since Flemming's work as the direct antecedents of the lymphoid cells. The latter, which are identical with the lymphocytes of the blood, are accu-

mulated in quantities in the meshes of the reticulum. The origin and relations of all those phagocytic, mononuclear, wandering cells which appear in so many inflammatory processes is discussed in an earlier chapter, where it is suggested that they are not so closely related to lymphoid cells as we at one time thought.

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#### EFFECT OF INJURIES TO THE RED CORPUSCLES AND THEIR FORMATIVE ORGANS

It is naturally impossible that there should be any extensive alterations in the red corpuscles without some accompanying changes in the closely associated white corpuscles and vice versa; nevertheless the disturbances affect so predominantly one type of cell or the other that we may confidently speak of these diseased conditions with regard to the cells chiefly affected, referring to the changes in the others as accessory.

In the normal blood the number of red corpuscles per cubic millimetre is about five million, while the number of white corpuscles taken together is about five or six thousand. Any great variation from these numbers usually indicates the influence of some abnormal condition. An increase in the number of red corpuscles or *polycythaemia* may occur, but is by no means so common as the opposite effect, a decrease in their number, *oligocythaemia*, loosely called *anaemia*.

**Polycythaemia.**—The rapid loss of fluid from the body, such as may occur with severe diarrhoea or Asiatic cholera or even with profuse sweating, leads to such inspissation or concentration of the blood as to raise the number of red corpuscles per cubic millimetre to six or seven million. This is naturally a transitory phenomenon if the patient survives, since with the absorption of water from the digestive tract the blood returns to its normal concentration. There are other conditions, however, such as chronic cyanosis from cardiac insufficiency or from emphysema, in which there is a lasting polycythaemia apparently due to the actual need for more blood to nourish and oxygenate the tissues properly. This is especially marked when the chronic passive congestion has existed since infancy, as in congenital heart lesions. In persons who live at high altitudes there is a similar increase in the number of red corpuscles which appears after even a short stay in the mountains or, it is said, after or during an aerial voyage. More interesting still and more difficult to explain are those cases of *polycythaemia rubra* (Osler), or *erythræmia*, in which the blood becomes actually thick and viscous

from the presence of such enormous numbers of red corpuscles (10 million or more). There is increase in the total volume of blood, cardiac hypertrophy, great enlargement of the spleen, and hyperplasia of the bone-marrow. The cause is quite unknown and the patients go on to die of haemorrhage or of some intercurrent infection. It is a very curious phenomenon, perhaps analogous to leukaemia, since in spite of the fact that the blood-vessels are everywhere turgid with blood, the erythroblastic tissues of the bone-marrow are found to be in process of active hyperplasia and blood-formation, as though behaving quite independently of the needs of the blood which usually govern them.

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**Anæmia.**—On the other hand, agencies which destroy and diminish the red corpuscles are extremely common, and their action far more easily understood.

Decrease in the number of red corpuscles in the blood may be brought about in a very great variety of ways which perhaps fall into the following divisions:

1. Actual loss of blood through haemorrhage.
2. Destruction of blood and injury of the bone-marrow by poisons which are often those produced by bacteria or other parasites, often chemical substances taken as drugs or absorbed by workers in certain industries. Long-continued infections and the presence of malignant tumors are factors especially likely to bring about such results.
3. A peculiar, sharply defined disease known as *pernicious anæmia*, in which, despite the most active efforts toward regeneration, the red corpuscles continue to decrease in number.
4. *Osteosclerotic Anæmia.*—The attack may be more serious in that it is directed against the bone-marrow itself. While it is difficult to show that this is so in the case of poisons and infections which may also destroy the circulating red corpuscles, it is quite clear in those cases in which metastases from cancers of the prostate or breast occupy the whole marrow cavity of every bone to the mechanical exclusion of bone-marrow, or even in the cases of leukaemia in which the whole of the bone-marrow is given over to the production of the forerunners of white corpuscles, so that the erythroblastic tissue is crowded out of existence. In such cases there is extreme anæmia in spite of efforts toward extra-medullary blood-formation.

**Secondary Anæmias.**—1. *Post-hæmorrhagic anæmias* depend in their severity upon the extent of the haemorrhage and upon the frequency with which it is repeated. A single great haemorrhage is followed by a series of symptoms due to the incomplete filling of the blood-vessels—fainting, nausea, weakness, collapsing pulse, etc.—but the concentration of the blood and the proportion of corpuscles immediately after the

haemorrhage is naturally exactly what it was before. Very rapidly, however, fluid passes from the tissues or from the digestive tract to dilute the blood and make up its quantity. Within a few days after such haemorrhage the fatty bone-marrow of the long bones becomes so filled with newly formed cells that the fat is crowded out and the marrow assumes a red color and cellular consistency. In such marrow there are found abundant nucleated red cells rapidly giving rise to red corpuscles, and also quantities of myelocytes; this is not followed, however, by the pouring out of any extraordinary number of leucocytes, although the proportion of these cells in the blood is somewhat increased.

Such extensive haemorrhages occur, of course, in mechanical injuries in which large blood-vessels are cut or torn, but they also occur in advanced pulmonary tuberculosis from the erosions of a branch of the pulmonary artery, in ulcers of the stomach or in cases of cirrhosis of the liver in which there is a rupture of the dilated veins in the oesophagus, in the rupture of an extra-uterine pregnancy, or in ordinary pregnancy at childbirth. But even more profound degrees of anaemia may be produced by slighter but frequently repeated haemorrhages, such as those which come from recurrent nose-bleed, bleeding haemorrhoids and ulcerated submucous myomata of the uterus, and, possibly, in the case of certain intestinal parasites which suck the blood, although, as has already been said, this is of somewhat doubtful occurrence in human beings and the anaemia caused by these parasites seems rather due to a poison which they produce.

2. *Destruction of the blood-corpuscles* (haemolysis) may be caused by a great variety of chemical substances, of which ricin and benzol have already been mentioned. Nitrobenzol, toluylenediamine, lead, and a host of other substances have a similar effect. Particularly interesting are the specific haemolytic sera which have been experimentally produced, and we are even yet very imperfectly informed as to the part which similar elusive substances may play in human pathology. There are many bacteria which produce strong haemolytic poisons, and acute infections are therefore common causes of intense anaemia. For example, the haemolytic streptococci can cause the destruction of a great proportion of the blood-corpuscles in a brief period, and even the less actively haemolytic *S. viridans* produces an endocarditis and general infection which runs its course with the development of extreme grades of anaemia. The anaemia which accompanies typhoid fever, chronic tuberculosis, and syphilis is apparently due to similar processes, while in chronic nephritis and the cachexias which accompany the presence of tumors, especially perhaps when they are ulcerated, the nature of the poison is more difficult to ascertain.

The extreme anaemia brought about by malaria is in great part due to the mechanical destruction of the corpuscles by the parasites, but in the case of bothriocephalus and uncinia it appears that a recognizable haemolytic material can be extracted from the worms and that this is probably diffused into the blood and tissues.

Such anaemias, which together with those caused by haemorrhage, are often called secondary, since their cause is known, resemble one

another closely in the character of the blood changes. The red corpuscles may be reduced to less than a million per cubic millimetre, and tend to be rather small and pale, or poor in haemoglobin, and show some irregularities in size or form. Normoblasts are present in the circulation, often appearing in great numbers, at intervals corresponding with what seem to be crises of activity in the bone-marrow. Megaloblasts are seldom seen. There is nearly always an accompanying leucocytosis except in the case of such diseases as typhoid fever and malaria, in which

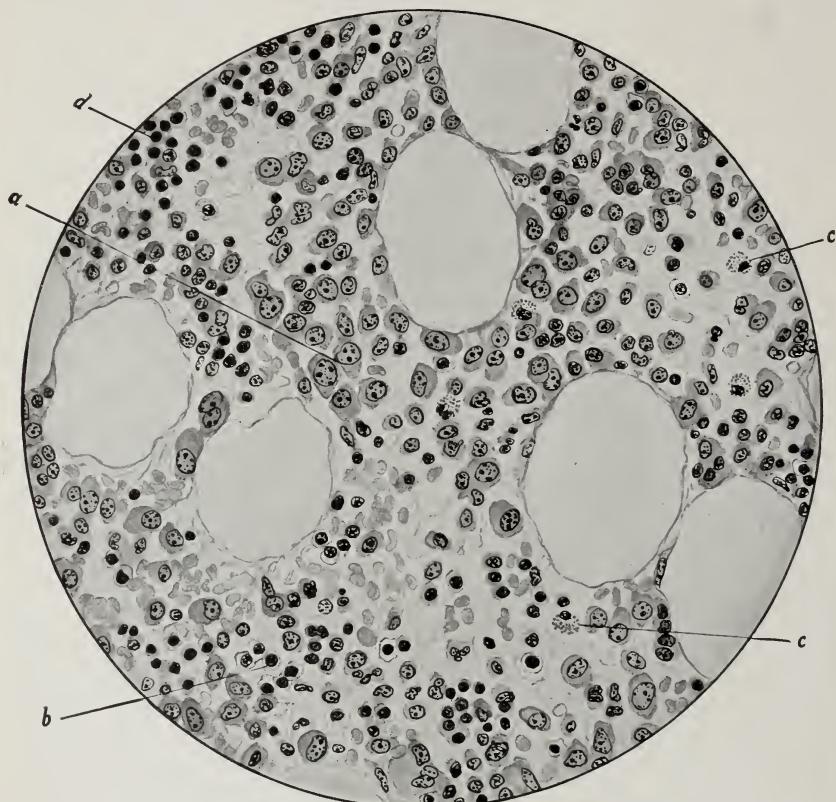


Fig. 480.—Bone-marrow in secondary anaemia, showing intense regenerative hyperplasia: (a) Myelocytes; (b) normoblasts with occasional megaloblasts; (c) eosinophile myelocytes; (d) lymphoid cells.

the leucocytes are decreased in number. (Longcope: Bull. Ayer Clin. Lab., 1905, ii, 1.)

The changes in the bone-marrow are those already described as characteristic of hyperplasia, which appears in response to the dearth of red cells, but associated with similar hyperplastic changes in the myelocytic group (Fig. 480). When, however, the anaemia is caused by some poison which attacks the bone-marrow itself, the reparatory changes are even more striking, as shall be detailed later. In the spleen,

which may be somewhat enlarged, one finds no especial change in the Malpighian bodies, but in the splenic pulp, myelocytes, erythroblastic cells, and other elements corresponding to those of the bone-marrow are to be found. Similarly in the capillaries of the liver, and sometimes outside them in the liver substance itself, such groups of cells may occur. The lymph-glands and lymphoid tissues are practically unaffected in secondary anaemias. Scattered haemorrhages are common, and oedema of the ankles or of the tissues under the eyes forms a characteristic accompaniment. Other anatomical changes, aside from the pallor of the organs in which little or no blood-pigment is deposited, are inconstant. Very often there is an accumulation of fat globules in the heart muscle and in the kidneys. The disabilities produced by such anaemia are those consequent upon diminution of the bulk of the blood and of its oxygen-carrying capacity. Weakness, faintness, etc., have been mentioned, but, curiously enough, whether from the increased efforts of the heart and more rapid circulation, or other cause, the respiratory interchange is not decreased and the nitrogenous output not characteristically altered.

Some mention should be made of the rather rare cases of *aplastic anaemia* which run a more precipitate downward course to a fatal result because no effort toward regeneration of the blood takes place in the bone-marrow. Instead, the marrow of the long bones is found at autopsy, in spite of the most profound anaemia, to be entirely yellow and fatty without any of the cell hyperplasia seen in the ordinary cases.

This seems to be most frequently the effect of the injurious action of such a poison as benzene inhaled by workers in some technical procedures, or by arsphenamine, etc., in the treatment of syphilis, so that it is perhaps best regarded as a secondary anaemia.

A secondary anaemia is the banal result of all sorts of injuries which destroy the blood-corpuscles, just as cardiac decompensation may rise from the most varied injuries to the heart. The changes in the bone-marrow are the ordinary or routine efforts of the body to repair this injury, just as new epithelium grows to cover a defect. We need not feel surprised, therefore, in finding the type of reparatory reaction the same in all. If we can remove the cause by stopping haemorrhage, by expelling parasites, by extirpating tumors or withdrawing chemical poisons, the rapid production of red corpuscles in the bone-marrow proceeds until the anaemic circulation once more has its normal amount of normal blood, after which it quiets down and the cellular marrow resumes its fatty character in the long bones.

**Hypochromic Anaemia.**—Chlorosis, which has now practically disappeared, has been described in discussing the metabolism of iron. In recent years there has been recognized a form of anaemia to which the name hypochromic has been applied. It seems, in a sense, related to the old familiar chlorosis inasmuch as it appears to depend upon an inability to assimilate iron in adequate amounts to maintain the haemoglobin content of the red cells. The question arises as to whether this is because of insufficient iron in the diet, inability of the stomach to render it absorbable or some defect of the bone-marrow which fails to

accomplish the normal formation of cells which can take up haemoglobin. This last is, as will be seen, the essential defect in pernicious anaemia but here it seems rather that an insufficient supply of iron is the fault. There is still the possibility that the building up of haemoglobin from the absorbed iron may present difficulties and that the normal formation and size of the red cell is dependent upon available haemoglobin for in the hypochromic anaemia the red cells are smaller than normal, as well as being poor in haemoglobin.

Hypochromic anaemia is an affection chiefly of women between the ages of 30 to 40 years. It is a chronic, non-fatal condition in which the skin is very pale and not yellowish, as in pernicious anaemia, nor greenish as in chlorosis. There may be atrophy and inflammation of the tongue and some sore throat and the gastric juice is poor in hydrochloric acid and pepsin. The spleen is generally enlarged, the bone-marrow hyperplastic. There are no changes in the central nervous system although there may be paraesthesiae in the extremities. The blood shows irregularity in the size of the red corpuscles which are in general smaller than normal (anisocytosis, microcytosis) and have a low color index because they contain too little haemoglobin. The leucocytes are as a rule normal.

Nothing is clearly known as the cause of this disease but, of course, the condition of the gastric secretion is suspected. Liver feeding does nothing to cure it nor does feeding with beef which has been digested with normal gastric juice. Iron-rich food seems not capable of improving the anaemia but when such food rich in iron is digested in normal gastric juice and then fed to the patient, the red corpuscles increase and approach the normal. Iron given as ferrous salts or in organic combination together with hydrochloric acid has a phenomenal effect in restoring the blood to a more normal state and dispelling all symptoms.

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**Pernicious Anaemia.**—This, although so difficult to distinguish from other types of severe anaemia by any single criterion, is quite obviously an independent and definite disease which we recognize with certainty, and of which we can foretell the course as surely as we can in a case of typhoid fever. Briefly, there is extreme decrease in the number of red corpuscles, each of which, however, contains an abnormally large amount of haemoglobin, so that, sometimes, in spite of the oligocythaemia, the haemoglobin of the whole blood is not greatly lowered. The corpuscles are very irregular in form (poikilocytosis) and in size (anisocytosis), there being not only small forms but very large or giant corpuscles, also tinged deeply with haemoglobin. The presence of these large forms together with the high color-index is distinctive, since these do not occur in secondary anaemias where the color-index is low. Nucleated red

corpuscles are found sometimes in large numbers and megaloblasts are often abundant. Indeed, the finding of megaloblasts in the circulating blood is much relied on in the diagnosis of this disease. The leucocytes are decreased in number and there may be only 1500–2000 per cubic millimetre. Since the lymphoid structures in the body are unaltered, the percentage of lymphocytes rises and they may assume a proportion of as much as 60 per cent. The great decrease is in the polymorphonuclear neutrophiles. Myelocytes and myeloblasts are occasionally found. The decrease in the red cells is often such as to give the blood a peculiar watery appearance, although the high color-index tends to keep it red. In actual numbers the red cells may sink far below one

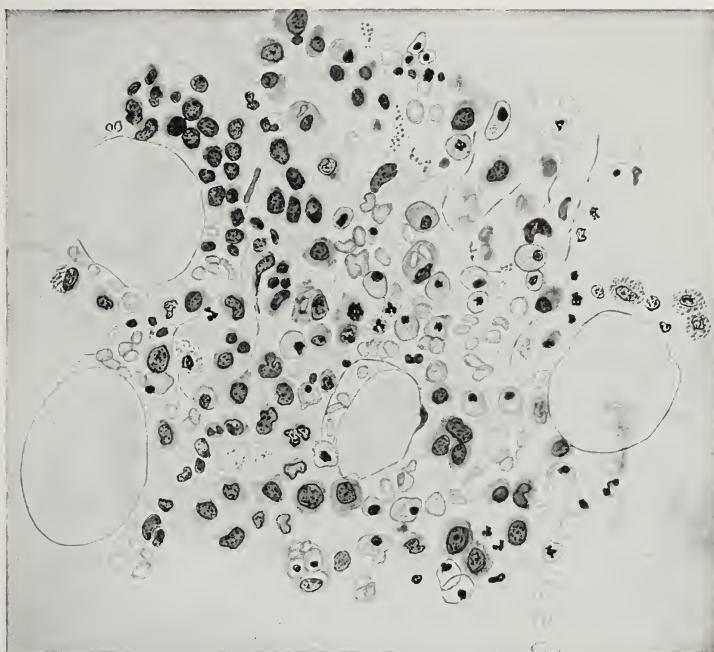


Fig. 481.—Bone-marrow in pernicious anaemia. Normoblasts and numerous megaloblasts occur, together with many neutrophile myelocytes. There are phagocytic cells and some finely granular pigment.

million. (For details of the blood-changes consult the works of Cabot, Naegeli, Lazarus.) This distinctive alteration of the blood is perhaps not enough to mark out pernicious anaemia as an independent disease, but the occurrence in middle-aged people, the complete lack of any recognizable cause, the continued good nutrition of the patient, the progressive deepening of the anaemia with intermissions during which great improvement occurs, the yellow pigmentation of the skin, the lesions in the central nervous system, and the practically uniform fatal outcome are enough to establish its identity.

At autopsy the body is found well nourished, the subcutaneous fat

and, indeed, all the fat tinged a rather deep yellow. The muscles are dark red. The diminution in the amount of blood is striking, and there may be found minute ecchymoses and local oedemas, especially in the lungs. The heart is soft, and through the myocardium there shines the yellow streaking which indicates the presence of much fat in the muscle-fibres. The liver, cortex of the kidneys, heart muscle, and the lungs are pigmented with iron-containing blood-pigment, even to the extent of assuming a rather distinct chestnut-brown color. Immersed in ferrocyanide of potassium and weak hydrochloric acid, they become grayish-blue in color.

The mucosa of the stomach is markedly altered, sometimes throughout, sometimes rather in patches. The changes are not striking on gross



Fig. 482.—Bone-marrow in pernicious anaemia. An island or group of megaloblasts with adjacent myelocytes and a few normoblasts.

inspection and do not appear in the form of distinct ulcerations with thickened margins but rather as a widespread atrophy so that the mucosa is thin, smooth and flattened out. It is, of course, of great importance to determine precisely what cells or what specific granules are lost, in view of the newer work of Castle and others which point to this as the key of the whole situation, but up to the present this has not been accomplished. In our own cases the destruction has been so general that it is impossible to say which loss is important. The oxyntic cells are destroyed and the granules characteristic of the remaining cells, including those at the outlet of the glands and such as are found in the

pyloric glands, are all in large part lost so that achylia, which in itself is less important, results. In the mouth, too, there are often lesions of the mucosa of an inflammatory character associated with haemorrhages which cause pain, especially when acids are taken into the mouth. On the tongue there are brownish patches at the sites of haemorrhages.

The *bone-marrow* is dark red and rather gelatinous. Its fat is replaced by the abundant hyperplastic tissue which in general resembles that found in secondary anaemias. The character of this can be conveyed better by a drawing than a description (Fig. 481). There is extensive new formation of myelocytes and myeloblasts. Newly formed lymphoid cells are present, and there are abundant groups or islands of erythroblastic cells among which megaloblasts are conspicuous. Ehrlich made the statement that the presence of megaloblasts in the hyperplastic bone-marrow was peculiar to pernicious anaemia, and that it

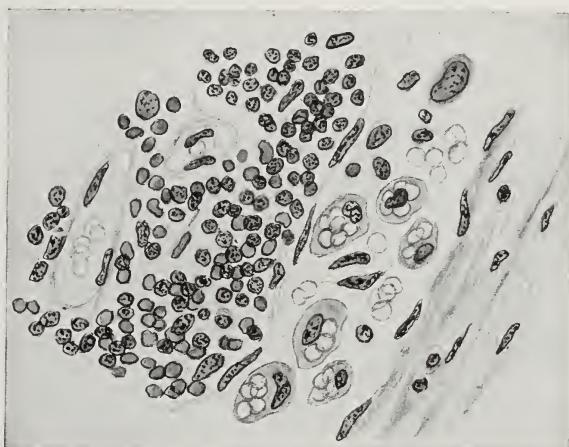


Fig. 483.—Pernicious anaemia. Lymph-gland with phagocytes in the peripheral sinus, containing red corpuscles.

indicated a return to a distinctly embryonic type of erythrocyte formation, in sharp contrast with the normal formation, which is by way of the normoblasts. The appearance of megaloblasts in the blood and of megalocytes or large, deeply colored, non-nucleated red corpuscles was equally characteristic, and one must regard pernicious anaemia as a condition in which there was being formed a different sort of blood derived largely from abnormal cells, the megaloblasts, proper to embryonic life, but obsolete in adult life. Naegeli and Lazarus and most German writers have accepted this view of the obsolete nature of megaloblasts and the consequent peculiarity of the bone-marrow in pernicious anaemia. Certainly the presence of megaloblasts in the circulating blood is indicative of very severe anaemia, and although these cells occur in other forms of anaemia, they are far more common in pernicious anaemia. But any one can convince himself of the presence of megaloblasts in any hyperplastic bone-marrow, and the experiments of Bunting,

in which, by repeatedly injuring the bone-marrow with ricin, he produced an anaemia practically identical with pernicious anaemia, showed further that in the bone-marrow there were quantities of megaloblasts which formed the centres of erythropoietic islands. They formed red corpuscles by development through the intermediate normoblasts which lay peripherally. It is Bunting's idea that this is practically the normal relation, and that the erythrocytes are given off peripherally, but that in the case of such serious injury to the bone-marrow as may be produced with ricin or as exists in pernicious anaemia, not only the more peripheral normoblasts, but the central megaloblasts themselves, may

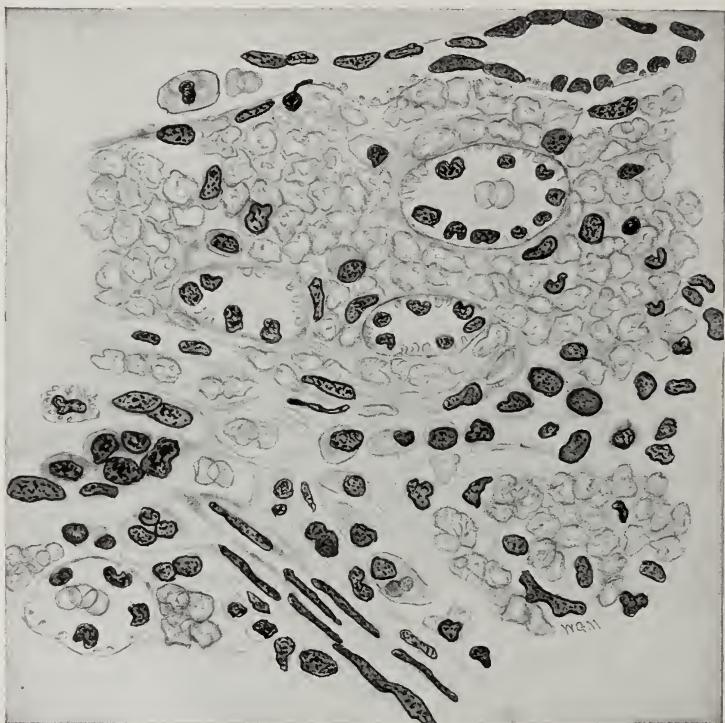


Fig. 484.—Pernicious anaemia. Spleen showing red corpuscles between the venules and small group of myelocytes in the reticulum of the pulp.

be hurriedly discharged. It is quite true that in the bone-marrow of pernicious anaemia it is exceedingly difficult to outline any such groups of cells, since they are intimately intermingled with adjacent groups of other sorts of cells. Nevertheless, the relative concentration which can be made out, and the analogy with the perfectly clear-cut islands of regenerating cells in bone-marrow made aplastic with benzol, leads us to believe that Bunting's conception is a true one (Fig. 482). Numerous large phagocytic cells are found in the sections, loaded with red corpuscles and with the shadows of such corpuscles, together with occasional fragments of nucleated cells. These have been described by Sternberg

and are conspicuous also in the spleen and in the lymph-nodes (Fig. 483). They at least indicate the activity of blood-destruction.

The *spleen* is usually slightly enlarged, and in some cases, but by no means all, shows a rusty tint on its cut surface. The Malpighian bodies can be seen plainly and the splenic pulp is not very greatly increased in bulk. Occasionally the organ is larger and firmer than normal, the increase being evidently in the splenic pulp. Microscopically there is strikingly little change from the normal (Fig. 484). The venules are clearly outlined with intact endothelial cells; the intervening reticulum of the pulp is more abundantly loaded with red corpuscles than in the normal, and many of these appear to be disintegrating. The mono-nuclear cells which normally occupy this position seem to be relatively few. Both within and between the venules there are moderate numbers of large phagocytic cells with débris of red corpuscles in their protoplasm. The myeloid change described by Meyer and Heineke and others is by no means so conspicuous as one might be led to expect from the severity of the anaemia; indeed, it is necessary to search through the sections to find any myelocytes, and then they occur only in small groups of two or three, both inside and outside the venules. Many of them are found in the margins of the Malpighian bodies or in the walls of the larger blood-vessels. Nucleated red cells are also inconspicuous, but are occasionally found in the splenic pulp. In reality, the alterations of the spleen in severe secondary anaemias may be much more marked than in this condition, both with regard to the increased number of wandering cells in the pulp and the accumulation of myeloid cells, but that is probably to be explained by the influence of the infectious or toxic process which stands as the cause of such secondary anaemia and which in itself may produce changes in the spleen (*cf.* acute splenic tumor in infectious diseases).

The lymph-glands show no striking alterations, but, as stated above, may contain in their sinuses many of the large phagocytic cells loaded with red corpuscles. The immunity of the lymphoid tissue from alteration in pernicious anaemia is evident in some cases in the presence of a slight degree of lymphoid hyperplasia in the bone-marrow and in the relative increase in the numbers of lymphoid cells in the blood.

The liver is said by Meyer and Heineke to show accumulations of myelocytes and erythroblastic cells. Much more striking is the fine, dust-like sprinkling of iron-containing pigment in the liver-cells themselves (Fig. 60, page 131). This pigment, which is readily colored blue by the ferrocyanide method, lies about the fine bile canaliculi in the centre of each strand of liver-cells. There is some pigment also in the Kupffer cells of the capillaries, but it is far less noticeable.

Another lesion characteristic of pernicious anaemia is found in the white matter of the spinal cord. Especially in the posterior tracts there occur focal areas of degeneration of the nerve-fibres and neuroglial scarring which, by interrupting these tracts, produce irregular, ascending, secondary degenerations. These, described by Lichtheim, Minnich, Nonne, Milne, and others, bring about very distinct sensory disturbances

during life, sometimes amounting to ataxic phenomena closely resembling those of tabes.

Similar lesions have been found in the white matter of the brain, especially in the motor areas. Such changes are not improved by any therapy.

The recent studies have been most enlightening as to the nature of pernicious anaemia. Whipple, beginning with a study of bile production for which haemoglobin is necessary, transferred his attention to anaemia produced by the withdrawal of blood and in the maintenance of such experimental animals found that a diet of liver was far more effective than any other. The liver in cases of pernicious anaemia is particularly rich in this material, so that Whipple concludes that in this disease there is a lack of something so that the marrow cannot produce the needed red cells and the haemoglobin-building material heaps up in the liver storehouse. Minot and Murphy found that by feeding liver to these patients they could restore them to a state of wellbeing.

The solution of the problem has been almost reached in a quite different way by Castle and his co-workers, although it cannot be said to be complete. Castle has shown that in the diseased stomach in pernicious anaemia something is lacking in the secretion but that this is not pepsin, hydrochloric acid, rennin nor lipase. Beefsteak, eggs, autolyzed yeast, wheat germs, etc., incubated in normal gastric juice will, if fed to the patient with pernicious anemia, start at once the improvement in symptoms and rapid regeneration of the blood. But the food alone, or the gastric juice alone, will give no such effect. Even gastric juice freed from hydrochloric acid, pepsin and rennin and then incubated with beefsteak, will produce the same response so that there is a specific factor in normal gastric juice which Castle calls the intrinsic factor which must act upon certain substances in the diet which he calls the extrinsic factor to produce a material necessary to the normal functioning of the bone-marrow in producing normoblasts and normocytes instead of megaloblasts and distorted red cells. Apparently the question of haemoglobin production is not especially concerned and the store available is more than adequate if only the red cells can be produced in proper form.

This combination of intrinsic with extrinsic factor seems to be stored at least temporarily in considerable quantity in the liver and hence the beneficial effect of feeding liver, although in Whipple's experiments the good effect in producing haemoglobin in his anaemic dogs was rather the result of the storing in the liver of haemoglobin-building material—quite a different chain of events.

The nature of the intrinsic factor is completely unknown and even its source in particular cells of the gastric mucosa remains obscure although Meulengracht finds that the extracts from the pyloric glands are active while those from the fundus and cardiac portion are inactive.

It is important that the extrinsic factor has also a specific character for while beef and eggs and wheat germs contain it, casein, gluten and purified nucleoproteins do not. Strauss points out that the occurrence of this intrinsic factor is much like that of the antipellagra Vitamin

$B_2(G)$  although it is not identical with it. Indeed, this may explain the occurrence of pernicious anaemia or a condition practically the same in some cases of sprue, pernicious anaemia of pregnancy or the macrocytic anaemia of the tropics described by Wills. Strauss also emphasizes the failure of absorption of the product of the interaction of the two factors from the intestinal tract in cases where extreme obstruction has been produced by strictures or multiple intestinal anastomoses or by dysentery.

This seems to put pernicious anaemia into an almost unique position since it appears to be the result of the lack of combination of some internal secretion with a specific dietary constituent to form a substance necessary for the proper development of the red corpuscles. It is more complex perhaps than vitamin deficiencies and not exactly analogous with the activities of internal secretions. In addition to the good effects of feeding liver, or the various extracts made from it, West has analyzed to some extent the effective substance stored in the liver and has brought about clinical improvement with the crystalline material that he obtained. But still we are not informed as to the cause of the destructive changes in the central nervous system.

Recently, Miller and Rhoads have found that, by feeding swine a diet which causes canine black-tongue, something resembling pernicious anaemia is produced with loss of the anti-pernicious anaemia activity of the gastric secretion and as before relieved by feeding liver.

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**Sprue.**—This is a complicated condition long known to occur in some tropical countries but more recently recognized in temperate zones, although there is even yet some question as to whether the tropical and non-tropical forms are identical. Most striking are the disturbances of the digestive tract. The tongue and mucose of the mouth are ulcerated, the small intestine dilated in places, narrowed in others, but in general the colon greatly distended. There is diarrhoea with pale stools loaded with fat, the so-called *steatorrhœa*. There is extreme anaemia, sometimes microcytic but more often megalocytic as in pernicious anaemia. Wasting, low blood-pressure, and weakness are characteristic and there

may be signs of rarefaction of the bones, as in osteomalacia. The calcium of the blood is reduced and the excretion of calcium in the intestine increased. This may well explain the tetany which is frequently associated. The organs are extremely anaemic and heart, liver, spleen, and other structures are atrophied. The stomach can still secrete hydrochloric acid which is one feature which distinguishes it from pernicious anaemia which in so many respects it closely resembles. Castle and Rhoads studied it in Puerto Rico and found the changes in the blood and in the bone-marrow practically identical with those in pernicious anaemia in that there is a proliferation of megaloblasts and suppression of maturation of the normoblasts. They found no evidence that it is caused by infection with *Monilia psilosis* as had been stated by Ashford, but thought it due to the lack of either extrinsic or intrinsic factor or of ability to absorb the haematopoietic combination of these when given. But liver extract produces a rapid cure of all the symptoms in most cases, although iron is necessary in some.

It seems that this condition is not quite identical with pernicious anaemia but is rather the result of a complex disturbance of the digestive system which allows the escape of various necessary materials—not only the essential haematopoietic combination but quantities of unutilized fat and other nourishment and an excessive amount of calcium, all of which losses have their specific effect upon the body, producing anaemia, wasting and tetany.

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**Sickle-cell Anaemia.**—This is a disease, recently recognized, affecting negroes exclusively, and occurring as an inherited condition obeying Mendelian laws as a dominant character. It may be latent and during a long, active life there are no symptoms, although the red corpuscles have the tendency to assume the peculiar elongated or crescentic form which gives it its name, or for some reason as yet quite unknown it may become active, and with extreme anaemia, swelling of the spleen, jaundice, urobilinuria, and excess of faecal urobilin and cutaneous ulcers, generally over the shins, lead to death. In many respects it is similar to haemolytic jaundice, especially resembling the congenital form, but there is no decreased resistance of these sickle-shaped cells to hypotonic salt solution. The latent form has been recognized by Rich in cases undiagnosed clinically, by the peculiar changes in the spleen which are identical with those in the spleens of the active cases studied in the wards and diagnosed during life. Later study of the relatives in these latent cases has shown that in each family there were others whose blood revealed the same peculiarities. There must be some abnormality of the bone-mar-

row to produce such red corpuscles, but it is not yet recognized. The spleen shows pools of extravasated blood about the Malpighian bodies and the splenic venous sinuses are collapsed by the great accumulation of blood between them. The Malpighian-body cells and the cells of the splenic pulp are often greatly decreased in number. The haemorrhages encircling the Malpighian bodies Rich explains as due to abnormality

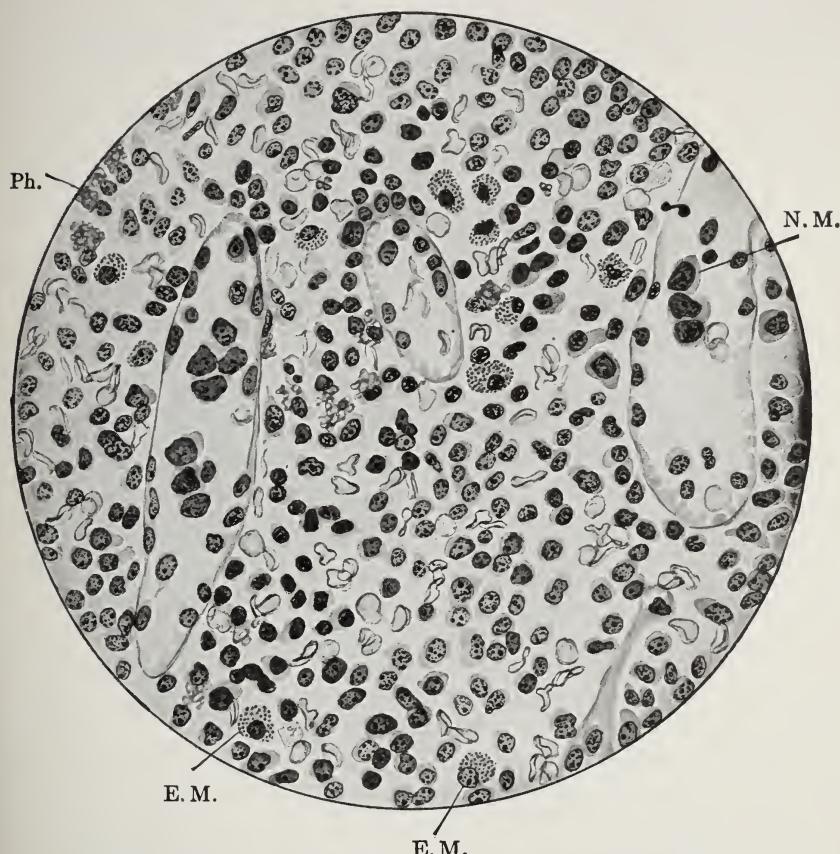


Fig. 485.—Myeloid alteration of the splenic pulp in osteosclerotic anaemia from destruction of bone-marrow by metastases from a carcinoma of the prostate. N. M., Neutrophile myelocytes; E. M., eosinophile myelocytes; Ph., pigment-holding phagocytic cells.

of the ampullæ which are located especially there, the rupture of which allows the extravasation. There is much iron-containing pigment in such phagocytic cells as remain and scars follow the extravasation of blood and obstruction of blood-vessels. Such a change in the spleen can be recognized at a glance and is peculiar to this disease, although it does resemble the condition seen in haemolytic jaundice. Liver and kidneys also contain pigment derived from blood-destruction in the active cases.

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**Anæmia Following Mechanical Destruction of the Bone-marrow.—**

Although the technically impossible experimental destruction of all the bone-marrow has often been discussed, some light on such a condition is furnished by those cases in which a tumor, such as a carcinoma of the prostate or breast, metastasizes to the marrow cavity of practically every bone in the body, and there, by occupying space in the rigidly enclosed cavity, destroys the bone-marrow. There is much uniformity in these cases, and we have recently studied two in which literally every bone was found to be completely occupied by the tumor. The cavities of all the long bones were filled with a solid tissue, for these tumors cause the formation of enormously thick laminae of new cancellous bone which lie in a close network and contain in their meshes only the epithelial cells of the tumor. The ribs, vertebrae, pelvic and other bones were also solidly infiltrated by the bone-forming tumor. The effect was to produce the most profound anaemia in which the red blood-corpuscles sank to 600,000 per c.mm. There was a parallel reduction of the granular leucocytes. It is in such cases that the greatest need arises for extra-medullary blood-formation and, indeed, they furnish the best and least complicated examples of myeloid change in the spleen and liver. The development of blood in the spleen and liver in one of these cases is shown in Figs. 485 and 486.

A similar effect, as far as the red corpuscles are concerned, is produced by the crowding out of the erythrogenic tissues by the enormous overgrowth of myeloid cells in myeloid leukæmia and of the lymphoid cells in lymphoid leukæmia. Of course the destruction is by no means so complete in these cases, and the existence of the myeloid change in other tissues is less clearly defined since they are already overwhelmed with the hyperplastic elements from the bone-marrow itself.

**Banti's Disease.**—There is a form of anaemia with great swelling of the spleen and usually accompanied by haemorrhages which has long been described by clinicians as *anæmia splenica*. Banti has studied these cases anatomically and his name is associated with the complex lesions, although it is claimed by others that not all the cases progress, as Banti describes them, to a stage in which cirrhosis of the liver and ascites are features. Nothing is known of the cause. The spleen becomes greatly enlarged and there is a secondary type of anaemia intensified by haemorrhages from the stomach. There may or may not be cirrhosis of the liver, but there is a peculiar and specific type of alteration in the spleen which is not like that due to chronic passive congestion nor even like the one associated with forms of cirrhosis of the liver which do not obstruct the portal blood-stream. It may reach a weight of 1 to 3 kg., and during

life is distended with blood. The veins are enormously enlarged and numerous huge collateral channels appear, especially in adhesions between the spleen, the stomach, and the diaphragm. There is often thrombosis of the main splenic vein, a condition which I have seen three times. When the spleen is extirpated it shrinks and collapses with the escape of blood and becomes a rather flabby elastic mass which, on section, shows a grayish-pink translucent cut surface that sinks a little below the capsule. The Malpighian bodies are not visible. Microscopically there is found to be moderate atrophy and scarring of the

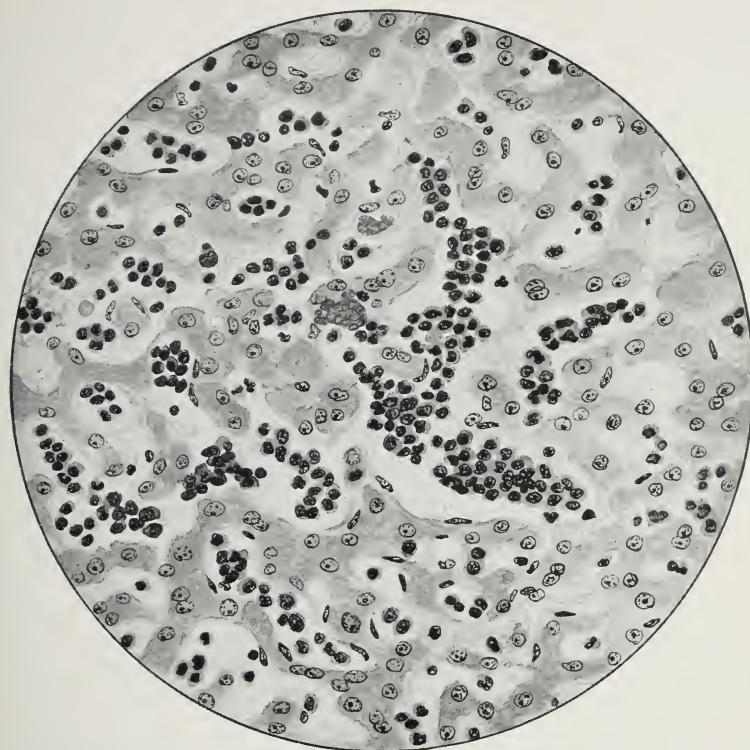


Fig. 486.—Osteosclerotic anaemia following destruction of bone-marrow by metastatic carcinoma. Clumps of myelocytes in the liver capillaries. The endothelial cells are intact.

Malpighian bodies, and in the pulp the venules are separated by quite abundant loose fibrous tissue in which there remain very few of the original pulp cells. The whole spleen is thus impoverished in cells and has assumed an empty appearance, being composed essentially of fibrous tissue in which the venules are embedded. The liver, in the late stages, is said by Banti to become distinctly cirrhotic. In our rather numerous cases it has frequently appeared normal and in a few instances has shown advanced cirrhosis. The bone-marrow is moderately hyperplastic. We are thus very ignorant of this condition, but it is quite clear that it is

a definite and constantly recurring disease and that it is easy to recognize the typical anatomical changes. Extirpation of the spleen appears to cure the whole malady, if it does not kill the patient through uncontrollable haemorrhage at the operation.

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**Hæmophilia.**—This is a peculiar hereditary condition in which the clotting of the blood is deranged and so slowed that the slightest wound may result in a severe, perhaps fatal haemorrhage. It affects males only, but is transmitted by females. Its occurrence in several royal families in Europe has given scope for much dramatic literature and the complications arising are well told in "Die Frauen von Tanno," by Mann.

The platelets are apparently resistant and do not swell and disintegrate to produce thromboplastic substance as they should, so that the clotting is long delayed. Of course, every possible treatment has been tried. It has even been stated that the lack of female sex hormone is the cause, and ovarian extract has been injected, but without effect. Of the whole range of haemostatic drugs, all have been tried and McFarlane and Barnett suggest the venom of a viper as the best.

**Purpura hæmorrhagica** is a condition in which haemorrhages into the skin and mucous membranes and elsewhere occur with frequency. Various types exist and different names are given, for example, Schoenlein's purpura with arthritic symptoms and sometimes pericarditis, Henoch's purpura with colic and the morbus maculosus of Werlhof. In the latter, at any rate, a decrease in the number of platelets in the blood is thought responsible for the slow clotting, but this alone can hardly account for the haemorrhage, and it is thought by others that an increased permeability of the capillary wall is especially important. The decrease in the platelets has been thought to be due to their consumption by phagocytes, perhaps especially in the spleen, and splenectomy has in many cases produced a sudden remarkable improvement in the condition. No especial changes in the bone-marrow have been found and the case of Lawrence and Mahoney, in which metastases from a carcinoma of the stomach filled the lymphatics about the bronchi and vessels, and even the capillaries of the alveolar walls in the lungs, with extreme thrombopenia, might support the recent theory of Dr. Howell that platelets are formed in the lungs. Muller finds a severe disturbance of calcium metabolism and changes in bones which possibly have a bearing on coagulation time of the blood. Greenwald suggests snake venom in the control of thrombocytopenic purpura, the injection of this in high dilution apparently causing a rapid rise in the number of platelets.

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**Hæmatoporphyria.**—Porphyrins, which are pyrrhol compounds recognizable spectroscopically, may occur in excess in the blood either as congenital or acquired hæmatoporphyria. Some porphyrins occur naturally in animal and plant cells and especially in feathers. The exact origin of the excess in man is not clear but while some may be ingested, it is thought that it is either abnormally synthesized or derived from haemoglobin. Fischer thinks it comes from muscle haemoglobin. In the acquired form it seems to result from poisoning with such drugs as veronal, sulphonal, trional, acetanilid, or even from lead poisoning.

Hæmatoporphyrin solutions absorb ultra-violet light and are fluorescent. Animals injected with such solutions are sensitized to light so that sunlight causes acute inflammation and necrosis of the exposed skin, rapid respiration and heart beat, coma and death. This extreme sensitization to light is true of the cases of congenital hæmatoporphyria but not of the acquired form. There is pigmentation of bones and teeth and the urine is dark red. There is increased tonus of the intestine with spasms, nausea and vomiting, and nervous disturbances with ascending paralysis and muscle atrophy, which seem to depend upon demyelinization of nerves and destruction of ganglion cells in brain and cord.

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**Hæmolytic Jaundice.**—Hæmolytic jaundice is an uncommon affection, evidently hereditary and due to peculiar constitutional changes of which probably the extreme fragility of the red corpuscles is most important. In the blood there are found very small corpuscles (microcytes) and distended spherical forms (spherocytes) which are perhaps such as can be produced by exposing normal corpuscles to a hypotonic solution. The anaemia is marked and causes great activity of the bone-marrow. Apparently the essential of the process is the destruction of the fragile corpuscles in the spleen, setting free abundant material for the formation of bile-pigment which in excess stains the tissues and the faeces, but is not present in the urine so that it is often called acholuric jaundice. Whether this is entirely the result of the fragility of the blood cells is questionable since removal of the spleen promptly cures the condition although the fragility remains. The excess of bile-pig-

ment is doubtless concerned in the cholelithiasis which so frequently accompanies this condition, but there are also bone changes, ulcers in the skin and other complications. Deformities in the skull ("Turmschädel"), due to early closure of the coronary sutures with anomalies of the face and some evidences of genital infantilism, further confirm the idea that this inherited disease is transmitted as a dominant Mendelian character.

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## CHAPTER XLVIII

### EFFECTS OF INJURIES TO THE BLOOD AND BLOOD-FORMING ORGANS (Continued)

*Leucocytosis; leucopenia. Lymphocytosis; eosinophilia. Agranulocytosis.*

*Diseases of blood-forming organs with corresponding changes in blood. General characters; attempt at classification. Chronic and acute lymphoid leukæmia. Mikulicz's disease. Recent studies of aetiology. Infectious mononucleosis. Leucosarcoma and chloroma. Lymphoid myeloma. Lymphosarcoma.*

THE blood-forming organs respond promptly in the production of white corpuscles when the occasion demands it, just as they do in the case of red corpuscles. But in this case the causes of their activity are different and it is toward the flooding of the blood with abnormally great numbers of these white corpuscles that their efforts tend, rather than to the mere replacement of those which have been destroyed in the circulation.

The appearance of an excessive number of white corpuscles in the circulation is called hyperleucocytosis, commonly shortened to *leucocytosis*, while their decrease is known as *leucopenia*. So specific are the different types of white cell of the blood that each may separately be thus affected, and it is necessary, in order to understand the nature of the change, to know not only how many white cells are present in each cubic millimetre of the blood, but in what proportion the different cells are present. Through common use the far more frequent excess in the absolute number of polymorphonuclear neutrophile leucocytes has come to be spoken of loosely as "*leucocytosis*" *par excellence*. But the terms lymphocytosis, eosinophilia, myelocytosis, etc., are also used to express the predominant increase in the corresponding cells, and these terms may be properly used even though the total number of leucocytes is not increased. In the following we shall use the term leucocyte to refer to any of the circulating white cells of the blood, specifying in each case the particular type meant. The details of the changes in the relative proportions and absolute numbers of leucocytes must be studied in the special works on the clinical examination of the blood, and only an outline shall be given here in connection with the description of the changes in the blood-forming tissues.

#### LEUCOCYTOSIS AND LEUCOPENIA

*Neutrophile leucocytosis* is the common outpouring of polymorphonuclear neutrophiles into the blood, so familiar in almost every sort of acute inflammatory process. These cells have to a great extent the function of attacking and engulfing bacteria and other injurious substances and of producing a proteolytic ferment which acts best in an alkaline medium. They appear in increased numbers in the course of

digestion, after the use of certain drugs (quinine, etc.), after haemorrhage, during some forms of toxic injury to the tissues, but especially and in greatest abundance as a response to the invasion of bacteria. Thus in pneumonia, endocarditis, septic infection, and in nearly every sort of acute inflammatory process, the neutrophile leucocytes rise in number until the white corpuscle count reaches 20,000 to 30,000 or 40,000, or in some cases as much as 150,000, per c.mm. In such cases the other leucocytes are not correspondingly increased, and the neutrophile cells assume a proportion of 98 or 99 per cent. There are notable exceptions to this in the case of typhoid fever, measles, tuberculosis, and protozoan infections, such as malaria, in which the leucocyte count does not rise, or in the case of trichiniasis and allied parasitic infections in which the eosinophile cells are especially increased.

*Lymphocytosis.*—The lymphocytes are relatively and sometimes absolutely increased in number in typhoid fever and several other infections, and the important work of Murphy\* has apparently shown that their presence is really of the very greatest value in antagonizing such infections. Animals deprived of their lymphocytes by exposure to  $\alpha$ -rays, etc., are much more susceptible to tuberculosis than normal animals, and the zone of lymphocytes which is so constantly found gathered about growing tumors is evidently of great importance, for in animals without lymphocytes implanted tumors grow rapidly, although they are destroyed in the controls. Hence we must assume that the so-called round-cell infiltration which is so striking a feature of the late stage of an inflammatory reaction and predominant in the more chronic forms, is an expression of the ability of the lymphocytes to act in the process of warding off and annulling injuries. Relative lymphocytosis occurs not only in typhoid fever but in malaria, small-pox, exophthalmic goitre, and in many affections of childhood.

*Eosinophilia* has been mentioned as occurring in trichiniasis, unciniariasis, and other infections with parasitic worms, in asthma, in various skin diseases, in scarlet fever, etc. Other cells, such as myelocytes, myeloblasts, and mast-cells are found at times in the circulating blood but usually only in connection with leukaemias, except in certain severe infections in which myelocytes are swept into the blood in the wake of the leucocytes.

The changes in the blood-forming organs in these states of the blood are not as satisfactorily studied as one could wish. Descriptions of the spleen and bone-marrow are particularly meagre except in a few instances.

In neutrophile leucocytosis there is a strong hyperplastic reaction in the bone-marrow, which naturally consists essentially in a great new production of neutrophile myelocytes, which leads to the formation of the leucocytes. As a rule, the leucocytes are discharged so rapidly that the myelocytes become the most prominent feature of the bone-marrow section (Fig. 487). Undoubtedly the spleen is deeply affected in this process and commonly assumes the peculiar softness and richness in cells which has already been described as the acute splenic tumor of

\* Murphy and Ellis: Jour. Exp. Med., 1914, xx, 397.

infectious or septic diseases. It appears that in such spleens there is a great increase in the characteristic cells of the pulp combined with an accumulation of the débris of cells, and phagocytes loaded with such fragments. The lymph-glands and lymphoid tissues are not necessarily much affected except by local conditions in which they take up the products of inflammation.

The cause of the changes in the bone-marrow in inflammatory leucocytosis has been much discussed. It is evident that the appearance of such great numbers of leucocytes must depend upon the ability of the

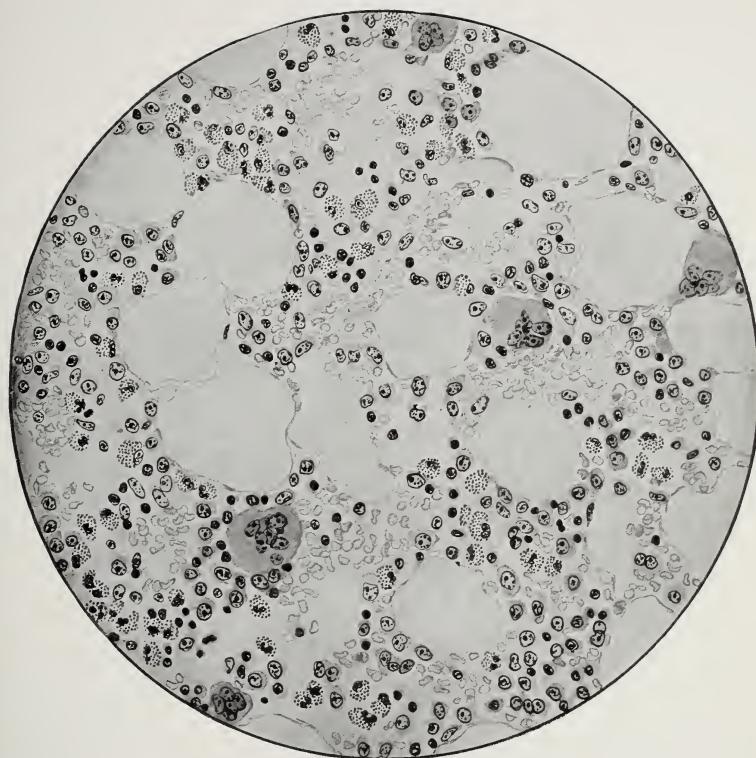


Fig. 487.—Bone-marrow from a case of staphylococcus septicæmia with leucocytosis. Myelocytes are abundant, but there are few leucocytes in the marrow.

bone-marrow to produce them rapidly. The idea that the leucocytosis is a response to the need caused by the destruction of many of their number is scarcely different from the idea that they are drawn to the general circulation and thence to the site of the inflammation by a chemotactic substance which itself gains entrance into the circulation. That some such chemical stimulant must not only attract the leucocytes but also stir the bone-marrow to increased formation of these cells seems to be clearly shown by the extremely rapid and ready increase which takes place in infections as contrasted with the much less striking

leucocytosis which appears after a severe haemorrhage, that is, after the actual mechanical removal of the leucocytes. It is most important to realize the fact that an extremely violent poisoning, such as occurs in many severe infections, may not be followed by any leucocytosis. On the contrary, the bone-marrow seems to be so injured by the strong stimulus as to be incapable of producing the cells. It is probably exactly the same thing on a somewhat different plane when, in a debilitated old person, there is no leucocytosis in pneumonia or other infection, for then a degree of poisoning which might be readily met by a leucocytosis

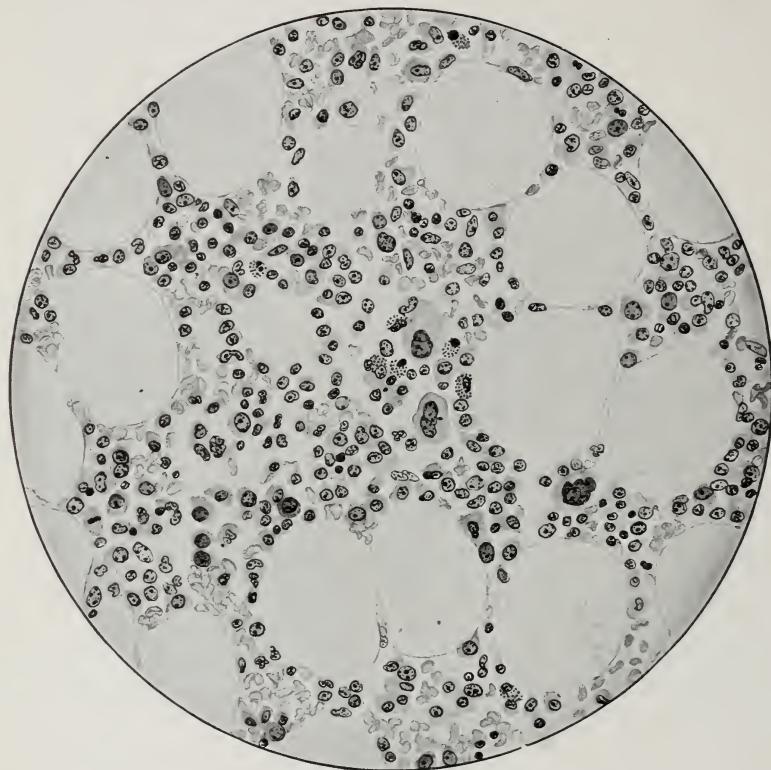


Fig. 488.—Bone-marrow in typhoid fever.

in a young and strong person is sufficient to paralyze the feebly reacting bone-marrow of the old man. Clearly then the prognosis in any infection may be judged to some extent by the efficiency of the leucocytic response; when there is a failure on the part of the bone-marrow to produce abundant leucocytes the disease is likely to prove fatal.

In *lymphocytosis* of infectious diseases the spleen and lymph-nodes are usually enlarged, but this enlargement is generally due to local causes, as in typhoid fever, and not especially to their participation in the production of lymphocytes, although the lymphoid tissue is undoubtedly active in this way. In the bone-marrow there is very definite

hyperplasia and the bone-marrow of the femur becomes red or grayish-red and cellular. Here, however, the new formation of myelocytes and neutrophile cells is found to have sunken to a relatively far less important position. It is true that the typhoid marrow still shows numerous myelocytes, but the striking feature, as Longcope has shown, is the relatively abundant new formation of lymphoid cells there. A comparison of Figs. 487 and 488 will show this. In typhoid fever the myelocytes seem unable to respond to such stimuli as usually produce neutrophile leucocytosis. The advent of pneumonia or other similar infection in the course of the disease does not necessarily bring out the corresponding leucocytosis, and, indeed, those things which usually produce an abscess have failed to do so in a person sick with typhoid fever, although the occurrence of furunculosis with typhoid fever is familiar. This, however, comes on in a late stage and corresponds with the experiment of Bauer who could produce no abscess by injecting turpentine subcutaneously during the height of the typhoid fever, although when the fever disappeared in convalescence the belated abscess appeared at the site of the injection.

In *eosinophilia* there is a relative and absolute increase in the eosinophile myelocytes of the bone-marrow. This statement is made without hesitation since it has been shown experimentally by Opie to be so, although there are as yet no conclusive reports as to the appearance of the bone-marrow in human beings in those infections (trichiniasis, etc.) in which the eosinophiles are so abundant in the blood. With regard to the analogous conditions in leukaemia we shall speak presently.

*Agranulocytosis—Agranulocytic Angina*.—Schultz, in 1922, recognized a condition in which patients developed an intense pharyngitis, tonsillitis and laryngitis with evidences of general infection and upon examination of their blood the polymorphonuclear neutrophiles were found greatly decreased in number or practically absent. The history of this affection which he called agranulocytic angina, is interesting since many cases were reported from that time up to 1934 with much speculation as to the cause. It was realized that the myeloid tissue of the bone-marrow had somehow ceased to function satisfactorily and the idea developed that there was for some reason a defect in the maturation of the myelocytes, together with a failure in the passage of leucocytes into the circulation. Naturally the effect of this was recognized as an ominous failure in the defensive mechanism which explained the fatal outcome in such infections as followed. Hamburger, Roberts and Kracke and others in this country, and Brogsitter and Kress in Germany, studied the condition and the pentnucleotide therapy suggested by Reznikoff, in 1930, was tried. In 1934 there suddenly appeared a great many papers calling attention to the fact that these patients had been taking one or other of the more recently developed drugs to alleviate pain and among these amidopyrine, pyramidon, antipyrine, and allonal, all closely related substances chemically, were most frequently recorded. Several authors, Sturgis and Isaacs, and others, proved the activity of amidopyrine by giving small doses to patients who had recovered from the severe condition following its habitual use. Combinations with the

barbital group were suspected but it appears (Madison and Squier) that the barbiturates alone have no such effect. Other substances have been inculpated also, especially dinitrophenol and neoarsphenamine, and some gold compounds such as solganol. Kracke and Parker feel that in the case of such drugs as amidopyrine, allonal, dinitrophenol and solganol, the harmful end-product resulting from oxidation is quinone. It seems that it is impossible at the present to feel sure as to the precise portion of these various compounds that is actively harmful. Further, it is evident that there is some kind of idiosyncrasy involved, for it is only in certain persons that the destructive effects have been observed, although it is obvious that thousands of people are habitually swallowing tablets of one or other of these drugs. The exact nature of this sensitiveness of the blood-forming tissues remains to be studied but the gross effects of the granulopenia, as some prefer to call it, is a defenseless state which allows the rapid spread of a fatal infection of some sort which would be easily repelled by a normal person.

The rôle of endocrine disturbances thought by some writers to be responsible, demands further study.

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#### DISEASES OF THE BLOOD-FORMING ORGANS

We approach in this section a series of extraordinary affections involving the blood-forming organs, and consequently the blood, in which the morphological changes from normal are very minutely studied, but in no single one of which we know anything of the cause. We do not even know whether they should be grouped together. The study of these diseases is made more difficult by the fact that while there are type forms which are fairly distinct, one meets with many individual cases in which there are wide variations from these types or even transitional forms. They are affections of the lymphoid tissue, on the one hand, or of myeloid tissue on the other, and such is the specific distinction between these tissues that we find no mixture of the two. They are essentially hyperplasias of the blood-forming tissues, and while in some cases this does not involve any striking change in the circulating blood, in others such quantities of new cells are emptied into

the blood-stream as to be completely subversive of its ordinary composition.\* Perhaps this should not be regarded as a distinction of importance between these cases, because it is said to happen that in some forms the blood, after having been normal through a long period in which disease of the myeloid or lymphoid tissue was well developed, may suddenly be flooded with an excessive number of cells representing the particular hyperplastic element. Such cases, however, are rare, although great modifications in the quantity of cells poured into the blood occur from time to time in those in which the blood shows distinct changes. It is probably correctly claimed that the classification of such diseases should be based not upon the number of cells swept into the blood, but upon their character and, therefore, upon the character of the hyperplasia in the blood-forming organ concerned. Still, the setting free of the cells or their retention in the place of their formation is so nearly constant a feature of each form that we must assume that there is something peculiar about the way these cells are held together in the tissue, which brings about these different results. It is difficult, if not impossible, to see in the sections of bone-marrow or lymphoid tissue anything which in one case would make the escape of cells impossible, in another facilitate it; but perhaps with finer technique this may be discerned.

There may be a qualitative change in the white cells of the blood without any increase in their number, such as to suggest the existence of changes in the lymphoid or myeloid tissues characteristic of leukæmia. The term "aleukæmic leukæmia," often used to mean this, is awkward and contradictory, and it would be preferable to speak of "aleukæmic lymphadenosis" or "myelosis."

In some types it appears that the hyperplasia of one sort of cell occurs strictly within the normal limits of the myeloid or lymphoid tissue, as the case may be, even though these cells may escape into the blood. In others the hyperplastic tissue extends like a tumor, so as to invade and destroy adjacent tissue, even breaking through the cortex of the bone or spreading far and wide from the normal limits of the lymphoid tissue. On account of this many authors have looked upon these hyperplasias as tumor growths. Indeed, even when there is no obvious tumor, but great quantities of cells are found circulating in the blood, it seems that these cells may form colonies in other organs and there give rise to new cells of the same sort. This is the point in dispute in the question of myeloid metaplasia, other investigators holding that such colonies of cells are formed *in situ* by a true metaplasia, and not derived from the usual site of their formation in the blood-forming organs. The question is hard to settle satisfactorily, but in the one case the new formation of cells in an unaccustomed organ, such as the liver, would resemble the mode of distribution and proliferation of a tumor;

\* Leukæmia or leucocythaemia, was first observed almost simultaneously by Bennet in Scotland and by Virchow in Germany (1848). Virchow recognized the lymphoid nature of the cells in one type and their granular character in the other, and called them lymphatic and lienal forms. Neumann first pointed out the importance of the bone-marrow in their production.

in the other we must assume that the tissues of the capillary walls of the liver, the splenic pulp, etc., are capable of reacquiring the power of blood-formation which, as all agree, they possessed during embryonic life. To me the idea of the transplantation and growth of cells seems more plausible, although there is some good evidence in favor of the idea of metaplasia.

It appears, then, that if we know accurately all the cellular types existent in the bone-marrow and in the lymphoid tissue, which are the blood-forming tissues concerned, and if we assume that each is capable of undergoing an independent hyperplasia, we should be able to construct a tabulation of all the possible diseases arising in this way. This has indeed been done, just as it was possible for Rokitansky to foretell what types of malformation of the heart might occur on the basis of the embryological development of that organ, and then years later to meet with cases, hitherto unknown, which realized each member in his scheme. The possible existence of unknown tumors has been foretold in the same way on a histogenetic basis.

Sternberg has made such a table, but I should prefer another division, perhaps equally open to criticism, but separating as the main groups the affections of the lymphoid from those of the myeloid tissue.

*A—Hyperplasia of lymphoid tissues:*

*a—With leukæmic blood—*

- (1)—with swelling of lymphoid tissue and lymphoid infiltration of organs.....*Chronic lymphoid leukæmia;*  
*Acute lymphoid leukæmia.*
- (2)—with tumors originating in various situations and invading tissues.....*Leucosarcoma; Chloroleucosarcoma (Chloroma).*

*b—Without leukæmic blood—*

- (3)—with tumors involving bone-marrow.....*Lymphoid or plasma-cell myeloma.*
- (4)—with general swelling of lymphoid tissue.....*Pseudoleukæmia, aleukæmic lymphadenosis.*
- (5)—with regional invasive tumor-like growth.....*Lymphosarcoma.*
- (6)—with stigmata of general maldevelopment.....*Status lymphaticus.*

*B—Hyperplasia of myeloid tissue:*

*a—With leukæmic blood—*

- (7)—with myeloid infiltration of organs.....*Myeloid leukæmia; Myeloblastic leukæmia.*
- (8)—with tumors of the myeloid tissue.....*Chloromyelosarcoma (Myeloid chloroma).*

*b—Without leukæmic blood—*

- (9)—with tumors of the myeloid tissue.....*Myeloid myeloma.*

**Chronic Lymphoid Leukæmia.**—The onset is insidious, with painless enlargement of some of the lymph-glands and occasionally with haemorrhages from the mucosæ. Examination of the blood shows an increase in the leucocytes without necessarily any change in the red corpuscles. Among the leucocytes the small lymphocytes occupy the important place and are proportionately greatly increased. This state may continue for years with gradually progressing anaemia, continuous intermittent increase in the number of white cells, and slow enlargement of the lymph-

nodes, spleen, and sometimes of the liver. The lymphocytes may constitute 95 or 99 per cent. of all the white cells and there may be several hundred thousand of these per c.mm. Naegeli mentions one case in which the haemoglobin was 25 per cent. and there were 621,000 leucocytes, of which 99.6 per cent. were lymphocytes with only 0.14 per cent. of neutrophiles. The symptoms are due chiefly to the presence of infiltrations of these lymphocytes in various places where they often produce pressure phenomena, and to haemorrhage. In the nervous system



Fig. 489.—Chronic lymphoid leukæmia. Infiltration about the gall-ducts and portal vessels.

and eyes destructive changes may occur in this way. Dyspnœa follows similar obstruction in the lungs, which, together with the changed character of the blood, makes aeration difficult. In the skin there are sometimes tumor-like masses. Death follows from the cachectic condition itself or from acute exacerbation or intercurrent bacterial infection.

At autopsy the *lymph-nodes* are found enlarged and converted into homogeneous masses of soft, grayish-white cellular tissue, without any marks remaining to indicate their structure. In one case which I watched for several years the axillary, inguinal, and retroperitoneal nodes finally

formed huge masses in which the separate nodes had grown to the size of apples. They were so large as to hold the arms away from the sides, but showed no tendency to invade the surrounding tissue. The tonsils and pharyngeal lymphoid tissue may become enlarged late in the disease, but this is not invariable. The intestinal lymphoid tissue is astonishingly little affected. The *spleen* is generally enlarged, although not to the maximum degree. It may still show Malpighian bodies on section sharply outlined against the grayish or brownish-red splenic pulp which is loaded with lymphoid cells. The *bone-marrow* is no longer fatty in the shaft of the long bones, but forms a solid cellular tissue of gray or grayish-red color, often with patches of dark red. The liver, which is usually rather swollen, shows grayish lines accompanying the bile-ducts and portal veins (Fig. 489). Gray infiltrations are found elsewhere too, as in the thymus, which may be markedly enlarged, or in the kidneys, adrenals, testes, etc. Following the blood-vessels in the retina are sheaths of lymphocytes with which haemorrhages are often associated.

The histological changes are all occasioned by the extraordinary over-production of lymphocytes from the lymphoid tissue, wherever that occurs, in the lymph-nodes, lymphoid apparatus of the respiratory or digestive tracts or skin, or in the bone-marrow. It is impossible, as a rule, to make out just where it started to undergo hyperplasia in these chronic cases, although there is a better opportunity in the acute cases to be described later. Naegeli makes a special point of saying that such hyperplasia cannot occur in the bone-marrow lymphoid tissue alone, but that all the lymphoid tissue is equally involved.

The cells, in most of the chronic cases, are small lymphocytes. Nevertheless, in the lymphoid tissue in which they are being formed one finds almost always a mixture of these with rather larger lymphoid cells.

In the lymph-nodes all signs of the original architecture with lymph-nodules and sinuses have disappeared, being obscured and covered in or pushed aside by the overwhelming growth of one kind of cell, so that the tissue appears as a solid, uniform mass of lymphocytes. In the spleen, at first sight, it seems that the same thing is true, as though the Malpighian bodies had spread to occupy everything, but closer examination shows that the structure of the pulp is still discernible and the venules and interspaces are found filled with lymphocytes. In the older cases, in which the spleen is hard, there is much new fibrous tissue between the venules. This was true in the very chronic case mentioned above and is shown in Fig. 490. In the bone-marrow there is usually almost complete replacement of the ordinary cells by spreading masses of lymphoid tissue, but in many cases there are areas of myeloid tissue left unchanged with erythroblastic and myeloblastic cells. These appear to be the dark red patches which are visible in the gross and are, no doubt, responsible for the relatively good maintenance of the red cell content of the blood.

**Acute Lymphoid Leukæmia.**—In our experience this is a more common affection than the chronic form, and must be distinguished from it because of its more violent and severe symptoms and rapid course, and also because the cells concerned are in most cases larger. In relatively few cases only are they of the same small size as in the chronic forms.

It must be noted here that certain of the cases which were formerly classed as acute lymphoid leukæmia are now known to be not lymphoid leukæmia at all, but myeloid leukæmia in which the non-granular myeloblast is the cell that is especially abundant, and some authors, such as Gulland, express doubt as to the existence of acute forms of lymphocytic leukæmia.

In contrast to the chronic form of lymphoid leukæmia this one begins suddenly with intense symptoms: fever, hæmorrhages from the mucosæ, and rapidly developing anæmia. Hæmorrhages in the retinæ are almost

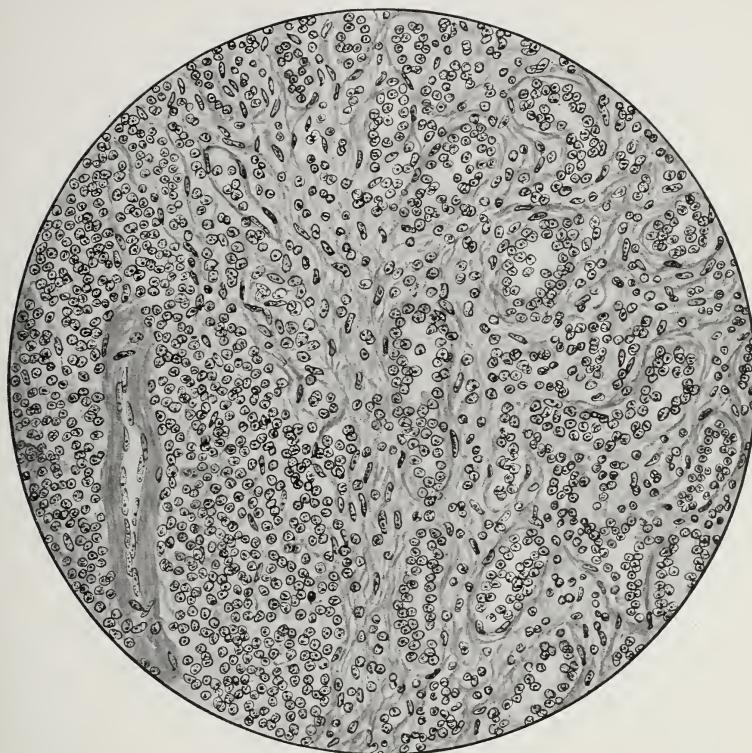


Fig. 490.—Chronic lymphoid leukæmia. Spleen showing a Malpighian body and part of the pulp in which there is much induration and infiltration with lymphoid cells.

constant, while those in the conjunctivæ, over the face and over the whole body, are often very extensive and gradually pass through the ordinary changes of color to become pigment spots that finally disappear. The hæmorrhages in the mouth, vagina, and digestive tract often become converted into gangrenous areas which leave deep ulcers. The tonsils and the rest of the pharyngeal adenoid tissue frequently become greatly enlarged and deeply ulcerated. The *lymph-nodes* may, in some cases, even in a rather advanced stage, be relatively slightly enlarged, but usually they are palpable or even form prominent packets. In a case now under

observation what seems to be the thymus has become greatly enlarged in the course of a few days. A radiograph reveals the fact, however, that this is a retrosternal mass of lymph-glands. The spleen is generally enlarged but does not reach as a rule the huge dimensions seen in some other forms. The blood in some instances shows no decrease in red corpuscles but usually the anaemia advances rapidly and in the case mentioned is already under 1,000,000. Occasionally such blood shows regenerative forms resembling those of pernicious anaemia, but often there

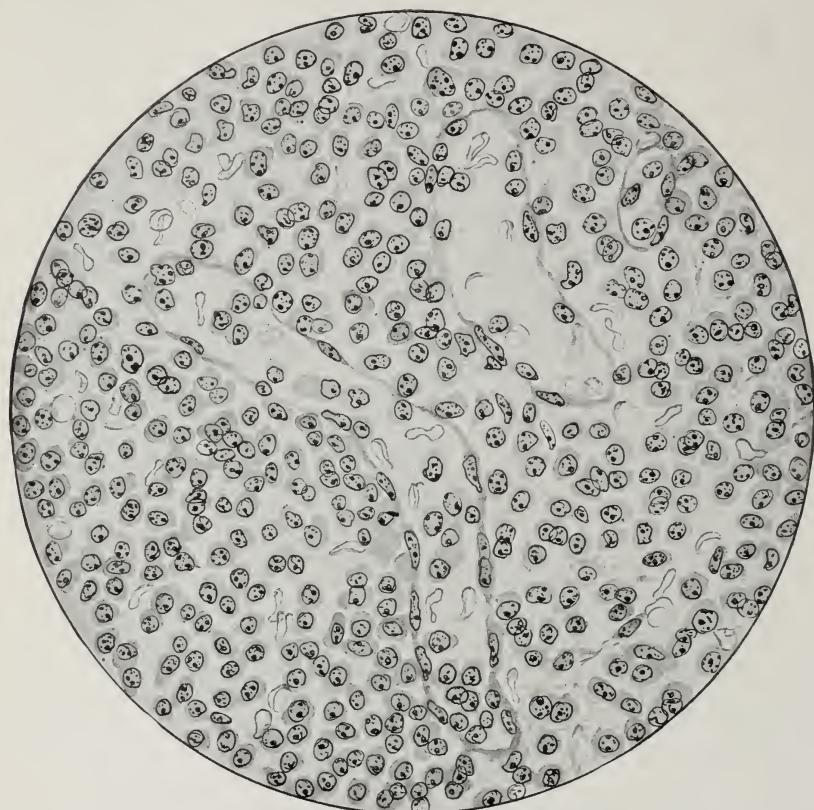


Fig. 491.—Splenic pulp in acute lymphoid leukaemia. The cells of the pulp are practically entirely replaced by large lymphoid cells.

seems to be no attempt at regeneration. The leucocytes reach high numbers, ranging from 50,000 to 250,000 or more, and the increase is represented by the lymphocytes, which may constitute 98 or 99 per cent. of the cells. As stated above, these lymphocytes are in most cases larger than those of normal blood. Death results from a terminal infection, from haemorrhage, or from the disease itself.

At autopsy the lesions are found to resemble those of the chronic form except that since the course of the disease is so much briefer, there is not time for the development of such great accumulations of lymphoid

tissue. The lymph-glands are nevertheless enlarged, and show on section a homogeneous, grayish-white cellular tissue rather softer than that found in the chronic cases. The presence of haemorrhages in these glands is very characteristic. Microscopically one may find the architecture still recognizable, although the sinuses contain great quantities of lymphocytes. Occasionally, however, the whole structure appears as a mass of lymphoid cells. There are usually similar changes in the adenoid tissues of the throat, and sometimes in those of the digestive tract, so that swellings comparable to those in typhoid fever are found in the solitary nodules and Peyer's patches. Since, with haemorrhages, these may become ulcerated, the resemblance may be close.

The spleen may be moderately enlarged and fairly firm, dark grayish-red, sometimes with conspicuous infarctions. Microscopically the splenic pulp is packed with the large lymphoid cells (Fig. 491), but usually these are so different in appearance from those of the lymphoid tissues that the Malpighian bodies stand out sharply (Fig. 492).

It is noteworthy that in this, as in other forms of leukæmia, the endothelium of the venules of the spleen to which so many functions have been ascribed is perfectly intact and shows no evidence of playing any part in the extraordinary changes going on round about.

In the bone-marrow (Fig. 493), which is gray or grayish-red and cellular, often with red, gelatinous patches, the conditions vary. Usually practically all the myeloid elements are crowded out of existence, except perhaps in the red patches just mentioned, by the great compact swarms of lymphoid cells. Naegeli is very dogmatic in stating that there are, and can be, no cases in which this process begins in the bone-marrow alone—that it is essentially a systemic disease affecting all the lymphoid tissue. Nevertheless, in one such case reported by Dr. Reed we found the lymphoid tissue throughout the body entirely unaffected except that, in the manner of a sieve, it had retained many of the circulating lymphocytes in its vessels. The bone-marrow was practically entirely composed of lymphocytes. Ehrlich, in studying the preparations from that case, expressed his opinion (1902) that such a leukæmia might originate from any substratum of lymphoid tissue, such as that in the skin, in the intestinal wall, or in the bone-marrow. The other changes are the effects of infiltration and localization of large quantities of lymphocytes in the organs. In the liver this deposit does not, in the brief span of the disease, reach macroscopical dimensions, but in the kidneys there have been cases in which such quantities of cells have gathered in the interstices as to enlarge the organ greatly and give it the appearance of a huge white kidney. In the nervous system and retinae similar accumulations accompanied by haemorrhages cause functional and anatomical disturbances. It is important to note that in neither of the forms of lymphoid leukæmia do the circulating lymphoid cells, or the cells of this sort in the tissues, give the oxydase reaction which is shown by Schultz to be characteristic of the myeloid cells. Nor, according to Longcope, are they capable of producing a proteolytic ferment. The contrast in the case of other forms of leukæmia, to be described later, is very striking.

There is another condition essentially like an acute or subacute lymphoid leukæmia in which tumor-like swelling of the salivary glands and of the lachrymal glands is very conspicuous. This is the so-called *Mikulicz's disease*, named for the distinguished Breslau surgeon who described it. We studied such a case at autopsy recently and found all the salivary glands and the lachrymal glands greatly enlarged and converted into masses of lymphoid cells in which the gland elements were widely separated.



Fig. 492.—Spleen in acute lymphoid leukæmia. The splenic pulp and blood vessels are filled with large lymphoid cells contrasting with the lymphocytes of the Malpighian bodies.

It has been shown by Ellermann and Bang that leukæmia occurring in chickens can be transmitted to normal fowls by injection of emulsions of the organs, or the blood of the leukæmic chicken or even by Berkefeld filtrates of this blood. That strain of the causative agent was studied by several others but Schmeisser in this laboratory had the same results with a new strain and more recently Furth and his associates, and MacDowell and others, have carried on the work much further. The types of leukæmia vary, showing in some cases lymphocytes, in others myeloid cells. Furth with one strain from a so-called leucosis in chickens, and, indeed, with a filtrate passed through a Berkefeld N filter so that there

were no viable cells, could produce leukæmia with various localizations in the tissues. These were myeloid leucoses or erythroleucoses but not lymphoid leucoses. Oberling and Guerin, beginning with the Rous tumor of chickens, produced leukæmia with the tumor growth but in some cases after many transfers the fowl developed only leukæmia. Inoculation of such blood, however, in further transfers produced sarcoma-like tumors. The question arises, since Furth also produced tumors by inoculating leukæmic blood or the filtrate, as to the aetiological relation of leukæmia to tumor growths. No further study of what to them seems to be a virus has really established its nature but MacDowell and his associates.



Fig. 493.—Bone-marrow in acute lymphoid leukæmia.

have been able to produce a degree of immunity in mice against a transplantable leukæmia. Furth has also studied leukæmia in mice and speaks of malignant lymphocytes which can produce lymphomatosis or tumor-like masses of lymphoid cells, but only when viable cells are injected. He thinks these cells are not lymphoblasts but pathological malignant lymphocytes which multiply with the same characters which enable them to invade and produce tumors and to transmit the disease to other mice. Later, a transmissible strain of myeloid leukæmia in mice could be inoculated by injecting live cells into the circulation—when injected subcutaneously or intraperitoneally it produced a tumor of basophilic myelocytes.

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**Infectious Mononucleosis.**—This condition, the so-called glandular fever of Pfeiffer, Türck, Marchand and others, has been extensively studied in recent years without even yet any recognition of its cause. In the early stages there may be difficulty in distinguishing it from acute lymphatic leukæmia but it is an affection of short duration and ends in complete recovery. The name infectious mononucleosis was given by Sprunt and F. A. Evans who described it as an acute febrile illness with enlargement of the cervical and other lymph-nodes and the spleen. There is a great increase in the lymphoid cells of the blood so that they may form 90 per cent of all the white cells which may reach as high a count as 30,000 per c.mm. Tidy, in an excellent review, speaks of it as an acute infectious disease with fever, severe inflammation of the mucosa of the upper respiratory tract, glandular enlargement and mononucleosis. It is most frequent in children and young adults and he divides it into three types, the glandular or Pfeiffer type; the anginal form, and the febrile type with the maculopapular rash. The cells in the blood are somewhat variable but usually they are large atypical basophilic lymphocytes with nuclei which have a coarse chromatin pattern unlike the delicate structure of the nuclei of immature lymphocytes or lymphoblasts. These cells do not give the oxydase reaction. In the lymph-nodes they are massed in great quantities with much proliferation of large pale cells which are regarded as reticulo-endothelial. The fever, enlargement of the nodes and the changes in the blood persist for ten to twenty days after which the whole condition gradually returns to normal. Much interest has been aroused by the diagnostic test of Paul and Bunnell who found that during the illness the blood contains heterophile antibodies which agglutinate the red corpuscles of the sheep. No good explanation of this extraordinary phenomenon is offered, and although the disease is very obviously of infectious nature, nothing has been learned as to its cause.

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**Leucosarcoma or Chloroleucosarcoma.**—This term, introduced by Sternberg, is meant to designate those cases in which a definite, tumor-like

mass is developed in some organ or tissue, and is composed of lymphoid cells which seem to escape into the blood-stream, giving rise to leukæmic alterations of the blood. Naegeli and others refuse to recognize this as anything distinct from lymphoid leukæmia, in which, as they say, there may be extensive tumor-like infiltrations of the tissues. Sternberg, who finds the tumors in the dura mater, in the mediastinum, in the breast or in connection with the tissues of the orbit, denies that such growths occur in ordinary leukæmia, and brings forward the cases studied by Paltauf and by Buschke and Hirschfeld in which the tumor was well developed before any changes occurred in the blood. Several cases which

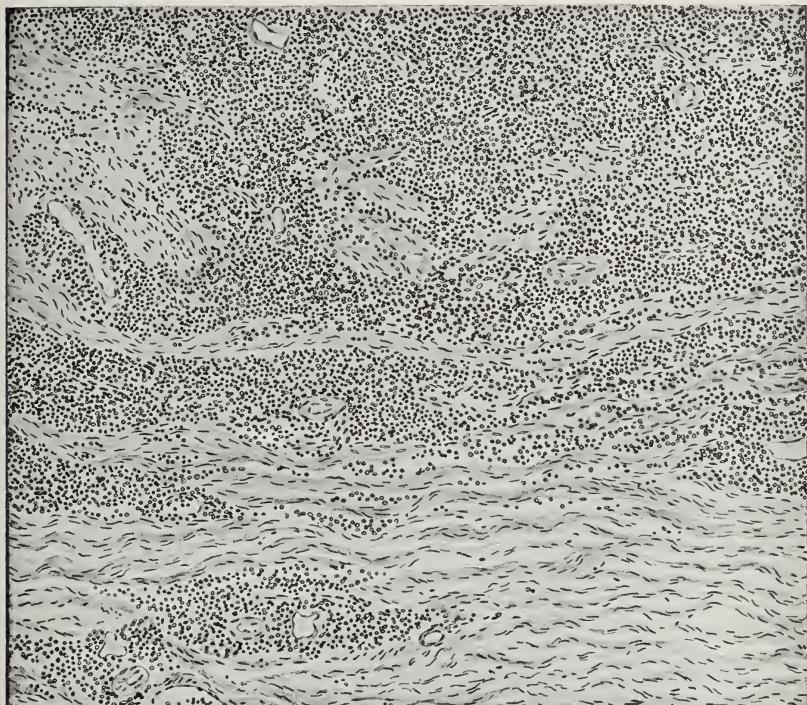


Fig. 494.—Leucosarcoma. Tumor-like nodule in the substance of the cervix uteri. This was associated with lymphoid leukæmia.

we have studied, even though this very point was neglected, have seemed to me to occupy so distinct a position and to begin so definitely with the formation of a localized tumor-like mass that I am inclined to accept Sternberg's nomenclature. In one of these cases there were two circumscribed "lymphomatous" nodules in the breast, which were removed by the surgeon. It was only after their removal that examination of the blood was made and revealed the presence of 250,000 lymphocytes per c.mm. Another case showed a lymphoid nodule in the cervix uteri (Fig. 494) extending to the vagina, with ulceration and bleeding. It was at first thought to be a carcinoma, but the autopsy revealed areas of in-

filtration of lymphoid cells in many of the organs in association with the leukæmic condition of the blood. The cells in this form also fail to show the oxydase reaction.

Intimately related to this, if not identical with it, is one of the forms of *chloroma*, so named for the green color which the tumor-like nodules show when first exposed at autopsy. There are two sorts of chloroma, one composed of large lymphoid cells, the other of myeloid cells. The lymphoid type differs in no important particular from the leucosarcoma except in its green color, and perhaps in its arising usually in connection with the periosteum, and especially with that of the bones of the face and head. The green color is inconstant, failing in some parts of the same nodule, and is not to be regarded as sufficient basis for the separation of these cases; hence Sternberg classifies them as chloroleucosarcoma. No good explanation of the jade green color has been found, and efforts at the isolation of the pigment have failed, perhaps partly because it fades very quickly on exposure and disappears. The myeloid form is named by Sternberg on the same basis chloromyelosarcoma; it will be referred to later.

**Lymphoid or Plasma-cell Myeloma.**—A myeloma is a growth springing up in the bone-marrow and evidently occurring as a systemic affection of the marrow-cells, since it appears simultaneously in many bones and nowhere else. Unless we assume the existence of cells which can grow only in bone-marrow, it is hard to imagine such wide-spread multiple growths as due to transportation of cells. There are again two kinds, this one composed of lymphoid cells, and another, to be described later, composed of myeloid cells. In their biological behavior they are almost exactly alike. The lymphoid myeloma is gray or reddish gray on section, while the myeloid form is deep red and soft, but both encroach upon the cortex of the bone and erode it, causing fractures at such weakened spots. In both types there occurs in the urine a peculiar albumose (Bence-Jones protein), the mode of formation of which is much debated. In neither form is there any constant or characteristic alteration of the blood in the sense of a leukæmic flooding with lymphoid or myeloid cells, but in one of the three cases of the lymphoid form which we have observed there were excessive numbers of large lymphoid cells with the morphology of plasma cells in the circulating blood.

In two of these cases there were prominent tumors projecting from the ribs, vertebrae, and long bones. On sawing through the bones it was found that the involvement of the marrow was far greater than could be realized from the surface. Where the tumors showed, the enlargement was partly due to lifting up of the cortex, partly to its actual erosion, and the protrusion of the tumor. There were several fractures of the weakened bones. In the third case, in which the albumosuria was absent, there were no tumors springing from the bones, but nearly all the ribs were broken and the thorax collapsed. The marrow was entirely replaced by masses of lymphoid cells, and the same was true of the marrow of the long bones where the bony cortex had become greatly thinned. There was no leukæmic change in the blood. The cells (Fig. 495) are non-granulated mononuclear cells with basophilic protoplasm, and are

very similar to the plasma-cells, with which they are regarded by most writers as identical.

**Pseudoleukæmia.**—Cohnheim employed this term to describe a case in which there was marked lymphoid hyperplasia in the lymph-glands and other lymphoid tissue, but no leukæmia; in other words, a condition identical with lymphoid leukæmia, but without the blood changes. Since that time every sort of obscure affection of the lymph-glands has been called by this name, usually in the lack of any clear idea of the nature of the case, and it has been particularly confusing in the case of Hodgkin's disease. At the 1912 meeting of the German Pathological Association in



Fig. 495.—Lymphoid myeloma. The cells closely resemble plasma-cells.

Strassburg this was made the subject of discussion. Fraenkel and Sternberg agreed that such a condition as Cohnheim described existed, and that it differed from lymphosarcoma and Hodgkin's disease, but that in some cases there arose a sublymphæmic condition of the blood or even a leukæmic condition, after which it could no longer be distinguished from leukæmia. In the long discussion which followed no one referred specifically to any case of this disease nor did any one seem familiar with it. It is unquestionably a very uncommon affection, and the instances which are referred to are usually those in which there has been clinical study only. Nevertheless, one does meet with cases in which

there is swelling of the glands which form bulky packets, enlargement of the spleen, and no blood change. If such cases at autopsy prove to be due to a true hyperplasia of lymphoid tissue without leukæmia and without invasion of the tissues, they will fulfill the definition of pseudo-leukæmia, or aleukæmic lymphadenosis.

**Lymphosarcoma.**—Kundrat was the first to give a clear description of the disease which he outlined as lymphosarcomatosis. In this he recognized a more or less wide-spread growth arising from a group of lymph-glands (more rarely from a single one) or from a tract of lymphoid tissue such as occurs in the intestinal wall, pharynx, etc. Such a growth is composed of a delicate reticulum in the meshes of which lie cells of a lymphoid character. It fails to respect the capsules of the lymph-glands but grows rapidly and invades and infiltrates adjacent tissues. Isolated

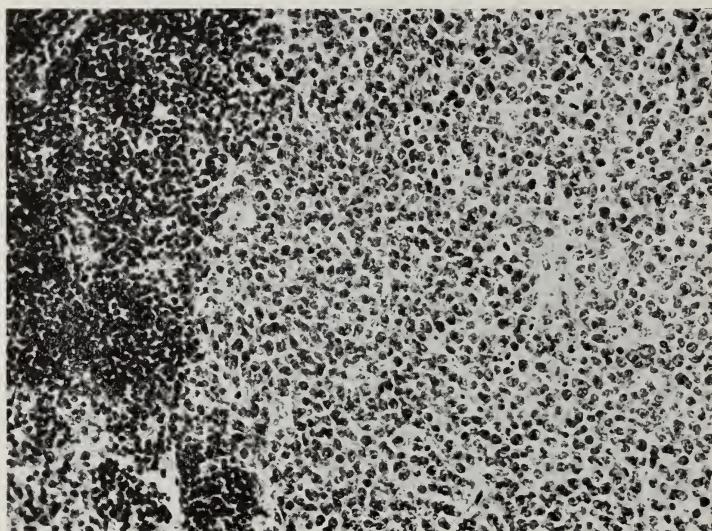


Fig. 496.—Lymphosarcoma showing contrast with smaller lymphoid cells of the invaded lymph-node.

metastases in distant organs are rare, but the adjacent lymph-glands may be involved; otherwise the growth tends to spread in loose tissue and in film or plate form over serous surfaces. Throughout, Kundrat recognized the regional character of the growth. Where the tumor appears in the form of a metastatic nodule in such organs as the heart or kidney, the sharply outlined nodule seen with the naked eye proves to be a localized infiltration of cells (Fig. 496). Eight cases which we were able to study seemed to fall into two groups. Three showed thoracic masses apparently derived from mediastinal lymph-glands and limited in their extension to the thorax, while five were equally limited to the abdominal cavity. They differed slightly in the form of the cells, which in the thoracic type were small ( $4\text{--}6 \mu$ ), while in the abdominal type they measured  $8\text{--}12 \mu$  and were associated with a few

scattered phagocytic cells of large size. The thoracic type formed great masses of solid tissue surrounding the heart and compressing the lungs. In one case these had actually penetrated the heart-wall and hung in polypoid lobules in the cavity of the right ventricle. The abdominal or intestinal type, as already mentioned, either formed great ring-shaped masses at intervals along the intestine, penetrating into its lumen and obstructing it until ulceration again opened the channel, or else they infiltrated the whole wall diffusely for a long way, and by making it rigid and inactive might have caused a so-called paralytic ileus. The intestine comes to look like a stiff piece of garden hose, and the folds of mucosa are all greatly swollen and stand up stiffly (Fig. 497). In such intestinal cases it is not uncommon to find organs such as the adrenal

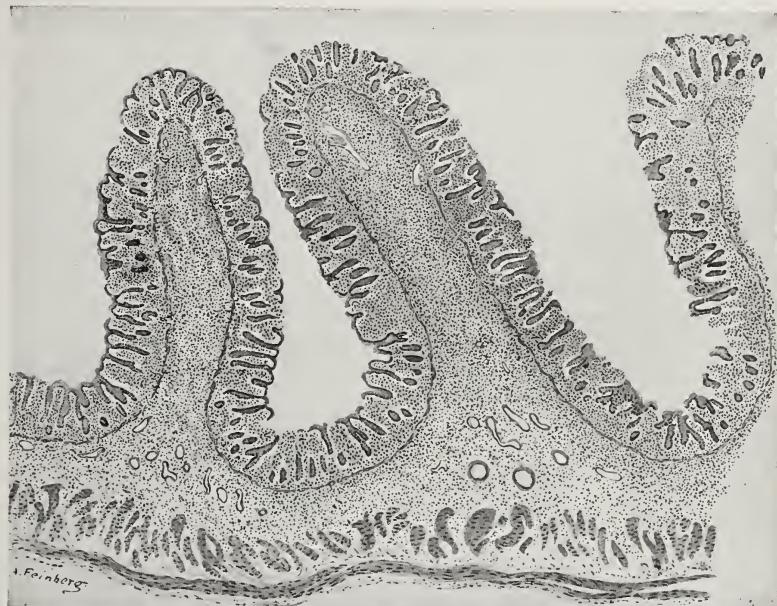


Fig. 497.—Lymphosarcoma. Infiltration of valvulae conniventes of the jejunum.

and pancreas completely buried in an infiltrating mass of the tissues. The mesenteric glands are usually greatly enlarged by a similar infiltration. The spleen shows no especial alteration in either of these types, nor do the more distant lymph-glands. It is generally stated that the bone-marrow is quite unaffected and that there are no alterations of the blood. In two of our cases there was hyperplastic bone-marrow in the long bones and there were many cells which resembled precisely those of the tumor growth, and formed solid masses of tumor tissue. Further and more modern study of the bone-marrow in such cases must be made. Lymphosarcoma arising from other groups of lymph-glands occurs as mentioned above and presents similar characteristics.

The characters which distinguish a lymphosarcoma from other conditions which resemble it in a confusing way may be best set down in a

comparative form. From a single section it would probably be impossible from a study of the cells to distinguish between an involvement of a gland by chronic lymphoid leukæmia, leucosarcoma, lymphosarcoma, and small round-cell sarcoma. In chronic leukæmia the glands become enlarged but remain discrete, there is dissemination of lymphoid cells in the capillaries of organs otherwise practically unchanged, and there is the leukæmic state of the blood. In leucosarcoma there is an invasive lymphoid tumor and there may be nodular infiltrations, but once more there is the leukæmic state of the blood. In lymphosarcoma there is an invasive or infiltrating lymphoid growth which has a peculiar regional way of spreading and is rather limited either to the thorax or the abdomen. It is much like leucosarcoma except that there is no leukæmic change of the blood. Round-cell sarcomata offer much less difficulty: they start anywhere in the connective tissue (not in the lymph-glands especially) as a single tumor nodule which invades the surroundings and metastasizes by way of the blood-stream, forming new discrete nodules in distant organs, such as the lungs, liver, etc. When they lodge in a lymph-gland they produce a solid nodule with an outline, outside which some remnant of the gland may be found unchanged. All the others cause a complete replacement of the gland, although occasionally a localized lymphosarcomatous infiltration may leave the rest of the gland intact. With round-cell sarcoma there is no leukæmia.

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## CHAPTER XLIX

### EFFECTS OF INJURIES TO THE BLOOD AND BLOOD-FORMING ORGANS (Continued)

*Chronic myeloid leukæmia. Acute myeloid or myeloblastic leukæmia. Monocytic leukæmia, myeloid chloroma, myeloid myeloma.*

#### CHRONIC MYELOID LEUKÆMIA

THE beginning of this disorder is usually gradual and unnoticed, with weakness and loss of weight, after which anaemia and slight haemorrhages appear. Many of the patients suffer no particular discomfort and show no anaemia until late in the disease, but apply for relief from a large abdominal tumor which proves to be the enormously enlarged spleen. Examination of the blood shows a very great increase in the number of white cells which are easily seen to be large granular cells. They may reach a count of over 1,000,000 per c.mm. More careful study reveals the fact that while at first the polymorphonuclear neutrophiles are still the predominant cells, there is later a great increase in the neutrophile myelocytes which usually become the most numerous cells. Eosinophile myelocytes also appear in great numbers, while eosinophile leucocytes, though absolutely increased, like the neutrophile leucocytes, do not attain to any great proportion among all the cells. Mast leucocytes with their basophile granulations and basophilic myelocytes are abundant and conspicuous. Lymphocytes are present in small numbers and form a very small proportion of the total. The appearance of such blood with its huge numbers of large granular myelocytes is most astonishing even when compared with the much altered blood of the lymphoid forms of leukæmia. In late stages, when the alterations have become most intense, non-granular myeloblasts may appear in considerable numbers. These, like the granular cells just mentioned, sometimes give the oxydase reaction although in some cases they do not. As might be expected, the blood in this condition is rich in proteolytic ferments. There may be no reduction in the red corpuscles until quite late in the disease. Then, partly as a result of the haemorrhages, their number sinks and normoblasts appear in the circulation. In some cases megaloblasts are found and the form of the red corpuscles (anisocytosis, poikilocytosis) recalls that seen in pernicious anaemia. Megalocaryocytes are sometimes found.

With the advance of the disease there often occur rather extensive haemorrhages from the mucosa or into the retinae or other organs. Death from apoplexy seems to be relatively common. Extensive necrotic and gangrenous processes sometimes appear here just as in the lymphoid cases.

There have been reported a few instances, such as those of Thompson and Ewing, Burckhardt, and others, in which such myeloid leukæmia

with predominant myelocytes in the blood has arisen acutely and quickly led to sudden death, and in these cases evidences of haemorrhage and necrotizing processes are most striking. They are mentioned here because there is another group of acute myeloid leukæmias to be discussed later in which myeloblasts form the predominant cell in the blood.

At autopsy, in cases of chronic myeloid leukæmia, the blood is found clotted in the heart and large vessels and is so peculiar in appearance that it suggested to Virchow the name leukæmia or white blood. When it clots



Fig. 498.—The spleen in chronic myeloid leukæmia.

slowly, as in the heart, the upper part of the clot is whitish or greenish and rather opalescent on account of the great number of leucocytes. In a typical case which we have studied, the clots evidently formed more rapidly for they were of a quite uniform pale chocolate color. The most striking phenomenon at autopsy is the great enlargement of the *spleen* (Fig. 498), which is smooth and firm and often deeply notched at its edge. In some cases it is adherent to the diaphragm and abdominal wall. It stretches downward toward the right and may reach the symphysis pubis, filling a great part of the abdominal cavity and appearing to rest

on the right ilium. In the case just mentioned it weighed 1550 grams but it may weigh as much as 10,000 grams. On section it is grayish-red and finely granular and opaque; the Malpighian bodies have disappeared but the trabeculae can usually be fairly clearly seen. Sometimes, however, in the later stages it is very fibrous and dense and the whole structure assumes a rather uniform appearance. Infarcts are quite common. The bone-marrow in the long bones is no longer fatty, but firm, opaque, yellowish gray or pinkish gray, and homogeneous. It can be cut out in blocks and is evidently a solid mass of cells. The liver is enlarged and rather pale, but usually without any grossly visible change in the structure. However, in the case mentioned there were several opaque grayish nodules embedded in its substance and reaching 5 to 8 mm. in diameter,

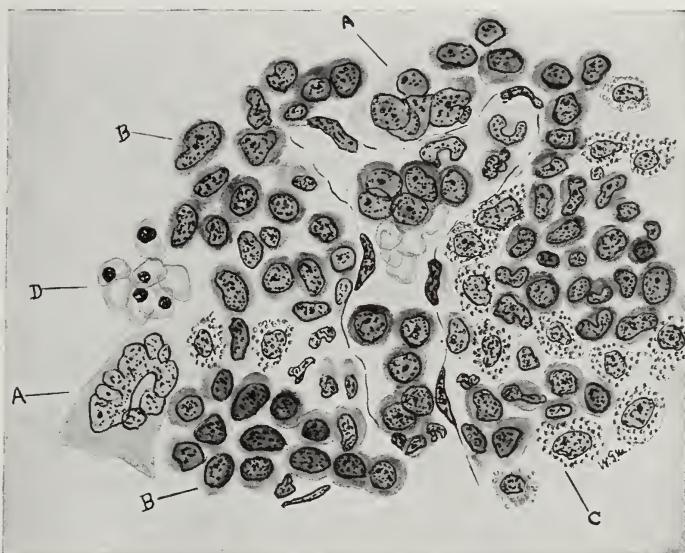


Fig. 499.—Bone-marrow in chronic myeloid leukæmia. There are very abundant neutrophile (*B*) and eosinophile (*C*) myelocytes, megakaryocytes (*A*), and a few normoblasts (*D*).

which proved to be masses of myeloid tissue. The other organs show no characteristic gross changes except the effects of the anaemia, which are seen in the general pallor of the organs and in accumulations of fat in the heart, kidneys, etc. The lymph-glands are not enlarged and with the rest of the lymphoid tissue appear to play no part in the process. Apoplectic haemorrhages in the brain have already been mentioned. Thrombosis of various veins is not uncommon. When complicating infections occur the leucocytosis which attends them may be quite normal and the reaction about the bacteria and injured tissue typical. In such cases the whole blood picture can change so that the leukæmic character disappears, and in place of the horde of myelocytes there are found the neutrophile leucocytes. Such a change does not last, however, and when the occasion for leucocytosis is over the leukæmia returns. I have not

seen such a case, but it would appear to offer an interesting field for study of the nature of leukæmia. Microscopically the *bone-marrow* is the tissue of prime interest. It appears as a solid array of cells among which the capillary vessels can be made out with some difficulty (Fig. 499). Within these vessels there are great numbers of neutrophile myelocytes, eosinophile myelocytes, leucocytes of all kinds, and red corpuscles. Outside, but evidently able to enter the blood-channels pretty easily, are masses of neutrophile myelocytes with somewhat smaller num-



Fig. 500.—Spleen in chronic myeloid leukæmia. Space between two adjacent venules, showing numerous myelocytes of neutrophile and eosinophile type. Many cells, emigrating from the venules, of which some appear to be nucleated red corpuscles.

bers of eosinophile myelocytes. Basophile myelocytes are also present in great numbers, and there are other non-granular mononuclear cells of rather large size which are probably myeloblasts. Neutrophile leucocytes are there in rather large quantities too, but there is not much to be seen of red blood-cells or of erythroblastic tissue. Normoblasts are present here and there in small groups but must be searched for. From this it seems that the progressive anaemia in this, as in other types of leukæmia, may be due to the actual crowding out of the erythroblastic

tissue rather than to the haemorrhages, which are not always very evident. In this respect it would resemble the osteosclerotic anaemia mentioned above. The spleen (Fig. 500) in this disease has almost the same composition in respect to the cells present as the bone-marrow; it resembles in an exaggerated way the myeloid spleen found in the osteosclerotic anaemia. As shown in the drawing, the venules of the splenic pulp (Malpighian bodies are almost crowded out of existence) are intact and in themselves unaffected. They are full of myelocytes and in

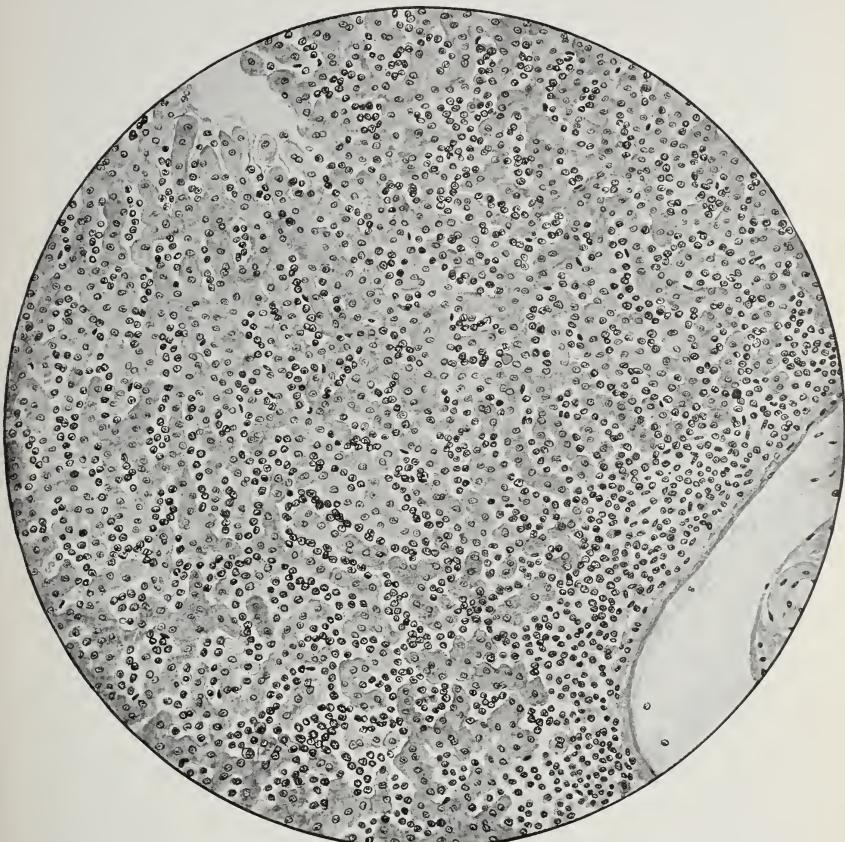


Fig. 501.—Myeloid leukæmia. General infiltration of the liver with myeloid cells.

the intervening spaces myelocytes of all kinds are crowded together with some red corpuscles and a few nucleated red cells. Myeloblasts, nucleated red cells, and even lymphocytoid cells are constantly found passing through the walls of the venules, which seem to be as open as so much mosquito netting.

In all the other organs the microscopical alterations consist essentially in the filling of the capillaries with myelocytes, etc., from the leukæmic blood (Fig. 501). In the liver the capillaries may be hugely distended with clumps and masses of these cells. It is interesting to note that

no necroses occur in the liver-cells or even among the packed myelocytes themselves. In this the myelocytes differ from the cells found distending these capillaries in typhoid fever, which seem unused to life within the vessels and in addition carry seeds of death with them. In the nodules mentioned above there are huge pools of myeloid cells and the

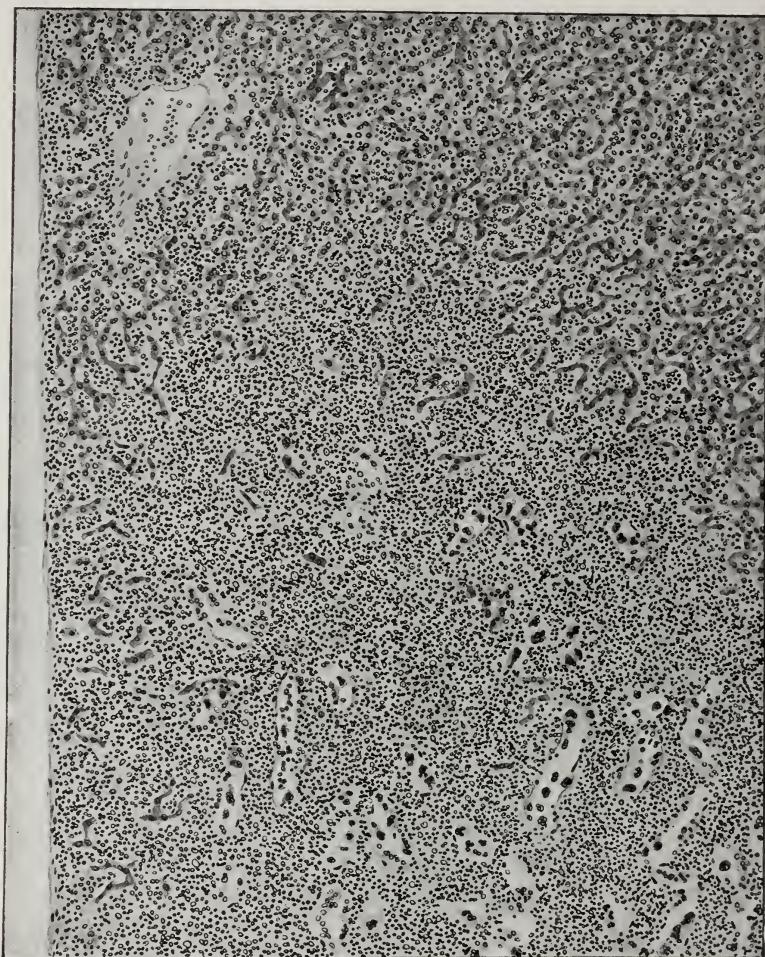


Fig. 502.—Myeloid leukaemia. Myeloid area in the liver, showing displacement of liver-cells by the abundant myelocytes, and in the endothelium-lined capillaries many megakaryocytes.

liver-cells are compressed into flattened rows or squeezed out of existence entirely. Some of the wide capillaries contain megakaryocytes in groups, and the whole area has assumed the exact appearance of bone-marrow (Fig. 502).

Other organs are also thickly infiltrated with myelocytes (Fig. 503), but, as a rule, show little of actual myeloid colonization. The lymph-

glands merely participate passively in this process—occasionally their sinuses are stuffed with the cells of the blood.

The nature of the process is quite as obscure as in the other forms, but it seems clear that the changes are primary in the bone-marrow, and that those of the spleen and other organs are secondary. Nevertheless

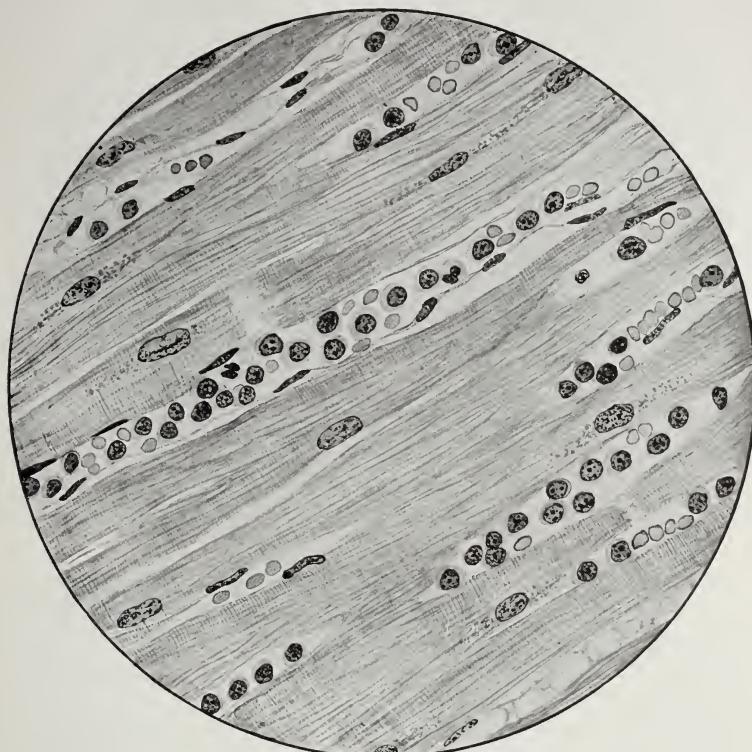


Fig. 503.—Myeloid leukæmia. Heart showing the overfilling of the capillaries with myeloid cells.

it is also pretty clear that new formation of cells goes on in the myeloid accumulations of tissue in spleen and liver, although not, it seems to me, as the result of activity on the part of splenic or hepatic endothelium.

#### ACUTE MYELOID LEUKÆMIA—MYELOBLASTIC LEUKÆMIA

We have already mentioned the existence of cases in all respects like the chronic myeloid leukæmia except that their fatal course is very rapid and marked by the occurrence of more extensive hæmorrhages and ulcerations of mucosæ. In another and larger group of these acute cases whose symptoms are not to be easily distinguished from those of acute lymphoid leukæmia, the differences lie in the fact that the non-granular mono-nuclear cells which are predominant in the blood and tissues are not lymphocytes, but myeloblasts, as shown by their possession of a proteo-

lytic ferment action in an alkaline medium and by their positive oxydase reaction, although in many cases the cells show no such oxydase re-



Fig. 504.—Acute myeloblastic leukæmia. Focal infiltrations of the kidney with haemorrhage. Great accumulation of myeloblasts with haemorrhage in the tissues of pelvis and ureter.

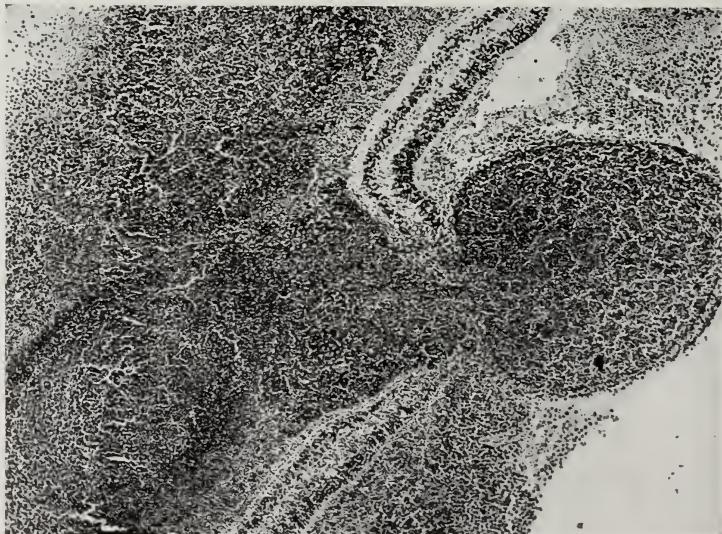


Fig. 505.—Myeloblastic leukæmia. A mass of myeloblasts lifting up and breaking through the retina.

action. In these cases there is a great overflowing of the blood with white cells, most of which are myeloblasts; the bone-marrow shows a

myeloid hyperplasia in which they are prominent, and there are myeloid changes in the spleen and liver. Hæmorrhages (Fig. 504), necrotic and ulcerative stomatitis, etc., are common. Lymph-glands may be enlarged, but commonly are not. The whole condition has the appearance of an acute infectious process, and, indeed, infections often exist, but whether as cause or as incidental accompaniment it is difficult to say. Sternberg, however, is so impressed by this that he proposes to exclude the myeloblastic leukæmia completely from the group of leukæmias and to regard it as an infectious process—the more so since it has been shown that a number of extremely severe infections can cause the appearance of huge numbers of myeloblasts or myelocytes in the circulating blood. These, however, are not progressive processes, and the myeloid cells disappear with recovery from the infection.

The question of the relation of infection to the whole group of leukæmias is one which we can hardly discuss as yet with profit. All of them have something of the character of infections, and the work of Furth and others gives promise that with a firmer knowledge of their aetiology we shall be able to make a rational classification.

### MONOCYTIC LEUKÆMIA

The character of the monocyte has been discussed in a former chapter with some reference to the differences of opinion which prevail as to its origin and identity. It was pointed out that while it seems probable that it is of the same nature as the so-called histiocytes, macrophages, reticuloendothelial cells or clasmatoctyes which are the names given to the phagocytic mononuclear wandering cells of the tissues, there are those who on account of the fine neutrophile granulations of the cytoplasm and the positive oxidase reaction, would relate it to the myeloid group. Others, such as Maximow, derive it from the lymphocyte while Doan, Sabin and Cunningham separate it from the clasmatoctye which they think is of endothelial origin and ascribe its origin to the reticular cells.

Cases have occurred in which these cells appear in great numbers in the circulating blood and are present in even greater numbers in the spleen, lymph-nodes and other tissues. In the liver and kidneys great accumulations of such monocytes appear in such a way as to compress and destroy some of the normal tissue. These cells are markedly phagocytic with faint bluish-gray cytoplasm, with fine granules and indented nuclei. The oxydase reaction is variable but in our recent cases was negative. The condition has been well discussed by Clough.

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**MYELOID CHLOROMA—CHLOROMYELOSARCOMA**

The justification for the isolation of this group is much the same as in the case of the lymphoid chloroma or chloroleucosarcoma, and the same arguments have been raised against it. The peculiar feature consists in the formation of tumor-like growths within the bone-marrow or extending through the cortex of the bone to spread over the periosteal surface. Some of them spring apparently from the periosteum. They may or may not have a bright grass-green color, and, as in the lymphoid chloroma, the inconstancy of this color makes it seem an inadequate basis of classification. The tumors allow the myeloid cells to escape in great numbers into the circulation and are thus accompanied by a leukæmic state of the blood. The bone-marrow, in Meixner's case, was partly red, partly occupied by masses of myelocytes which in the gross looked green. The lymph-glands were unaffected; the spleen much infiltrated with myelocytes.

**MYELOID MYELOMA**

In the previous chapter we spoke of multiple, rather invasive, tumor-like growths springing from the bone-marrow and composed of mono-

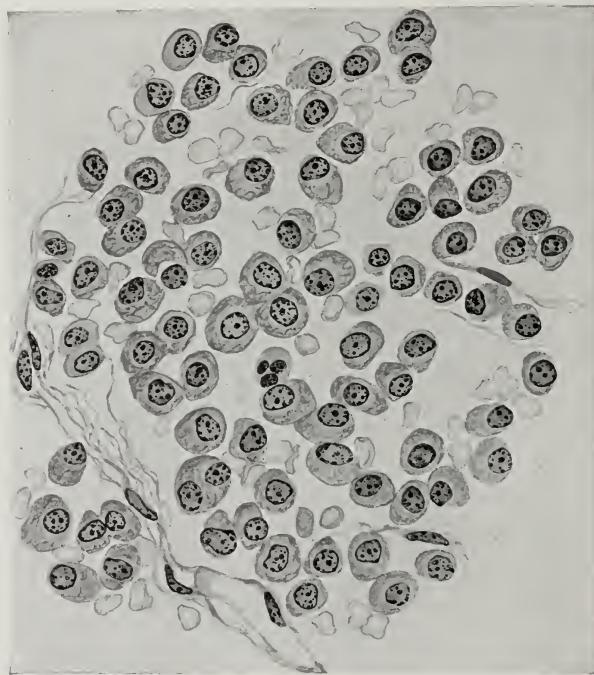


Fig. 506.—Myeloid myeloma. The cells are larger than those of the lymphoid myeloma (Fig. 495), which are drawn to the same scale. They show no definite granules, but would probably give the oxydase reaction.

nuclear cells which have been regarded as plasma cells. There are other cases, however, in which the tumors have in general the same distribution, but differ in appearance, being very soft and deep red in most parts.

They infiltrate and destroy the bones and give rise to repeated fractures. As in the other type, there is found the Bence-Jones albumose in the urine.

Boggs and Guthrie have shown that this albumose is by no means limited to cases of myeloma, and even that it may be absent in some well-defined cases of this affection. On the other hand, it is present in cases of carcinomatous invasion of the bone-marrow and in cases of chronic myeloid leukæmia. The mechanism of its production is as yet too uncertain to discuss here.

The cells which form these tumors have occasionally been demonstrated to be myelocytes or even erythroblasts (Ribbert), but in most cases they correspond with myeloblasts. In a case which I studied I thought that their identity with myeloblasts was proved (Fig. 506). It is to be hoped that in future the oxydase reaction will be applied to these cases to settle this point definitely. No leukæmic changes occur in the blood.

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## CHAPTER L

### HODGKIN'S DISEASE

*History. General character. Pathological anatomy. Efforts to discover causative agent.*

THIS common and fatal disease is set apart from everything else because it seems more like an infectious process than especially a disease of the blood-forming organs. On the other hand, its gross appearance is rather that of an invasive tumor. Since we know nothing of its cause or true nature it may be considered separately.

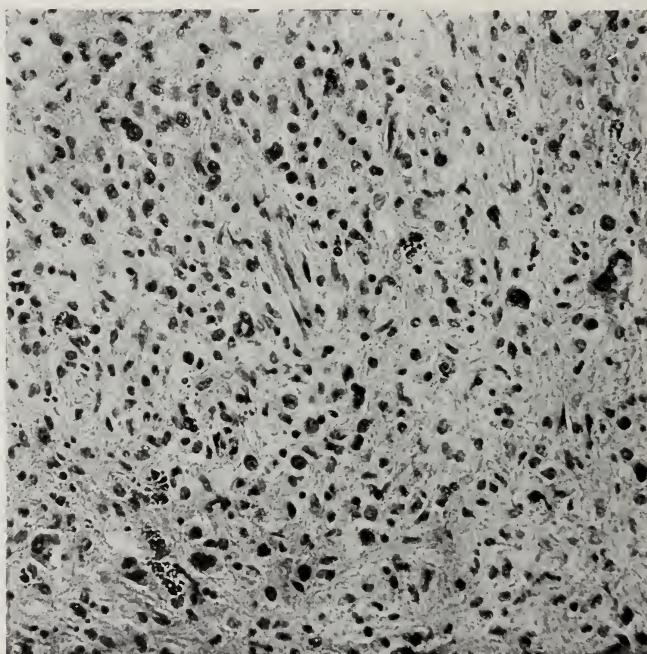


Fig. 507.—Photograph of section from one of Hodgkin's original cases. Guy's Hospital.

Described by Hodgkin together with a number of other conditions in 1832,\* much confusion existed as to the nature of the process until the work of Sternberg, Reed, LongCOPE, Ziegler, and others established the fact that there is a peculiar and specific histological picture which sets it apart as a separate disease.

\* Through the kindness of the staff of Guy's Hospital we have been able to study sections of material from one of Hodgkin's original cases, and find that it still stains well and shows brilliantly the characteristic histological structure.

The affection is commonly found in rather young persons and far more frequently in men than in women. Beginning with painless swelling of the superficial lymph-glands, it progresses with gradual enlargement of these glands and signs of similar enlargement of others within the thorax or abdomen, and usually with increase in size of the spleen. Anæmia appears and may reach a profound degree. There may be evidences of mechanical pressure exerted by the enlarged glands upon the veins, producing œdema of the face or other regions, upon the trachea, leading to emphysema in some cases, or upon some part of the alimentary tract, causing characteristic effects. Death is the result of one of these me-



Fig. 508.—Hodgkin's disease; early stage. Lymphoid and epithelioid cells with scattered eosinophiles and large multinuclear cells.

chanical influences, of some intercurrent infection, or of the anæmia and cachexia produced by the disease itself. It may be well to describe the peculiar change in the tissues, which is the same wherever it occurs, before discussing in detail the distribution of the lesions. The lesion is best seen (Fig. 508) in the lymph-glands where, in different nodules, it may be followed through the changes which it undergoes in the course of its development. In the smaller nodes the beginning of the process, as Dr. Reed pointed out, consists in a proliferation of the lymphoid cells, which is soon followed by the appearance of a coherent tissue formed of larger and paler cells with elongated vesicular and rather palely staining nucleus. They lie in no particular order, but they, together with the

lymphoid cells and others to be described, soon spread so as to replace the normal tissue of the whole gland, obliterating the distinction between lymph-cords and sinuses. Among these cells there are found much larger ones which constitute the most characteristic feature of the lesion. These are really quite large cells and, while they vary greatly, are many times the size of the lymphocytes. Their protoplasm is clear except for scattered, irregular stainable shreds, and their outline is rather ragged. They contain one or two or several large nuclei which are rounded or indented or lobed and usually lie close together. These nuclei are very sharply outlined with a deeply staining chromatin membrane within



Fig. 509.—Hodgkin's disease; early stage.

which the nuclear substance is relatively sparsely granular. In each nucleus there is a large nucleolus, sometimes two, and these nucleoli stand out very clearly with a deep stain. Besides the lymphoid, epithelioid cells and these large cells there are usually found many eosinophile leucocytes. Dr. Reed made much of their presence, but later agreed that they might be absent without lessening the certainty with which one might recognize the tissue. Occasionally, but in my experience rarely, there are found giant-cells of another type with many rather small nuclei arranged in a ring or horseshoe. These are much closer to the sort found in foreign body giant-cells or even to those of the tubercle. The reticulum, in the meshes of which these cells lie, is of

extreme delicacy and the whole mass thus forms a soft, rather translucent grayish tissue, which is quite elastic and in appearance quite homogene-



Fig. 510.—Hodgkin's disease. Partly scarred mass in which there are still areas of the characteristic tissue. The large nodule has undergone partial hyaline change.

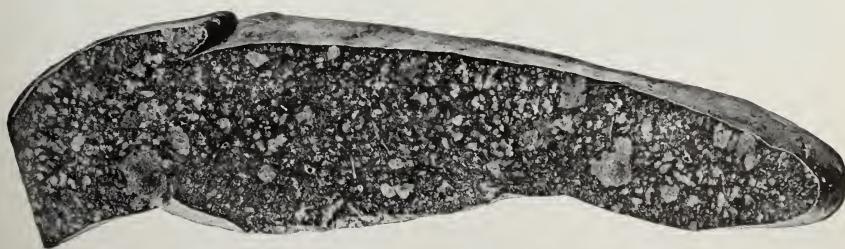


Fig. 511.—Hodgkin's disease. Multiple irregular nodules of specific tissue in the spleen.

ous (Fig. 509). This cellular condition is found in the earlier stages, but after a time there appears a progressive scar formation throughout

the gland coincident with the disappearance of the cells. Every step in the development of this change can be followed until finally there is left a dense mass of fibrous tissue in which, here and there, are to be found pockets or nests of such cells as have been described (Fig. 510). It should be noted that this change in the gland is one which even in the earlier stages involves the whole gland and obliterates its architecture by replacing the lymph-cords and sinuses with a uniform cellular tissue. In

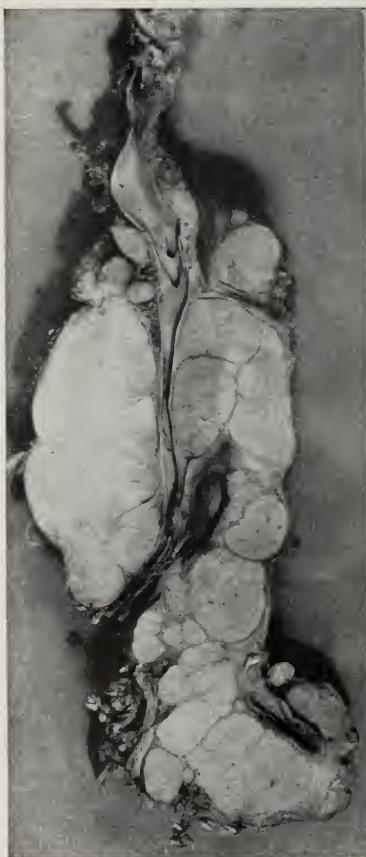


Fig. 512.—Hodgkin's disease. Involvement of retroperitoneal lymph-nodes.



Fig. 513.—Hodgkin's disease. Conglomerate masses in the lung, one of which projects into a bronchus. The lymph-nodes at the hilum are involved.

the neighborhood of such glands tiny new nodular clumps of lymphoid tissue are formed by a regenerative process, but these are no sooner developed than they are transformed into the same new tissue. The glands first affected are usually those at the root of the neck just above the clavicle, where they form a nodular mass almost like a sort of collar. Thence those higher in the neck are quickly involved; axillary and inguinal glands are only less frequently concerned. Sometimes they are

extirpated at operation, and it is then found that in the early stages they are oval or round, discrete nodes which, unlike tuberculous glands which adhere and tend to bind themselves together in a solid mass, can be easily pulled apart. The smooth glands on section show the grayish gelatinous elastic tissue described (Fig. 512), but in the somewhat later stage one very frequently finds in them dry, opaque, firm, yellowish-white areas of necrotic tissue with occasional haemorrhages. The old cases still show the glands in packets, loosely bound together, but as time passes there is more tendency to adhesion. The capsule and adjacent tissue may be especially thickly infiltrated with eosinophiles in these advanced cases. In the interior of the body the bronchial, peritracheal, and mediastinal glands are extensively involved and form such masses as to compress the trachea or impede the heart-beat. I saw one case in a woman in which huge masses existed in the place of the bronchial glands at the bifurca-



Fig. 514.—Hodgkin's disease. Huge enlargement of peripancreatic lymph-nodes.

tion of the trachea. From these the tissue extended into the lungs and there were numerous large discrete nodules scattered in the lung tissue (Fig. 513). In another, a negro boy, one lung was converted into a solid gray translucent mass closely bound by the much thickened pleura and showing no air-containing lung tissue, but only patches of collapsed alveoli in which the epithelial cells were loaded with fat. All the gray tissue was of the character just described, and though already rather fibrous, showed very distinctly all the types of cells. In the abdomen the retroperitoneal glands and perhaps more especially the peripancreatic and periportal glands are likely to be involved (Fig. 514). The periportal glands may be large enough to compress and obstruct the common bile-duct and produce jaundice. In the liver Dr. Reed described the wide-spread occurrence of perivascular and interlobular accumulations of the typical tissue, with its specific large cells, in strands and small nodules. This seems to be rather infrequent. On the other hand, the

spleen is pretty regularly involved, sometimes with mere swelling and with diffuse infiltration of the pulp; at other times, as shown in Fig. 511, with great enlargement and with numerous gray nodules composed of the characteristic tissue and sharply marked off from the deep red pulp. Occasionally such foci are found in the bone-marrow, which otherwise shows no change except the hyperplasia due to secondary anaemia. Nevertheless, I have recently found at autopsy in a man, who had been ill for a long time, a tumor-like invasion of many bones, including ribs and vertebræ, with extensive destruction of the cortex and pathological fractures.

Longcope describes the invasion of Hodgkin's tissue through the walls of the blood-vessels so as to penetrate the intima. There is, however, no leukæmic change in the blood from such invasion; instead there is a decrease in the red cells and usually a moderate increase in the leucocytes without much disturbance of their relative number. On the whole, we find in this disease an affection principally of the lymph-glands, which become greatly enlarged by the development in them of a peculiar tissue which rather rapidly takes the place of the original structure. Cellular and soft at first, this tissue in the course of time loses most of its cells and becomes scarred and hard. Hence the recognition of soft and hard forms of lymph-gland involvement. The growth is not limited to the lymph-glands but may extend into the adjacent tissues, such as the lung and pleura, or appear separately as a sort of metastasis in the spleen beginning perhaps in the Malpighian bodies and extending to the pulp.

It is evident that this is not a hyperplasia of the essential lymphoid cells of the gland, nor is it anything like the myeloid hyperplasias described above. It has some of the characters of a tumor growth, but by far the greater weight of evidence is in favor of its being an infectious process involving simultaneously much of the lymphatic gland system. As to the portal of entry of the infectious agent nothing can be said. The tonsils are most often unaffected.

Nor can anything definite be said as to the nature of the causative agent. Sternberg maintained for a time that this is a peculiar form of tuberculosis, but all efforts to demonstrate tubercle bacilli or to infect guinea-pigs with the tissue were in vain, unless, of course, as was true in Dr. Reed's first case, there was a coincident infection with tuberculosis, and tuberculous lesions and those of Hodgkin's disease lay side by side. Afterward Sternberg and others thought it due to a weakened tubercle bacillus but this seems unlikely in view of the case just cited and also because a weakened tubercle bacillus ought to produce injuries less destructive than those caused by a virulent one and not necessarily fatal. Hodgkin's disease produces lesions quite unlike those of tuberculosis but is always fatal. Fränkel and Much have described certain granular Gram-positive rodlets which they find frequently and consider that they have found the cause of the disease. On the other hand, Bunting and Yates have found a pleomorphic diphtheroid bacillus which they think is the cause. It is too early to decide as to the merits of these different organisms, but the impression is strong that Hodgkin's disease is an infectious process.

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## CHAPTER LI

### DISEASES DUE TO INJURIES OF THE ORGANS OF INTERNAL SECRETION

*Survey of relations of endocrine functions. Controlling influence of hypophysis.*

IN considering the diseases which depend upon disturbance of the activities of the organs of internal secretion we must usually speak of a disease in which one of these organs is most prominently affected, because it is known that they seem to coöperate in such a way that the disabling of one disturbs the others.

Diabetes mellitus is an example of this, for while we find the pancreas most prominently concerned, we are not yet sure of the part played by adrenal, thyroid, hypophysis, etc. Nor are we sure in the case of exophthalmic goiter whether thyroid or thymus or some other organ is chiefly responsible for the disease.

Indeed, the recent great flood of literature has brought so many new statements as to the interrelations of the organs of internal secretion that their interdependence has become quite bewildering. The old diagrams of Falta seem now quite inadequate and the established facts, even about such things as insulin which had become familiar to all the world, are subjected to new explanations. For example, the whole problem of the chemical changes in muscular activity has been solved in a new way and the processes of reproduction in the female have been shown to be curiously under the control of the pituitary gland. We must accept with reserve each new result and wait for time and concentrated work to put the whole matter in a clear and stable form.

#### DISTURBANCES OF ENDOCRINE FUNCTIONS

In a study of the pathological conditions arising from abnormalities of the organs of internal secretion, or endocrine glands, it seems best to begin with the hypophysis since the recent investigations show that it controls in a remarkable way the activities of all the others. But, as yet, there is very incomplete knowledge of the part played by the several elements which make up this complex structure. The results of histological and experimental studies are very contradictory in many particulars, perhaps because of the difficulty in determining precisely which parts of each of these organs are affected, perhaps because extracts or implanted tissues in the experimental studies contain the active principles from several types of cell at once. It seems, too, that there is risk in applying the results of experiments upon lower animals without reserve to man, since the relations may not be exactly the same. Whatever conclusions are stated must therefore be regarded as present knowledge, very liable to change from future investigations. One receives the impression that, complicated as it is, this is a nicely balanced system in which the control is in general a quantitative one in which

actual antagonism between two functions hardly occurs, although in the literature much emphasis is laid by some workers upon the idea that one secretion is planned to neutralize or oppose the action of another. It seems to be true that the introduction, or injection, of an excess of one secretion may diminish the activity of the organ which normally produces it and, indeed, it is perhaps possible that in such a case when the extract is derived from another animal that the opposing substance produced may have the character of an antibody just as the body tissues react to the introduction of any foreign protein. On the other hand, if an organ such for example as the thyroid, is destroyed or ceases to function, there may be an intensification of the action of the hypophysis in producing the secretion which normally stirs the thyroid to activity. So, too, in the cyclic changes in the reproductive system, the succession in functional activity seems to be due to quantitative changes rather than to the antagonism of one secretion for another.

The rôles of the eosinophile, basophile and chromophobe cells of the anterior lobe of the hypophysis are not specifically determined although

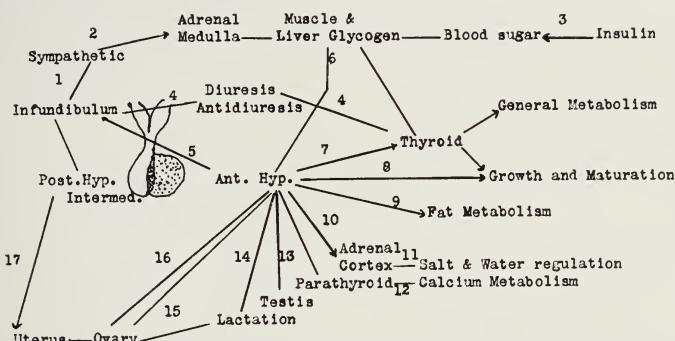


Fig. 515.—Chart constructed from the literature up to 1935 to indicate the widely accepted ideas as to the interrelations of the hypophysis and other organs.

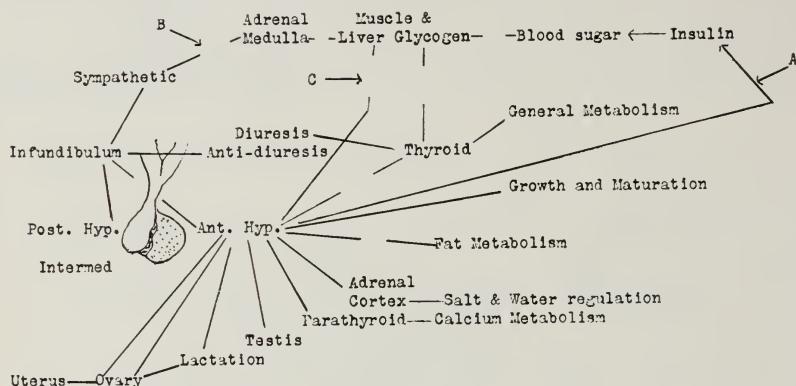
the weight of evidence shows that the eosinophile cells are prominently concerned with growth. The cells of the pars intermedia which are indistinctly marked out from the anterior lobe, surround colloid-filled spaces and extend into the posterior lobe and up along the stalk into the tuberal portion, are not yet well understood but their activities are apparently far more important than has hitherto been thought. It is well known that they produce a secretion which controls the melanophores in the skin of frogs and other animals. They are not identical with the basophile cells of the anterior lobe as is clearly shown by a copper haematoxylin stain and when they are in great excess, as in the tumors of Cushing's syndrome, they cause extreme functional disturbances such as hypertension, obesity, diabetes and osteoporosis.

It begins to seem probable that they may be responsible for the effects ascribed to extracts of the posterior lobe—hypertension and contraction of uterine muscle. The non-glandular structure of the posterior lobe suggests this. There have been many functions ascribed to the various components of the floor and walls of the third ventricle—the

supraoptic, paraventricular and tuberal nuclei, but there, too, final conclusions must await further investigations.

Although the hypophysis is regarded as the controlling organ, it is true that under certain conditions of activity or inactivity of the more peripheral glands, slight histological changes appear in its cells—thus, in pregnancy there appear large numbers of cells with fine, slightly eosinophile granules in the anterior lobe while in castration the basophile cells seem more conspicuous there and are vacuolated. But, so far, no fundamental change in function depending upon these microscopic alterations has been definitely recognized.

If the evidence from the literature be weighed as critically as possible it seems that some lines of activity stand out as fairly well established and for the purpose of presenting to the eye these relations



A. Houssay. *Klin. Woch.* 1932.11.1529.

B. Lucke. *Ergeb.d.inn. Med.u.Kinderheilk.* 1934.46.94.

C. Cope and Marks. *J. Physiol.* 1934.183.157.

Fig. 516.—Chart showing various ideas as to the relation of the hypophysis to carbohydrate metabolism in diabetes. A.—Anti-insulin action; B.—interruption of stimulus via sympathetic system to adrenal medulla; C.—interruption of action of hypophysis rendering liver glycogen susceptible to action of adrenalin.

in the simplest possible form a chart has been constructed which has, of course, no pretense to permanence.

With regard to the carbohydrate metabolism, Houssay found that the hyperglycemia and glycosuria that follow pancreatectomy may be stopped by removal of the anterior hypophysis and claimed a direct antagonistic effect of a secretion of the anterior hypophysis upon insulin, but this might be explained as a failure of the activity of the adrenal medulla in setting free glucose from the glycogen of the liver upon its stimulation from the anterior lobe by way of the sympathetic system through the splanchnic nerves, a failure also produced by paralyzing these nerve endings with ergotamine (Lucke (5-1-2)).\* Others refer

\* Figures refer to lines on the chart (Fig. 515) and to the corresponding literature references.

this to the posterior lobe (1-2). A more convincing explanation is that of Cope and Marks who find that a secretion of the anterior hypophysis is required to make the glycogen susceptible to the action of the adrenalin (6), the lack of which results in hypoglycaemia.

Under the influence of the anterior hypophysis the thyroid is said to promote diuresis (4) while one of the functions of the posterior hypophysis, or perhaps of the pars intermedia, is to control the loss of water (antidiuresis). When there is injury to the infundibulum, or certain portions of the floor of the third ventricle, this control may be interrupted and there is diabetes insipidus.

The anterior hypophysis sends the so-called thyrotropic hormone (7) to maintain the structure and function of the thyroid which would atrophy without it. The effect of the thyroid on metabolism, growth and to some extent the liberation of sugar from the liver, is thus insured. In this sense it must aid in the more direct action of the growth hormone (8) which controls the actual growth and maturation of the young animal and in excess may produce gigantism insofar as it may act before growth has already attained its natural maximum and the epiphyseal lines closed. Later, an excess produces distortions and over-growth of the bones of the face and extremities (acromegaly). Failure of this growth hormone leaves the so-called pituitary dwarf, just as failure of the thyroid (possibly because of lack of the thyrotropic hormone) results in stunted growth. It has been shown that the anterior hypophysis produces a hormone which promotes the metabolism of fats (9), giving rise to an excess of the acetone bodies. It is difficult to understand the enormous obesity of those in whom a tumor presses downward upon the infundibulum, or partly occupies the anterior lobe while the more extreme destruction of the anterior lobe results in great emaciation (Simmonds' disease). The anterior lobe maintains the integrity of the adrenal cortex which, without this corticotrope hormone (10), wastes away. Without the cortex the disposition of salt and water in the body is disturbed and the loss of these by the kidney leaves the blood concentrated or inspissated (11). Whether the adrenal cortex has anything to do with fat or carbohydrate metabolism remains uncertain. Again, the anterior hypophysis appears to have some influence upon the parathyroid (12) and upon the testes (13) although the studies in these respects are not as yet completed. Upon the ovary the action of the gonad-stimulating hormones of the anterior lobe (15-16) is very well worked out. One, the gonad-stimulating hormone A, causes ripening of the ovarian follicle and the production of theelin. Then the gonad-stimulating hormone B stirs the maturation of the corpus luteum with the production there of progestin which acts after ovulation to produce the pregestational proliferation in the uterine lining. In the absence of fertilization upon the exhaustion of this progestin, and possibly on inhibition of the gonad-stimulating hormone production by theelin, menstruation occurs, but if there is fertilization and embedding of the ovum, the progestin continues so as to stir the formation of the placenta. Finally, with the end of pregnancy the posterior

hypophysis pours out its oxytocic hormone (17) which stimulates uterine contraction. In the meanwhile theelin has caused growth of the mammary gland and a few days after birth prolactin (14) from the anterior hypophysis gives rise to the secretion of milk.

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## CHAPTER LII

### DISEASES DUE TO INJURY TO THE ORGANS OF INTERNAL SECRETION (Continued)

*Effects of disturbances in the hypophysis. Structure, relations with central nervous system. Distinctions among cell constituents. Experimental studies by partial extirpation, implantations, testing of extracts, etc. Relation with products of other endocrine organs. Effects of hyperactivity and hypoactivity at different periods of life. Gigantism, acromegaly, Cushing's disease, dwarfism, Simmond's disease. Fröhlich's syndrome. Diabetes insipidus.*

#### EFFECTS OF DISTURBANCES IN THE HYPOPHYSIS

**STRUCTURE:** The hypophysis lies enclosed in the sella turcica, separated from the brain by the dura but continuous with the floor of the third ventricle by its stalk. It develops partly from an epithelial structure in the roof of the pharynx in the embryo, partly from the tissue of the central nervous system and even in the mature animal there may be found remnants of a craniopharyngeal canal embedded in the sphenoid bone. Remnants of this epithelium, especially in connection with the stalk, may in later life give rise to tumors of a peculiar type quite like the adamantinomata which spring from the enamel organ of the jaw.

In order to study the composition of this complex mechanism it is best to make serial sections in a horizontal plane upward through the whole gland and the stalk, even through the third ventricle. It is found, most surely by the application of stains composed of methyl-blue or pyrrhol-blue and eosin, that there can be distinguished the anterior lobe, the pars intermedia continuous with the outer layer of the stalk, the posterior lobe extending in the stalk up to the floor of the infundibulum. There, in the walls of the third ventricle, attention must be devoted to the supraoptic nuclei, the paraventricular nuclei, and the tuber cinereum, although as yet the precise relations of all these structures are not entirely clear.

In the anterior lobe there are readily distinguished the chromophobe cells, sometimes surrounding small colloid accumulations, the eosinophile cells rather larger and more sharply outlined, and the basophile cells with their deeply staining blue granules. These, too, are rounded and sharply outlined and lie in no particular architectural arrangement, often in masses.

The pars intermedia is relatively inconspicuous in man, although much more prominent in some lower vertebrates. It is made up of cells sometimes closely associated with those of the contiguous anterior lobe, generally in part forming the lining of irregular follicles which are filled with a thin colloid, extending in radiating strands laterally into the posterior lobe and distributed as a rather irregular outer layer upward on the stalk.

The posterior lobe with the greater part of the substance of the stalk seems to be composed of loosely arranged neuroglial tissue without distinct nerve elements or epithelial cells other than those which extend into it from the pars intermedia. It is thought by many to serve chiefly as a conduit for the secretion of the glandular elements but much stress has been laid on the potency of specific extracts of the posterior lobe by others.

As to the exact functions and even anatomical relations of the several nuclei in the walls of the third ventricle, investigations are still under way and the conclusions already reached must be regarded critically at least.

Extracts have been made by various methods from the different lobes, each supposed to be separated cleanly from the rest. This, on account of the intimate anatomical relations, seems at once a probable source of error. The chemical methods of separation of special secretions on the basis of solubility, filtrability, heat resistance, precipitation at a special pH, etc., seems more reliable but then arises the problem of assigning that particular active substance to an origin from a special cell. The other chance of recognizing the activity of a cell type arises when a constant group of symptoms or bodily changes is associated with a tumor growth composed of that type of cell—but even then the compression and obliteration of the other cell types by the tumor may cause confusion. Indeed, it may be said that at the present time there is no agreement among authors as to the special function of any of the cells in the hypophysis, except perhaps that most authors agree that the control of growth is related to the eosinophile cells of the anterior lobe since acromegaly and gigantism are regularly associated with an excessive increase of these cells. Attention is being directed to the pars intermedia from which up to the present only one extract has been recognized—that which controls the chromatophores and by expanding them gives the dark color to the skin of a frog which without it becomes a silvery gray.

Great advance has been made recently in the study of the anterior lobe but it is still rather confused, partly because each author gives a different name to some hypothetical hormone to represent each effect. Out of the enormous literature one may gather the following, although it must be clearly realized that all these ideas are new and not yet readily crystallized, as they doubtless will be.

Philip E. Smith and Engle showed that by transplantation of the anterior lobe of the hypophysis sexual maturity could be rapidly brought about in immature or infantile animals. This action affects the gonads directly and the accessory genital organs through their intermediation.

Dandy and Reichert extirpated the anterior lobe and kept the young animals alive. They failed to grow and remained sexually infantile. Reichert continued this and restored normal development by implantation of anterior lobe tissue. Philip E. Smith showed that extirpation of the anterior lobe prevented the development of the thyroid and interfered with metamorphosis in tadpoles. Evans and Long showed that there are two principles in the anterior lobe, one governing growth, the other sexual development and ovulation. With an excess of the extract of

this lobe they could produce giant rats. Putnam and his associates, by long continued dosage, converted a normal bulldog puppy into an acromegalic dog. As to the effect upon the genital sphere, apart from the rapid sexual maturing of infantile animals shown by Smith and Engle, there appears a complex interrelation with the various products of those organs.

For a long time efforts have been made to discover the function of the posterior lobe, especially by testing the effect of extracts. Schaefer found that an extract caused a rise in blood pressure, and this has been repeatedly confirmed by many workers. Dr. Abel has produced a purified extract which is immensely powerful, and Geiling, in a series of studies, has emphasized the other main property of the extract, namely, its oxytocic effect—that is its power to cause violent contraction of the uterine muscle.

These have been mentioned before but may be stated in a little more detail. Zondek and Aschheim found that the anterior hypophysis is active in producing two hormones which they named prolan A and prolan B. Later workers have spoken of them as gonadotropic hormones, or gonad-stimulating hormones. Of these the first stimulates the ripening of the ovarian follicle with the production of a secondary substance, recognized by Frank and later studied by Allen and Doisy, which is now known generally as *theelin* although many other names have been suggested. This is the estrogenic substance, the principal action of which is to stir the proliferation of the tissues of the genital apparatus. Its presence can be recognized by the rapid growth of squamous epithelium in the vaginal wall, as seen in smears of the cells taken from that surface, but it also produces changes in the uterine lining cells.

The second gonadotropic hormone acts upon the ruptured ovarian follicle to convert the granulosa into the lutein cells of the corpus luteum which in turn produces *progestin* which seems to prevent further ovulation and to so affect the uterine wall and its lining as to prepare for the implantation of the ovum. If there is no impregnation, it lasts only a short time and the altered uterine mucosa disintegrates with bleeding (menstruation). If the ovum is fertilized and implanted, it, with the developing placenta, produces a substance which maintains the corpus luteum. The precise part played by the placenta in this is still under discussion. The breasts during this time are affected by theelin which causes their proliferation and preparation for lactation. This, however, does not begin until after the birth of the child when it is stirred by a recognized hormone from the anterior lobe of the hypophysis, *prolactin* (Riddle and others).

*Androsterone*.—It is found that under stimulus from the anterior hypophysis, the testis produces a hormone which has the function of maintaining the accessory genital organs, prostate, seminal vesicles, etc., and the secondary sexual characters in the body. Whether this is a single hormone is not certain as yet, nor is it quite clear, although probable, that it is produced by the interstitial cells of Leydig. It is present in very small quantity in blood and urine and can be extracted only in very small amounts from testes of animals or from male urine. But

it has been analyzed and even synthesized by Butenandt, and a structural formula given. This hormone, named androsterone, is also described by Ruzicka and Tschopp, the structural formula given being somewhat like that of folliculin.

Of course, the injection of such a hormone, as in the case of every other gland of internal secretion, does not stir the activity of the producing gland but rather tends to stop its activity since it replaces its normal secretion. It is only by the injection of a gonadotropic hormone from the hypophysis that the activity of the testis could be accentuated.

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The study of the changes in the hypophysis in human diseases should include a careful consideration of the alterations in the other organs of internal secretion, as well as the disturbances of metabolism and the functions of other organs and tissues which may be only secondarily concerned. Thus, pregnancy brings about, as Erdheim and Stumme showed, the appearance of masses of cells in the anterior lobe of the hypophysis which are quite unlike the eosinophile cells proper but stand out because of a very fine palely eosinophile granulation. In castrates the basophile cells are found increased in number and curiously vacuolated. But in most conditions it seems that the tissue of the hypophysis is primarily altered and that the changes in its functions affect the other organs. These changes in its tissues may consist in the appearance of tumor-like masses of cells of one type which accentuate that hormone production or, on the contrary, extraneous tumors, haemorrhages, etc., may destroy the gland in part or for reasons less obvious, it may atrophy and become insufficient.

**Gigantism.**—An eosinophile adenoma appearing in the anterior lobe of the hypophysis in childhood stirs the growth of the bones and other tissues so that the child grows to a stature far above that of ordinary people. Commonly this is accompanied by a failure of the genital organs to develop normally, and the secondary sexual characters also remain in abeyance.

An illustration taken from Cushing's work will convey more than any description (Fig. 517). This one, aged thirty-six, was rather weak, had a high sugar tolerance, was sexually impotent, and showed at autopsy a much reduced hypophysis converted into a cyst. Evidently the activity of growth under the influence of the hypophysis, which began to increase at the age of fifteen, gave place, after the ossification was complete, to glandular insufficiency. Such *gigantism* (Fig. 518) is not entirely limited to those in whom the activity of growth

stops with the completion of ossification, but may be combined with the effects of overgrowth which occurs after the epiphyseal lines are ossified, and thus may play a part in the changes in cases of acromegaly.

**Acromegaly.**—When the anterior lobe, through hyperplasia or increased activity, causes excessive growth in adult life the result is *acromegaly* (Marie, 1886). Again an illustration of a typical case will convey more than a description (Fig. 519). The bones of the face and



Fig. 517.—Note the narrow chest; large joints; hypotrichosis. Also the large size of the hands compared with those of Dr. Crowe, whose height is 5 feet 8 inches (Harvey Cushing).

those of the hands and feet become enlarged, the jaw projects, and the soft parts of the face, hands, and feet become greatly thickened (Fig. 521). For a time there may be glycosuria, or at least a lowered sugar tolerance. This hyperglycaemia and glycosuria appears to be resistant to the influence of insulin. The sexual function is not impaired in this stage. Some acromegalics are also giants, evidently because the stimulus to growth existed before ossification was complete, although there may

have been a long interval after the increase in stature before the distorting growth of the facial bones and extremities took place. Such remissions in the activity of the gland are recognized. The condition, acromegaly, is permanent, but in most cases, owing to subsequent impairment of the hypophysis, symptoms of insufficiency (obesity, impotence, high sugar tolerance, etc.) appear.



Fig. 518.—Gigantism. Man with evidences of hypophyseal disturbance, shown in contrast with a normal negro man, 5 feet 8 inches tall.

At autopsy in cases of acromegaly there is usually found a tumor-like enlargement of the hypophysis which may be in the form of a circumscribed adenomatous mass composed especially of the eosinophile cells. It is apparently the pressure caused by the growth of this mass within the rigid sella turcica which, even though the space is greatly

enlarged, finally causes degenerative changes and destruction of much of the secreting tissue. The pressure of the tumor upon the adjacent optic chiasm produces a characteristic partial loss of vision, usually



Fig. 519.—Acromegaly. Great enlargement of face, with heavy features. Great increase in size of hands, with thickening of the fingers.

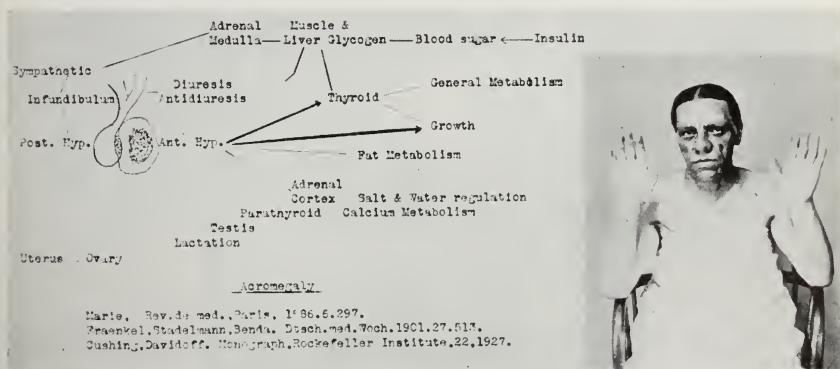


Fig. 520.—Chart showing emphasis of hypophyseal growth hormone and stimulation of thyroid in acromegaly. Illustration from Thayer.

temporal hemianopsia. The thyroid is generally enlarged and shows adenomatous nodules. The pineal, parathyroids, and thymus are said by some writers to be enlarged, but we have not observed this, nor the

hyperplasia of the adrenals which is said to occur. But there is a general enlargement of all the organs perhaps consistent with the great skeletal and muscular growth. The hair grows much more abundantly



Fig. 521.—Advanced acromegaly. (Dr. D. Lewis.)



Fig. 522.—Skull from same case as Fig. 521. x-Ray taken after death. Great enlargement of sella turcica. (Dr. D. Lewis.)

than before over the body and tends to become darker in color. The skeletal changes are remarkable in that the bones of the face, hands, and feet become much enlarged with irregular exostoses about the ends

of the phalanges. These exostoses are prominent in the skeleton of one of our cases at the margins of all the vertebræ and about the ends of the long bones. There is usually a marked kyphotic curvature high in the thoracic region.

**Cushing's Disease.**—One of the most remarkable syndromes arising from disease of the pituitary is that described by Cushing and since then recognized by writers in all parts of the world. It begins with a rapidly increasing obesity involving the face and trunk but not the

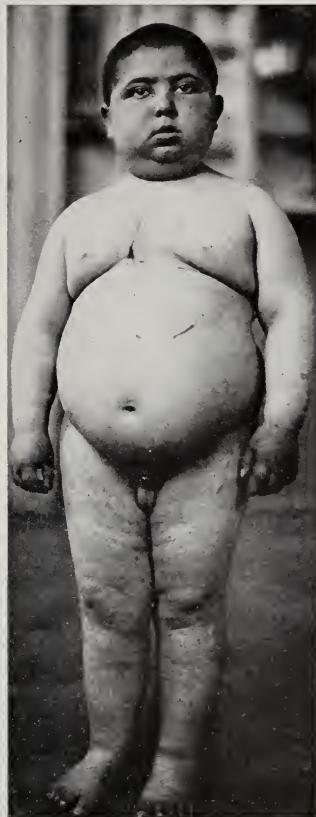


Fig. 523.—Preadolescent hypophyseal insufficiency in a male (Cushing, after Neurath).



Fig. 524.—Adult pituitary insufficiency with hypophyseal tumor. Feminine habitus (Cushing).

extremities. This tears the skin in broad lines over the abdomen and thorax, leaving jagged red bands. There is hypertension, hyperglycæmia and glycosuria, cessation of gonad function with amenorrhœa, polycythaemia and a little later osteoporosis so that the back becomes bowed from the softening of the vertebræ. In addition, there may be enlargement of the adrenals and, indeed, in several cases, a similar condition has been found as a result of changes in the adrenals alone. But in most instances at autopsy there was demonstrated a small tumor in-

vading the anterior lobe of the hypophysis. This, since its cells took the blue stain, was regarded as a tumor of the basophile cells of the anterior lobe and the functional disturbances therefore referred to the increased activity of the basophile cells. But in a typical instance which we were able to study, it proved that the cells of the tumor, although they stain blue like the basophiles of the anterior lobe, are morphologically different and resemble closely those of the pars intermedia.

The cells of the pars intermedia stain blue also with the usual stains but with copper haematoxylin which stains the basophiles black in the anterior lobe, the cells of the pars intermedia do not stain at all—nor do the cells of the tumor. It seems, therefore, that the tumor is really derived from the pars intermedia and the functional disturbances due to accentuation of the activity of that tissue. This suggests the necessity for further study of the function of the pars intermedia since up to the present only the chromatophore hormone has been ascribed to it.

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Inactivity of the hypophysis beginning before puberty, causes such changes as are observed in puppies after hypophysectomy, namely, stunting of growth, great obesity, high sugar tolerance and failure in

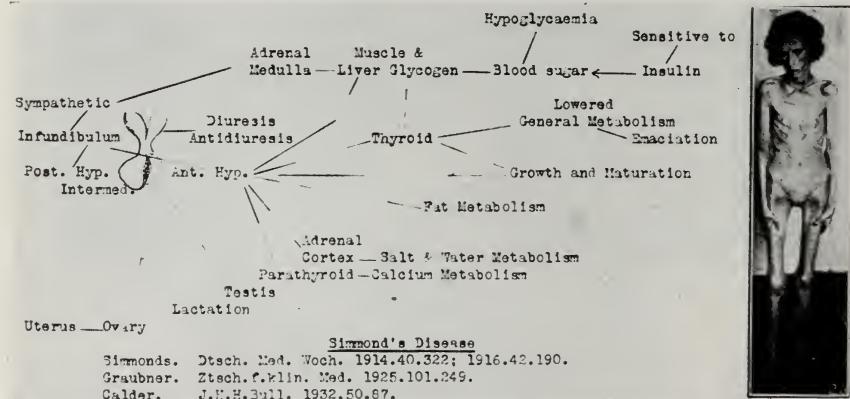


Fig. 525.—Chart suggesting interruption of various influences in Simmonds' disease with atrophy of anterior lobe of hypophysis. Illustration from Penfield.

the development of the sexual glands and in the appearance of secondary sexual characters. Mental dulness is a frequent accompaniment.

**Hypophyseal Nanosomia.**—Erdheim was the first to recognize the hypophyseal origin of a dwarf-like stunting of growth which may occur

with the very early destruction of the hypophysis by a tumor—in his case a teratoma. The skeleton in such cases remains like that of a young child with open epiphyseal lines, and there is atrophy of thyroid and testes and adrenals. This is evidently due to the loss of the anterior lobe and especially of the eosinophile cells.

**Simmonds' Hypophyseal Cachexia.**—Simmonds has described in adult women a peculiar wasting and premature aging with dryness of the skin, apathy, and somnolence, sometimes with delirium and convulsions. This, in further studies, has proven to be due to atrophy and almost complete disappearance of the cells of the anterior lobe of the hypophysis which brings with it a cessation of gonad function and hypoglycæmia which is responsible for the convulsions. This is of the character discussed in connection with experimental hypophysectomy and is perhaps best explained as the result of the lack of that hypophyseal hormone which renders the liver glycogen susceptible to the action of adrenalin.

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**Dystrophia Adiposogenitalis, Fröhlich's Syndrome.**—These are the fat boys that one sees so frequently, fairly bursting from their clothes. They have a peculiar feminine habitus with wide hips, knock-knees, and especial collections of pads of fat in the pectoral regions and on the hips (Fig. 523). Even in adult life there is no beard and hair is scanty over the body. If there is any pubic hair it has the feminine distribution (Fig. 524). This is due to an injury of the hypophysis in early childhood before the epiphyseal junctions are completed and before the maturation of the genital glands. Various injuries to the hypophysis or to the adjacent basal portion of the brain may be concerned, tumors of different sorts involving the gland itself or the floor of the third ventricle, or tumors far removed in the brain substance which cause pressure and hydrocephalus, or even a fracture of base of the skull. The essential injury is one which impairs the activity of that complex region in which the hypophysis is included. When the deficiency of the hypophyseal activity begins late in life there is still an approach to this condition, and although the character of the skeleton is already established and the genitalia developed, there comes obesity with the great heightening of the sugar tolerance and there is gradual or rapid loss of sexual functions. It is possibly with these cases that we should class those extraordinary instances of adiposis dolorosa or Dercum's disease in which there are great and often irregular accumulations of adipose tissue with neuralgic and joint-pains.

**Diabetes Insipidus.**—This is an affection in which extreme thirst and polyuria form the most striking features, but in which, as its name tells us, there is no glycosuria. It has been thought to be due to some sort of injury to the posterior lobe of the hypophysis, but from a recent study of H. Bourquin it appears that it can be produced experimentally by cauterizing the floor of the third ventricle.

The most diverse explanations of the various features of diabetes insipidus are offered and it seems that its true nature is still obscure. Hann thought it due to destruction of the posterior lobe with the anterior lobe still active, which lowered the concentration ability of the kidney—that is, the ability of the convoluted tubules to reabsorb the water—and caused polyuria. Richter found that total removal of the hypophysis produces temporary diabetes insipidus while it is permanent after total removal of the posterior lobe, leaving part of the anterior lobe. He finds that the withholding of water does not at once stop the polyuria. Barath and Weiner think the secretion of the posterior lobe regulates the oncotic pressure in the blood and tissue fluids and hence the direction of the movement of water. High oncotic pressure in the blood causes polyuria. Landau and Wajsman, in much the same way, think that extracts of the posterior lobe increase the "hydrophilia" of the tissues and so reduce polyuria, and refer again to the inability of the kidney in diabetes insipidus to reabsorb water, and especially to the difficulty in the passage of sodium chloride from the blood to the tissues. This, with the insufficiency of renal concentration and the free passage of water through the kidneys, frequently causes hyperchloraemia. Dreyfus rejects the German theory that diabetes insipidus depends upon inability of the kidney to concentrate and eliminate salt. Suppression of salt in the diet ought then to stop the polyuria.

Very careful study with more precise experimental methods capable of stimulating or destroying individual centres in the hypothalamus have shown that unilateral damage is ineffectual but bilateral injury to the supraoptico-hypophyseal system, causing atrophy of the supraoptic nuclei and of the posterior lobe, produces permanent polyuria. This can be restored to normal by injections of pitressin and, of course, by withholding water. Diabetes insipidus seems, therefore, to be caused by a deficiency in the secretion of the antidiuretic principles of the posterior or more probably of the intermediate lobe of the hypophysis, the cells of which extend up the stalk to the tuberal region. The supraoptic nuclei send secretory impulses to these cells so that interruption of this system at the nuclei, in the fibre tract, or in the pars intermedia and pars neuralis, results in diabetes insipidus. Such are the experimental results of Fischer, Ingraham, and Ranson. Biggart had an opportunity to study three cases in which the lesions were situated at different points and his diagrams are most instructive. Interruption of the hypophyseal stalk produces polyuria by cutting through the supraoptico-hypophyseal tract, but the gland cells about the pars tuberalis will hypertrophy and later suffice to control the polyuria. A lesion in the supraoptic nuclei cuts off secretory fibres from the whole epithelial investment of the pars nervosa and tuberalis and leads to permanent diabetes insipidus controllable by injection of pitressin since the effective pathway from the nuclei of the tuber cinereum are intact. But a lesion which destroys the tuber cinereum or this pathway from the tuber downward results in a permanent polyuria refractory to treatment with pituitrin. This seems still to leave the matter in some confusion unless we agree that the tuber cinereum by way of the tracts in the

medulla and cord and the sympathetic or parasympathetic system restrains the kidney from overactive secretion and is itself maintained in its activity by the secretion from the pars intermedia and tuberalis of the hypophysis. Interruption of this mechanism at any point would appear to set free the kidneys to overactivity or rather to deprive them of all power to restrain the escape of water. Zadek explains it by suggesting the control of water binding by the tissues as the effect of the hypophyseal secretion but on this basis the tuber and its pathways would seem superfluous.

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## CHAPTER LIII

### DISEASES DUE TO INJURY TO THE ORGANS OF INTERNAL SECRETION (Continued)

*Diabetes mellitus: General character, relation to islands of Langerhans. Experimental studies. Insulin. Relation to action of hypophysis. Carbohydrate metabolism. Relation to fat metabolism. Pathological anatomy. Symptoms. Metabolic disturbances. Fat and carbohydrate in diet. Hyperinsulinism. Von Gierke's disease. Accumulation of glycogen in tissues.*

#### THE PANCREAS

##### DIABETES MELLITUS

This is a disease upon which for many years the most intense study has been concentrated with the application of every possible experimental and quantitative chemical method, and still it is largely clouded in obscurity. It is essentially a derangement of carbohydrate metabolism which is interrupted at one point because of the lack of a ferment or hormone necessary at that point. Where the intervention of the ferment occurs cannot be said with security yet, but the hormone is insulin, and if that is injected, the whole thing comes right at once and proceeds normally.

In the lack of insulin, sugar is not used at all. Of course, it is taken into the body, but it merely circulates in the blood in excess and is excreted in the urine. For the necessary supply of energy which the sugar normally affords, the fats are attacked, but since they can be properly oxidized only in conjunction with the oxidation of sugar, poisonous by-products arise and cause coma and death. These three things, hyperglycæmia, glycosuria, and acidosis, or acetonæmia, are perhaps the most familiar features of diabetes. Any understanding of the disease involves knowledge of the cause, that is, of what caused the failure of the insulin, and secondly, of the normal course of carbohydrate metabolism, so that the nature of the abnormalities may be appreciated. Many accessory features must be considered, too, but these are the main things, and the disease is really a classical demonstration of the opportunity offered us to learn the nature of a normal process by watching the result when it is interrupted at one point. But, as will appear, we have not yet succeeded in interpreting all these phenomena.

While these paragraphs are left as a brief statement of the conclusions arrived at a few years ago, the more recent observations, which are given at the end of this section, throw a different light on the whole situation.

As to the cause of the failure of the insulin, the following may be said:

v. Mering and Minkowski showed that extirpation of the pancreas is followed regularly by all the phenomena of diabetes, and this, of

course, led to the prevailing view that the pancreas is of predominant importance in this disease. If a part of the pancreas be left, it protects the animal from diabetes even though its duct be tied or even though the fragment be transplanted to some other part of the body. It has long been known that the islands of Langerhans have a character different from the cells of the acini which produce the digestive secretion. Bensley and Lane have shown that their cells contain at least two kinds of granules quite different from the zymogen and other granules



Fig. 526.—Hyaline island of Langerhans from a case of diabetes.

in the acinar cells. And it is known that they are not connected with the ducts of the pancreas, although they probably originated in connection with them. There has been much dispute about this and about the independence of their function, but it is perfectly clear that when the ducts of the pancreas are ligated, or obstructed, the acini atrophy and disappear, while the islands remain intact.

Opie found a case of diabetes in which the pancreas appeared normal, but microscopically almost all of the islands of Langerhans were found to be converted into a hyaline material and thrown out of func-

tion (Fig. 526). This suggested at once that the islands constituted the organ of internal secretion which controlled carbohydrate metabolism.



Fig. 527.—Pancreas of guinea-pig one year after ligation of the ducts. The islands of Langerhans alone remain, embedded in fat.

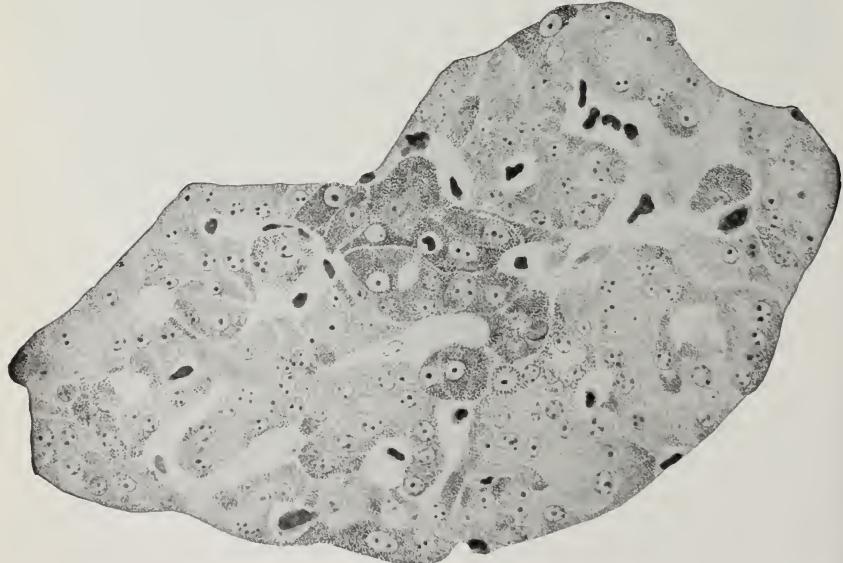


Fig. 528.—Island of Langerhans enlarged from Fig. 527. The sharp differential staining of the granules shows that the cells are intact.

We ligated the duct of one-half of the branching pancreas of a dog and left the animal, which seemed perfectly normal, for a year. Then

it was found that the obstructed part was reduced to a thin transparent film in the mesentery. Extirpation of the intact half of the pancreas was followed by transient glycosuria, but after one day the animal showed no symptoms whatever and could assimilate large amounts of sugar or starch without hyperglycaemia or glycosuria. After a month the transparent film which represented the other half of the pancreas was extirpated and then the animal was plunged into the severest diabetes. In such an animal the film contained only islands of Langerhans, as was proved in a guinea-pig by the special stain of Bensley (MacCallum, Johns Hopkins Hosp. Bull., 1909, xx, 222; Kirkbride, Jour. Exp. Med., 1912, xv, 101) (Figs. 527, 528).

Banting and Best used this plan of ligation and atrophy to procure a tissue from which they might extract the essential principle of the islands of Langerhans, and with complete success, as all the world knows. Afterward, at Collip's suggestion, they neutralized the digestive ferments of the rest of the normal pancreas, by merely extracting with acid alcohol.

It seems unnecessary to recount the earlier hopes and failures. Hedon found that the introduction of the blood of the pancreatic vein of a normal dog into the portal vein of a depancreatized dog would reduce very greatly the amount of sugar in the blood and urine, as though a necessary ferment were secreted by the pancreas into the blood.

Admont Clark made a fundamental contribution by showing that if Locke's solution, containing known amounts of sugar and kept free from bacteria, were perfused through the pancreas alone, there was no disappearance of sugar. When passed through the beating heart alone very little was lost, but when passed first through the pancreas and then through the heart there was a great consumption of sugar. A sugar-free solution which has passed through the pancreas alone contains something of a ferment nature which when added to a sugar-containing solution used to perfuse the beating heart, enables the heart to consume much sugar. The perfusion also changed the optical rotating power of the dextrose to some extent.

But now it is clear that insulin is the long-sought hormone, which when it is injected replaces, for as long as it lasts, the lost secretion of the diseased islands of Langerhans. It is found, it is true, but in much less concentration, in other tissues, and similar substances are found in plants, but that need not detract in any way from the first conclusion, that it is the essential hormone and that it is formed in the islands.

Are we then to conclude that diabetes is clearly and definitely and exclusively the result of disease or destruction of the islands of Langerhans? Opie's case was very impressive and there have been many others in which such hyaline changes in the islands have been found, but in our routine autopsies upon cases of diabetes we seldom find any obvious disease of the islands of Langerhans. Nor do we find disease of the pancreas in any visible form.

Of course, it is true that Cecil studied the pancreas in a large number of cases of diabetes including our material, and found pancreatic lesions in more than 87 per cent., and showed that in these the islands of

Langerhans were always affected and that in about 12 per cent. the islands alone were injured. But certainly most of the islands look normal, and in most cases one must search for a hyaline island; and in other cases in which there is no diabetes such hyaline islands are often found. The matter needs further study and it is a pity to detract from such a satisfying explanation without supplying a better one.

Kindell finds upon extracting the pancreas obtained at autopsy in fatal cases of diabetes, that the content of insulin as shown by animal tests is far below the normal. He suggests that the arteriosclerosis and general scarring may have some significance in this connection.

Bensley and Lane have shown, as was said, that in the islands some of the cells have a type of granule which they designate A, the rest another type, B. Homans, in studying the condition of islands in portions of pancreas left after extirpation of the rest, finds that the evidences of their inadequate function shown by glycosuria are parallel with loss of B granule in the swollen islands.

Thus, while it is not invariably possible to demonstrate the existence of lesions of the pancreas in cases of diabetes, the whole symptom complex can be produced by extirpation of the organ and not in any other way, although transient glycosuria may have many other causes. More attention should be paid to the condition of the granules in the cells of the islands in cases of diabetes which come to autopsy soon enough after death to allow such a study to offer any chance of success, but, after all, there are many tissues whose functions become deranged without our being able to see any morphological evidence of this disability.

At this point it must be said that recent work has produced evidence that diabetes as such is influenced by other mechanisms since the utilization of glycogen and the consequent setting free of glucose into the blood depends on the activity of other organs. Houssay was the first to show that in pancreatectomized animals (toads) the removal of the anterior lobe of the hypophysis stopped the hyperglycaemia and glycosuria while implantation of tissue of the anterior lobe brought the diabetic condition back again. He spoke of it as a contra-insular hormone antagonizing the action of insulin. But Lucke found that section of the sympathetic nervous system at any point on its course to the adrenal medulla, or poisoning of its terminations there with ergotamine would produce the same effect and concluded that because of this the anterior lobe of the hypophysis is no longer able to stir the pouring out of adrenalin which ordinarily acts upon the glycogen in the liver to set free from it glucose in the blood. Hyperglycemia and glycosuria were therefore so reduced that a minimal action of insulin was adequate. On the contrary, Claude Bernard's piqûre may be thought of as a stimulus to this tract which for a time stirs the outpouring of more adrenalin than normal and consequently more sugar is poured into the blood than can be used by the tissues with the aid of the normal insulin production. Lucke's theory presupposes action of the anterior hypophysis by the way of the sympathetic system which is at least an unusual path for a hormone. Another idea is that of Cope and Marks who show that the hormone from the anterior lobe

of the hypophysis acts upon the glycogen in the liver to make it susceptible to the action of the adrenalin—it is resistant in the absence of this circulating hormone and remains unchanged even when adrenalin in excess is injected into the blood-stream. This seems a more plausible idea but the situation must be further studied. In a recent case we found that a severe diabetes mellitus had gradually disappeared so that there was no hyperglycaemia nor any trace of glycosuria. Death occurred months later from some other cause and at the autopsy about half the islands of Langerhans were hyaline and about half of the anterior lobe of the hypophysis had disappeared through atrophy of the cells. It is evident at any rate that the islands of Langerhans are not alone concerned in the control of carbohydrate metabolism. Indeed, Anselmino and Hoffmann have recently described a product of the hypophysis which they say regulates carbohydrate metabolism in general. Loss of the cells of the anterior hypophysis as seen in Simmond's disease results in such lowering of the glucose content of the blood that the patient may die in hypoglycaemic convulsions but could be saved by prompt enough administration of sugar.

Whatever the explanation, it seems that a quantitative disturbance in the balance of insulin and adrenalin is more plausible than any antagonism between the hypophyseal hormone and the insulin.

**Carbohydrate Metabolism.**—Before describing in more detail the symptoms of diabetes and the chemical disturbances that occur there, it is necessary to make an attempt to survey the confused and indefinite ideas that we possess as to the normal metabolism of carbohydrates, fats, and some other substances which are concerned. Before the discovery of insulin all this seemed simple enough, and instead of clearing the matter up, the study of the effect of insulin has only shown us what gaps really existed in our knowledge. They are still slurred over by nearly every writer, and it seems almost impossible to gather any consistent account of the whole matter from the recent literature. In the following it is sought to do this from the writings of Macleod, Fletcher and Hopkins, Hill, Embden, Laquer, Brugsch, Shaffer, Knoop, Euler, and many others, but so much is contradictory, so much is left vague and incomplete and so much is referred to purely hypothetical substances and agents that it is feared that in many points their thoughts may here have been misunderstood or wrongly interpreted.

Formerly it seemed clear that starches and sugars taken into the alimentary tract reached the blood of the portal vein as glucose, this was transported through the liver, largely stored there as glycogen, and reached the other organs for oxidation partly directly, but partly after having been restored to the blood as glucose by the reconversion of the glycogen by a diastatic ferment.

Now it appears that the carbohydrates do reach the blood as glucose and perhaps in a form suited for transport and not very ready to react chemically. Two forms of glucose are recognized with a slightly different structure. Of these,  $\alpha$ -glucose is very strongly dextrorotatory and highly reactive. It is a sort of nascent glucose, while  $\beta$ -glucose is very feebly dextrorotatory and very inert. It is perhaps a mixture of these

which assumes an average dextrorotatory power and chemical activity, and it is possibly in this form that it is transported through the blood. Polymerization into the more complex colloidal form, glycogen, results in its deposit in the liver and also in the other tissues, especially in those which are very active, as the heart and muscles. No precise statement appears as to the way in which this polymerization occurs, nor as to the nature of the ferment involved, nor as to whether the deposition of glycogen in the liver affects all or only a part of the sugar which comes from the intestine. It seems that much of that stored in the liver is not for its own use, but it is tacitly assumed that the other tissues are not so altruistic and use for themselves whatever glycogen they can store. For this reason it is supposed that another ferment breaks down the glycogen in the liver into glucose which is carried on by the blood to the other tissues. It might be imagined that such newly liberated glucose would be in the alpha form. Whether it enters the tissues and becomes once more glycogen there, or is used directly, is not clear. Many writers casually make the statement that glycogen is the first step in the actual metabolism of sugar, and most of the schemes of sugar utilization begin with glycogen. It would simplify the matter if one could feel sure that the ultimate using of sugar invariably depends upon its being in the form of glycogen, but there seems to be hardly time for that modification to be formed. If an animal is in a state of extreme lowering of the blood-sugar, so that it is about to die for lack of glucose, the intravenous injection of that substance brings it back to normal almost instantly, but then there may be other explanations of this, because it is possible that the glucose neutralizes some poison. It is with regard to the ultimate consumption of the sugar that there is most uncertainty. Many have sought for a still more labile form of sugar in the blood, and the terms  $\gamma$ -glucose, neo-glucose, and enol-glucose have been invented for supposed substances of this sort, but none have been really shown to exist.

The consumption of sugar has been most intensively studied in the muscle, and the work of Fletcher and Hopkins, Meyerhof and Hill, and of another group with different ideas, beginning with Embden, are most interesting.

Essentially it appears that the ideas of the English investigators result in the conclusion that glycogen in the muscle is decomposed into lactic acid with a loss of  $\text{CO}_2$ , that some of this lactic acid is oxidized, but more of it neutralized by sodium protein compounds and ultimately reconstituted as glycogen. Hill describes it as follows: "In an isolated muscle, stimulated in oxygen, lactic acid is set free, but vanishes again during a subsequent resting period. During this recovery process  $\text{CO}_2$  is produced equivalent in amount to the oxygen used, heat is liberated, and glycogen is restored. The amount of glycogen gained is not equivalent to the lactic acid lost; a certain amount of one or the other is oxidized, presumably to provide the energy to drive the endothermic reaction.

"Sodium lactate + protein  $\rightarrow$  sodium protein + glycogen. According to Meyerhof, about one molecule in four of the lactic acid removed in

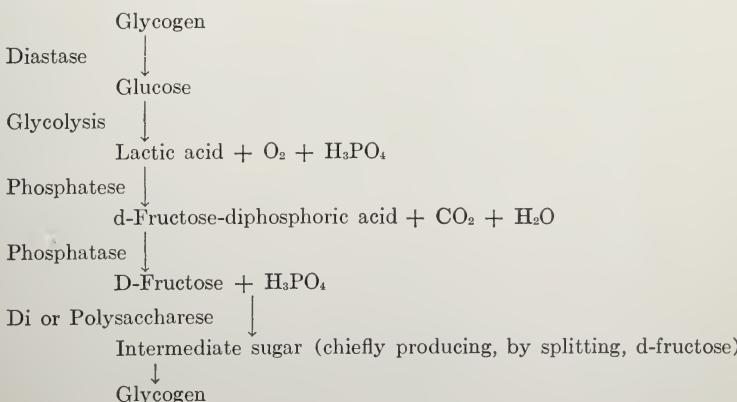
recovery is oxidized, the remaining three molecules reappearing as glycogen."

This is not very satisfactory, and in another place he says it is impossible to say what kind of reaction occurs in the recovery process.

Another idea is that which was introduced by Embden and his associates which emphasizes the part played by inorganic phosphates or phosphoric acid in the utilization of sugars. Harden and Young had shown that in the fermentation of sugar by yeast there are two ferment, a thermolabile zymase and a thermostable coenzyme, and that in this process inorganic phosphates are essential in that the sugar in the presence of phosphoric acid is decomposed into carbon dioxide, alcohol, water, and hexose diphosphoric acid. A similar phosphorizing process occurs, according to Embden, in the use of sugar in animals, and from glucose through splitting into lactic acid and combination with phosphoric acid a laevorotatory laevulose-diphosphoric acid is formed which is labile. Two molecules of lactic acid are reconstituted to d-laevulose and combined with phosphoric acid, part of the lactic acid being oxidized to  $\text{CO}_2$ . The d-laevulose-diphosphoric acid is decomposed in all organs by another ferment, giving once more d-laevulose and phosphoric acid, and the laevulose is reconstituted to glycogen. Lack of insulin interrupts the process at the stage of glycolysis, or conversion of glucose into lactic acid, although even in a diabetic animal laevulose can be polymerized to glycogen (Brugsch and Horsters).

A great deal has been written, chiefly by the German investigators, upon the importance of this intervention of the phosphates which they seem to think is established, although the English and Canadian investigators look upon it with some suspicion. Essentially it seems to mean that with the aid of many hypothetical ferment and beginning with glycogen, a labile glucose is formed which decomposes into lactic acid—part of this is oxidized to  $\text{CO}_2$ , the rest combines with phosphoric acid to d-laevulose-diphosphoric acid. The laevulose set free from this is recombined to glycogen, while the phosphoric acid is liberated for new combination with lactic acid.

Brugsch and Horsters give the following scheme:



In all these interchanges it would seem that there is an extraordinary amount of fermentative decomposition and resynthesis, with a minimal amount of oxidation and actual consumption of the carbohydrate.

It has always been known that the oxidation of carbohydrates renders easier the complete combustion of fats, and in its absence this is imperfect, the oxidation of the fatty acids, at any rate those with an even number of carbon atoms, takes place by the oxidation of the third carbon atom (that is, in the  $\beta$ -position) and the splitting off of the terminal carbon atoms. In this way  $\beta$ -oxybutyric acid can be formed from all the ordinary fatty acids, palmitic, stearic, and oleic (Knoop).

Shaffer finds that diacetic acid is the first to appear and that some of it may be oxidized to acetone and some reduced to  $\beta$ -oxybutyric acid. Some product of the oxidation of glucose not yet identified combines with diacetic acid to form a compound which is readily oxidized further and destroyed, thus obviating the formation of  $\beta$ -oxybutyric acid or acetone. This would at least justify the old statement that "fats burn in the fire of carbohydrates."

It is evident that all this is very confused and unsatisfactory, but the activity of the last years in this field makes one feel that before long it will be clear. Since this was written a detailed review of the whole subject has appeared in O. Fürth, Lehrb. d. Physiol. u. Path. Chemie, 1927, II, 184, and to this the student may be referred.

Since this was written the whole question has undergone a change, inasmuch as it has been shown especially by Meyerhof, Lundsgaard and other co-workers that lactic acid may be excluded from the process and that heat production goes on with muscle activity through the intervention of a phosphate-creatine combination which they name phosphagen. For this the student is referred to the papers by Meyerhof, Hill, and others.

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**Pathological Anatomy.**—The nature of the disease diabetes is not much cleared up by anatomical study at autopsy, for, as has been stated, there are usually no gross changes which seem capable of explaining the complete upset of the metabolism, and even the microscopical alterations of the islands often seem inadequate.

The liver is devoid of glycogen or nearly so. That usually found in globules or granules in the cytoplasm of the liver-cells is gone and the nuclei of the cells which are swollen now contain whatever glycogen remains in the organ. The muscles have also lost their reserve of glycogen, and this is true of all the tissues except the heart muscle, the leucocytes, and the renal epithelium, particularly, as pointed out by Baehr, that in the terminal part of the first convoluted tubules (lesion of Armanni). The blood contains an excess of sugar and often of various fats. Arte-

riosclerosis is common, but by no means invariable, and is perhaps associated with the disturbance in fat metabolism. In a few cases large lipoid-holding cells have been conspicuous in the spleen (M. Smith).

The pancreas is sometimes atrophic and scarred, but this is by no means constant or even frequent. The changes in the islands have already been discussed, and when they are present they are eagerly seized upon as the obvious cause of the disease. Winternitz described the case of a child in which steatorrhœa had existed since birth without diabetes. On the death of the child no pancreas was found, but only a thin strip of tissue, which contained nothing but islands of Langerhans. This is the opposite side of the picture and, although it is difficult to make an obvious demonstration in every case of diabetes, we shall go on believing in the pancreatic origin of the disease until an extrapancreatic cause is demonstrated.

In view, then, of what we know of carbohydrate metabolism and of the anatomical disturbances in diabetes, how far can we understand the symptoms and chemical derangements?

The name *diabetes* suggests "a running through," or polyuria, and the term *mellitus* refers to the glycosuria, to distinguish it from diabetes insipidus, in which there is polyuria without hyperglycæmia or glycosuria. These were the outstanding features of the disease, but it was known that the patients exhibited excessive appetite and thirst, polyphagia, and polydipsia. Further, it has always been known that the whole disease is more violent and rapidly fatal in children than in old people, and that death results in coma with all the signs of acid intoxication, forced respiration, acetone odor of the breath, etc. Older people especially show an extreme susceptibility to bacterial infections which make enormous strides in a short time. Tuberculosis especially seems to be greatly favored in its inroads by the existence of diabetes, but other infections, such as those which accidentally arise in fingers or toes, spread rapidly. Arteriosclerosis of the vessels of the extremities is often extreme, and this, possibly in conjunction with infection beginning in a toe, frequently leads to gangrene which extends upward rapidly so that the leg must be amputated. Clinicians recognize the fact that insulin apparently loses its effect in diabetics in whom there is infection. No explanation is offered, but it is known that in fever the store of glycogen in the liver is depleted and there may possibly be some connection.

In most cases the patient learns that he has diabetes through the discovery of sugar in the urine. With careful restriction of the diet this may disappear and he lives a normal life. Excesses in the consumption of starches and sugars may recall the disturbed state, however, and so exaggerate it that the tolerance for sugar becomes extremely low and evidence of acidosis from the distorted oxidation of fats appears. The problem presents itself as to why the presence of sugar which is not being used should interfere with the process of fat-sugar oxidation which was going on well enough when less sugar was available. Glycosuria is, after all, only a sign of the presence of an amount of sugar in the blood above the threshold of the kidney. In the absence of disease one can make the kidney excrete sugar by taking too much by mouth (alimentary

glycosuria), and, in general, hyperglycæmia and glycosuria can be brought about by many other causes than those commonly at work in diabetes. Injury to the brain (the so-called piqûre of Claude Bernard) and tumors of various sorts within the skull, and perhaps especially those related to the hypophysis, may produce it. Stimulation of splanchnic nerves will cause glycosuria apparently through the intermediation of the adrenals, just as injection of adrenalin causes it. There is much discussion as to the point of action of adrenalin, and especially in relation to insulin, which seems to act in an antagonistic manner. Apparently the secretions of several of the organs of internal secretion have a bearing upon carbohydrate metabolism, for in the absence of the thyroid it is difficult to produce hyperglycæmia, while it may appear spontaneously when an excess of the secretion of thyroid or hypophysis is thrown into the circulation. Glycosuria may also be produced by caffeine, strychnine, sensory stimuli, and asphyxia (which, in its turn, may be brought about by various narcotics, ether, chloroform, morphine, etc.). In other cases (renal poisons or phloridzin poisoning) it seems that there is no hyperglycæmia and that glycosuria arises as the result of renal changes. For information concerning the complex effects of phloridzin poisoning Lusk's papers may be consulted.

But in diabetes mellitus the hyperglycæmia is more profound and lasting than in the case of any of these transient effects. Even when sugar is withdrawn from the diet and nutrition is dependent upon proteins and fats, certain of the amino-acids derived from the decomposition of proteins can give rise to sugar, which then continues to circulate in the blood, while glycerol, from the decomposition of fats, may perhaps also go to the formation of sugar, although there has long been dispute as to whether carbohydrates can in any way be derived from fats.

The sugar which circulates in the blood in diabetes is not stored in the liver and other tissues as glycogen and is but little used by the tissues, although it can be used to some extent if violent muscular work is demanded. Instead, proteins are called upon, their carbohydrate product being wasted and excreted in proportion to the nitrogen excreted (the so-called D:N ratio). Fats, too, are especially utilized, and it is perhaps in connection with this that lipæmia is common in diabetes, fat streaming in visible form in the blood in such a way as to make the serum milky. The origin of this fat is not clearly known, but at first there is increase in lecithin and throughout a still greater increase in cholesterol.

As has been explained, the absence of combustion of carbohydrates makes impossible the normal oxidation of fatty acids which should go by way of the destruction of a combination of diacetic acid with a labile oxidation product of glucose. It has even been suggested that this interaction with fats is a normal and possibly essential step in the oxidation of carbohydrates. At any rate, in its absence diacetic acid is largely converted into  $\beta$ -oxybutyric acid and partly into acetone.

$\beta$ -oxybutyric acid .....	$\text{CH}_3-\text{CH OH}-\text{CH}_2-\text{CO OH}$
Diacetic acid .....	$\text{CH}_3-\text{CO}-\text{CH}_2-\text{CO OH}$
Acetone .....	$\text{CH}_3-\text{CO}-\text{CH}_3$

These are the so-called acetone bodies, which tend to appear more readily in herbivorous and omnivorous animals than in the purely carnivorous. Diacetic acid and acetone rarely occur in any great amount in the urine, but the  $\beta$ -oxybutyric acid may reach 50 to 100 grams a day or more. With such disordered fat combustion, toxic phenomena appear which are known as the symptoms of acidosis or acid intoxication. They are quite similar to those produced by the feeding of inorganic acids to rabbits or other herbivorous animals, and consist in a peculiar violent deep respiration or air-hunger and coma. These symptoms may be much relieved by the introduction of large quantities of an alkali, such as sodium bicarbonate. During the gasping for breath the blood is bright red and contains very little carbon dioxide; instead, the tissues are loaded with carbon dioxide which the blood is unable to remove, presumably because the acid injected has combined with the sodium of the blood, so that it is no longer able to aid in the transport of the carbon dioxide to the lungs. Ordinarily it passes to the lungs as bicarbonate, where it is decomposed into the carbonate, liberating  $\text{CO}_2$ , and returns to the tissues for more. Exactly the same preëmption of the alkali of the blood results from the presence of the organic acids that arise from the decomposition of the fatty acids, and the diabetic dies in coma largely as a result of this kind of asphyxia unless the alkali is supplied rapidly from the outside.

Some explanation of the polydipsia and polyuria is offered by the studies of Klein, who finds that in the extreme diabetic, water taken alone is retained, while if carbohydrate is given at the same time it is promptly excreted. If insulin is given at the same time, water alone is excreted at once, while it is retained in large part if carbohydrates are given too.

Insulin given to a person with diabetes immediately restores the whole metabolism to normal by correcting the primary error upon which all the others follow in regular sequence. Naturally, it does not cure the disease, but it shows what has been the essential defect, and as long as it lasts it replaces the missing hormone. It stops the glycosuria by reducing the blood-sugar, partly by promoting the formation of glycogen and partly by making possible its utilization in the tissues. In a normal animal it reduces the blood-sugar to such an extent that it effects the withdrawal of glycogen from the liver to make up the loss. Of course it stops the abnormal oxidation of fatty acids because it restores the normal combustion of carbohydrates.

The problem which remains unanswered is as to the exact point at which it acts. Macleod has shown that it has no effect upon glycolysis of sugar in the blood, and thinks it must cause removal of the sugar to the tissues, and since the respiratory quotient quickly reaches the figure characteristic of the oxidation of carbohydrate, it must indicate that the sugar is oxidized there. Brugsch thinks that insulin is the thermo-stable coenzyme of the phosphatase, *i. e.*, the ferment which promotes the phosphorization of sugar in the organs, but Euler as strongly opposes this. It seems most probable that it is important in the conversion of glucose into lactic acid which immediately precedes the phosphorization,

and that because of its absence the glucose persists as such. Geelmuyden and Laufberger think the action of insulin is essentially upon fat metabolism, inhibiting the formation of fat, which according to them, is the striking feature of the metabolism of diabetes which would perhaps fit in with the idea that the combined oxidation of fats and carbohydrates is essential, but it is by no means clear.

The effect of insulin seems to be more or less independent of any action it may have in promoting the storing of glycogen in the liver, for it acts to reduce blood-sugar in the absence of the liver. Given in excess it produces hypoglycæmia as intense as that which follows extirpation of the liver, and the animal dies with convulsions followed by coma, although it may be immediately restored to normal by intravenous injection of glucose. Macleod explains this as due to a rapid removal of glucose by the tissues, but this seems hardly a satisfactory explanation, since, after all, it must be the tissues which need the sugar and not the blood, and it seems possible that some toxic substance is developed which may be neutralized by sugar.

In the last years there has been a change based primarily upon the experience of clinicians (Geyelin and others) which showed that with the aid of insulin much larger quantities of carbohydrate could be given to diabetics without any resulting glycosuria or hyperglycæmia, provided the intake of fat and lipoid substances be kept at a very low level. This suggested that in some way fats could be converted into carbohydrate and there are experimental studies which show the mechanism of this conversion (Remesow, Jost, Henze). But the matter is still confusing for the general tendency is to show that insulin favors the conversion of fats into carbohydrate, although these authors use rather the expression that insulin regulates the conversion of lipoids into carbohydrates. Hunt shows that insulin maintains cholesterol at a nearly normal value. Geelmuyden, in his review of 1931, states that: "Insulin has no direct effect upon carbohydrate oxidation and by itself does not increase the total metabolism or heat production. But indirectly it can influence in several ways the carbohydrate utilization and heat production, both increasing or inhibiting it. By affecting other endocrine activity or by the synthesis of fat or glycogen it increases the consumption of carbohydrate. But its most important action is to inhibit the formation of carbohydrate from non-carbohydrates so that energy must come from the consumption of preformed carbohydrates. It thus controls the pathological increase in new formation of sugar from non-carbohydrates in diabetes." It seems therefore that the question is not yet completely solved and that further study is necessary to clear it up. The experiments of Admont Clark seem inconsistent with the idea that insulin affects prominently anything but the carbohydrate consumption.

Study of recent reviews and papers upon the mechanism of insulin action fails to reveal any penetration into this mystery. It becomes clear through the work of Geyelin that the production of insulin is stirred to an increase by giving a much greater proportion of carbohydrate in the diet with less fat—a reversal of the method of Allan who restricted carbohydrates. This seems analogous to the increased effort of other

organs when their function is taxed more heavily. It is clear, too, that much oxidation can occur in the tissues of animals deprived of the pancreas. But as to the precise point at which insulin acts in connection with glycogen formation, with glycogenolysis into dextrose, with the oxidation of dextrose and with the prevention of the harmful decomposition of fats, no satisfactory conclusion has been reached. It would seem tempting to think of it as concerned in the newly recognized process of muscle metabolism in which phosphorus plays a part as shown by Meyerhof and Lundsgaard.

Wilder and others describe a case of carcinoma of the islands of Langerhans with metastases in which hourly doses of dextrose were necessary to prevent convulsions and coma from hypoglycæmia. It was clearly shown after the patient died that the tumor and especially the metastases were producing insulin. The liver at autopsy contained 8.25 per cent of glycogen, but it had been found impossible to mobilize this during life with epinephrine, or in that way or with pituitary extract, to neutralize the effect of the excessive insulin. Since this, there have been reported many cases in which an adenoma of the islands has been shown to produce the same effects.

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**von Gierke's Disease.**—In 1929 von Gierke recognized an extraordinary condition in a child in whom the liver was greatly enlarged, smooth and hard, a change which was found at autopsy to be produced by a storage of glycogen in its cells. In that case the epithelial cells of the kidney tubules were also loaded with glycogen. There was no glycosuria and the blood-sugar was reduced. Since then numerous authors

have described cases but it is not a common disease and we have recognized at most two cases. It seems to be a congenital affection although the great enlargement of the liver appears slowly.

The essential features are briefly as follows: There is hypoglycæmia with acetonuria. Injections of adrenalin have no effect in mobilizing the glycogen or increasing the blood-sugar, but do increase the ketosis and the production of lactic acid. When glucose is given by mouth there is no glycosuria; there is normal tolerance for galactose and fructose. Insulin produces an even greater hypoglycæmia so that the cases are regarded as hypersensitive to insulin. Study of the ferments concerned shows that diastase is normal in blood and urine, but there is no glycogenolysis and even after death the glycogen in the tissues persists unchanged for a long time when the conditions of temperature, etc., favoring autolysis, or exposure to watery fixing fluids are such as to cause the disappearance of the glycogen from any normal tissue. There

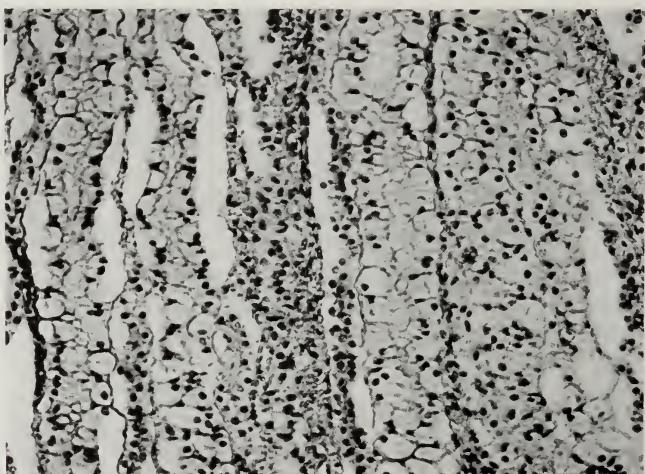


Fig. 529.—von Gierke's disease. Epithelium of renal tubules loaded with glycogen.

is some fundamental change in the glycogen which makes it unassailable by the usual agents which cause its depolymerization with its reduction to glucose and the explanation of this has been sought in various ways. It is stated that foetal glycogen behaves in this way and is different from that of the adult but this is equally obscure. The excretion of diacetic acid,  $\beta$ -oxybutyric acid and acetone, which is so constant a feature of these cases, must depend upon the inability of the body to utilize carbohydrates. Protein utilization seems normal.

What explanation can be offered for this situation? The most varied ideas are expressed—that there are abnormal types of sugar or of glycogen; that there are combinations of protein and glycogen; that diastase cannot reach the glycogen, etc., but there is no convincing evidence for any of these suggestions. That diastase is abundantly present is proven by Hertz, and lipases are even increased. One statement is of interest

and suggests a possible explanation. It was shown by Faber that an emulsion of normal liver mixed with the liver from von Gierke's disease will promote the conversion of the resistant glycogen. This suggests the existence in the normal liver of some factor which affects the glycogen to make it susceptible to the action of the normal agents. It was pointed out by Cope and Marks that loss of the anterior lobe of the hypophysis makes the adrenalin unable to liberate glycogen. Injection of adrenalin, then, causes little or no hyperglycæmia but injection of extract of the anterior hypophysis restores an even increased response to adrenalin. Fluch, Greiner and Loewi confirm this by experiments with perfusion of the liver of frogs with Ringer's solution to which adrenalin is added and found that hypophysectomy decreases glycogenolysis, and Hertz strengthens this argument by finding von Gierke's disease combined with hypophyseal dwarfism which he speaks of as suggesting a combination of embryonal conditions in which, as is known, the glycogen is resistant.



Fig. 530.—von Gierke's disease. Heart muscle fibres distended with glycogen.

On the whole it seems that the most plausible explanation may lie in a defect in the secretion of the anterior lobe of the hypophysis which, as Cope and Marks have shown, is necessary to make the glycogen susceptible to the action of adrenalin. When opportunity offers, a precise study of the hypophysis should be made.

The cases vary in that in some the accumulation of glycogen is chiefly in the liver while in others the kidneys are enlarged and choked with glycogen and occasionally the heart seems to be equally involved in this storage and greatly enlarged. Recovery is rare but death usually results from some terminal infection, although at all times the patient is on the borderline of hypoglycæmic shock. Other cases described by Debre and Grenat in which the liver is greatly enlarged are quite different since the enlargement is due to great accumulation of fats in that organ. This recalls the fact that several authors have suggested an analogy between

von Gierke's disease and those in which various lipoids are stored, such as Gaucher's, Niemann-Pick's disease, etc.

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## CHAPTER LIV

### DISEASES DUE TO INJURIES OF ORGANS OF INTERNAL SECRETION (Continued)

*Disturbances of the functions of the thyroid gland. Anatomy and physiology. Chemical studies of secretion. Relation of iodine. Relation to hypophysis. Effect of loss of thyroid function. Myxaedema. Colloid formation. Goitre, various forms, aetiology, relation to iodine consumption. Cretinism. Riedel's ligneous thyroiditis. Exophthalmic goitre. Symptoms, pathological anatomy. Theories of origin and nature. Effect of iodine.*

#### DISTURBANCES OF THE FUNCTIONS OF THE THYROID GLAND

THE thyroid, arising from the branchial arches, is composed finally of two lateral masses in some animals, of a fused organ in others, the isthmus of connection in man crossing in front of the trachea. The original duct opening at the root of the tongue is interrupted by the growth of the hyoid bone, but occasionally there are remnants of glandular tissue left about the foramen cæcum, which represents its outlet. The alveolar structure of the mature gland, its relation to blood-vessels and its colloid secretion, and the surmises about the fate of that secretion are discussed in all text-books of histology and physiology.

The function of the thyroid is generally assumed to be well known, but there are many things about it, especially in its relation to other organs of internal secretion, which are obscure. In embryonic life it is made up of more or less solid strands of epithelium which later take the form of alveoli and begin to contain colloid. In the mature gland the question of the secretion of colloid, and more particularly of its distribution into the rest of the body, offers difficulties which are doubtless repeated in other organs of internal secretion. Rienhoff, who has made beautiful studies of the lymphatics in the thyroid, feels that the colloid is not carried away by them but that the secretion of the thyroid must enter the blood-stream by way of the capillaries which form a far finer network about the follicles. Most difficult is the decision as to whether the gland is actively secreting or not, and this becomes of importance in the consideration of various pathological conditions, for the alveoli may be distended with colloid so that the lining cells are flattened, and then from the general symptoms it is thought to be relatively at rest, or the alveoli may be empty and its walls lined with high epithelium thrown up into folds, and then from the symptoms it is thought to be vigorously overactive and that all the secretion is discharged as fast as it is produced. There are contradictory features in this, however, as will be detailed.

The colloid contains iodine, as shown by Baumann, and this is in protein combination as thyreoglobulin (Oswald). It has definite effects upon an animal increasing the metabolic rate and the heat production when injected, and in excess producing nervous excitability, tachycardia, etc. No other constituent of the colloid than the iodine-containing thyreoglobulin will do this. Kendall has isolated in pure form a less complicated iodine-containing substance, thyroxin, which is apparently the essential principle of the thyroid secretion, and recently Harington has synthesized this. It seems a new triumph of chemistry to be able to put together elements to form the actual substance secreted by this gland.

Harington's work has gone on to show that thyroxin is a tetraiodo derivative of thyonine which is the parahydroxyphenyl-ether of tyrosine but that this forms only 40 per cent of the total iodine content of the thyroid. The remaining 60 per cent occurs in the acid soluble fraction apparently as 3:5 di-iodo tyrosine which, alone, is physiologically inactive but very active when linked with thyroxine and other amino-acids and built up into thyroglobulin which is stored as colloid.

Iodine taken into the body is almost at once fixed in the thyroid but the elaboration of these specific combinations requires time.

Most of the studies are concerned with the iodine content of the thyroid and with the morphology of the follicles and their lining epithelium. But probably some of the confusing results might be cleared away by study of the distribution of the secretion throughout the body. Briefly, when the thyroid appears most vigorously active, its cells are hyperplastic but its follicles are empty of colloid and it contains little or no iodine. Under other conditions, especially in regions where it is known that iodine is deficient in food or water supplies, the follicles become distended with colloid to the great enlargement of the thyroid. While the immediate withdrawal of iodine may empty the thyroid of its colloid and stir its hyperplasia, this gradual partial insufficiency of iodine in the alimentary intake might perhaps be thought of as leading to the storing of a colloid ineffectual in some respects, so that it remains stored. Indeed, in old goitres one can observe differences in the consistency and staining properties of different levels in the colloid of the most distended follicles so that some of it is hard and can be broken, suggesting its retention as useless material which cannot be secreted into the body at large.

Administration of iodine allows the perfection of part of the colloid at least, and the softening and secretion of that, although it seems probable that the inspissated part will remain since the thyroid is not returned to a normal state. Marine holds that all such colloid-distended goitres begin with hyperplasia of the epithelium of the follicles, and emphasizes the irregularity in the growth of the tissue which is focal and results in circumscribed nodules—the so-called *adenomatous* or *nodular goitres*.

When part of the thyroid is removed, the remainder is rapidly changed into an overactive gland with proliferation of the cells and complete secretion of the colloid, as shown by the experiments of Halsted. This change in structure can be prevented by the administration of iodine which evidently makes adequate secretion possible by the remain-

ing tissue which then continues to show normal follicles filled with colloid.

It is known that the thyrotropic hormone of the anterior hypophysis, if given in excess, will temporarily stir the thyroid to hyperplasia and rapid and complete secretion of its colloid. It is not agreed, however, by most authors, that this is the basis of this change as it is seen in exophthalmic goitre. But even there, as was shown by Kocher, in 1907, and has more recently been emphasized by Plummer, the sudden administration of a large dose of iodine will restore the colloid to the depleted follicles and stretch out the hyperplastic epithelium to line the smoothed out walls while it apparently modifies the secretion in some way so as to relieve the patient of the disturbing symptoms long enough to allow the surgeon to extirpate part of the thyroid. The great difficulties in the explanation of this situation will be referred to later.

Many questions remain as to the complex relations of the thyroid. It is evident that its function is of great importance to the body and that it requires material especially in the form of iodine to carry out this function. Further, that it can be stimulated by the hypophysis but is also stimulated by the needs of the body. Throughout it seems that the symptoms or bodily changes produced by insufficiency or excess of this secretion in its relation with other endocrine products or the functional activity of the organs, are the result of quantitative changes and not of the production of any abnormal toxic substance. Hence, it seems improper to speak of toxic goitre or thyrotoxic symptoms.

The reciprocal changes in other endocrine organs such as the enlargement of the anterior hypophysis with decrease of acidophile cells upon extirpation of the thyroid seem also determined by a disturbance in the normal balance since thyroid dosage will restore the hypophysis to normal.

#### MYXŒDEMA

Gull noticed, in 1874, the relation of atrophy of the thyroid with thickening of the skin, loss of hair and loss of mental and physical vigor and Ord called this condition myxœdema, thinking that mucin accumulated under the skin. Then Kocher found that the same result followed extirpation of the thyroid and many authors have observed it in persons in whom goitres have evidently become completely inactive through degeneration and destruction of the active tissue. Such are the cretins whose stunted growth and imbecility are generally associated with still greatly enlarged thyroids.

This may occur in children in whom the thyroid is atrophic. The rate of metabolism is greatly decreased and all the functions of the organs are retarded. Mentally the child remains at this stage at which the destruction of the thyroid found it and sexually it ceases to develop.

Such children may become very obese, but they do not grow in stature, because the process of bone formation is retarded, not merely at the epiphyses, as in chondrodystrophy (*q. v.*), but throughout, so that a delicate small skeleton is produced in which all the cartilaginous epiphyseal lines and junctions remain as cartilage until very late in life.

In one case dissected some years ago a few of the permanent teeth

had appeared, crowding inside the milk teeth, all of which were still present. The sternum was in several parts at fifteen years of age, and the three pelvic bones were still joined only by cartilage in the acetabulum. The thyroid was reduced to a minute mass of distorted alveoli about the foramen cæcum, and two extremely small cystic nodules somewhere in the position of the lateral lobes. These were smaller than the parathyroid glands, which were perfectly well preserved. The hypophysis was rather large, and gave the impression of being in process of hypertrophy. This girl was an idiot with the intelligence of a young infant.

In adults, except when the thyroid is removed at operation, there appears to have been hyperplasia with colloid accumulation before the exhaustion and atrophy of the thyroid occurs and development of the body stops at the stage already reached. Any further growth is stopped, and mental and sexual activity rapidly recedes, so that these people quickly become sexually impotent and mentally dulled. They grow sluggish and cold, appetite fails, metabolism is decreased, the skin becomes dry and scaly, and in a curious way thickened and dense. Heavy pads form in a characteristic way below the clavicles and elsewhere, and over the face and forehead the skin may feel as though there was a thick, pasty elastic infiltration in its deeper layers, so that it cannot be easily pinched up into a fold.

There are all imaginable grades of this thyroid insufficiency, and the slighter ones are difficult to recognize, but in the more complete degrees the effects are overwhelming. In a relatively short time if there is no therapeutic intervention the patient sinks into a state of idiocy and physical torpor such that one is reminded rather of the life of a vegetable than that of a human being.

The proof that all this is due to the loss of the thyroid lies in the fact that the daily long-continued administration by mouth of an extract of the thyroid of some animal will restore such an inert being to life and activity. The child grows and develops and brightens into a normal person. The adult is transformed to his old self, the whole machinery quickens its rate, the skin becomes thin and moist, and the hair grows. The face loses its dull, bloated appearance, and the tongue its thickness and sluggishness, and words and ideas come back. It is as though the regulator of an engine were reset at the normal point. The same effect has sometimes been attained by the transplantation of thyroid tissue into the patient, or has appeared gradually with the increase in size through compensatory hypertrophy of some fragment or accessory nodule left intact.

In these persons, as in animals, it is found, by studying the metabolism, that the output of nitrogen in the urine is greatly decreased, that the intake of oxygen and the discharge of carbon dioxide are similarly on a lower level.

Unless the appetite is greatly decreased, there is apt to be a gradual increase in weight under these circumstances, and most of this is in the form of fat. Since the oxidation is thus decreased in the restricted metabolism of the muscles and other organs, the production of heat is

diminished, and this may reach the point where the regulatory mechanism is unable to maintain the normal standard of bodily temperature, so that it falls even several degrees.

Carbohydrate metabolism is affected in such a way that it becomes practically impossible to produce an alimentary glycosuria, that is, to cause the elimination of sugar in the urine by feeding it in excessive amounts. Even those drugs and nervous disturbances which ordinarily produce glycosuria fail to do so, or succeed only when pushed to extremes. Adrenaline, which in relatively small doses produces hyperglycæmia and glycosuria, fails to do this in the absence of the thyroid, or does so only when given in far larger doses. Even the glycosuria of depancreatized animals is greatly modified by the loss of the thyroid, although not entirely abolished. This is apparently due to the lowered utilization of the carbohydrates for excessive thyroid feeding increases glycogenolysis and lowers the glycogen content of the liver. Partial removal of the thyroid, leaving enough to carry on the function fairly well, may produce no such symptoms, but the offspring of such an animal may have exceptionally large thyroids as though to compensate for the lack in the mother. Dr. Halsted found that the remaining portion of the gland after a time showed a structure quite different from that of the part removed, in that instead of rounded colloid-filled alveoli with flattened epithelium, the alveoli are of various sizes and extremely irregular in form with diverticula and projecting folds, lined with high cubical or columnar epithelium and devoid of colloid. He recognized this as a compensatory hypertrophy and thought it represented an extreme effort on the part of an insufficient mass of thyroid tissue to function adequately. This has been confirmed by everyone and is the basis of the idea that when the thyroid is secreting so actively, the secretion is all discharged in response to the demand from the body, leaving the alveoli empty.

With regard to the colloid secretion which contains iodine, we can hardly imagine that in every case the concentration of iodine is the same, or the quality of the colloid in other respects maintained at an absolute standard. It is possible, therefore, that a thyroid distended with colloid may be poorer in the active factors than one that contains relatively little. Marine found that upon analysis such a hyperplastic thyroid as has just been described in compensatory hypertrophy is much poorer in iodine than a normal thyroid. That might well be explained by the discharge of the secretion. But it is not quite so easy to explain the fact that when he gave iodine to such an animal its thyroid quickly returned to a state resembling the normal with rounded alveoli distended with iodine-rich colloid, unless we assume that he gave so much iodine and rendered the power of secretion of normal colloid so active that the thyroid not only satisfied the needs of the body, but could store a great reserve of secretion.

Marine really studied especially dogs in the environs of Cleveland where nearly every street-dog has an enlarged thyroid, showing the type of tissue seen in the compensatory hypertrophy. This he thought due to lack of iodine in the food or water because administration of iodine quickly converted them into normal looking colloid-containing thyroids.

### GOITRE

Great changes occur in the size and appearance of the thyroid under conditions which are very little understood. In general, we use the word "goitre" to indicate any enlargement of the thyroid, but there are many different types which are obscurely related.

Wegelin, to whose excellent discussion of the whole subject the student is referred, classifies them as follows:

In infants there are congenital goitres, which may be parenchymatous, telangiectatic, or colloid.

In children and grown persons there are found diffuse goitres which may be parenchymatous (composed of small alveoli) or colloid (with large alveoli distended with colloid). There are in other cases small areas of hyperplasia, and in still others, cysts. But more common than



Fig. 531.—Nodular goitre. The adenoma-like nodules are soft, opaque, and granular.

these are the nodular or adenomatous forms of goitre, among which he distinguishes parenchymatous types, with trabecular, tubular and small alveolar nodules, and colloid types with simple large alveolar nodules, and others with papillary growths in the alveoli.

The congenital forms are not common in this country except perhaps in certain "goitre regions," where they also occur in newborn calves and other animals. They are probably the result of thyroid insufficiency in the mother. Nor are the diffuse thyroid enlargements with small alveoli commonly found in grown persons. On the other hand, there are a great many cases in which the thyroid is very much larger than normal because each alveolus is greatly increased in size and distended with a glairy colloid, to such a degree that the lining epithelium is flattened until it looks almost like endothelium. This is the diffuse colloid goitre (Fig. 533), and on section the gland is rather soft and translucent like amber and nearly uniform in appearance throughout, although it

may be lobulated, and there are often haemorrhages or necroses or the scars that result from them. One can easily make out the large colloid-filled alveoli with the naked eye.

The nodular forms of goitre are more common, sometimes combined with the colloid enlargement, often apparently arising in normal thyroid tissue, which is then stretched and flattened by their pressure. These nodules, which seem to begin in young persons about the time of puberty and to progress slowly, are commonly called adenomata, although it is very doubtful whether that is an accurate use of the word. They vary greatly in size and number and gross appearance, but they

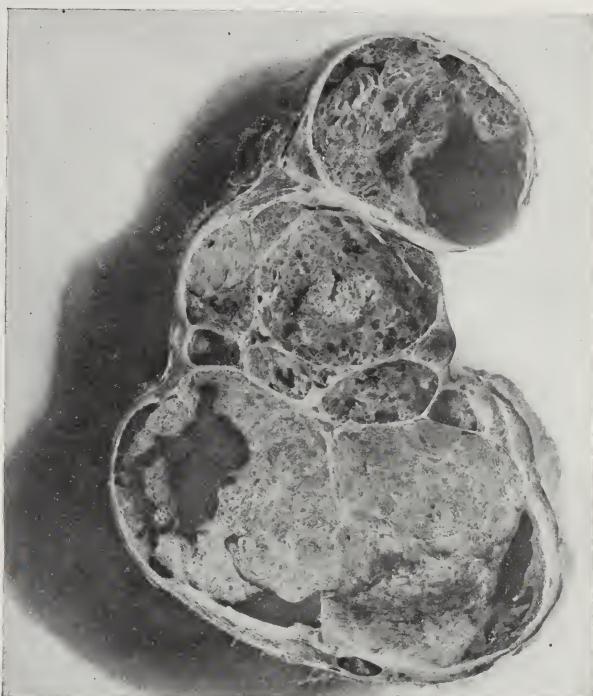


Fig. 532.—Large goitre with colloid adenomata, in some of which there are great pools of colloid. These stretch and compress the remnant of normal tissue.

are always quite easily distinguished from the surrounding tissue. In their fresher states they are elastic and show a smooth, swelling, finely granular or velvety surface which is grayish white or pink, often with small haemorrhages (Fig. 531). Microscopically such a nodule is seen to be made up of many small, round alveoli, lined with rather high cubical epithelium enclosing a small lumen which usually contains little or no colloid (Fig. 534). The alveoli are not, as a rule, closely packed together, but are separated by an abundant rather oedematous-looking stroma rich in blood-vessels from which interalveolar haemorrhages often arise. After a time necroses occur in the central portion, the alveoli disappear, and a hyaline stroma is left, often with haemorrhage or areas

of calcification. Often the whole centre becomes liquefied and a cyst is formed with turbid and blood-stained liquid contents which in time may become a clear yellow fluid. The rind of the nodule persists often with extensive calcification or even bone formation and is deeply pigmented with haemosiderin.

The other kind of nodule with large alveoli distended with colloid may be associated with those just described to form a large coherent mass between and about which only stretched-out remnants of the original thyroid tissue can be seen (Fig. 532). Their structure is much like that of the diffuse colloid goitre, but the surrounding stroma seems denser and they are more prone to circulatory disturbances and necrosis—the central part breaks down into a pigmented and calcified cyst. The papillary forms are relatively uncommon, but they, too, may sometimes be associated with the other kinds.



Fig. 533.—Colloid goitre. The alveoli are all enlarged and contain colloid.

Wegelin does not agree with Wölfler, who called the small alveolar nodules "foetal adenomata," a term which we also reject, because Wölfler saw only surgical specimens and had no experience with their beginnings, and thought that this was a remnant of embryonic tissue. He agrees rather, with Hitzig and Michaud, that these nodules arise in later life from the thyroid tissue.

The functional activity of the nodules has been much studied and Goetsch conceived the idea that the abundance of mitochondria in their cells indicated an excessive secretory power, but it appears that these structures are just as abundant in the cells of the most inert nodules. As far as their iodine content is concerned, scarred nodules with little gland tissue or colloid, contain no iodine, nor do the trabecular or small alveolar

nodules, but the colloid-rich nodules may contain a good deal. Marine and Graham also found no iodine in the parenchymatous nodules, while those which contain abundant colloid show varying amounts of iodine, but always less than the normal thyroid. The action on tadpoles (Guder-

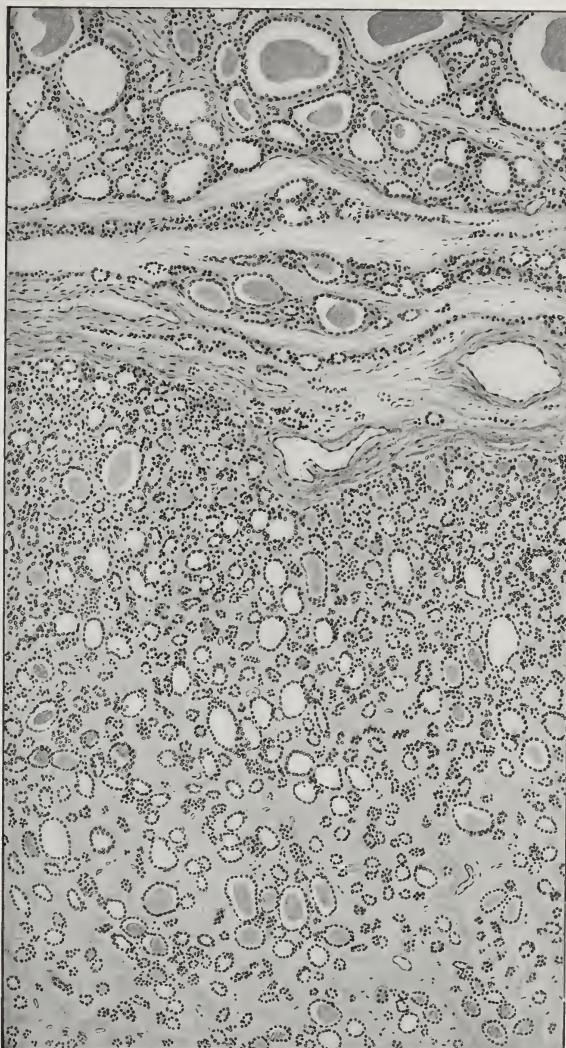


Fig. 534.—Circumscribed adenomatous nodule of the thyroid. The surrounding tissue is somewhat compressed. The alveoli of the nodule are small and round, and are embedded in abundant stroma.

natsch) is less than that of the normal thyroid, but qualitatively they are like the normal thyroid in their biological action.

From the experiments detailed above, one would expect the administration of iodine to turn the parenchymatous nodules into colloid-rich

nodules with large alveoli, but this is not true. Marine finds that the "fœtal adenomas" remain unchanged and absorb little iodine, while those with large alveoli behave like normal or hyperplastic thyroid tissue. So, too, cancerous tumors of the thyroid have no capacity for absorbing iodine. In a case of myxœdema following removal of a cancer of the thyroid metastases did not improve the myxœdema. v. Eiselsberg's case, always quoted as an example of the relief of myxœdema by a metastasis, was really only the subsidence of tetany which in those days was thought referable to thyroid.

Although the functional activity of such enlarged and distorted thyroid glands may not be strikingly disturbed, the mechanical effects upon the neighboring organs are often serious. The goitre may be so large as to be very unsightly, and impede the movements of the head, but more important than this are the results of pressure upon the trachea, the œsophagus, and the circulatory organs.

Lateral pressure upon the trachea frequently reduces its calibre to a narrow slit, with distortion and softening of the cartilages, so that extreme dyspnœa, emphysema of the lungs, etc., may ensue. Dysphagia from compression of the œsophagus is far less common, but the circulation is sometimes embarrassed, so that palpitations and tachycardia and, finally, cardiac hypertrophy are brought about.

Minnich, who has made a study of such goitre hearts, points out the mechanical strain offered in the lesser circulation by the effects of dyspnœa, but thinks that even more frequently the circulation is disturbed by alterations in the secretions of the thyroid, which affect the nervous regulators of the heart, diminishing especially the action of the depressor and allowing the heart to be overworked.

An interesting if rare form of enlargement of the thyroid is the so-called plunging goitre, which hangs down behind the sternum and moves up and down, in and out of the thorax, with respiration.

As to the aetiology in the case of goitres, there has for ages been discussion and dispute and the most fantastic theories have been proposed. It has been known for centuries that goitre is actually endemic in certain regions, usually in high valleys, as in the Himalayas, in the Alps and Austria, and in the Andes. But there are other endemic areas not so elevated, as in Norway and about the Great Lakes in North America. Some investigators have thought that this resulted from living and drinking the water upon certain geological formations; others, that particular springs (*Kropfbrunnen*) produced goitre; others, that intestinal infection common in those regions was the cause. There is little evidence for any of this, although it is clear that there is some rather mysterious cause in those places. Goitre is extremely common in such districts (McClendon), affecting more than half the people in some places, and there have been observed waves of increased frequency lasting over years. Wegelin feels that heredity has much to do with its perpetuation, as the children of goitrous parents start with a tendency to goitre and an already enlarged thyroid. But since the discovery of the intimate relation of iodine to the function of the thyroid and to its histological form, attention has been turned to that. Marine with his co-workers, after experimenting as de-

scribed upon dogs and finding that he could make the abnormal thyroid of the dogs in the Cleveland goitre region assume the normal form and colloid content by administering iodine, experimented further with school children. To 2000 children in one region where goitre was known to be prevalent he gave minute doses of iodides—so that each child received in all 2 grams of sodium iodide twice a year. Of these, only four or five developed goitres, while of 2000 others not so treated, 475 developed goitre.

In Switzerland and Austria the same thing is recognized, and great efforts are being made to induce the whole population in affected districts to use an iodized salt which is furnished by the government. Since in some countries salt is a government monopoly this can be done accurately. Indeed, it was worked out carefully in France by Chatin sixty years ago and, although in that experiment too high proportions of iodine were used and through political reasons and apathy the attempt was abandoned, the principle was exactly the same.

de Quervain states that the Swiss Goitre Commission recommends a dose of iodine of 16 to 20 mgm. per year, which amounts to 5 mgm. of iodine to 1 kgm. of cooking salt. In addition, the administration of iodine under medical supervision to school children is being carried out and much is hoped for in the way of prevention of goitre in coming years. Such amounts of iodine seem much smaller than those administered by Marine, and the question of the production of symptoms of thyroid intoxication after giving iodine is much discussed. Apparently there is some risk in very sensitive persons and in those already affected with exophthalmic goitre of accentuating the symptoms or even of bringing them on, but this seems extremely slight and, for the most part, a traditional fear which came from Rousseau's warnings.

All of the Swiss workers say that the lack of iodine alone can hardly be regarded as the single cause of goitre. Organic poisons of some sort are still vaguely suggested, as was done by Marine and Gaylord. Excess of calcium in the diet has been thought to play a part and it is possible that it may interfere in some way with the final action of the thyroid secretion. Other factors in the food should be recognized also—excess of proteins and fat, and perhaps especially liver, may cause hypertrophy of the thyroid and Chesney and his co-workers have shown that a diet of cabbage will produce goitres in rabbits. Methyl cyanide increases the effect of the cabbage.

Marine himself says that the factors in goitre centre about iodine, the normal and abnormal requirements, substances preventing its absorption, and its actual lack in food and water supplies.

It seems possible, however, that the secretion and, therefore, the function of the thyroid are more complex than we have thought, and that the lack of some other element than the thyroxin may be responsible for some effects which are not easily cleared up by the administration of iodine.

**Cretinism.**—In these endemic goitre areas there occur among the general throng of goitrous people certain cases—very numerous in the more central parts of the regions—which seem to represent a far more

severe affection. These are the cretins. They usually have goitres, although some have only very small soft thyroids, but unlike the people of the more outlying regions who have goitres but are not especially disabled, the cretins show every degree of myxoedema—even to complete idiocy, with the corresponding stunted growth and stagnant metabolism, and are very often completely deaf and dumb. They are the ones best described as leading the existence of a vegetable, the stunting of growth, the extreme distortion of the thyroid, which is poor in iodine, and all the derangements of metabolism and development of the organs have, in most cases, gone so far that it is too late for thyroid extract to produce much change and, of course, iodine alone would probably be equally ineffectual. There is probably no other reason why cretins should not be rescued as well as the sporadic cases of myxoedema, but most workers

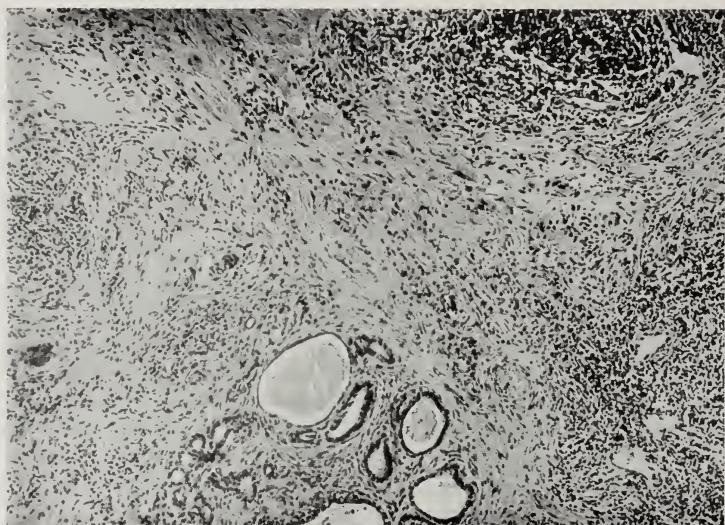


Fig. 535.—Riedel's ligneous thyroiditis.

have been pessimistic about the effects of thyroid medication on them.

The student should consult the illustrations in Virchow's early papers or in those of Bourneville or Jeandelize to appreciate the extraordinary appearance of cretins. I think they hardly occur in this country.

*Riedel's ligneous thyroiditis*, or *Riedel's struma* should be mentioned as a peculiar scarring of the thyroid with accumulations of lymphoid tissue, often with giant-cells and with great loss of actual thyroid tissue. The cause is unknown but it seems to be essentially a chronic inflammatory process in which there are finally formed wide bands of dense scar tissue in which only scattered groups of thyroid follicles are found (Fig. 535). The extreme hardness of the mass has suggested the name.

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### EXOPHTHALMIC GOITRE

Most interesting of all the diseases which affect the thyroid is this so-called Graves' or Basedow's disease, in which, at least, there are active symptoms in place of the sluggish effects met with in the diseases following upon deficiencies in the thyroid gland. But here the nature of the relation of the symptoms to the thyroid is not so clear, although it is commonly looked upon as the effect of overactivity of the gland.

The disease is common, occurring sporadically everywhere without recognizable relation to any particular district, and much more frequently in women than in men. Extremes of age have been reported, but it is essentially an affection of young and middle-aged adults. It



Fig. 536.—Exophthalmic goitre. The patient shows a goitre of moderate size; great exophthalmos, smooth forehead, and abnormal expression.

begins without any very obvious causes, after recovery from some infection or often after some violent emotional disturbance or fright, sometimes appearing suddenly in its full intensity, more frequently developing gradually. The more prominent disturbances of function are briefly as follows: there are nervousness and irritability, the patient being agitated and perturbed by occurrences which would produce little impression on a normal person; the skin is flushed and moist, and the patient feels hot; the heart beats very rapidly and forcibly, and the peripheral vessels are distended and thump. There is tremor; the eyes protrude abnormally, so that the eyelids may fail to cover them properly; there are disturbances in the motility of the eyelids and of the forehead (Fig. 536).

There is often, though not always, enlargement of the thyroid, and finally, in spite of the good appetite, the patient wastes away. Nitrogenous metabolism is increased, as judged by the excretion of nitrogen in the urine; the calorimeter shows an increased dissipation of energy. The tolerance for sugar is lowered, and glycosuria is readily brought about or occurs spontaneously, since the storage of carbohydrate is so unstable.

After operation, especially when the thyroid has been much handled, the patients sometimes show great intensification of the symptoms for a short time.

Such patients are more or less incapacitated, but some of them go on for years and die of an intercurrent affection. Others develop symptoms of such intensity that they die from the disease itself, often with mental derangement, with cardiac dilatation, with excessive vomiting, or with exhaustion from any of these.

At autopsy fairly constant changes are found in the thyroid, in the thymus, and in the lymphoid structures. The heart is frequently hypertrophied, but there are no very obvious changes in the other organs. The brain, in spite of most diligent search, has shown nothing constant.

**The Thyroid.**—Many descriptions of the thyroid alterations have been given and many subdivisions made, but it is doubtful whether these classifications have any great significance. Many stages or degrees of alteration are found in the gland, and these must be studied in detailed reports on this subject (A. Kocher, etc.). There is not always a great enlargement of the gland, and sometimes it cannot be palpated. When the thyroid is exposed at operation, it is found to be very richly supplied with blood, and over the surface course huge distended veins whose walls tear readily, so that the risk of haemorrhage is great in these operations. After removal, when the blood runs out, the gland appears pale, dense, and hard, and on section its cut surface is both finely and coarsely lobulated, opaque, and of pale, grayish-pink color (Fig. 537). Little or no colloid can be found. On the other hand, there are some cases in which colloid is abundant, so that the characteristic gross appearance of opacity is not produced.

In a very considerable proportion of the cases there are circumscribed adenomatous nodules in the thyroid. These are of various types—they often contain colloid in large alveoli, but in other cases they have the ramifying alveoli of the same type as makes up the rest of the gland, or else they may be the granular nodules of small alveoli with much stroma.

Microscopically, there is found in the most typical cases an alteration of the gland (Fig. 538) which closely resembles that recognized as a compensatory hyperplasia in the remnant of the thyroid of a normal animal, some time after a large part of the gland has been extirpated. The alveoli are no longer uniform in size or shape, and contain little or no colloid. What they do contain is no longer homogeneous or refractive, but granular or shreddy, like a thin, coagulated fluid. The epithelium, instead of being flattened or low cubical, is high and often distinctly columnar, and is so increased in amount that it is thrown into folds, giving to the alveolus an irregular outline, with papillary ingrowths

encroaching greatly upon the cavity. Commonly many very small alveoli are associated with each larger one, and one sometimes receives the impression that many of these are merely cross-sections of the bays which project from the larger ones. The stroma is frequently but not always fortified by scar tissue, sometimes to such an extent as suggest a cirrhotic condition. Definite lymphoid nodules are often found scattered through the gland, an appearance which, while fairly characteristic of this disease, is rarely if ever seen in the normal thyroid.

These changes may sometimes be recognized as beginning in patches scattered through the normal gland or in adenomatous nodules, but in most cases they appear gradually and diffusely throughout the organ. They are constantly found, in some stage of development, although in

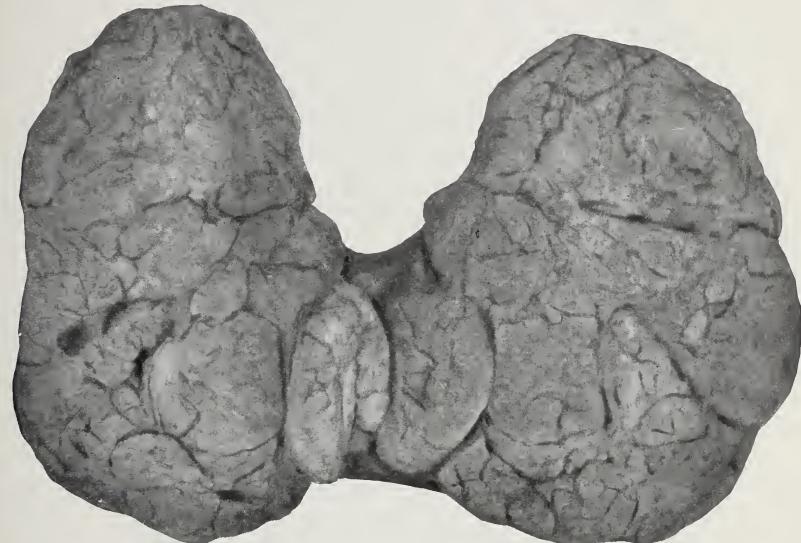


Fig. 537.—Exophthalmic goitre. Gross external appearance of the thyroid.

any large series one finds several cases in which, although the symptoms are definite and intense, the alveoli of the thyroid are still large and fairly uniform in outline and filled with colloid. The various modifications of this anatomical picture which involve reduplication of the epithelial lining, distortion and irregularity in the form of the cells, desquamation of the epithelium, etc., must be read in such papers as that of Kocher.

The thymus, which is ordinarily atrophied in adult life except for microscopical remnants, is found to be greatly enlarged. This has been constant in the autopsies which I have seen, and in some cases it has presented itself as an organ almost the size of one's hand. Hassal's bodies persist, and the small cells are in such excess that the ordinary distinction between medulla and cortex is obscured. Dr. Halsted discusses its importance in connection with the symptoms and the favorable effect of its extirpation.

The adrenals are described as somewhat atrophied in both cortical and medullary portions in some cases, and it seems possible that this may in some way be connected with the hyperplasia of the thymus, for, as mentioned in another place, Marine has found that extirpation of adrenals retards the involution of the thymus in animals, but that thyroidectomy prevents this effect. The extraordinary prominence of the thymus should receive more attention than has been accorded to it. It seems to point to a more extensive involvement of the organs of internal secretion than has been generally thought to occur.

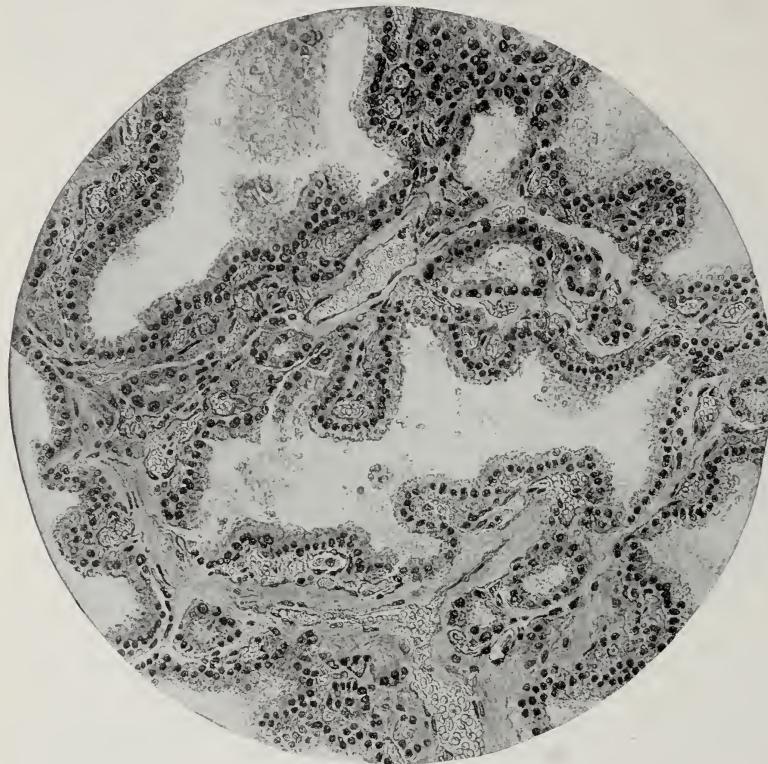


Fig. 538.—Exophthalmic goitre. Alveoli are irregular in form, lined with columnar epithelium, and almost devoid of colloid. The stroma is increased in quantity.

The lymph-glands, especially in the neck, are often markedly enlarged. In some cases this increase in the bulk of the lymphoid tissue occurs throughout the body, even the solitary nodules in the intestine projecting as gray prominences. Together with this, which corresponds with the finding of new lymph-nodes in the substance of the thyroid, there is a distinct lymphocytosis (Kocher), which is reduced to normal when the thymus is removed (Capelle and Bayer). The liver is said to show anatomical changes in some cases leading to destruction of much of its tissue but we have not observed this in the cases which have come to autopsy.

**Conceptions of Nature and Cause of the Disease.**—In spite of all investigation the nature of this disease is still in doubt. Since the statements of Möbius it has been most commonly thought of as the effect of hypersecretion or perhaps an altered secretion on the part of the thyroid, without any further curiosity being shown as to what might cause this altered activity of the thyroid. The main support for this lies in the recognition (by the acetonitrile method of Hunt) of excess of thyroid secretion in the circulating blood, in the increased nitrogenous metabolism during the disease, in the harmful effects of thyroid extract, and in the peculiar hypertrophic changes in the thyroid itself. The lack of colloid there is ascribed to the rapidity of its removal by the lymphatics or the passing blood. Further, the view is supported by the beneficial effects of removing part of the thyroid or of ligating the thyroid arteries.

Opposed to this view are the following facts: the thyroid gland and the colloid contain less iodine than the normal gland; after extensive operative extirpation, or even in the natural course of the disease, symptoms of myxoedema which surely indicate insufficiency may arise, while the symptoms of exophthalmic goitre are still present and intense. Nor do the symptoms of exophthalmic goitre disappear with any precision upon the removal of half or more of the gland, as they should if they were merely the result of an excessive secretion. What actually happens is that the recognized influence of the thyroid in promoting nitrogenous katabolism is halted by the loss of the gland, and for a time the patient, in spite of her other symptoms, gains weight. Nevertheless, with the compensatory growth of the thyroid the weight sinks again. Further, it is impossible to reproduce exactly the whole symptom complex by administering an excess of thyroid secretion, although some of the phenomena can thus be brought about.

On the whole, it seems clear that while the thyroid is profoundly affected, and through the disturbance of its function does cause many of the symptoms, it is not alone responsible, but forms part in a chain or circle in which notably the sympathetic system and the chromaffine system, and probably the other organs of internal secretion, perhaps especially the thymus, are concerned. This is true, as we have seen in most of the diseases which involve these organs, and in their study we are more and more impressed with their close interrelation.

Cannon has recently reported an ingenious experiment which may shed much light on the affection, although in itself it must be regarded as a purely artificial imitation of the disease. He anastomosed the phrenic nerve, which sends an impulse with every breath to the diaphragm, with the cervical sympathetic, which gives sympathetic fibres to the thyroid. After the time necessary for the functional union of the two nerves had passed he found that the animals (cats) showed practically all the symptoms of exophthalmic goitre, tachycardia, diarrhoea, greatly increased appetite, emaciation, an increase of 150 per cent. in the nitrogenous metabolism, exophthalmos, and, while in the dark, a rhythmic expansion and contraction of the pupil with each breath.

On the basis of such experiments he thinks that in exophthalmic

goitre there may be a lowering of the threshold which normally limits the passage of sympathetic stimuli to the organs, and that the over-activity of the thyroid and the consequent symptoms are due primarily to a disturbance of the central nervous system and the preponderance of the sympathetic over the autonomic stimuli. It is true that others have been unable to confirm these results.

The more recent studies, beginning with Loeb and Basset, Allen, Smith and others, which have demonstrated the existence of the thyrotropic hormone of the anterior lobe of the hypophysis capable of stirring the thyroid to such hyperplasia as is seen in exophthalmic goitre, tempts one to believe that this disease may be the result of some change in the hypophysis which accentuates that influence. This idea has been discussed by many but nearly all reject it on the ground that as shown by Collip, this effect cannot be maintained in experimental injections of the hormone but soon gives place to a retrogression to a normal state of the thyroid, apparently from the development of some sort of neutralizing substance in the blood. That the action is not by way of the sympathetic nervous system is shown, however, by the fact that the thyrotropic hormone acts equally well on implanted fragments of thyroid tissue, or even on thyroid tissue growing in tissue culture in vitro. It seems that the objections raised to the idea of the hypophyseal origin of exophthalmic goitre are not absolutely and finally convincing but a decision must depend upon further studies.

Plummer and Wilson and others have made the statement that much milder symptoms of excessive thyroid secretion without exophthalmos and some of the other features of Graves' disease may be caused by nodular adenomatous masses in the otherwise normal thyroid, which they call toxic adenomas.

In general, Kocher, in his London address in 1907, showed that although he had believed that the symptoms of exophthalmic goitre are greatly aggravated by iodine, the sudden administration of rather large doses relieves them for a time. Plummer has since repeated this and it is in general use as a pre-operative measure, especially to protect the patient from the intense accentuation of the symptoms which sometimes followed the operation. If Lugol's solution of iodine and potassium iodide be given for ten to twenty days in rather large doses the symptoms are remarkably diminished, and operation can be performed with much less risk and with better result than otherwise. But this effect is very transient and cannot be produced if the patient has been taking iodides for a long time. Its value is essentially in preparation for operation so far as it is now understood. Rienhoff has found by first excising a small piece of the thyroid and then giving the iodine for days prior to excision of a lobe of the gland, that the hyperplastic thyroid with its empty alveoli is changed for the time into an almost normal-looking thyroid with rounded alveoli filled with colloid. He regards this as responsible, especially in those instances in which the hyperplastic alteration of the follicles is in scattered patches, for the production of adenoma-like nodules with large follicles distended with colloid. Although he recognizes the existence of nodules of another type,

such as have been described above, which appear more like actual new growths, he thinks that the numerous masses of large alveoli which are often found in cases of exophthalmic goitre which have run a long course with remissions and exacerbations, may be the result of an analogous process.

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## CHAPTER LV

### DISEASES DUE TO INJURIES OF THE ORGANS OF INTERNAL SECRETION (Continued)

*The parathyroid: Anatomy, physiology. Tetany; hyperexcitability of nerves. Relation to calcium metabolism. Effect of excessive action by parathyroid tumors or by renal insufficiency. Osteitis fibrosa.*

*Thymus: Anatomy. Evolution and involution. Effects of extirpation. Hyperplasia. Thymus in exophthalmic goitre, in myasthenia gravis, in status thymico-lymphaticus. Effect of extracts upon growth and maturation.*

#### DISTURBANCES OF FUNCTION OF THE PARATHYROID GLANDS

THE parathyroid glands arising from the walls of the third and fourth branchial clefts come to lie in man in various situations along the posterior edge of the thyroid, and are usually four in number. They are brown and soft, with conspicuous peripheral veins, and are composed of anastomosing strands of cells many of which have a very clear protoplasm in early youth, while in later life the predominant cells have a slightly granular cytoplasm, a few groups standing out by reason of their small dark nuclei and their bright eosinophile protoplasm. Differences in the function of these cells are not understood.

**Physiology.**—When the parathyroids are completely extirpated, a period of twelve hours to several days elapses during which there are no symptoms, but then there appear the evidences of the so-called tetany, which may quickly reach the greatest intensity. Twitchings of various muscles appear, and soon there is a continuous quivering or vibration of the tense muscle, which can be felt as a thrill interrupted by violent convulsive jerks. The whole body becomes rigid, the jaws snap, and every muscle is thrown into violent clonic convulsions. Smooth muscle is said to be affected also, but its participation is inconspicuous. Such convulsions involve the most extreme labor on the part of the muscles, and the temperature rises to fever heat because the dissipation of heat cannot proceed rapidly enough. In the dog respiration becomes very rapid, because that is its way of dissipating heat. Death may occur in such a convulsive seizure, or the tetany may pass off for a time and recur until death follows from complete exhaustion. Sometimes a sort of continuous milder twitching persists for a long time, the animal rapidly wastes and becomes infected, and dies in a kind of cachexia.

All this depends upon the most striking and constant feature of tetany, the hyperexcitability of the motor nerves, with which there appears to be associated a similar hyperexcitability of the sensory nerves.

This hyperexcitability is easily shown, in that a muscular jerk is elicited by a galvanic shock applied over the motor nerve, so weak that it would have no effect under normal conditions. The direction of the

current and the character of the shock, whether due to opening or closing of the circuit, must be considered, and the following table will give an average comparison between the shocks necessary to produce a visible muscular contraction in a normal and a tetanic animal.

	NORMAL MILLIAMPERES	TETANY MILLIAMPERES
Kathode closing . . . . .	0.3	0.05
Kathode opening . . . . .	6.0	0.6
Anode closing . . . . .	1.8	0.8
Anode opening . . . . .	2.0	0.8

It will be seen that the greatest and most characteristic change is in the reaction to the kathode opening shock; that is, where the kathode of the battery is put on the nerve and the current broken. Practically all the other symptoms seem to depend upon this hyperexcitability of the nervous system.

It was found (MacCallum and Voegtlin) that injection of a salt of calcium would abolish the hyperexcitability and cure all symptoms of tetany, even to the extent of keeping the animal alive and well for months if regularly administered, and it was suspected that a lack of calcium in the circulating fluids and tissues might explain the hyperexcitability of the nerves. As a matter of fact, the blood and nerve tissues of animals in tetany contain a decreased amount of calcium. It was shown (MacCallum) that if an isolated extremity of a normal animal be perfused with blood from another in the height of tetany, the excitability of its nerves would be increased to the tetany level, returning to normal when again perfused with normal blood. Conversely, if one extremity of a dog in tetany be perfused with normal blood, the excitability of the nerves of that leg becomes normal, and that leg ceases to twitch, although the excitability rises and the twitchings begin again if the femoral vessels are reanastomosed with their stumps, so that the leg is again flooded with its own "tetany blood." This blood is poor in calcium, and it seems that the hyperexcitability of ganglion-cells of the central nervous system throughout, as well as the nerve endings, is produced by this, for if one remove calcium from the blood by dialysis (MacCallum and Lambert), and then perfuse an extremity with that blood, exactly the same hyperexcitability is produced. Further evidence in favor of the conception of the parathyroid as an organ presiding in some sense over the calcium metabolism is presented by Erdheim, who finds that in chronic tetany in rats, produced by extirpating almost all of the numerous scattered glands, calcium fails to be deposited in the constantly growing teeth, so that they become soft and break off. Fractured bones heal with only a soft callus, and thus fail to unite firmly. Reimplantation of parathyroid tissue restores the ability of the dentine to calcify and harden, and reestablishes the ossification process as long as the graft lives.

The influence upon the sympathetic system is not yet worked out, although there are vague indications of hyperexcitability of those nerves after the destruction of the glands.

An enormous literature has sprung up about tetany in late years, much of which has been due to an effort to discover some poison in the blood. I have been quoted as insisting upon the existence of a poison because tetany can be relieved by intensive bleeding and replacement of the blood with salt solution, but this does not prove that there was a poison in the blood, but only that such bleeding and infusion reduces the excitability of the nerves to a point at which it requires a very much greater stimulus than normal to produce a muscular contraction. It is quite as true of normal animals.

Noel Paton and his school have found various guanidine compounds in the blood in tetany, and, indeed, methylguanidine when injected will produce symptoms practically identical with those of tetany. They are not specifically counteracted by calcium, however, nor by parathyroid extract, so that it is at least not identical with the tetany that results from destruction of the parathyroids, nor with the ordinary forms of human tetany. Greenwald fails to find guanidine in the blood of experimental animals in tetany and Major confirms this result.

Others have studied the tetany that arises from excessively forced breathing (hyperpnoea) which by driving off carbonic acid leaves the balance on the alkaline side. The forced introduction of alkaline phosphates or carbonates may have the same effect. But while these things may interfere with the proportion of free calcium in the blood, there is little evidence that tetany is in nature due to alkalosis. Tetany in infants is quite common with symptoms analogous to those in animals deprived of their parathyroids, although by no means so severe. Howland and Marriott found that this is always associated with rickets and shows a lowering of the calcium content of the blood. There is often a lowering of phosphorus, too, and sometimes this may be even lower than the calcium. Howland found that one or other might be as high as normal, but if the product of phosphorus and calcium content in milligrams be less than 40, tetany would supervene. These low figures were thought to be due to inadequate absorption from the intestine and the condition can be cured with cod-liver oil or exposure to ultraviolet rays. Calcium in the serum does not increase with irradiation in parathyroprival tetany as it does in infantile tetany, so that there is some difference in their character.

Recently a great epoch in the study of the parathyroid has been initiated by Collip's discovery of an efficient method for extracting the active principle of the parathyroid. This new extract is extremely powerful and immediately removes all the symptoms of parathyroid tetany or of infantile tetany. It brings back calcium into the blood (it has no effect on guanidine twitching) and does so with such vigor that it must be administered with great care; otherwise, from the excess of calcium, the blood becomes thick and dark and will not circulate freely, and the animal dies.

Later work carried out especially by Aub and his co-workers has done much to throw light upon the quantitative relations of calcium and phosphorus as influenced by the parathyroid glands and the rôle of phosphorus as suggested years ago by Greenwald, has become more

prominent. When the parathyroids are extirpated the calcium of the blood is decreased but not because of its excretion in the urine, for that is also decreased. On the other hand, the phosphorus in the blood is increased and its excretion decreased. When a potent extract of the parathyroid (parathormone of Collip) is injected, there is a sudden increase in the urinary phosphorus excretion and a lowering of the phosphorus content of the blood. Calcium increases in the blood and is excreted in increased amounts in the urine. All this, worked out carefully in a patient with parathyroid insufficiency by Albright and Ellsworth, is in accord with the results of Albright, Bauer, Ropes, and Aub in experimental animals. It is their impression that the vigorously increased phosphorus excretion is the primary effect of the administration of the parathyroid extract.

When too great a dose of the extract is given and the calcium has reached a very high point, a secondary phenomenon occurs. Phosphorus is no longer excreted in the urine and serum phosphorus rises abruptly, producing an increased amount of calcium phosphate which leads to calcium phosphate precipitation in various tissues (Albright, et al.).

The high proportion of calcium in the serum is evidently due to the action of the parathyroid extract in withdrawing calcium from the bones, the chief storehouse. If this condition is protracted as in the cases in which a tumor-like enlargement of the parathyroid constantly pours into the blood an excess of the parathyroid secretion, it becomes evident that calcium is being removed from the bones which show the changes known as *osteitis fibrosa*.

*Osteitis fibrosa*, or von Recklinghausen's disease, is an affection in which with pain and disability followed by a succession of fractures and distortions of the bones, examination of the blood shows a great excess of calcium and diminution of phosphorus. Roentgenological study reveals the great rarefaction of the bones, often with areas in which it is evident that cysts have been formed. These bones, if opportunity arises for this histological study, show not only extreme thinning of the cortex and laminæ with a partial replacement of the adjacent tissue by connective tissue, sometimes with many large osteoclasts, but also abundant active osteoblasts attempting to repair the loss of bone substance. Osteoid tissue is not conspicuous, instead there are masses of fibrous tissue replacing areas of cancellous bone near the ends of long bones, much pigmented and generally with cysts which are mere accumulations of gelatinous blood-stained fluid in this tissue. In contrast with this rarefaction of the bone is the extraordinary deposit of calcium in the walls of blood-vessels and in various organs throughout the body, perhaps especially in the lungs and kidneys.

Such a combination of numerous fractures of rarefied bones with increased urinary excretion of calcium and phosphorus and heightened serum calcium with low serum phosphorus, is generally due to the existence of a tumor-like enlargement of the parathyroid which is pouring out an excess of parathormone. Surgical removal of such a tumor results in a prompt return of the calcium-phosphorus balance in the blood

to normal, and in time the bones tend to return to their normal solidity. Teeth are not decalcified in such a process.

An enormous literature has arisen in the last years concerning such tumors of the parathyroid with their excessive action upon the calcium and phosphorus metabolism. A few cases of parathyroid tumor have failed to show such an influence but perhaps this is because usually only those which cause the absorption of calcium from the bones are searched for at operation. It suggests the possibility that these benign or adenomatous tumors may arise from different types of parathyroid cells in different cases but as yet no one has recognized any such histological differences between active and inactive tumors. Analogous adenomatous tumors affecting intensely the metabolism ordinarily governed normally by the cells from which it arose, are found elsewhere as for example in



Fig. 539.—Extreme atrophy of kidneys following ureteral obstruction and infection, resulting in osteoporosis.

the tumors arising from the islands of Langerhans which produce hypoglycaemia. Nothing is known as to the cause of their growth. Erdheim at first suggested that the enlargement of the parathyroid might be compensatory and brought about by an increased demand for the functional activity but this was disproven by the discovery that parathormone in such cases intensifies the symptoms while the extirpation of the large mass cures them—of course, provided that other parathyroid tissue or even a fragment of the tumor is left behind to avoid post-operative tetany. It seems, therefore, that in most cases at least the tumor arises as a single large mass while the remaining three parathyroids are unchanged. Such a tumor described by me, in 1905, in a case of extreme chronic nephritis, has stirred the comment that no study of the bones was made. No obvious change was found but a more

careful study of sections, made since the rise of interest in the bone changes, shows a moderate rarefaction of the cancellous bone with osteoclasts and Howship's lacunæ in great numbers. But while there is apparently no doubt of the independent origin of such a single nodule, the other parathyroids remaining normal, there occur other cases in which it is difficult to escape the conclusion that the enlargement of the parathyroids is compensatory for some disturbance. Such is the case, shortly to be described by Remsen and Shelling, in a boy with extreme atrophy and destruction of the kidneys with renal calculi and ureters so thickened and folded as to be practically obstructed (Fig. 539). The bones were in this case rarefied, fractured and displaced in every direction so that the patient with astounding distortions of the skeleton lay helpless in bed. At autopsy all four parathyroids were uniformly enlarged which practically forces upon us the idea of hypertrophy rather than tumor formation. It is difficult to imagine how excessive activity of the parathyroids could be useful in a case in which urinary excretion is practically obstructed. It is perhaps conceivable that the retention of an excess of phosphorus requires the increased activity of the parathyroid in removing calcium from the bones, but even if this is not already calcium phosphate, it, in combination with the retained phosphorus, is widely deposited in the tissues causing conspicuous calcification of artery walls and various organs.

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**DISEASES DUE TO THE DISTURBANCES IN THE FUNCTION OF THE THYMUS**

The thymus arises in man as a paired ventral outgrowth from the entoderm of the third and fourth branchial clefts, the main portion of the gland being derived from the third cleft.

Its original form is that of a flat pouch. With the gradual thickening of the walls of the sac the original lumen is obliterated, but vestiges of the original canal may be found even in the fully developed organ. In embryos of 30 to 40 mm. the rapid increase in size leads to great convolution of the surface, but although the form of the gland becomes more complicated, the parenchyma maintains its continuity. The right and left lobes remain separate, but there is no formation of isolated lobules.

Two types of cells are distinguishable in the thymus—one, resembling the lymphocyte, being concentrated in especial abundance in what thus becomes the cortex of the organ, while the other, recognized as epithelial in nature, occurs throughout, but is less masked in the central or medullary part.

Long dispute has occurred as to the nature of these cells and their origin, and the controversy is not yet finished. For many years the lymphocytic nature of the small cells was unquestioned, but their origin was attributed by one school (His, Stieda, etc.) to an early invasion of the epithelial elements by wandering mesenchymal cells, by another to a direct differentiation of the epithelial cells into lymphocytes identical with those of the blood-stream and lymphatic tissues (Beard, Kölliker, Prenant, etc.).

Stoehr, in 1906, declared that the small thymus cells were neither genetically nor functionally lymphocytes, but true epithelial cells, while more recently Hammar and Maximow have demonstrated an early invasion of the epithelial cells by migrating lymphocytes which accompany the ingrowing blood-vessels.

Morphologically and biologically the small cells resemble in almost every respect the lymphocytes.

The greater portion of the medulla and the reticular framework of the cortex are formed of derivatives of the original epithelial cells. They tend to arrange themselves in concentric fashion to form the Hassall bodies, which are not vestigial structures, but are constantly being newly formed from hypertrophic epithelial cell complexes. The protoplasm of the epithelial cells has a fibrillary character, and gives rise in places to intracellular fibrils resembling neuroglia fibrils.

There is no fibrous reticulum within the substance of the organ, and only a delicate sheath accompanying the blood-vessels. Opinion is divided as to the significance of the thymus as a blood-forming tissue, aside from its importance as a site for the production of lymphoid cells.

The thymus is thus, if we accept the prevailing view as to the lymphocytic nature of the smaller thymus cells, an organ composed of two genetically distinct types of tissue. These two types of cells, lymphoid and epithelial, are intimately commingled, and in the normal gland there constantly occurs a destruction of the lymphoid cells and

phagocytosis of the degenerating cells and pyknotic nuclear fragments, by the larger epithelial cells.

**Normal Evolution and Involution.**—The thymus reaches its maximum development coincidently with the maturation of the sexual organs, and then gradually atrophies. This is the normal involution, but since the work of Waldeyer it has been known that even in senescence there are regularly found the strands of thymic tissue containing presumably functioning thymic cells.

In early childhood cortex and medulla cannot be distinguished, as the lymphoid cells are predominant throughout. In later childhood the differentiation between cortex and medulla becomes more pronounced, but from adolescence on there is a progressive reduction in the amount of the parenchyma, the Hassall bodies are brought together, and the interstitial tissue and fat form a large part of the volume of the organ.

Hammar gives a table of normal weights at various ages, from which the following may be extracted:

	GRAMS
New-born .....	13.26
6-10 years .....	26.1
11-15 years .....	37.52
21-25 years .....	24.73
56-65 years .....	16.08
66-75 years .....	6.0

**Effects of Extirpation.**—Many efforts have been made to show the nature of the function of the thymus by extirpating the organ, but these have given variable and unsatisfactory results. Probably most, if not all, were really incomplete extirpations, and while some authors describe retardation of growth and rachitic changes in the bones, Park, in his review of the literature and description of his own experiments upon guinea-pigs, concludes that results such as his own, which were quite negative, are most trustworthy, and that developmental anomalies in the dog after such operations are not due to the loss of the thymus, but to confinement, unsuitable food, etc.

For a discussion of this whole question the reader is referred to the paper of Park and McClure in the American Journal of Diseases of Children.

**"Hyperplasia," "Abnormal Persistence" of the Thymus.**—Since thymic tissue can be demonstrated in normal individuals at any age, the term abnormal persistence should be dropped, but there are cases in which the thymus fails to undergo involution at the proper time, and others in which there is a renewal of growth after involution has been established. In these latter cases it may attain a weight several times that of the normal organ.

Such hyperplastic glands are found in infants usually unassociated with general lymphoid hyperplasia, in older individuals in connection with various derangements of the organs of internal secretion, particularly thyroid, adrenals, hypophysis, and genital organs, in the so-called myasthenia gravis, and finally in individuals presenting the

anatomical features included under the conception of *status thymico-lymphaticus*.

In the form found in infants the thymus may reach a weight of 60 grams at birth, and may actually constitute an obstruction to the respiratory passages or great veins. In older persons the evidence is against the possibility of any such mechanical obstruction, although the literature is full of contradictory statements concerning thymic asthma and other effects of pressure. Nevertheless, the immediate relief of the suffocative attacks which follows the partial removal by the surgeon of the enlarged gland is pretty strong evidence in favor of the idea. There is no evidence that the enlarged thymus can interfere with the function of the vagus, phrenic, or recurrent laryngeal nerves.

**The Thymus in Exophthalmic Goitre.**—Reference has already been made to the enlargement of the thymus which, according to Capelle and Matti, occurs in 75 to 79 per cent. of the cases. That it is an actual enlargement is clear from that fact that its weight may greatly exceed the normal limits at the height of development. The descriptions of the histological changes are most contradictory, but it seems that they may represent an accentuation of the condition corresponding to the age at which the disease developed. In a young person (twenty-three years) the appearance was that of a child's thymus, the hyperplasia being essentially in the lymphoid elements. The interpretation of the rôle it plays and of the beneficial effects of its operative removal is as yet entirely speculative.

Hyperplasia of the thymus in Addison's disease and acromegaly and in genital hypoplasia or eunuchoidism has been frequently observed and it has been experimentally proven that the involution of the thymus is greatly delayed after castration at an early age. Evans and Simpson find that long continued injection of the gonadotropic hormone from the hypophysis causes atrophy of the thymus, but not when testes or ovaries are removed. This is due to the action of the interstitial cells and not to the germinal epithelium, in the case of the testes, since atrophy is still produced in cryptorchids, or in vitamin E deficiency.

**Myasthenia Gravis.**—In about 90 per cent. of the cases of this peculiar disease the thymus is enlarged into a bulky mass, variously regarded as a new-growth or as simple hyperplasia. There are found lymphoid infiltrations in the skeletal muscles and sometimes in the myocardium, adrenal, and liver.

**The Thymus in Status Thymico-lymphaticus.**—This condition, difficult to recognize before puberty, is more definite in adults. There is at least a certain group of individuals who are characterized—(1) By anomalies in the hair distribution; (2) by the rounded conformation of the limbs; (3) by the smooth texture of the skin; (4) by a general lymphatic hyperplasia; (5) by hypoplasia of the aorta and other arterial trunks, and (6) by hypoplasia of the adrenals and the entire chromaffin system.

It is generally assumed that enlargement of the thymus forms a part of this rather vaguely outlined condition, but it requires further study to be sure of this. Pappenheimer, analyzing 28 cases of sudden

death in subjects up to thirty-five years of age with the anatomical features of status lymphaticus, found that the beginning of involution of the thymus is delayed to the third decade. The histological picture is in no sense characteristic, although Schridde claims that there is hyperplasia of the medulla with underdevelopment of the cortex. The possibility that there may have been previous involutional changes, thinning the cortex, must be remembered.

There is no proof that the thymus is concerned in the development of status lymphaticus or in the sudden death which sometimes occurs in these persons. It is more logical to believe that it is the incomplete differentiation of secondary sexual characters, which causes the failure of the thymus to undergo involution, and possibly all the other features of status lymphaticus may be best explained in this way too. Nor is there convincing evidence that the sudden death, increased susceptibility to acute infections, trauma, emotional stress, and anaesthesia, is in any way due to hyperfunction or disordered function of the thymus. Hammar, in his most recent paper, finds from prolonged statistical study that the weight of the thymus in cases of sudden death from accident is quite as great as it is in these cases of supposed status thymicus and intimates that the result is mistaken for the cause and that there is very little support for the doctrine of status thymicus. This is also the conclusion reached by Young and Turnbull.

**Involution.**—Starvation, acute and chronic wasting disease, infections, and exposure to *x*-rays produce rapid degenerative changes in the thymus, leading often to extreme atrophy.

The histological picture produced in this condition, which Hammar has called "accidental involution," varies with the acuteness and severity of the injury and the previous state of involution of the gland.

Recent work of Asher and his co-workers shows that an extract of thymus which he calls thymocrescin, causes, on long continued injection, a great increase in growth in rats even when on a diet poor in vitamin D which would otherwise decrease their growth. This especially increases the development of the sex organs. Rowntree and his associates, using an extract of thymus prepared by Hanson, caused a great increase in growth in rats and especially in succeeding generations produced large animals reaching sexual maturity at an early age.

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## CHAPTER LVI

### DISEASES DUE TO INJURIES OF THE ORGANS OF INTERNAL SECRETION (Continued)

*The Adrenals: Anatomy, functions of medulla and cortex. Extracts of medulla, adrenalin or epinephrine. Extract of cortex, cortin. Influence upon electrolytes. Addison's disease. Tumors of cortex. Effect upon reproductive system. Aplasia in anencephalic monsters.*

#### DISTURBANCES IN FUNCTIONS OF THE ADRENAL GLANDS

THE adrenal glands are complex structures the functions of which have long been the subject of intense study with many revelations of surprising character in the work of recent years but even yet there are great uncertainties and differences of opinion and it can hardly be said that any of the results are finally established.

The adrenals are known to be intimately related to many minute masses of tissue which are scattered chiefly along the course of the chains of sympathetic ganglia, and known as chromaffin bodies. These chromaffin bodies are of the same character as the medulla of the adrenal glands, which is itself enveloped in a cortical covering of very different nature. In children the so-called Zuckerkandl organ is a mass of medullary or chromaffin substance situated near the bifurcation of the aorta. The carotid glands are said to have the same chromaffin quality, absorbing chrome salts and thereby stained brown, but it is not known that they actually belong to this system. Practically the same relations exist in other animals lower than man, but in some fishes, such as the sharks and rays, the two types of tissue are not so intimately intermingled; instead, the cortical substance forms one mass between the kidneys (interrenal body), while the other tissue (the adrenal bodies) is distributed in a series of nodules with the sympathetic ganglia. On this account it is feasible to carry out on these animals isolated extirpations not possible in the higher animals, where cortex and medulla or interrenal and adrenal substances are too inextricably entangled.

In the early development the cortex arises as a new formation from a portion of the mesodermal ridge, while the medulla appears in the form of tiny groups or balls of cells which arise with the sympathetic ganglia and from common forerunners. These cells wander into the substance of the cortex and take up a central position, where they constitute the medulla.

They retain the most abundant and intimate connections with the sympathetic system, receiving quantities of fibrils from the cœliac ganglia.

Accessory or aberrant masses of cortical material occur sometimes in man in kidney, tissues about the spermatic cord, and elsewhere.

The normal histology of the adrenal need not be described here, but attention should be called to the peculiar involution through which it passes in early life. It is a relatively large organ in the new-born infant, and in the first two weeks during which the medulla, which is then an extremely inconspicuous collection of cells, begins to grow, the innermost zone of the cortex is destroyed and converted into a highly vascular and often haemorrhagic connective-tissue layer which collapses. Consequently it requires some time for the adrenal to reach again the size it had at birth, and this growth is partly effected by the extension of the medulla into this collapsed framework which represents the inner layer of the original cortex (Thomas, Pappenheimer, and Lewis).

The medullary cells, while they are in themselves colorless and appear gray and translucent in mass, have, as stated above, the property of absorbing chromium salts and assuming a bright chestnut-brown color. No adequate stains have been found to distinguish the cells of the glomerular layer of the cortex from those of the fasciculate or the reticulate layer, but this would seem very desirable since these three types of cell appear to behave differently under various circumstances. It is true that silver salts will stain the cells of the cortex on account of the presence there of the so-called ascorbic acid, but even that has not been extensively utilized as yet in pathological conditions.

The cortex is particularly rich in globules of anisotropic lipoids (cholesterine esters), as well as ordinary fats, which, however, as the experiments of Landau, Hueck, and Rothschild show, cannot be taken as evidence that these organs produce the lipoids, nor even that they effect the combination of cholesterine with fatty acids. Cholesterine fed to herbivorous animals is stored in quantity in the adrenal cortex. It is abundant there normally, and especially so in pregnancy, but tends to disappear with infections, narcosis, etc.

**Functions.**—Recent work is succeeding in distinguishing fairly sharply the functional activities of cortex and medulla. It has become clear that the medulla is closely under the influence of the sympathetic system while the cortex is maintained in its normal anatomical structure and doubtless in its functional activity, by a hormone from the hypophysis. In the lack of this it atrophies but can be brought back to its original bulk and activity by injections of the extract of hypophysis which Evans and Collip and their co-workers describe as derived from the anterior lobe. It seems, however, more probable from the similarity in symptoms brought about by certain enlargements of the cortex, and the tumors described by Cushing in the hypophysis, that the hormone may be derived from the pars intermedia of the hypophysis.

It was shown by Oliver and Schafer that the medulla produces a substance active in raising the blood-pressure and after that first indication, Abel undertook the study of this material and isolated and synthesized epinephrine. This highly purified material, which is an amino-alcohol, upon injection stimulates the heart to increased activity and raises blood-pressure by causing constriction of the small peripheral vessels. On the other hand it dilates the coronary arteries of the heart and relaxes the bronchioles and intestinal musculature inhibiting peris-

talsis. In the eye it causes dilatation of the pupil and in the uterus contraction of the muscle. But, while these are the results of injecting relatively large doses, very minute doses seem to have an opposite effect and blood-pressure appears even to be maintained for a time after complete extirpation of the adrenals, if other symptoms are obviated.

The influence of epinephrine, or adrenalin, as it is also called, upon the carbohydrate metabolism, is especially interesting. It was observed long ago by Herter and Wakeman that application of adrenalin to the

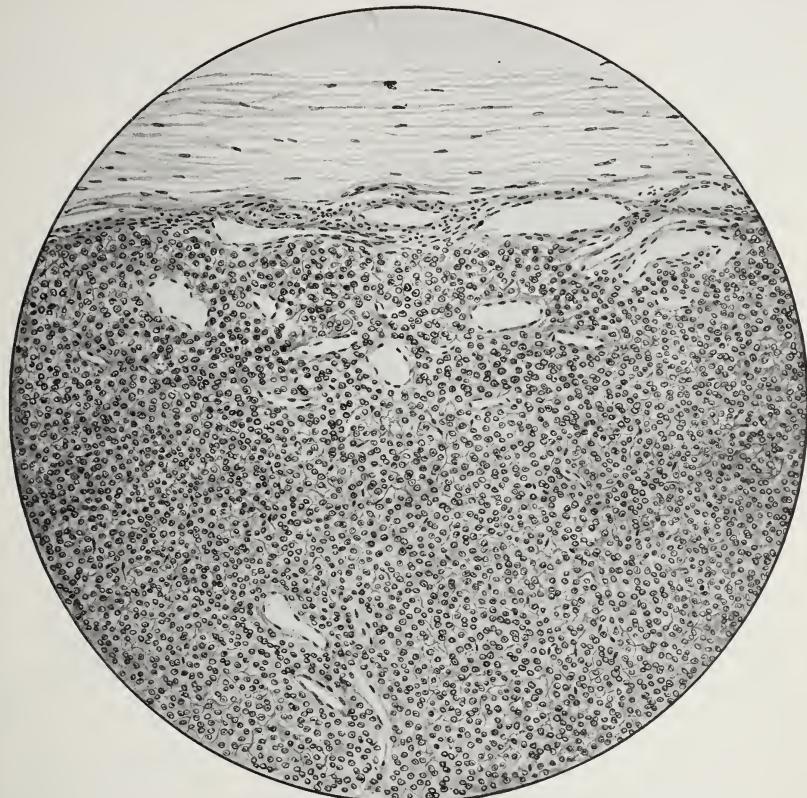


Fig. 540.—Tumor of adrenal cortex from a female child who showed masculine characters.

pancreas produced hyperglycæmia and glycosuria. This may have been caused by vasoconstriction in the islands of Langerhans but it is also known that injection of adrenalin sets free sugar into the blood by decomposing the glycogen store in the liver. This seems to be favored by the thyroid and is less marked in its absence. It may result in hyperglycæmia and glycosuria which must be regarded as a quantitative disturbance of endocrine balance since the sugar thus poured into the blood is for the moment too much for the normal output of insulin to deal with.

That the sympathetic system is intimately concerned in this is shown

by the stimulus produced by the picture of Claude Bernard. Lucke has shown that the influence of the sympathetic system on the adrenal medulla can be interrupted by section at various points, or by poisoning with ergotamine which stops the production of adrenalin, lowers the glycogenolysis and lessens the blood-sugar when the normal amount of insulin may even bring about hypoglycæmia. The work of Cope and Marks shows further that a secretion from the hypophysis is required to make the glycogen susceptible to the action of adrenalin so that in cases in which the anterior hypophysis is atrophied or destroyed, hypoglycæmia occurs.

Tumors composed of adrenal medulla tissue have been described by several authors and we have studied one or two. In these there is evidently a very great production of epinephrine which produces a high



Fig. 541.—Addison's disease; complete atrophy and disappearance of cortex of adrenal with preservation of the medulla.

blood pressure, often with paroxysmal increases. Removal of such a tumor restores a normal condition.

The functions of the cortex are even more complex and only beginning to be comprehended. As already stated, we have no trustworthy methods for distinguishing the activities of the different types of cells which make up the three layers although it seems evident that they behave differently. Szent-Györgyi has isolated from the cortex a peculiar substance which he has purified to crystalline form and which has the power of reducing nitrate of silver so that if the fresh cut surfaces of an adrenal are immersed in a weak solution of this salt, the cortex is blackened. He has recognized it as hexuronic acid, or ascorbic acid, so-called from its supposed curative action in scurvy from which it is also called cevitamic acid.

More certain are the results obtained by Swingle, Pfiffner, Hartman and others, from the extractions of a principle from the adrenal cortex which they call cortin, which will maintain in health animals deprived of both adrenals and restore to activity animals dying in coma from the loss of the adrenals. This has been studied recently by Kendall and his associates, who find that there may be two types of extract differing in that one promotes muscular activity while the other controls the excretion of urea and salt. Various theories as to the action of the extract have been put forward but it appears that the work of Loeb and of Harrop and their associates is most convincing. They find that the cortical hormone is predominantly concerned in the metabolism of sodium chloride which in adrenalectomized animals is so rapidly excreted. Indeed, they have found that adrenalectomized animals can be kept alive and well by the administration of large quantities of sodium chloride, with some sodium bicarbonate alone, without any adrenal extract. When the animal is left without treatment after adrenalectomy, there is great excretion of sodium salts with water—potassium salts and urea are retained in excess. All of this is restored to normal by replacing the sodium chloride and water but in extreme cases it is necessary to add the cortical hormone to maintain the normal plasma electrolyte levels. But this is merely a mechanical method of restoring the electrolyte composition of the body fluids which can be done as well by the cortin alone. It is evident, therefore, that blood-concentration and the normal exchange of sodium and the corresponding water are maintained by the secretion of the adrenal cortex. No influence in carbohydrate metabolism is found.

**Addison's Disease.**—Addison described in 1855 a symptom-complex which is now known by his name, and found to depend upon chronic destructive disease of the adrenals. The patients become gradually weak and easily fatigued, the circulation is enfeebled and the blood-pressure low, the heart beats rapidly, irregularly, and feebly, there are vomiting and anorexia, and the skin becomes pigmented at first only about the usual areas of greatest pigmentation; later the whole skin may become brownish or deep bronze in color. In a state of the most extreme weakness and prostration the patient dies. The autopsy reveals most commonly a tuberculous infection which has attacked especially the adrenals and converted them into necrotic caseous masses, but there are other cases in which some other destructive process has so injured the adrenals as to leave only scars or calcified nodules in their places. No conclusion as to the tissue whose loss is responsible for the symptoms can be drawn from this, but more recently there have been described instances of typical Addison's disease in which the medulla of each adrenal seems unchanged while the cortex has been destroyed. Such cases were described in 1904 by Karakascheff and later by Kovaes, Wells, Barnard, and others. We have recently studied two instances in which the adrenals were found with difficulty but on section had preserved in miniature their normal form but showed no trace of cortical tissue (Fig. 541). These patients, kept alive for a long time with doses of Swingle's cortical extract, showed also a distinct enlargement of the

thymus. Nicholson, who has studied the hypophysis in adrenalectomized dogs, finds no changes. This is also true in Addison's disease produced by tuberculosis of the adrenals. But in the cases in which the cortex is lost while the medulla of the adrenals is unaffected the hypophysis shows a loss of basophile cells, which suggests that the Addison's disease in such cases is the result of a primary injury to the anterior hypophysis with consequent atrophy of the adrenal cortex.

With regard to the pigmentation of the skin, the ideas are vague. Fürth has found that the ferment, tyrosinase, will produce a black pigment from adrenalin, but it is difficult to understand how, in the absence of the adrenal, such a reaction could aid in the enormous production of pigment seen in Addison's disease. Bauer thinks it a derivative of uric acid. Spohr and Moore have analyzed the pigment from such a case and found that its formula is that of melanine. (See discussion of pigment formation under Nævi.)

The close relation of the adrenal cortex with the functions of the genital glands has long been known and is shown in various ways.

In a number of cases tumors arising in the adrenal cortex and containing no adrenalin have produced abnormal precocity in sexual development. Children with such tumors (Fig. 540), may appear as mature sexually as adults. When the tumor, as in a case described by Tuffier, appeared late in life, after the menopause, the woman assumed male characters, heavy beard, baldness, ability to perform heavy labors without fatigue, etc. Gordon Holmes describes a case in a young woman in whom feminine characteristics were gradually replaced by a masculine appearance with cessation of menstruation, etc., and on removal of the tumor of the adrenal cortex, the whole condition reverted at once to normal. Dr. H. H. Young has recently studied several cases in young girls in whom anatomical and functional changes suggesting a form of hermaphroditism appeared. Operative removal of greatly enlarged adrenals has been carried out and microscopically these show marked hyperplasia of the cortex, especially affecting the reticulate zone but extending also into the fasciculate layer. Many such instances have been described but we have yet to learn the exact relation of this to changes in other endocrine organs.

The atrophy of the hypophysis which gives rise to the so-called Simmonds' disease, also results in atrophy of the adrenal cortex which may add to the symptoms of that disease.

In anencephalic monsters in which the medullary groove remains open and the brain in a rudimentary state, aplasia of the adrenals is a fairly regular accompaniment. This was observed also in a recent case in which although the skull was well formed, it contained a large quantity of fluid with only a small mass of nervous tissue to represent the brain. In another case of complete anencephaly the hypophysis was fairly well preserved and the adrenals but little altered. Therefore, it seems probable that in these cases the failure of development of the hypophysis may account for the lack of proper development of the adrenal cortex. Medulla is probably present although difficult to find.

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## CHAPTER LVII

### DISEASES RELATED TO SPECIFIC DIETARY DEFICIENCIES

*Vitamins. Their occurrence in natural food. Chemical and physical characters.* Vitamin A: Relation to xerophthalmia, metaplasia of mucosæ. Vitamin B: Antineuritic. Beriberi. Pellagra. Vitamin C: Scurvy. Vitamin D: Rickets. Vitamin E: Fertility.

Rickets: Pathological anatomy. Effect of sunlight, irradiated ergosterol, etc. Osteomalacia. Scurvy.

IT was recognized by F. Gowland Hopkins years ago that animals could not live on pure protein, carbohydrate, and fat, even with the requisite amount of mineral salts, but that some other indefinable substance is necessary to their growth and health. Funk defined such substances more precisely under the name "vitamins," and it was perceived that a number of diseases already well known might be explained as the result of the lack of just such substances. It had been known for centuries that scurvy could be prevented if lemon juice or something similar were given to sailors who had to go for a long time on salt-beef and biscuit. In the last years great advance has been made in the comprehension of these things, with their chemical nature but their mode of action is still almost entirely obscure. Only the barest outline can be given here, and the student must be referred to the works of McCollum and his collaborators, Stepp, Hess, Pappenheimer, Mellanby, and others.

Adequate amounts of proteins, carbohydrates, and fats, with mineral salts in proper proportions, must be available, but the vitamins are necessary in some cases for their proper utilization, in other cases they seem necessary in other ways as yet little understood.

Vitamin A, fat-soluble, is found especially in the liver and in parts of the body fat where it is held in reserve, but it comes in food in green plants, in milk, and butter, and especially in cod-liver oil which contains three hundred times as much as butter even when that comes from cows feeding on green grass. The lack of this vitamin, which is called antixerophthalmic, causes the atrophy of the lachrymal and lid glands and drying up of the cornea with softening, ulceration, and infection (xerosis, keratomalacia). Salivary glands also fail to function, blood-platelets are decreased in the blood, and there is night-blindness from loss of visual purple. Growth ceases also, but all of this can be prevented by adding butter or cod-liver oil to the diet, or by proper doses of  $\beta$  carotin.

It has been isolated in pure form, its chemical constitution determined and its relation with the carotins recognized. The carotins act as Provitamin A and are converted by the animal organism into the Vitamin A. Pure  $\beta$  carotin has been adopted by the International Vitamin Conference of 1934 as the standard substance for medical use.

Wolbach and Howe have shown that in animals fed on this deficient diet the lack of Vitamin A causes a keratinization of the epithelial cells

of mucosæ, lining of ducts, etc., which can be reversed by feeding once more an adequate amount of the vitamin. In some recent autopsies we have observed this change especially in the bronchi and in the pancreatic ducts with effects which suggest a partial obstruction of the lumina and sometimes a secondary infection.

Vitamin B is the antineuritic vitamin found in green plants, the tissues of animals, and in brewer's yeast. It is so wide-spread that it is lacking only in the diet of those who live almost entirely on polished rice from which the thin silver skin and the embryo have been removed. Eijkmann, familiar with beriberi in prisoners and others in the East, noted similar symptoms in fowls fed on polished rice. The disease *beriberi* is especially characterized by peripheral neuritis with spastic symptoms and paralysis. There are acute and chronic forms with or without extreme œdema, usually with evidences of great wasting and with cardiovascular disturbances, in addition to the paralysis. The hypertrophy of the right side of the heart is very constant and striking and has been discussed especially by Wenckebach who agrees that it is due to the great œdema of the musculature of the heart wall, involving the muscle fibres, and interfering with their activity. It is probable that this œdema is due to the inadequate protein content of the diet since the addition of abundant protein tends to relieve it. Villela shows that the serum albumin is lowered while the globulin is slightly increased which would tend to produce œdema.

Whether the condition is due solely to lack of Vitamin B has been the subject of much discussion. The idea of an infectious cause has been held by many and in the Pasteur Institute in Saigon Noel Bernard showed me pigs in which he had produced all the phenomena of beriberi by a combination of avitaminosis with inoculation with a bacterium which he had isolated. McCarrison finds beriberi in certain districts regardless of the diet and feels that an unknown toxic factor acts together with the deficiency of vitamin and this is widely believed. A so-called rice disease is also recognized in which the peripheral neuritis with its consequences is the same as in beriberi, but the cardiac complications do not appear.

The so-called *epidemic dropsy*, sometimes confused with beriberi, appears to be due to the eating of rice which has decomposed on long standing and evidently contains some toxic material. There is no neuritis or cardiac failure but gastro-intestinal symptoms with fever, and skin rash together with œdema. Of course, this, as shown by Shanks, is quite different from beriberi. It is evident from this that there is more to be learned about beriberi before we identify it completely with the lack of Vitamin B.

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*Pellagra* is a disease which is also related to the deficiency in Vitamin B but is so different from beriberi that the subdivision of Vitamin B into

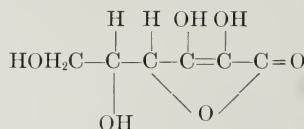
at least two forms has been carried out. These are known as Vitamin B<sub>1</sub> and Vitamin B<sub>2</sub>, also sometimes called Vitamin G. The lack of B<sub>1</sub> is responsible for beriberi, but it is the insufficient supply of B<sub>2</sub> or G which causes pellagra. This is found in yeast, liver, milk and green vegetables and can be separated from B<sub>1</sub> by several methods.

Pellagra is a widespread affection, perhaps commoner in the South in certain districts. It has been studied by Goldberger in milltowns in the Southern states where the diet is largely cornmeal, molasses and fat pork, with but little of green vegetables. There has long been an idea that a poison produced in deteriorated corn is the cause of pellagra and it has been suggested that because of the intense changes in the skin of parts exposed to the sun, it may be a photosensitizing substance analogous to that supposed to exist in buckwheat. This remains doubtful but the disease can be prevented or even cured by adding yeast to the diet.

The symptoms are severe, the most striking being the symmetrical pigmentation of the hands, arms, face and neck insofar as they are exposed, sometimes with ulceration and crust formation. Mental disturbances and digestive anomalies generally with constipation are also found. The anatomical changes in the internal organs are not distinctive.

Vitamin C.—The most brilliant studies have been made in the last years as to the nature of Vitamin C which has been known to be essential in the prevention of scurvy. It is found in vegetables especially—the juice of oranges and lemons, limes, mangos, tomatoes, potatoes, etc., and in paprika. It occurs also in animal tissues, particularly, as will be pointed out, in certain organs, but it is so readily changed by methods of preservation and cooking that the amount available in food is rather dependent upon fresh milk, and vegetables and fruits.

Szent-Györgyi first recognized this substance in the adrenal cortex and called it hexuronic acid—later it was called ascorbic acid or even cevitamic acid. Quite recently, after prolonged studies by many chemists, it has been synthetized by Reichstein and also by Haworth with their co-workers, and given the following structural formula



which is L. ascorbic acid. It can now be made from L. sorbose and can be administered, even intravenously, in very dilute solutions, for the cure of scurvy.

It is a substance of high power as a reducing agent and therefore any attempt at its recognition or titration by histological or chemical methods must begin by guarding it against all oxidizing agencies. Several chemical methods have been devised for its measurement in extracts of vegetables or animal tissues and so far its recognition in histological sections has been reached by treating them after various precautions, with silver nitrate which is precipitated by the reducing action in the form of black granules. By these methods the ascorbic acid has been

found to exist under normal condition in the cortex of the adrenal, especially in the fasciculate layer, in the hypophysis, especially in the anterior lobe, and according to others, in the pars intermedia, in the cells of the corpus luteum and theca externa of the follicles of the ovary, and in the Leydig cells of the testis. It has been found in the lens of the eye and in the pulp of teeth.

It is absent in thyroid, thymus, pancreas, salivaries, stomach and muscles, but present in small amount in the intestine, liver and kidneys. It is evident, therefore, that the tissues commonly used as food are not those rich in this substance.

The main function of this vitamin will be discussed with scurvy but it has some bearing on blood-formation and on the coagulation of the blood and is thought to oppose the action of the thyroid, but all of this is still rather vague.

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Vitamin D, also fat-soluble, is found in cod-liver oil too, and can be separated from Vitamin A by oxidation which destroys the anti-xerophthalmic vitamin. This was suggested by the fact that butter will cure the xerophthalmia, but not rickets, against which Vitamin D, which is scantily present in butter but abundant in cod-liver oil, is a specific cure. In rickets the proportion of phosphorus to calcium in the blood is disturbed and generally the phosphorus is too low. Vitamin D, which is present in green plant food and in yolk of egg as well as in cod-liver oil, makes the phosphorus available, and increases its absorption until the proportion in the blood is normal.

It was found by Huldschinsky and others that ultraviolet rays will cure rickets, and later that there seemed to be some close relation between the activity of the Vitamin D contained in cod-liver oil and the action of these light rays of short length ( $290\text{--}300\ \mu\mu$ ). It was found by Hess and others that not only can the vitamin be produced in animal and vegetable tissues by exposure to these rays, but that cholesterin, milk, and even many indifferent oils can be given the same properties. Attention was especially directed to cholesterin, which Hess could render antirachitic by irradiation. Irradiated hens laid eggs the yolks of which had greatly increased antirachitic power (Hart and Steenbock). Since that, Hess in America and Rosenheim and Webster in England, in collaboration with Windaus, have shown that a particular substance, ergosterol, which is associated with cholesterol, is really the substance which is susceptible to the effects of the ultraviolet rays, and that it becomes enormously active and capable in extreme dilution of producing the antirachitic effect, but the exact physical process involved in this is yet to be explained.

Since this discovery in 1926, it has been found possible to isolate the Vitamin D in crystalline form and finally to approach the structural formula although this is not yet determined. The irradiation of ergosterol gradually produces the Vitamin D by various steps and may, if continued, overstep that stage and produce other substances, toxisterin, etc., which are not antirachitic. Toxic effects of the purified Vitamin D<sub>2</sub> or New Calciferol, as it is called, are seen when too great a dose is given. There seems still to be some doubt as to the identity of the natural Vitamin D and that produced by the photochemical treatment of ergosterol. The toxic effects especially of the latter consist in general disturbances of nutrition but especially in calcification of the tissues, most marked in arterial walls and rarefaction of the bones. This, it seems, is not to be confused with hyperactivity of the parathyroids as suggested by some writers, and we think that there is a fundamental difference between rickets and the so-called renal rickets, as will be discussed later.

Vitamin E.—Bishop and Evans have isolated from green leaves and seeds a fat-soluble, thick oily material resistant to heat, light, and oxygen, and free from phosphorus and sulphur. This antisterility vitamin seems necessary to maintain the proper course of reproduction. In its lack the females conceive and pregnancy goes on to a certain point, but is then interrupted by the degeneration of the embryo. In the male the production of spermatozoa ceases in the lack of the vitamin, and if this is continued long enough the testes atrophy. A very minute amount of the vitamin given at the beginning of pregnancy assures its normal course.

Since then Evans and his co-workers have crystallized Vitamin E, producing a substance of great potency. Analysis showed it to be a complex higher alcohol.

Hill and Burdet state that the worker bees feed the larva of the future queen bee with the so-called royal jelly which is thought to be pollen modified by the action of their pharyngeal glands. The queen bee is still fed in this way by the attendant workers when laying 2000 eggs a day. Both queen and worker are from fertilized eggs and a worker larva not more than three days old can be converted into a queen. This stirs up many speculations.

There is obviously much more to be discovered with regard to these things, and it is clear that even if an adequate supply of each vitamin is available in fresh green foods and in the various fats, most of us receive too little in ordinary urban life, for a moment's reflection will show how little part fresh salads and fresh fruits play in the diet of the majority of people in cold climates through a great part of the year.

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#### RICKETS OR RACHITIS

The name rickets is evidently a very old one, suggesting weakness of the bones, and rachitis only a high-sounding Latinization of the English word. It is an astonishing condition which begins in children between the second and third month and lasts in its active or florid state not later than the third year, although the deformities produced remain and the process of healing is protracted. It is often remarkable that the healing process can restore to the normal form bones which were at one time so greatly deformed. The signs of rickets in adults are rarely very disfiguring although in the case of the pelvis the deformity may have far-reaching consequences in the obstruction of childbirth.

Rickets is a disease which is seen chiefly in cold climates and in crowded cities when there is not much sunlight, and children are wrapped up and kept in the house a great deal. It seems to affect negro children especially in such climates, although in the tropics it is practically never seen except in India, where it is the custom among the better classes of Hindus to keep the women and children closely confined in the houses and not exposed to the sunlight.

The disease begins with changes in the bones of which the earliest is perhaps the thinning out of the back of the skull (craniotabes), a condition which may last for a while or give way to thickening, especially over frontal and parietal eminences. Then come thickenings of the costochondral junctions which are button-like (rickety rosary) and swelling or thickening of the ends of the bones. Some bending of the spine appears which seems due to muscular weakness. From the softness of the bones distortion follows the strain put on them which depends upon the posture of the child or its activities. Even the effort of breathing distorts the thorax.

Greenstick fractures—that is incomplete fractures in which one side of the cortex bends while the other is broken—are extremely common and occur without any remembered violence. But separation of the epiphysis from the shaft of the bone, such as is seen in congenital syphilis and scurvy, does not happen in rickets.

The abdomen protrudes, perhaps in part owing to atony of its walls, or of the intestinal walls. Flabbiness and softness of the skeletal muscles are striking.

As to the actual deformities of the bones, it is difficult to speak in any brief way and the student should read Park's chapter in Parson's Text-book of Children's Diseases.

The change from the normal form is the product of the softness of the growing bone, especially at the osteogenic region, and the force which



Fig. 542.—Rickets, showing the deformity of the costochondral junction which projects especially inward although it is apparent externally as the "rickety rosary."

acts upon it together with the compensatory effects of further growth. Thus, in the ribs the soft costochondral region is forced inward by inspiratory efforts so that the sharp end of the bony part of the rib forms a much greater prominence on the inside of the thorax than the swollen cartilage on its outer side. The cartilage comes to join the bony part of the rib almost at right angles and new cartilage is formed to fill up this angle. Again, in the lower end of the tibia the tendency is to bend backward so that ultimately the shin assumes an anterior bowing (sabre tibia) and the foot starting far back of the axis of the tibia becomes flattened. This, with a tendency to knock-knee deformity, is very commonly seen on the streets in Baltimore negro children.

Most cases, if the child survives, end with the gradual restoration of the normal consistency of the bones and afterward with the far more gradual rearrangement of the bony structure and readaptation to the

mechanical needs and normal form of the bones. There are some, however, in which such extreme distortion of the whole skeleton takes place in the florid stage that the deformity is never really overcome, and the patients remain permanently disabled. Such skeletons are seen in European museums showing grotesque bending and twisting of the long bones, but the very severe cases seem rare in this country.

At autopsy it is rather easy to cut with a knife down through the epiphyseal end of the bone deep into the shaft, and the cut surface presents an extraordinary contrast with the normal bone (Fig. 543). It is seen that in the normal bone the line of ossification is perfectly sharp, even, and really a narrow line. In rickets it is replaced by a wide

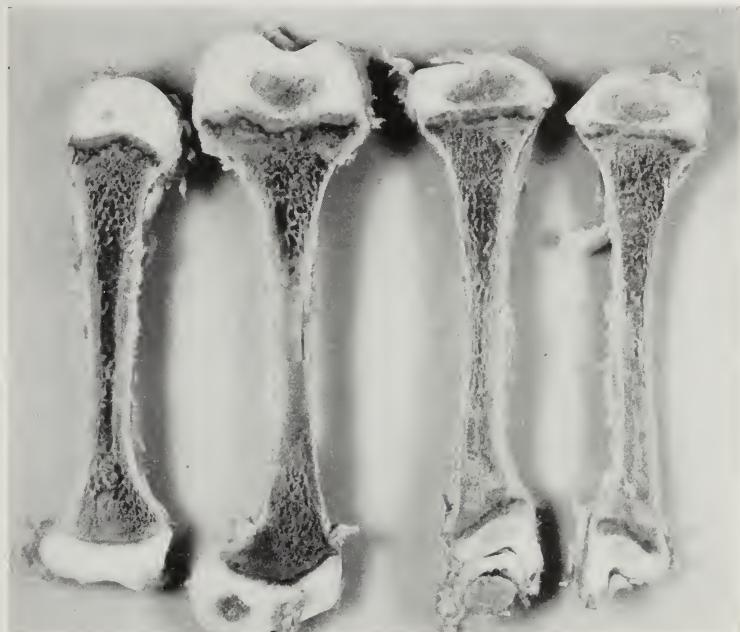


Fig. 543.—Rickets. Typical early changes in the region of the line of ossification.

irregular band of rather soft gray translucent tissue, in which white opacities and gritty particles represent the calcified lamellæ, but throughout which islands of bluish cartilage can also be seen. The cortex of the shaft often shows soft, spongy growths both inside and outside. These changes are especially well seen in the lower end of the femur, the upper end of the tibia, etc., but to a slighter degree they are found in every bone and are very prominent in the costochondral junctions of the ribs. A section through the epiphysis and shaft of such a bone shows (Fig. 546), on analysis of the confusing scene, that the cartilage, where it should border on the advancing marrow capillaries, is no longer regular in its columnar arrangement or uniformly subject to the provisional calcification. Instead there are patches of calcification, but the relatively unprepared cartilage is grossly invaded deep into its

substance by clusters of blood-vessels, so that the long tongues of cartilage seem to extend in the most irregular way far down toward the marrow cavity. Where the capillaries do lay open the cartilage cells and spread their osteoblasts on the remaining cartilage matrix, the result is the formation of highly irregular, thick laminæ, morphologically like bone (though much more bulky), but not calcified. This is the osteoid tissue described before, and this it is which makes up practically all of the thick grayish band which lies where the line of ossification should be. Where the capillaries grow far into the cartilage, they may surround themselves with zones or mantles of osteoid tissue. So, too, the margins



Fig. 544.—Extreme rickets. Line of ossification replaced by a broad band of osteoid tissue and cartilage as shown in Fig. 545.

of the cartilage masses left behind in the advance of the growth become changed into osteoid tissue, and when, in healing, this becomes bone, the rest remains as a cartilage island enclosed in bone. There is much of this osteoid tissue in the shaft of the bone also, making up the superficial layers of the laminae of the cancellous bone and of the periosteal exostoses. Even in the denser bone of the cortex one finds osteoid tissue, especially about the vessels which lie in the so-called perforating canals, but also at times occupying a quadrant or more of an otherwise well-calcified Haversian system. Another process characteristic of rickets is

the abundant ingrowth of blood-vessels into the epiphyseal cartilage from the perichondrium. These split up the resting cartilage in every direction, and end in a network of small vessels parallel with the transverse plane of ossification. Several such layers or "stages" of vessels may be formed, and may be visible at once, although as the irregular region of ossification advances they become, in turn, confluent with the vessels from the marrow cavity and lose their identity. As they lie in the cartilage ("cartilage marrow canals") the matrix around them loses its blue stain and assumes the power of staining with eosin. This collagenous material soon becomes converted by the accompanying osteo-



Fig. 545.—Extreme rickets. Islands of osteoid tissue and great widening of the ossification band. The skull in section shows periosteal new bone formation.

blasts into osteoid tissue, which finally adds itself to the mass of osteoid tissue formed by the marrow vessels.

The marrow is in itself changed into a tissue much more fibrous than normal ("endostitis fibrosa"), and laminæ of bone or osteoid tissue may be formed in this fibrous marrow. It is easy to see that an extremely complicated condition can be produced in this way, especially when it is remembered that similar processes in modified form occur in the shaft of the bone as well. It is remarkable that any adequate return to the normal architecture of the line of ossification is possible in the course of healing. The enlargement of the epiphyses is due not so much to any

excessive production of cartilage, as to the fact that ossification is extremely sluggish and the cartilage does not become converted into the calcified and less bulky bone. With the return of the normal process of



Fig. 546.—Rickets: Rib at site of line of ossification. The preparatory zone of cartilage is irregularly invaded by perichondral and marrow vessels. Calcification of cartilage lacking, except in two or three foci. Invading blood-vessels surrounded by osteoid tissue. Lamellæ of bone remain partly covered with osteoid tissue.

ossification which is perhaps the beginning of healing, there is a reappearance of the smooth, transverse line of calcium deposit in the cartilage—the so-called zone of provisional calcification—and with this a return

to the more regular approach of the capillaries from the shaft. The distorted osteoid laminae require a long time for reorganization into orderly bone laminae by processes of osteoclastic activity and reconstruction. The exostoses on the skull are soft, spongy masses of lenticular form composed of porous osteoid tissue which becomes partly calcified, and later may be absorbed in large part or completely converted into bone.

Great advance in the understanding of rickets has been attained in the last years. The approach has been so complicated by the maintenance of fixed ideas, however, that the literature is very extensive. The student may find the details in the review of Park and should certainly read that of Howland.



Fig. 547.—Skull in extreme rickets. Great new formation of soft bone or osteoid lamellæ, both inside and outside of the original skull.

The long groping after truth about the causation of rickets in which the names of Mellanby, Sherman, and Pappenheimer and their collaborators, McCollum, Simmonds, Shipley and Park, Howland and Kramer, and Hess and his co-workers, should be especially remembered has led to many remarkable discoveries. It is evident that the situation is controlled by certain ultraviolet light rays of short wave-length, about  $302 \mu\mu$ , which act upon various substances, but especially upon what has been called Vitamin D, which occurs in greatest abundance in cod-liver oil, is fat-soluble, and can be separated from the Vitamin A which also occurs there. Therefore, animals exposed to sunlight or to these ultraviolet rays do not develop rickets. Therefore, too, animals supplied with

Vitamin D which has at some time in its production been influenced by these rays will not develop rickets. The actual substance which at present is known to be particularly powerfully endued with this potent influence by exposure to ultraviolet rays is ergosterol, a cholesterine-like molecule with three binding links found in nature most abundantly in ergot, yeast, and other fungi, and in cod-liver oil associated with cholesterol.

While perhaps the organic food constituents—protein, carbohydrates, etc.—may have some influence, the actual condition among the mineral salts as found in the blood in rickets is, as shown by Howland and Kramer, the following: There is a disproportion in the amounts of phosphorus and calcium in the circulating fluids, although an analysis of the rickety bone shows the same proportions of phosphorus and calcium as shown in the normal bone. There should be 10 mg. of calcium and about 5 mg. of phosphorus per 100 c.c. of blood, but in rickets in the human being the phosphorus usually sinks to a low level; sometimes the calcium is very low, but in any case it is the relation of these two which seems important. Howland and Kramer find that if the product of the calcium and phosphorus figures is below 40, one is surely dealing with rickets. The curative effect of the vitamin or of radiation raises the phosphorus level and the calcium rises, too, until the relations are normal. Starvation will do the same thing in some obscure way. When the calcium is low, infantile tetany occurs and is, therefore, a natural accompaniment of rickets. It, too, disappears with the curative effect of the vitamin or the radiation.

It is evident that there is an inadequate disposition of calcium and phosphorus in the serum and that even this proportion is unstable and readily disturbed by excessive excretion. Some cases are especially deficient in calcium, others in phosphorus. It might suggest itself to anyone that in those cases in which calcium is low and there is tetany, the parathyroid is at fault although in most cases the parathyroids are said to be hypertrophied. Irradiated ergosterol (viosterol) will not cure this tetany and if the parathyroids are removed, viosterol will act to establish improved conditions only when given in huge doses. Parathormone is most useful when the calcium is low and phosphorus high—viosterol when the phosphorus is low and calcium high, so that they seem to supplement each other. At any rate, the curative effect of irradiated ergosterol in restoring the concentration and proper equilibrium of calcium and phosphorus in the blood, and controlling excretion, is magical. Under these conditions ossification returns to normal.

It is known that rickets appears not in the adult when growth is complete but only in growing bones and is intensified by increased activity of growth. The disturbance is essentially in abnormal ossification and probably the concentration of calcium and phosphorus in the serum would never have caused any comment except for this, so that one is led to wonder whether the effect of the ultraviolet rays is not rather a local one exerted upon that unknown factor in ossification which requires as its building materials an adequate supply of calcium and phosphorus.

**Osteomalacia** is a very similar disease which occurs in adults, especially in women, with exacerbations during pregnancy and lactation. It is thought by many to be practically identical with rickets, except that it occurs in persons whose endochondral ossification is complete. Otherwise the histological modifications of the bones are nearly identical. Here the softening of bones which were quite calcified and hard a short time before must be due to halisteresis, and in section the bones show clearly the osteoid margin along each lamina of bone, covering in the still calcified central part. The most extraordinary deformities through bending of the soft bones are produced during the florid stages, when the decalcification is at its height, and this is accentuated by the greater weight of the adult body. The pressure of the heads of the femora flattens the pelvis laterally and forces the symphysis pubis forward into a sort of beak. With returning rigidity such a pelvis is, of course, incompatible with childbirth. The loss of calcium may be relatively high in each day's excreta (Holtz's case, 0.1809 gm. daily; Sauerbruch's, 0.07 to 0.17 gm. daily).

Miles and Chih Tung Feng state that osteomalacia is comparable with rickets in that it is due to a deficiency in a fat-soluble vitamin together with lack of calcium, and that it can be cured with the vitamin. All the more recent work seems to support this idea. Maxwell points out that there is in the diet of the people who develop osteomalacia a shortage of calcium and of Vitamin D. They are protected to some degree by the action of sunlight upon the ergosterol present in the skin fat, providing Vitamin D which tends to maintain the calcium phosphorus ratio (Hess and Weinstock). So, the cases of osteomalacia improve in summer and women working in the fields are free from it in contrast with those who are confined to the ill-lit houses by purdah. It is essentially the deficiency in diet and the unhygienic living conditions which bring about the disease. Lack of Vitamin D disturbs the calcium relation, in contrast with the conditions found in osteitis fibrosa where excess of parathyroid secretion withdrew calcium from the bones. Hannon and others show that in osteomalacia there is lack of absorption of calcium from the intestine which is restored by Vitamin D which, in the form of cod-liver oil or irradiated ergosterol, is concerned in promoting the formation of bone when there is adequate calcium in the diet. Still, an overdose withdraws calcium from the skeleton.

#### SCURVY

Prolonged subsistence upon such food as salted meats, canned meat with biscuits or bread, and boiled or condensed milk, without fresh fruits, milk, vegetables, or fresh meat, is known to produce a complex disease characterized by anaemia, swelling and infection of the gums, painful haemorrhages in the joints and under the periosteum, and purpuric haemorrhages in the skin. This may lead to death, but can be cured by giving the so-called antiscorbutic substances which are contained in fresh fruits and vegetables and in fresh meat and milk. It is a disease which raged among sailors in times when it was difficult to carry these things, and voyages were of longer duration. In adults it is now

rather rare, and occurs only among the very poor, or in conditions of isolation where fresh food is not obtainable. It is still observed in children, especially when they must be artificially fed. The scurvy or scorbutus of adults seems to be identical with the infantile scurvy or Moeller-Barlow disease of children, except in some trifling details which depend upon anatomical differences, although the latter has usually been described as a combination of rickets and scurvy. It may be experimentally produced in animals by intentional feeding with a "scorbutic"

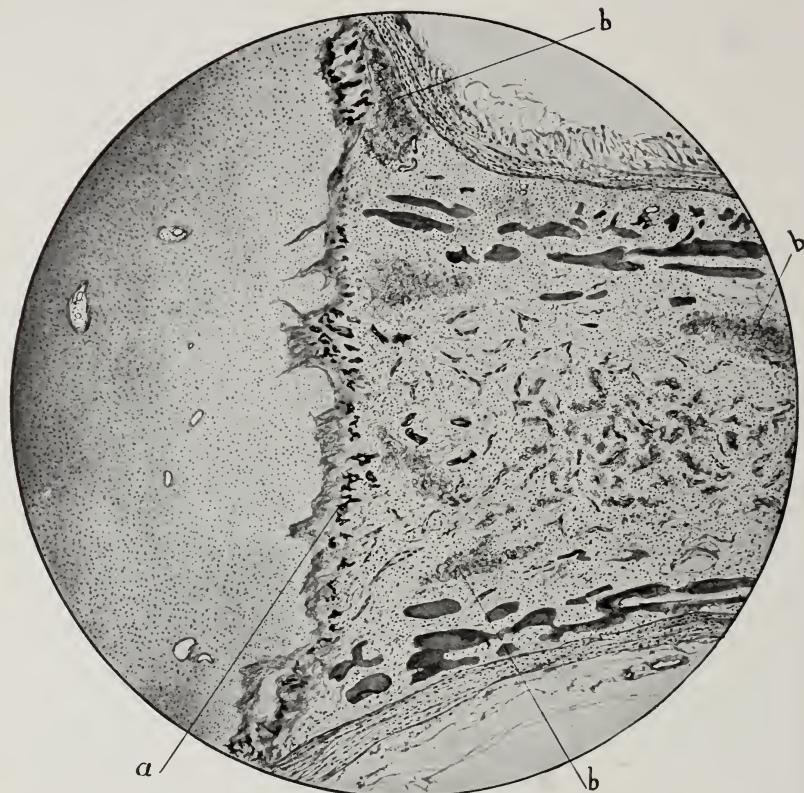


Fig. 548.—Infantile scurvy. Line of ossification of the lower end of the femur: *a*, Calcified cartilage; *b*, hæmorrhage in the fibrous bone-marrow. The process of ossification is almost entirely interrupted.

diet, and prevented or cured by giving the antiscorbutic substances. The lesions in animals are identical with those in man.

Among antiscorbutic substances lemon and lime juice are well known. Extracts of vegetables, such as cabbage and potatoes or dandelions, are effective, but deteriorate on standing, are alkaline, and are destroyed by heating. The beneficial properties of milk are destroyed by heat. Attempts to isolate the active substance have resulted, as detailed in speaking of Vitamin C, in the recognition of the chemical nature of the substance, the demonstration of the structural formula and its actual

synthesis. This artificially reconstituted ascorbic acid will cure scurvy just as does that found in lemon juice.

The lesions, which develop in the course of a few weeks or months of the unfavorable diet, affect chiefly the bones. The bone-marrow loses its blood-forming elements and becomes converted into an edematous fibrous tissue in which the blood-vessels and osteoblastic cells seem rela-



Fig. 549.—Infantile scurvy. Section of femur showing subperiosteal haemorrhages with periosteal bone formation. There are haemorrhages in the bone-marrow and distortion of the line of ossification at the lower end.

tively few. As a result, bone formation becomes almost stagnant everywhere, and since the resorption of bone goes on normally, the whole structure shortly becomes rarefied. At the epiphyseal line the lack of proper and orderly invasion of the cartilage columns is very marked. As shown clearly in the studies of Park and his co-workers, there remains a layer of calcified bands of matrix, very fragile and susceptible to fracture which he calls the lattice (Fig. 548, *a*). Sometimes there is irregular

or oblique invasion, and the zone of osteogenesis becomes broadened where there is a network of capillaries, but this is also an ineffectual method of bone formation. Usually only scattered laminæ are produced, and in some cases a sort of bony wall is formed transversely which obstructs further ossification. Haemorrhages occur as elsewhere in the body, in the joints, underneath the periosteum, and in the substance of the bone-marrow. The periosteum may be elevated from a large part of the shaft of the bone by the effusion of blood (Fig. 549). Periosteal growth of bone tends to replace the clot, but the cortex continues to be rarefied. The disturbances of ossification do not depend on the haemorrhages, since they precede them (Ingier).

There is also swelling of the gums with bleeding and loosening of the teeth, almost as in pyorrhœa, but while experimental studies in guinea-pigs in which the teeth are growing continuously, show separation of the odontoblasts, collection of fluid between that layer and the dentine and decalcification of dentine and enamel, these results cannot be applied at once to man except possibly in infancy when the teeth are being formed. Once complete, the teeth in man seem quite resistant and not affected by vitamin deficiencies of any kind.

Healing takes place after the proper food is once more given by the rearrangement of the disturbed cartilage cells in their columnar order and by the reappearance of blood-forming cells and abundant capillaries with osteoblasts in the impoverished bone-marrow, which then go on to the normal processes of ossification. The disease is quite different from rickets, in which the chief feature is the absence of calcification of the cartilage, and the consequent rapid ingrowth of capillaries which form osteoid tissue, in the lack of calcium.

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## CHAPTER LVIII

### DISTURBANCES OF LIPOID METABOLISM. LIPOIDOSES

THERE are, as we have said in preceding chapters, many conditions which seem to depend largely, if not exclusively, upon abnormalities in the metabolism of fats and lipoids and of these probably arteriosclerosis should rank as the most important. But there is separated here a group of peculiar ailments in which great accumulations of some special lipoid distort an organ or erode bones, or even produce tumor-like masses. It seems proper to discuss them together and even to accept the term Lipoidosis, suggested by Epstein, to define them, particularly because in each one there seems to be a specific disturbance.

**Gaucher's Disease.**—Gaucher described an affection lasting over years in which there is a great accumulation, especially in the spleen, of foamy cells containing a peculiar lipoid, kerasin, a cerebroside. The liver becomes enlarged and there may be anaemia. Details must be read in the papers of Bovaird, Brill, Mandelbaum, Risel, Pick and others but the essential facts are that it occurs in families, affecting several children, and that it produces a huge enlargement of the spleen and sometimes involves lymph-nodes and bone-marrow. In all these situations there are giant multinucleated phagocytic cells which are thought to be developed from the mononuclear phagocytic wandering cells. A case studied recently by Rich showed an extreme enlargement of the long bones which were occupied by the tumor-like mass of tissue composed of the large cells. Elsewhere this tissue behaved like a tumor invading the organs. From the interesting review of Epstein, who has studied all of the related diseases, it appears that it is only in Gaucher's disease that kerasin is found.

**Niemann-Pick's Disease.**—The second condition which has sometimes been confused with Gaucher's disease is that which was recognized by Niemann and later more thoroughly studied by Pick. Niemann-Pick's disease affects young children and is rapidly fatal. The lipoid material which accumulates is lecithin, generally associated with other phosphorus combinations. It is not limited to the spleen and blood-forming tissues, nor to the mononuclear phagocytes, but fills up with a foamy mass the liver cells, heart muscle, voluntary muscle, and epithelial cells of the kidney and thyroid, and even the ganglion and glia cells of the nervous system.

**Lipoidosis, Schüller-Christian Type.**—The third affection, reported by many authors of whom Hand was the first, shows peculiar defects in the skull in children, often with exophthalmos and diabetes insipidus. Rowland showed that this too is due to local deposits of lipoid material, not only in the skull but in the periosteum of other bones, in the lungs, pleura, liver, lymph-nodes, bone-marrow, and spleen. The lipoids are

predominantly cholesterol esters, as shown by Epstein and Lorenz, and are collected in large phagocytic cells. The localization, frequently in the neighborhood of the pituitary, determines mechanically the production of the diabetes insipidus. The subject has been well reviewed by Sosman who finds that while treatment with endocrine extracts is practically useless, healing can be attained by exposure to Roentgen rays.

**Xanthoma or Xanthelasma.**—Although commonly described with tumors, the term should be reserved for those yellowish masses which appear in the skin, mucosæ, and internal organs in cases of diabetes, jaundice, or other conditions in which there is hypercholesterinæmia.

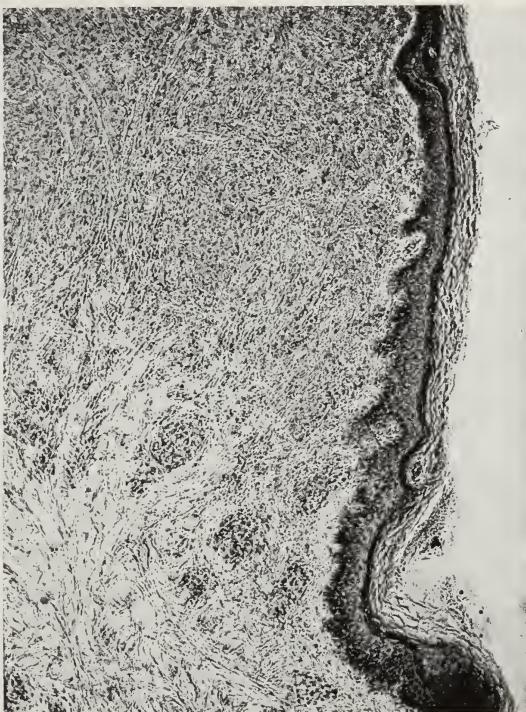


Fig. 550.—Xanthomatous mass in skin. The fat-laden cells are stained with sudan.

They occur as flat, slightly elevated, yellowish patches on the eyelids (*xanthoma palpebrarum*) or elsewhere on the skin, especially about the knees and elbows, or as larger tumor masses in connection with tendons and tendon sheaths, or with the joints. They are most common in persons of advanced age, although some types occur in children. Major has collected the literature on those especially associated with diabetes.

The nodules are ochre yellow and evidently contain much greasy lipoid material. On section they are found to be made up of masses of large foamy cells, often with several pale nuclei and loaded with doubly refractive globules of cholesterin esters, together with lipochrome pigments which give them their yellow color. In the skin they push aside

the sweat-glands and are not especially related to the sebaceous glands as shown in Fig. 550 from a case in which although there was no diabetes, there was a marked hypercholesterinaemia. These cells are apparently the large mononuclear phagocytes which may perhaps be concentrated in those areas by some slight trauma, or inflammatory reaction. Major observed their appearance following mosquito bites, and Levy suggests that they may be related to the local destruction of tissue.

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## CHAPTER LIX

### CONDITIONS OF UNKNOWN AETIOLOGY AFFECTING CENTRAL NERVOUS SYSTEM OR MUSCLES

*Syringomyelia. Pathological anatomy. Amaurotic family idiocy or Tay-Sachs' disease; eye changes. Myasthenia gravis, muscular infiltration, thymus tumor. Progressive muscular atrophy. Amyotonia congenita. Amyotrophic lateral sclerosis. Progressive muscular dystrophy. Myotonia congenita. Friedreich's ataxia.*

**Syringomyelia** describes a tubular thickening of the spinal cord. This is a condition variable in form and position of which the cause is not known and in which even the histological nature is in dispute. It appears as a mass of neuroglial tissue chiefly in the gray matter of the cord, but later growing out into the white matter and interrupting tracts. It may appear at any level from the medulla to the sacral region and becomes characteristically hollowed into a tubular form although the upper and lower ends generally remain solid. Some authors regard it as a congenital malformation with excessive glia formation and doubtful relation with the ependymal cells. Others, especially Hassin, think of it as the formation of a cavity in the glia with a later lining of connective tissue fibrils. Generally the cavity contains a turbid fluid and the walls are stained with yellow-brown pigment. It has been regarded also as a gliomatous tumor with secondary central softening but this is opposed by Tauber and Langworthy. Such a mass involves various nervous mechanisms and can produce extreme sensory disturbances, as well as atrophy and paralysis, or spastic conditions in the muscles.

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**Amaurotic Family Idiocy.**—Amaurotic family idiocy is an affection especially of Jewish infants and children, first described by Tay and Sachs and often known as Tay-Sachs' disease. Tay observed in the fundus of the eye a depigmented area with a red spot in the centre while Sachs found extreme atony or total paralysis with increased reflexes and spasms. The brain of these idiot children is loaded with lipoid substances and in some cases the liver and spleen are also enlarged with great accumulations of similar lipoids. Most striking is the distention of dendrites and axis cylinders with the fatty material as described by Schaffer and the demyelinization of the white matter of the brain. There has arisen a conflict of opinion as to whether the disease is due to a hereditary metabolic disturbance or possibly the effect of some hormonal abnormality as in Niemann-Pick's disease, or to

a secondary deposit of lipoids in cells as the result of some previous injury to these cells. v. Bogaert, Spielmeyer and others take the first view while Epstein and Schaffer feel that the amaurotic family idiocy is quite different from Niemann-Pick's disease inasmuch as the cephalin-lecithin infiltration of the tissues is less than normal while it is greatly increased in Niemann-Pick's disease. They think that the injury to the cells is primary while in the other group of diseases the lipid metabolism is primarily disturbed.

These children are blind in addition to the complete idiocy and the paralytic condition.

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**Myasthenia gravis** is a little understood condition first described by Wilks in 1877, and later by Erb and Goldflam in which the most striking symptom is the rapid fatigue of any muscles which are being used so that the most ordinary activities such as walking or even chewing of food become impossible after the briefest exertion.

The cause is quite unknown. In most of the cases the muscles show collections of lymphoid cells between the fibres in places but these "lymphorrhagias" seem not to cause any destructive changes in the muscle fibres, nor can any abnormality of the central nervous system or of the peripheral nerves or their endings in the muscles be found. In rather more than half of the cases there is found a tumor in the thymus, generally composed of rather pale cells with elongated nucleus, often arranged in rounded masses with central capillary vessel. There may be about such a tumor recognizable normal thymus tissue. Many theories as to the interrelation of these changes have been put forth with especially an effort to refer them to some endocrine disturbance, but so far without any confirmation. Various forms of therapy have been tried also, the most recent being the dosage with antuitrin, an acid aqueous extract of the anterior lobe of the hypophysis which is said to relieve the symptoms. In the one case which we have studied, there was a small sharply outlined tumor of the thymus and the characteristic lymphoid infiltrations of the muscles.

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**Progressive Muscular Atrophy.**—There is a group of diseases involving muscular disabilities, sometimes hereditary, sometimes sporadic,

of which we can make only passing mention. In no case is the aetiology known and in many of them there is difficulty in determining the exact relations of muscular and nervous alterations. The literature is enormous and the student is referred to the excellent review of Aring and Cobb. *Amyotonia congenita*. Two cases in twins were studied in the laboratory by Forbus and Wolf who found a reduction in the motor cells of the anterior horns, with extreme loss of nerve fibres in the anterior nerve roots. The muscles showed a few normal fibres but most of them were extremely small and of embryonic type. They thought it probable that there had been some injury to the developing embryo which affected especially the anterior horn of the spinal cord, the condition of the muscles being secondary. *Progressive muscular atrophy* shows wasting of the muscles with many small non-striated fibres and scarring. There is degeneration and atrophy of the cells of the anterior horn and secondary degeneration of the motor roots. This is an affection of middle age and seems closely related to *amyotrophic lateral sclerosis*, a disease of later life in which with the same muscular changes there is degeneration of the ventral horn cells and also of the pyramidal tracts even to the motor tracts of the cortex. More definitely hereditary are such diseases as *progressive muscular dystrophy* and *myotonia congenita*, or Thomsen's disease. There are several types of progressive muscular dystrophy sometimes with atrophy of some muscles while others appear greatly enlarged. These large muscles may be temporarily really hypertrophied or only rendered bulky by accumulations of adipose and fibrous tissue. The degeneration of the muscle fibres is progressive. No changes are found in the central nervous system. *Myotonia congenita* was described by Thomsen because he suffered from it himself and there were twenty-three other cases in his family. It shows itself in the lasting contraction that occurs when the patient attempts any voluntary movement after resting, although after a short time with continued effort the muscles relax from the spasm and he regains control. There are no changes in the central nervous system but the muscle fibres are enlarged and have more sarcolemma nuclei than normal and are sometimes vacuolated (Erb).

*Friedreich's ataxia* is a familial affection with muscular atrophy, fibrillation and cramps together with ataxia, nystagmus, speech defects, absent tendon reflexes and deformities of the feet and spine. Some cases were described by Marie as due to cerebellar lesions. The spinal cord shows degeneration, especially in the dorsal columns and dorsal roots but there may be also degeneration in the pyramidal tracts and in the ventral horns.

An effort has been made to refer some of these diseases to abnormalities in the endocrine glands but, so far, this is not convincing. They may be due to some exogenous toxin or infection but some are distinctly hereditary. Of course, the atrophies of muscle due to recognized aetiological factors, such as trauma, poliomyelitis, lead poisoning, etc., are easily separated from this group.

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## CHAPTER LX

### DISEASES OF UNDETERMINED ORIGIN AFFECTING BONES

*Chondrodystrophia foetalis. Osteogenesis imperfecta. Osteopetrosis, Legg-Perthes' disease. Osteitis deformans (Paget's disease).*

**Chondrodystrophia foetalis** is a disease of the cartilage occurring in foetal life, and leading to a partial or complete cessation of the endochondral ossification, while periosteal bone formation proceeds vigorously. The result of this is that the infant is brought into the world with extraordinarily shortened arms and legs and with other deformities, among which are distortion of the pelvis, malformation of the vertebral column and thoracic skeleton, and great enlargement of the skull, with retraction of the nose. Every one is familiar with the peculiar short-limbed dwarfs, with their large heads and characteristic faces, in which the nostrils seem directed almost straight forward. They are intelligent, active, and strong, and make their way in life, often as clowns in circuses, where their strength and agility find them occupation. They may reach an advanced age and bear children, although on account of the deformity of the pelvis these must be removed by Cæsarean section. That the disease is hereditary is seen from the fact that these are commonly also dwarfs, but cases of chondrodystrophia occur often enough in families in which no other instances are known.

The cause of the disease is quite unknown. The organs, including all the glands of internal secretion, are found to be quite normal, and all the changes are explained on the basis of the disturbances in the cartilages. Kaufmann distinguishes chondromalacic, hyperplastic, and hypoplastic alterations of the cartilage, but, as Siegert points out, all these may occur together in the same case. The epiphyseal cartilages are found abundantly penetrated by blood-vessels from the perichondrium (Fig. 551). The cartilage cells may be very small and widely separated by a rather soft fibrillar intercellular substance. Often they lie in great spaces which produce a spongy appearance. Along the line of ossification there is in patches a columnar arrangement of cells, while for the rest the cells are enlarged and totally irregular in their arrangement. In other instances the zone of columnar arrangement of cartilage cells is separated from the marrow cavity by other cartilage cells arranged in a network. Often, but not always, a lamella of periosteum with blood-vessels extends across the epiphyseal cartilage, just above the line of ossification, and causes a complete cessation of that process. Invasion of the cartilage by marrow capillaries is almost at a standstill, and usually the spaces are limited by a film of completed bone. Calcification of the cartilage is rather slight, but some remnants of blue-staining material are found in the centres of the terminal bone lamellæ. In spite of these anatomical conditions, which express the re-

sult, it is hard to say exactly why such slight obstacles are not overcome, so that growth of the cartilage into orderly columns and consequently ossification may proceed. Periosteal growth, building up and breaking down of the lamellæ of the diaphysis, and bone-marrow formation are normal. Premature synostosis of the portions of the sphenoid



Fig. 551.—Chondodystrophy in an infant. Median section of the femur, showing softening and displacement of the epiphyseal cartilage.

with one another and with the basilar portion of the occipital bone is common, and in sharp contrast with the condition in myxœdema or cretinism, in which this connection remains cartilaginous a very long time. It may be responsible in part for the retraction of the nose. Dandy has recently observed that there is a distinct hydrocephalus in these cases. There is a lumbar lordosis, and the promontory of the

sacrum projects into the upper strait of the pelvis, so as to make it very narrow. In adults of this type, as in the case of a woman aged seventy-five seen at autopsy, ossification is quite complete, and no trace of intermediary cartilage remains. Endochondral ossification with some growth does, therefore, go on to completion, but without adding much to the length of the bones. This condition is not to be confused with cretinism, in which the whole process of ossification is retarded, nor with rickets, in which there is a period during which osteoid tissue, and not bone, is formed abundantly.

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#### OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta is a condition in which, in infants and young children, multiple fractures of the ribs and long bones occur. Niklas, in describing a still-born infant in whom there were more than 60 fractures, most of them produced some time before birth, regards the process as different from osteopsathyrosis or osteogenesis imperfecta tarda, which occurs in adult life and the nature of which is still doubtful. Study of the bones in osteogenesis imperfecta shows normal cartilage with normal preparatory calcification, a normal line of ossification, with normal-looking osteoblasts. These, however, must function imperfectly, since the lamellæ of bone are extremely delicate and thin. Periosteal bone formation is greatly reduced, and many lamellæ of the cortex are disconnected and run transversely. Resorption of bone is normal in the presence of this faulty or deficient apposition—hence the numerous fractures. Fraser, Hirschmann and others agree that there is no endocrine disturbance but that the condition is hereditary, generally through the male. Blue scleræ are characteristic and there is an active period in childhood when fractures are most common, after which at puberty the bones become dense and strong—there is otosclerosis with deafness.

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#### OSTEOPETROSIS (MARBLE BONES)

This is another hereditary affection of which the etiology is unknown but it is thought not to depend upon any endocrine disturbance or deficiency factor. The cortex and spongiosa of bones become thickened and encroach upon the marrow cavity so as to interfere with blood formation. In one case described by McCune and Bradley the red corpuscles fell in three months from 4,390,000 to 967,000. The chemical constitution of the dense rather chalky bones is about normal and

while the calcium of the blood is only slightly changed, there is generally lowering of the serum phosphorus. There is a positive calcium and phosphorus balance.

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#### LEGG-PERTHES' DISEASE

The so-called Legg-Perthes' disease, or coxa plana, consists in a peculiar flattening of the head of the femur as the result of subchondral epiphyseal necrosis which seems to be brought about through a primary change in the tissues about the neck of the bone. The etiology is not known but it seems clear that it is not the effect of any endocrine disturbance, nor does it depend upon malformation of the acetabulum but perhaps on traumatic or other injury to the head of the femur.

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#### PAGET'S DISEASE (OSTEITIS DEFORMANS)

In 1876 Paget described a disease in which the bones of the extremities and of the skull became greatly thickened, and to some extent softened, so that bowing of the legs occurred. The enlargement of the head was extreme, and the person sank in stature. Many cases of this disease have been studied, and although the cause is still unknown, the anatomical changes are fairly clear. It begins usually after the age of forty, and progresses slowly with some pain and tenderness in the altered bones. In some cases the changes are unilateral or limited to one or two bones. In those in which the skull and facial bones are affected the condition is spoken of as leontiasis ossea. In them the softened bone may later assume an ivory-like hardness. The tibiae and femora commonly become thickened and bent forward. The skull (Fig. 552) may reach a thickness of 2 or 3 or even 4 cm., and, as a rule, the bone is easily cut with a knife. Since it is a disease of advanced life, there is no question of disturbance of ossification along the epiphyseal line. Instead, there are concerned especially extensive resorption of the normal bone by osteoclasts, and the excessive new formation of irregular bony lamellæ by the osteoblasts which accompany the fibrous marrow. The marrow actually loses its blood-forming elements and becomes converted into a vascular fibrous tissue which produces much soft, bone-like tissue. The architecture of the bone is disorganized, and the cortex loses its dense character and sharp outline. The marrow cavity is encroached upon or filled completely, and a thick subperiosteal layer is formed (Fig. 552). In this new tissue the lamellæ run in every direction. Occasionally there are cysts or spaces in it filled with fluid, or tumor-like growths may appear. There is no halisteresis, as in osteomalacia.

Various theories have been proposed as to the causation, and many infectious agents have been held responsible, including syphilis. There is little evidence for these views. Others have thought of it as an effect of the disturbance of some internal secretion. DaCosta and his co-



Fig. 552.—Paget's disease, or osteitis deformans. Thickened skull and cross-section of femur. Marrow cavity filled with osteoid tissue.

workers found that there is a retention of calcium, magnesium, and phosphorus, with excessive excretion of sulphur, and state that there have been analyses which show that, in spite of their softness, the bones are especially rich in calcium.

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## CHAPTER LXI

### ARTHRITIS DEFORMANS

*Confusion as to classification; infectious, traumatic, neuropathic, and gouty forms.*  
*Arthritis deformans: terminology. 1. Proliferative arthritis deformans or progressive polyarthritis; clinical and gross pathological characters; histology. Spondylitis of Bechterew and Marie. 2. Degenerative arthritis deformans. Clinical and gross pathological changes; histology. Malum coxae senile; spondylitis deformans.*

THE recent discussion of chronic affections of the joints at the International Congress of Medicine in London showed how confused our ideas are as to the classification of these affections. We have learnt that there are many infections in the course of which recognizable organisms lodge in the tissues of the joints and produce acute or chronic forms of arthritis and periarthritis. This is particularly true of the pyogenic micrococci, and perhaps especially of the gonococcus. There are also, as is well known, articular and periarticular inflammations due to the unknown infectious agent of rheumatism (and to avoid confusion we shall use the term rheumatism for that affection only in which fever, arthritis, and peri-, endo-, and myocarditis are found, often associated with tonsillitis and chorea).

The part played by the tubercle bacillus in producing destructive and reactive changes in joints had been dwelt upon, and there are other cases in which the spirochaeta of syphilis plays a similar rôle.

These are, with many others, the infectious forms of arthritis usually easily recognized to be the sequelæ of the existence of a focus of similar infection elsewhere. While this primary infectious lesion may sometimes be very evident, it is less so at other times, as, for example, those cases in which pyorrhœa alveolaris, or some nasal suppuration, is the real, though unsuspected, source of the spread of bacteria. The lesions of the joints are sometimes suppurative inflammations; sometimes there are only effusions of fluid; adhesions and even complete ankylosis of fibrous or bony character often occur. Traumatism, especially when bacteria are introduced into the joint cavity, is naturally often productive of an arthritis, and in haemophilia and allied conditions there arises haemorrhage into the joints which may simulate in its effects those of an inflammation.

In the course of some diseases of the spinal cord, notably tabes dorsalis, and syringomyelia, there occur curious changes in some of the joints, causing complete disorganization not only of the joint structures themselves, but of the neighboring bones, with the most deforming dislocations. The tabetic arthropathies have already been mentioned, and one of them at least represented in an illustration (Fig. 419).

A fourth type is that already described and figured in speaking of gout, in which the deposition of crystalline masses of urates in the joint

cartilages and in the periarticular tissues is the cause of intense inflammatory reactions (Fig. 41).

When all these forms of arthropathy have been considered, there still remain many which cannot be regarded as definitely belonging to any of those groups. These are commonly chronic and extremely persistent affections, which, although they may sometimes begin suddenly enough with pain and fever, and even in quite young people, drag on through years, and cause the most extreme deformities and disabilities, which are permanent. Indeed, they appear to be gradually progressive during all that time in producing atrophy and disorganization of the cartilages and of the bone itself, accompanied by extraordinary new formations both of cartilage and bone, as well as of scar tissue, in and about the joint.

It may as well be admitted at the beginning that, since every author who writes upon the subject seems to use a different terminology, it is extremely difficult to compare their results and to decide upon the limits of the disease and its most satisfactory subdivision. Barker has reviewed the subject, and in his tabulations he separates osteoarthritis deformans from chronic progressive polyarthritis (the rheumatoid arthritis of Garrod). German writers, such as M. B. Schmidt and Kaufmann, divide arthritis deformans into three groups: (1) *A. ulcerosa sicca*, which is often monarticular and is essentially a degenerative and destructive process; (2) *Arthritis adhæsiva*, in which many joints are involved, and while destructive in a sense, is especially characterized by the growth of granulation tissue forming adhesions and even a firm fibrous ankylosis; and (3) *Arthritis deformans*, in which atrophic or degenerative changes in the cartilage and bone are accompanied by extraordinary new formation of both bone and cartilage in such a way that the ends of the bone forming the joint become profoundly deformed and often dislocated. Nichols and Richardson regard all the cases as examples of one disease, but recognize an essentially degenerative form in contrast with another in which proliferation of connective tissue, cartilage, or bone is predominant. It seems that their proliferative form must correspond with the *A. adhæsiva*, while their degenerative form comprises the other two classes. In the same way in comparing their terminology with that of Barker it seems that the proliferative form is the same as the chronic progressive polyarthritis or rheumatoid arthritis, while the degenerative form is co-extensive with osteoarthritis deformans.

**Proliferative Arthritis Deformans.**—The first part of these, the proliferative form of arthritis deformans of Nichols, or progressive polyarthritis of other writers, begins often with fever and sudden pain in the joints, almost as in an attack of rheumatism. It affects young people as well as old, and quickly leads to lameness, disability, and stiffness of the joints. It affects many joints, including those of the knees, shoulders, etc., as well as those of the hands and feet. The joints become enlarged, but remain soft and doughy, without any irregular nodules (Fig. 553). *x*-Rays show rarefaction of the bone, which may be due to a withdrawal of calcium salts, but no exostoses. If

such a joint be opened, its articular surface is found partly covered with red granulation tissue and the synovial membrane generally thickened. At a later stage the cavity may be partly or completely obliterated by adhesions, and the cartilages partly replaced by new bone or by fibrous tissue. Fibrous or even bony ankylosis may occur, and in ex-



Fig. 553.—Proliferative arthritis; soft swelling of the joints of the hand.

treme cases the two bones become united with continuous marrow cavity. Partial dislocations are sometimes found, but even in such late stages there is no new formation of bony nodules about the joints.

Histologically, the following is found to occur. As a result, no doubt, of some primary injury, there is formed a layer of granulation tissue

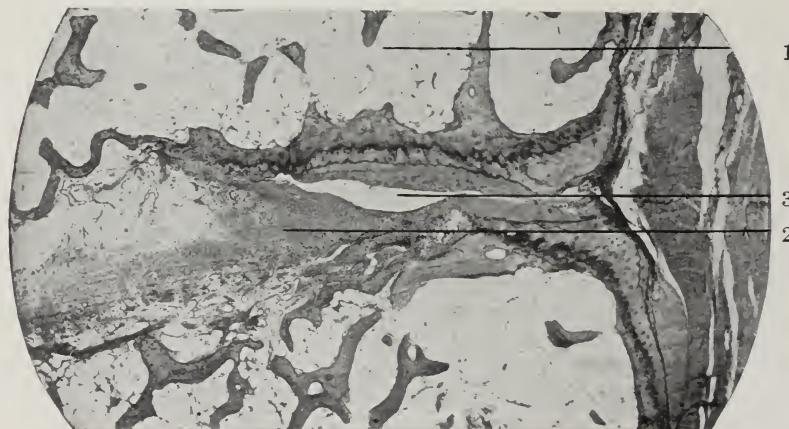


Fig. 554.—Proliferative arthritis with ankylosis of phalangeal joint. Spongy bone of the phalanx (1). Growth of fibrous tissue and fibrocartilage (2) has almost entirely obliterated the joint cavity (3) (Nichols and Richardson).

on the surface of the synovial membrane and spreading over the cartilage of the articular surfaces. This reduces the extent of exposure of the cartilage, and through adhering to the similar granulation tissue of the opposite side, causes partial obliteration of the joint cavity (Fig. 554). The granulation tissue also extends into the substance of the underlying cartilage and tends to destroy it. The bone beneath shows, for a time

at least, no morphological evidence of rarefaction, but the bone-marrow becomes converted into an oedematous fibrous tissue with many osteoblasts and capillaries. This invades the cartilage from below, causing its ossification as it goes, and may penetrate to join the overlying layer of granulation tissue. The activity of the osteoblasts may cause much condensation of the bone beneath the cartilage, but it also causes much new bone formation within and overspreading the cartilage, often with



Fig. 555.—Degenerative arthritis; characteristic deformities of the hands with nodular enlargements of the joints.

new cartilage formation as well, so that Nichols even pictures a bone in which, while part of the original cartilage remains, there is a layer of bone surmounted by cartilage covering it. All these things explain the tendency to the formation of dense fibrous ankylosis which may be more or less complete. One type of this disease which involves fibrous or bony ankylosis of the articular processes of the vertebræ, including the costovertebral articulations, is particularly striking. Occasionally



Fig. 556.—Degenerative arthritis; typical deformity of the hands, with ulnar deflection.

the ligaments are ossified also. The result is the solidification of the spinal column into a rigid curved structure, concave throughout on the anterior aspect. In the so-called Bechterew's disease the ankylosis is limited to the spine or part of it, beginning above, but in other cases the hip- and shoulder-joints are also involved (*spondylose rhizomelique* of Marie-Strümpell).

**Degenerative Arthritis Deformans.**—The second group, the degenerative form of Nichols or osteoarthritis deformans of others, is more par-

ticularly found in elderly people, and is often an affection of fewer joints. It usually begins insidiously, without fever, and progresses slowly to extreme deformities and disabilities of the joints. These become enlarged by the appearance of firm or hard nodules, and are tender and painful. The joints of the hands and feet often show the most striking changes, although the knees and hips and other large joints are equally characteristically affected (Fig. 555). The hands of these patients present an especially remarkable appearance. There is flexion of the fingers, as a rule, with deflection to the ulnar side. Great knobby enlargements of the knuckles and of the terminal phalangeal joints are often associated with relatively slight enlargement of the middle joints of the fingers, so that these tend, on account of the relaxation or atrophy of their ligaments, to bend backward (Fig. 556). Between the knuckles and the wrist-joint the back of the hand over the metacarpal bones sinks into a hollow over which the skin is extremely thin, like crinkled tissue paper, shiny and translucent, so that the veins show through distinctly.

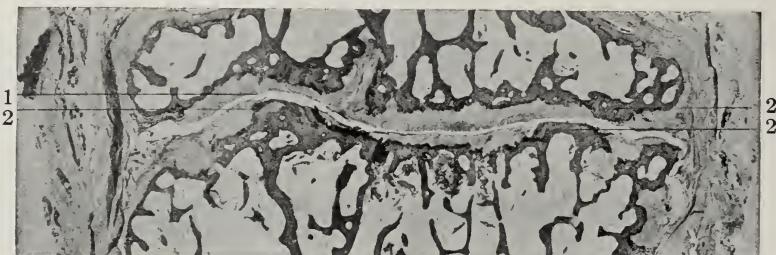


Fig. 557.—Degenerative arthritis. Phalangeal joint, showing irregular joint surface, (1) with exposed eburnated bone, (2, 2) (Nichols and Richardson).

On opening one of these joints no new growth of granulation tissue is found, nor any tendency to ankylosis. Instead, the changes are predominantly in the cartilage and secondarily in the bone. The cartilage is at first fibrillated and plush-like, so that its shaggy surface can be smoothed over from one side to the other. This causes such softening and disintegration that it is readily eroded away, leaving deep ulcers and sometimes exposing the bone (Fig. 557). In the gross specimen this uncovered bone is in most cases found to be smooth and hard. Opposite such an ulceration of the cartilage the cartilage of the other joint surface tends to thicken itself and fill up the space, often becoming partly or completely ossified in this process. But sometimes both of the opposed surfaces are denuded of cartilage and bone grinds against bone. Ordinarily this sets up the formation of much new bone in the substance of that which is exposed, and the surface layers become very compact and hard. In such joints as move like hinges these opposing surfaces of dense bone grind upon one another until they become brilliantly polished. Sometimes this condition arises only after inequalities in one surface have been filled up by overgrowth from the other which have become bony. Then the grinding produces parallel grooves, which

are fitted by ridges of the opposite side. In joints which work in many directions these parallel grooves do not appear (Fig. 558). Where the bone is very atrophic and unable to respond, or in retired places where the pressure is insufficient to stimulate much new bone formation, the



Fig. 558.—Arthritis deformans (degenerative form). Head of femur showing erosion and marginal osteophyte formation.

Fig. 559.—Arthritis deformans (degenerative form). Extreme erosion of the head of the femur, with polishing and exostosis formation.

surface does not become smooth and shiny, but remains porous, as though one had tried to polish pumice stone (Walkhoff).

All around the margin of the joint (Fig. 559), which is much enlarged thereby, there is usually formed a series of cartilaginous or bony nodular outgrowths. These may interlock in such a way as to limit



Fig. 560.—Arthritis deformans (degenerative form). Acetabulum with marginal osteophytes.



Fig. 561.—Arthritis deformans (degenerative form). Shallow acetabulum surrounded by marginal osteophytes. (Another view of Fig. 560.)

the motion of the joint very seriously. From the capsular synovial membrane there often hang villous, branched, fat-containing masses which are spoken of as *lipoma arborescens*. In this capsule, also calcified or cartilaginous masses of tissue may form and become pedunculated. Through constriction of their stalk they may come to be free in the cavity, where they cause much disturbance (*joint mice*).

Histologically the first changes are found in the cartilage, which loses its normal elasticity and homogeneous character and becomes vertically



Fig. 562.—Arthritis deformans (degenerative form). Erosion of head of femur with dislocation to a new flattened joint surface on the ilium.

split into fine fibrillæ. The cartilage cells degenerate and disappear. The whole layer may be ground away, exposing the bone, which has in the meanwhile, by the activity of the subchondral osteoblasts, become eburnated or condensed, so that the cancellous laminæ lie close together in a compact mass. Great proliferation of the remaining cartilage around the margin of the joint occurs, and into this cartilage the blood capillaries of the osteogenic marrow grow, converting it into bone. There is little or no formation of granulation tissue from the

synovial membrane or perichondrium over the surface of the joint, and ankyloses do not occur. The erosion can go much further than the mere thickness of the original layer of cartilage. The exposed bone is worn away deep into the head of the epiphysis until the most extreme deformity is produced, constantly made up in a futile way by the growth of the marginal osteophytes (Fig. 560). In the hip such changes produce a flattening of the head of the femur into a mushroom-like mass fringed with hanging osteophytes which plays in the partly filled-up and



Fig. 563.—Spondylitis deformans, showing fusion of the bodies of the vertebræ by exostoses which stretch across the intervertebral discs. The smaller articulations show no ankylosis, in which this condition differs somewhat from the spondylose rhizomelique.

very shallow acetabulum (Fig. 561), or the erosions may be more lateral and the head of the femur, now a laterally flattened mass, becomes dislocated to some point on the ilium where it lies against a newly formed acetabulum (Fig. 562). In all the more advanced cases of this type there is much rarefaction of the bones, and a dried femur is extraordinarily light as compared with one from a normal person. In one case which I observed for a long time the bones were so fragile that one of them broke on lifting the body of the woman from the bed

after death. A section showed the cancellous bone to be extensively atrophied and the cortex greatly reduced in thickness.

This group comprises, beside the forms in which the joints of hands and feet are affected together with other larger articulations, those in which erosion of the cartilage and atrophy of the bones found in one hip-joint (*malum coxae senile*), and those in which the cartilaginous intervertebral discs form the starting-point, and in which the production of exostoses and ecchondroses round the centra of the vertebrae results in a rigidity of the spinal column not dependent upon ankylosis of its smaller articulations (spondylitis deformans) (Fig. 563).

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## CHAPTER LXII

### DISEASES AFFECTING TEETH AND RELATED STRUCTURES

*Formation and structure of teeth; development. Influence of metabolic disturbances. Caries. Pyorrhœa alveolaris. Periapical abscesses. Relation to distant disturbances.*

SOME indication of the relation of the various elements that make up a tooth is necessary although for detailed description reference must be made to such works as those of Braus, Hopewell-Smith, Günther, Bödecker and others.

The outer coat of enamel which is produced by the ameloblasts or enamel organ, extends only a short way into the crevice between the gum and the tooth. It is continued in a sense by the cementum which covers the roots and is in contact with the peridental membrane which lines the alveolus of the mandibular bone. The enamel directly overlies the dentine which makes up the bulk of the tooth and is said to be itself covered at least in the teeth of young people by Nasmyth's membrane which is a remnant of the enamel organ and composed of an extremely thin homogeneous membrane with some flattened cells. It may show adherent bacteria but is thought to be a protective layer. The enamel itself is curiously formed in rods and in the striæ of Retzius is slightly pigmented. The dentine which is more opaque is hollowed out by the pulp cavity which extends in narrowed form into the roots. This cavity contains a soft connective tissue with abundant blood vessels and nerves which extend to and probably through the formative odontoblast layer which is directly applied to the dentine. The canaliculi in the dentine are by most authors thought to contain the elongated processes of the odontoblasts but Van der Sprenkel in an interesting paper describes non-medullated nerve fibrils which extend into those canaliculi and end in minute loops.

The teeth develop in human beings at different rates, the lateral incisors for example becoming complete only after two years while the central incisors, beginning at two to six months, are mature at one year.

In some animals, such as the rats so commonly used in experiments, Erdheim pointed out that while the molar teeth become mature and unchanging, the incisors grow continuously. This difference between the teeth of experimental animals and man must be kept in mind in the study of metabolic influences upon the teeth, for while many authors have maintained that once formed the teeth are as independent of chemical change in the body as so much foreign mineral material, others lay stress on their intimate dependence upon the calcium and phosphorus content of the body fluids and the influence of Vitamin D and of parathyroid activities.

Erdheim was perhaps the first to describe the effect of rickets upon the dentine in the continuously growing incisors of rats, and in the lateral teeth only if the influence was felt before their maturation was complete.

The matter is still being discussed without general agreement but such changes as are due to the abnormalities of metabolism are brought about by way of the blood and fluid supply to the pulp and dentine rather than by the action of the saliva. Mellanby found hypoplasia of dentine in experimental animals deprived of Vitamin D but Fish shows that once formed, the dentine retains its content of calcium in profound disturbances of the calcium metabolism, or after maximal doses of Vitamin D and calcium. Other maladjustments may arise, such as the retraction of the odontoblasts from the dentine in scurvy, as described by Wolbach and Howe. But in the early stages of development it is agreed that such conditions as rickets and tetany may cause imperfect formation of the enamel and to a less extent of the dentine. Such hypoplasia of the enamel leaves the affected teeth rough and nodular. McCollum and his co-workers find that lack of magnesium in the diet disturbs the proper growth of the teeth.

**Caries.**—Caries, or decay of the teeth, is, of course, of almost universal occurrence. It affects children as well as grown people, decreasing in advanced age perhaps because the more susceptible teeth are lost. It is astonishing that the cause and precise nature of dental caries are even yet unknown, although such definite advice is offered about the care of the teeth. It appears that among the Eskimos and native Africans and in some remote islands where no tooth brushes are known, there is no caries and it is perhaps possible that we overdo the application of powders and pastes.

Most authors agree that caries is not dependent upon metabolic disturbances although some people are especially susceptible while others seem almost immune. The rôle of diet has been abundantly discussed and it is thought that sugar in excess and other carbohydrates from which acid can be produced are important factors. It is especially pointed out that such coarse carbohydrates as may adhere in particles in crevices of the teeth favor, under the decomposing action of bacteria, the local action of acid on the tooth. Of the bacteria which occur, only the *Lactobacillus acidophilus* is thought to be important. Its mode of entry into the substance of the tooth through the enamel seems poorly explained by mere acid formation and it would appear more likely that some mechanical injury or fissure formation could allow entry to such bacteria. Still, the usual experience seems to be that decay begins in a recess between teeth where particles of food remain neglected for a time—perhaps allowing the concentrated production of acid there. The student should consult the papers of Bunting, Bibby, Hollander (reporting the work of the Columbia University Dental Caries Research), Hausman and Marshall and others.

**Pyorrhœa alveolaris** is a very common affection in which the tendency is toward a separation of the gum from the root of the tooth with consequent deprivation of the cement layer of its blood-supply.

It results from a purulent inflammation of those tissues caused by various bacteria, among which the spirochætes and fusiform bacilli of Vincent are prominent (trench mouth). Other bacteria of various sorts may be concerned, often with a deposit of calcium (tartar) about the surfaces and roots of the tooth.

**Periapical Abscesses.**—When the caries or decay of the tooth extends inward, with erosion of the dentine, to reach the pulp or so near to it as to allow the invasion of bacteria, the infection may extend destroying the nerves and blood-vessels through the pore at the apex of the root so as to produce there a localized abscess which is generally encapsulated by granulation tissue. Staphylococci or haemolytic streptococci are most often concerned and by drainage through the cavity in the tooth, it may be possible to clear away the infection, but in other cases the abscess may extend so as to involve the alveolar bone or even penetrate into the antrum of the maxilla, producing an inflammation of this sinus. Still more extensive involvement of the surrounding tissues may occur, such as the so-called Ludwig's angina which is an inflammation of the loose tissue in the neck. But the extirpation of teeth on the ground that supposed local infection is the cause of distant disturbances such as arthritis and a variety of other painful affections, seems to be greatly overdone. Günther, in a recent review, says "this exaggerated activity one might pass over in silence were it not dangerous. Many patients—not only in America—are deprived of all their teeth and their tonsils without any good result."

The changes in the teeth in congenital syphilis are described elsewhere (page 745), and the adamantinoma which arises from the enamel organ on page 1104.

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## CHAPTER LXIII

### TUMORS

*General nature of tumors; Difficulty of classification. Fibromata, keloids, lipomata. Chondromata. Osteomata. Myomata; leiomyomata, adenomyomata, rhabdomyomata.*

**General Nature of Tumors.**—It seems quite impossible to discuss the general nature of tumors or to attempt any definition of a tumor until after some survey of their varying anatomical characters and modes of growth is made. In the meanwhile it may be said that they are masses of tissue resembling, but not perfectly identical with, the normal tissues, which grow without any regard for the laws which govern and restrain the growth of normal tissue. They are supplied with blood-vessels and a sufficient supporting framework by the host, and derive their nourishment from the circulation of the host. Therefore, like any parasite, they are harmful to the person in whose body they grow, but the injury which they do becomes intolerable when they not only absorb this essential nourishment but also invade and destroy the normal tissues. In olden times they were actually looked upon as parasites foreign to the body, but such a vague idea was forced to disappear when Johannes Müller showed that they were always composed of tissue of their host. If, now, we speak of a fibrous tumor as a fibroma, a fatty tumor as a lipoma, and cartilaginous or bony tumors as chondromata or osteomata, it is rather because their tissues closely resemble fibrous, fatty, cartilaginous, or bony tissue, than that we can actually trace their origin to these tissues. Our classification is, therefore, rather a tissue of assumptions than one formed on a true histogenetic basis. Probably it is true that an epithelioma is definitely derived from the epithelium in which it began, and a fibroma from the preëxistent connective tissue. It would be difficult to conceive of any other explanation, but the absolute proof is not at hand. Classification is at best unsatisfactory on a histogenetic basis, since so often we cannot make a good guess at the tissue which the tumor most resembles, or the point from which it actually sprang. Study of the form and arrangement of cells in the course of embryonic development of a tissue sometimes gives a clue to the origin of a tumor from one of these stages, and this has been especially fruitful in the case of the tumors arising from the nervous system. But the most important thing is a knowledge of the life-history and behavior of a tumor which we learn from the clinical history, followed to its termination, and correlate with the gross and histological characters of the growth.

With this knowledge, and not without it, we may foretell with some certainty the course and behavior of another tumor of the same structure.

In general, we adopt a division in which the type of the tissue and the manner of growth in its conflict with the normal tissues of the body form the main lines upon which separation into classes is carried out. Such a classification will be given (p. 1198) after we have examined the tumors themselves.

### FIBROMATA

A fibroma is a tumor composed of tissue which resembles more or less closely one of the many types of normal connective tissue. There is such variety in the relations of intercellular substance and cells in

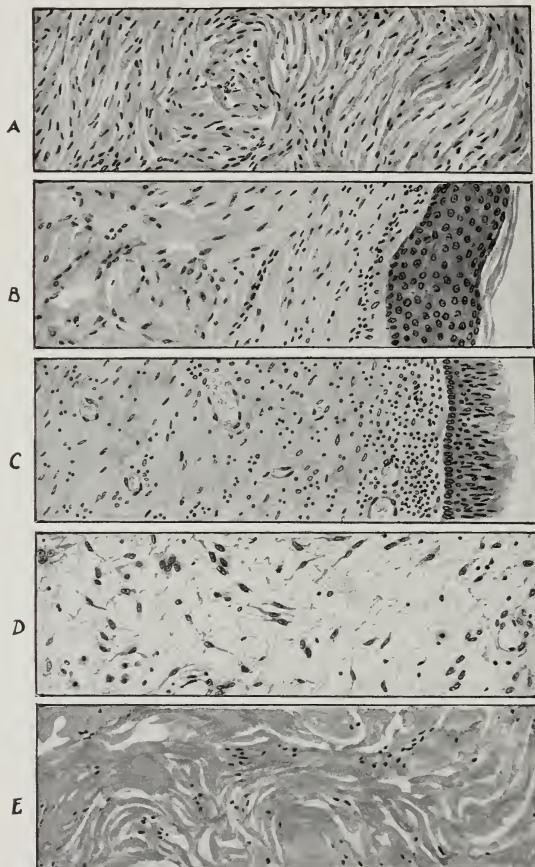


Fig. 564.—Types of fibroma. *C*, Nasal polyp or oedematous fibroma. The others (*A, B, D, E*) are fibromata of different consistence, formed in various situations in the body.

these normal types (tendon, fascia, areolar tissue, dermis, etc.) that it is not surprising that the fibrous tumors, which can diverge in every way from the character of the tissue from which they may be supposed to arise, may show a much greater variety. In every case one is impressed by the purposeless arrangement of the fibres, which stand in

no especial relation to adjacent tissues, as they do in normal connective tissue, but are merely woven together in a mass. Some fibromata are extremely soft and loose in texture—others are dense and hard (Figs. 564 and 565). When the intercellular fibres are little developed and the tumor is made up chiefly of closely packed cells, it may be found that its growth is rapid and invasive, and that the tumor should really be called a sarcoma. This is one of the points at which mere histological examination may fail to afford a correct interpretation and the biological

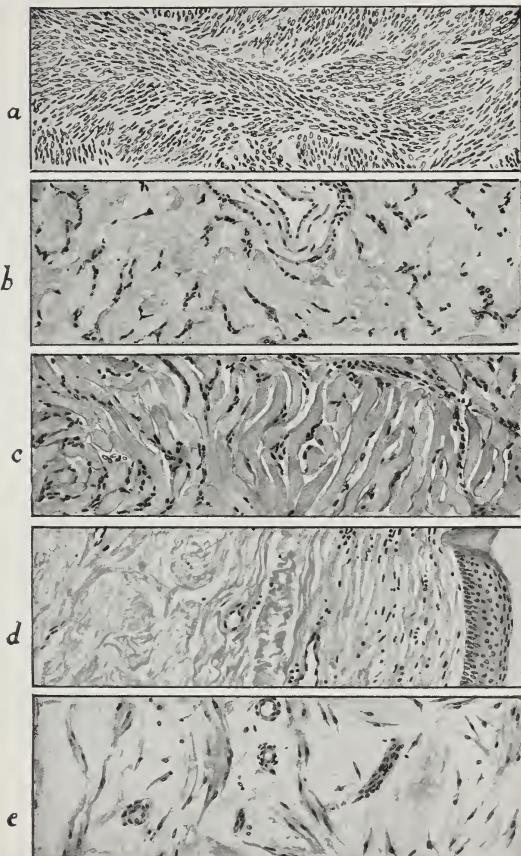


Fig. 565.—Types of fibroma: *a*, Cellular fibroma resembling a spindle-cell sarcoma, but benign; *d*, keloid.

characters must be known. To coin for such tumors the name fibrosarcoma is probably only to add to the difficulties of classification.

Fibromata occur almost anywhere in the body and are frequently multiple. They arise most commonly in the skin, the fasciæ, and the intermuscular tissues, about the joints or in connection with nerves. In the internal organs they are found in the submucosæ, in the kidney, ovaries, etc., but in many cases, especially in the breast and uterus,

the excessive growth of fibrous tissue accompanies that of other cells, such as epithelium or smooth muscle, and although such tumors are commonly spoken of as adenofibromata or fibromyomata, it seems probable that they are rather to be regarded as tumors of epithelium or muscle with merely a very abundant stroma. Fibromata of the skin are sometimes hard, solid tumors embedded deep in the skin and extending into the subcutaneous tissue (Fig. 566). One which was studied after its removal formed a thick cap over the whole scalp,

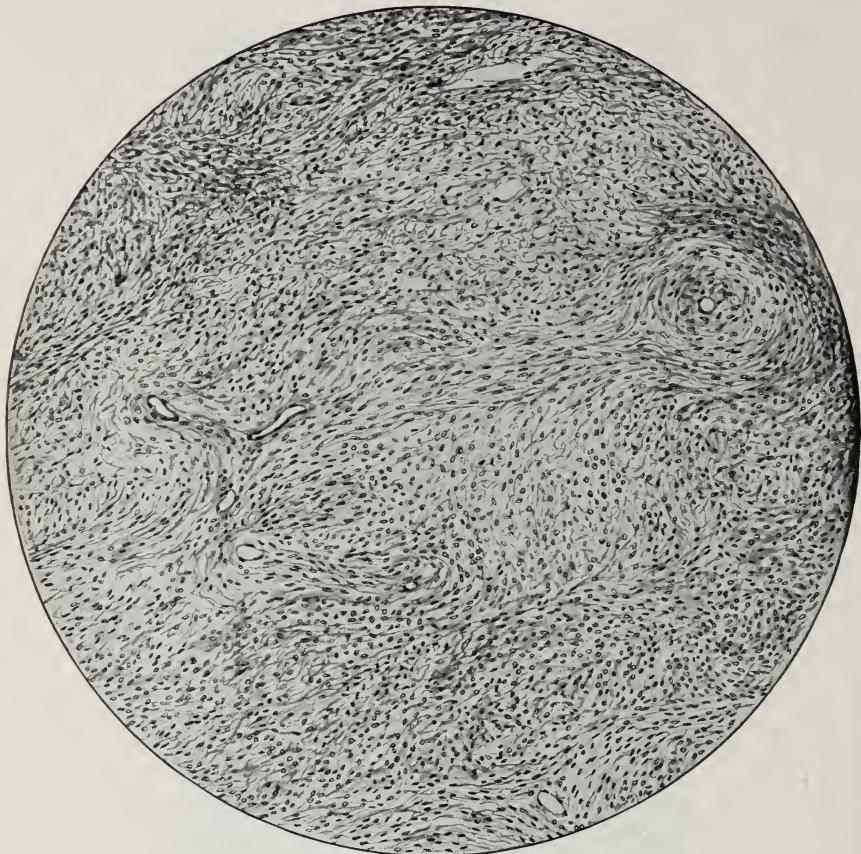


Fig. 566.—Subcutaneous hard fibroma.

projecting down with thick rounded edges as far as the ears. It was so rigid and so densely connected with the skin that much skin had to be grafted to cover the skull after its extirpation. Others are soft and project above the skin surface, often hanging by a relatively thin stalk (Fig. 567). Occasionally very large tumors composed of soft fibrous tissue are found hanging by a long stalk from the labium majus or from some other site about the external genitalia.

*Keloids* are extremely dense, scar-like tumors which appear in some people (especially in negroes) in the scars of wounds. Even when the

wound has been very slight great nodules may result. I have seen one or two negresses in whom puncture of the ear-lobes for earrings had set up the formation of great lobulated keloids. In other cases scratches, burns, or even healed acne pustules seem sufficient to start the growth. Extirpation leaves another scar in which, of course, the process may repeat itself. It seems that there must be some individual predisposition in such cases, for, of course, this does not happen in every one. The tumors are composed of very dense fibrous tissue in which blood-vessels and cells are far apart (Fig. 565, *d*).



Fig. 567.—Small soft pedunculated fibroma of the skin.

In the nose fibromata grow in clusters from the nasal septum, pushing up the Schneiderian membrane to cover them. These become extremely oedematous since they are loose in texture, and hang in the cavity of the nose as translucent, rather turgid rounded bodies almost like white grapes (nasal polyps). They cause obstruction of the air-passage and are exposed to trauma. Microscopically they are found to show sparsely arranged connective-tissue cells, but are infiltrated with all sorts of wandering cells, including many eosinophiles and the most beautiful mast cells (Fig. 564, *c*).

In connection with fasciæ, ligaments, and periosteum there are found larger, dense fibrous tumors in which the cells and their abundant inter-

cellular fibres are closely packed together in a hard mass which, on section, shows a shining, pearly white surface. These too may present softer areas, but usually the consistence is pretty uniform.

Pure fibromata are rare in the uterus and in the mammary gland. In the ovary they occur in the form of hard nodules which may reach a great size. These show microscopically closely arranged spindle-shaped connective-tissue cells with compact intercellular fibres. In the kidney there are often seen rather small, round, grayish-white glistening nodules embedded in the cortex or pyramids and crowding aside the tubules. These on section show an atypical fibrous tissue with varying proportions of cells and fibrous material. So, too, in the submucosæ of the alimentary tract firm gray nodules are found lifting up the mucosa. While some of these are true fibromata, most of them are made up of smooth muscle with a fibrous stroma.

#### LITERATURE

*Fibroma*.—Gergö: Virch. Arch., 1913, ccxiii, 317.

#### LIPOMATA

These are tumors composed of fat tissue and occurring in the form of circumscribed and sometimes lobulated flattened or rounded masses. Since fat tissue is not very sharply characterized histologically, it is difficult to make out differences between that which occurs in tumors and the normal fat. In some cases, however, the fat is associated with such a dense fibrous growth that the name *fibrolipoma* may be appropriate. In others an excessive vascular supply may suggest the name *angiolipoma*.

These tumors occur most commonly in the subcutaneous tissue, and especially over the back, the neck and shoulders, and the buttocks. They project as rather soft, lobulated masses which are sometimes quite tender or even spontaneously painful. They can be shelled out of their bed in the tissue and do not tend to recur. Microscopically there is merely fat in hugely dilated cells, arranged in compact lobules held together by the fibrous stroma. Coalescence of fat-cells with loss of their walls so that pools of oil are formed is an uncommon occurrence. Calcification or even ossification in necrotic areas is sometimes observed.

Other sites for lipomata are in the mesentery, the submucous and subserous tissues of the whole alimentary tract, in the kidney, heart, uterus, and even in the meninges: In the kidney the lipomata are usually rather small, but a few larger ones have been studied and have shown, besides the fat, an admixture with muscle and other elements, often with nodules of adrenal-like tissue.

Very interesting are the symmetrical multiple lipomata which have been mentioned before as related somehow with the irregular adiposis dolorosa of Dereum. These are often tender or painful, and are associated with mental, motor, sensory, and trophic disturbances of various sorts. Lyon thinks they shade off into the more general adiposis and may prove to be due to some disturbance of internal secretions.

Lipomata are practically invariably slow-growing tumors which in-

crease from within themselves, expanding so as to compress surrounding tissues or to project on the body surface.

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Keenan and Archibald: *Jour. Med. Research*, 1907, xvi, 121.  
Lyon: *Arch. Int. Med.*, 1910, vi, 28.  
Schridde: *Ergebn. d. allg. Path.*, 1906, x, 674.

#### CHONDROMATA

Tumors composed of cartilage of a somewhat irregular and atypical character occur in connection with preexisting cartilage in the joints, in the bones, or occasionally in the bronchi. Those which spring from the bone or skeletal cartilage appear as nodular tumors (Fig. 568) com-



Fig. 568.—Chondroma of phalanx.

posed of elastic, pale-bluish cartilage which is covered with a fibrous envelope and divided, as a rule, into lobules by a framework of connective tissue which bears blood-vessels. They are broadly connected with the bones or cartilage, or are partly embedded in the bone, occupying much of its marrow cavity and extending through the cortex to project upon the surface. The bone is often greatly distended by such a mass, and especially in the case of the fingers becomes greatly distorted (Fig. 569). Large tumors of this kind are not uncommon in the hand, where several fingers may be converted into unwieldy lumps

which become absolutely useless. In the pelvis enormous cartilaginous masses have been seen, projecting from the symphysis pubis or from the sacro-iliac synchondrosis, and so occupying the cavity of the pelvis as to obstruct childbirth. Similar tumors are described for the scapulae, the ribs, the hyoid bone, etc. Chondromata arising in the trachea or bronchi are often flattened clumps of tissue which, even though they lie in the spaces between the cartilaginous rings, are found to have a connection with them or with the perichondrium. In other cases large nodules have been observed blocking the bronchus or extending into the lung tissue.

Since normal cartilage is not vascular and depends for its nutrition upon the absorption of fluid from the vessels of the perichondrium, no great bulk of it can maintain itself alive. In the cartilaginous tumor, however, the tissue is in relatively small districts well supplied with nourishment from abundant blood-vessels which accompany its fibrous



Fig. 569.—Chondroma of phalanx. The tumor appears to begin in several places, perforating the cortex and lifting up the periosteum.

stroma. The inter-cellular substance is more variable in consistence and less dense than that of normal cartilage, and often shows a distinctly fibrillar structure. The cells vary greatly in size, and in their arrangement in groups, and thus differ markedly from those of normal cartilage (Fig. 570), but, on the whole, the resemblance is very close, and as a rule it is not easy to be sure of their tumor nature without recourse to information about the general features of the growth. Blood-vessels sometimes grow into the cartilage, as in normal endochondral ossification, and convert it into bone, so that the chondroma eventually becomes a kind of osteoma. Usually a layer of cartilage remains over the surface. In other cases extensive calcification occurs in patches, or the tumor may undergo a softening which leaves a cavity filled with a gelatinous, semi-fluid material in which large radiating cells are found. Actual cysts are formed finally if the liquefaction continues.

Virchow and others have attempted to show that since these tumors

are commonly found in young people, they may have arisen from congenitally misplaced cartilage or from disarranged cartilage islands cut off in the ordinary process of endochondral ossification. Such little islands do occur and remain unchanged. Virchow thought for a time that rickets, with its exaggerated and disorderly process of ossification, might present an especially favorable condition for such displacement of cartilage, but the cases seldom, if ever, show signs of healed rickets. It seems hardly necessary to insist upon the existence of such latent dis-



Fig. 570.—Chondroma with irregular blood-vessels and atypical bony areas.

placed cartilage islands, however, since periosteum and endosteum are so readily capable of producing cartilage whenever, as in a fracture, the new formation of tissue is required. Since we have other atypical tumor growths arising everywhere without special preparatory displacement of the tissue which exactly corresponds with them, it is not difficult to imagine the growth of a cartilaginous tumor from the cells which form bone by the way of cartilage. So, too, in the lung the new cartilage

growths, which are often called ecchondroses, when they seem to represent a mere hyperplasia, are easily derived from the perichondrium.

Combination of cartilage with other tumor elements is frequently found.

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*Chondroma*.—Boggs: Johns Hopkins Hosp. Bull., 1913, xxiv, 210.

Ehrenfried: Jour. Amer. Med. Assoc., 1915, lxiv, 1642.

Ribbert: Geschwulstlehre, Bonn, 1904.

#### OSTEOMATA

It has already been stated that at many points throughout the body ossification of tissue may take place if degenerative changes and deposition of calcium salts have occurred. At points in relation with cartilage and bones, instances have already been met with in which, as, for

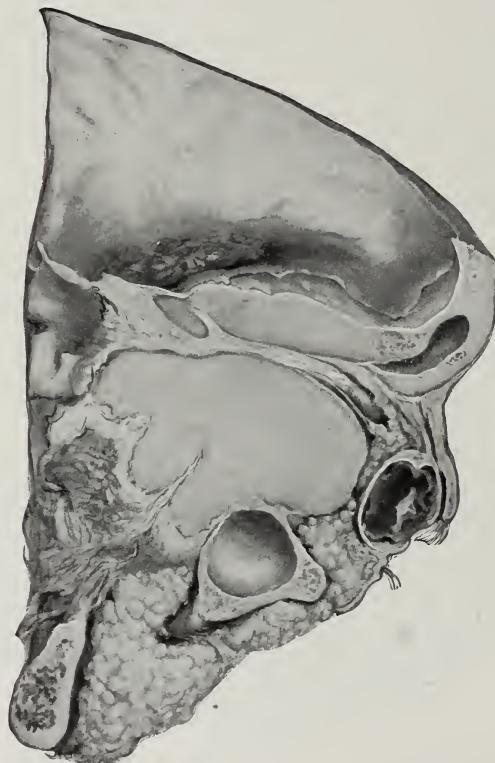


Fig. 571.—Large osteoma of very dense texture surrounding the elongated optic nerve, and dislocating the eye by extending into the orbit. The tumor bulged into the cranial cavity, and over it the brain was adherent.

example, in the case of arthritis deformans, rather extensive new bone formation occurs. Injuries to muscles and fasciae and inflammations of various sorts seem capable of giving rise to some change which finally leads to bone formation. Thus it is said that cavalrymen acquire bony plates in the muscles of the insides of their thighs, and soldiers and

others, similar plates in their deltoid muscles where gun or heavy burden rests. It is difficult to regard such things as tumors, since they seem to be merely an osteoplastic healing process which follows upon injury to the tissues. The so-called *progressive myositis ossificans* which, after inflammatory stages, ends in the formation of extensive bony shells in the muscles is doubtless similar in character.

More difficult to interpret properly are the multiple exostoses which appear about the epiphyses in young persons and are left along the shaft as the bone grows. They are often partly cartilaginous for a time, but in the end are bony. They can stretch some distance, and sometimes interarticulate in a way, with one another, or, by fusing, limit the motion



Fig. 572.—Ivory-like exostosis or osteoma of skull.

of the extremities. These growths are often observed to occur in one family and seem to have an hereditary element. Of course, any collection of bones will be found to present at least a few examples in which extensive exostoses are found in the form of irregular, rather thin, sharp outgrowths, but these are usually recognized to be the accompaniments of an old fracture or of some long-standing inflammatory disease. Growths of this kind from the surface of a bone are called *exostoses*; those which appear in the interior of a bone, *enostoses*, while a diffuse thickening of the bone is called *hyperostosis*.

The nodules of bone found in the lungs sometimes reach a considerable size. They are thought by many to depend upon preexisting inflammatory processes, and so too are those tiny bone masses which form in

the trachea and roughen its mucosa. These are not in direct connection with the tracheal cartilage rings.

Tumor-like growths of bony consistence, usually masses more or less closely connected with the bones, may be very compact and hard, "eburnated," or soft and spongy. Much has been said of such bony growths in other connections, and it will suffice to recall attention to the rounded masses of osteoid tissue which appear on the skull in rickets and later become hardened into bone; to the extensive new bone formation in chronic osteomyelitis around the areas of infection and in the neighborhood of ulcers which overlie such bones as the tibia. Chronic syphilitic forms of periostitis in the same way lead to the production of rough periosteal growths which deform the bone. Mention may also be made of the so-called osteophytes of pregnancy, which are thin, white, chalk-like deposits on the inner surface of the skull. These seem to be reabsorbed or merged with the cranial bones later, and are probably the result of changes in the distribution of calcium which characterize the altered metabolism of pregnancy.

Osteomata or bony tumors in which the bone is growing independently and without a limited aim are rare. They sometimes occur in connection with the long bones and sometimes with pelvis, shoulder-girdle, etc. Occasionally they are more independent of the skeleton and arise in tendons or muscles as actual growing nodules. It appears that the bones of the skull, especially about the nose and orbit and middle ear, offer the most favorable chance for their development, and it is not infrequent to find rounded masses developing in the nasal cavity from the ethmoid or other bones or in the accessory nasal sinuses. These sometimes become loose and are known as dead osteomata. One which we studied last year showed a compact, extremely hard mass, which had grown to occupy the upper maxilla, and part of the temporal bone, projecting far into the orbit so as to displace the eye. When sawed through (with great difficulty) it presented a perfectly smooth, ivory-like surface, and was seen to project in all directions so as to occupy space in the cranial and other cavities (Fig. 571). There are other ivory-like tumors which occur like buttons on the skull, and sometimes form hemispherical masses of considerable size. They are usually a little separated from the skull around the edges so as to appear pedunculated. These cause no especial inconvenience (Fig. 572).

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Zimmermann: Dtsch. Ztschr. f. Chir., 1900, lvii, 354.

#### MYOMA

The term myoma is applied to tumors which are composed largely of muscle, those in which smooth muscle or non-striated muscle constitutes the predominant tissue being called leiomyomata, while the rather more complicated tumors, which contain striated muscle, are spoken of as

rhabdomyomata. Since these types of tissue are not very closely related, it is not surprising to find that the corresponding tumors stand very far apart.

#### LEIOMYOMATA

Tumors composed of smooth muscle occur very commonly in the walls of the uterus. Although they are found elsewhere, as in the walls of the stomach and intestine, in the bladder, kidneys, skin, etc., they are only rarely encountered in those situations and constitute a group of little importance as compared with those of the uterus.

Myomata (or fibromyomata) of the uterus, often loosely spoken of as fibroids, appear as rounded or nodular tumors situated in the uterine wall, although they frequently project from the outer surface in such a way that they seem to be attached to the uterus by a slender peduncle only. The thin layer of uterine muscle which envelops them becomes more and more inconspicuous as they project in their growth from the uterine surface. On the other hand, there are also fibromyomata which project into the cavity of the uterus, carrying with them a very thin layer of the uterine musculature and the mucosa. They, too, become pedunculated and hang by this stalk in the cavity, sometimes projecting from the external os uteri. In these three positions the tumors are given the epithets intramural, subserous, and submucous.

Uterine myomata vary greatly in size, being found embedded in the wall, and no more than 2 or 3 mm. in diameter, while others reach enormous dimensions. Often several tumors of different size are found in the same uterus, and these may occupy all three situations (Fig. 573). In the cases in which large submucous myomata are found, the cavity of the uterus is greatly enlarged and distorted by the presence of the mass, and, indeed, this is true also in those cases in which large tumors occupy an intramural position.

They are dense, hard, pearly-white masses, which on section are found to be sharply marked out from the surrounding uterine musculature by projecting above the cut surface. They are further distinguished from it by their greater density and by their poverty in blood-vessels, for whereas the uterine wall is rather reddish gray and vascular, the tumor is usually composed of whorls of fibres intimately woven together so as to shine with a tendon-like lustre, reflected separately from each bundle, and is much more rigid than the surrounding tissue. Its blood-vessels, although sometimes rather large in the superficial zone, are quickly reduced to a very small calibre as they penetrate into the interior. Clarke has shown that this vascularization often becomes quite inadequate to nourish with blood the innermost parts, so that most extensive necroses appear, recognizable as hyaline areas or patches in which calcification or even bone formation has occurred. Great cyst-like cavities filled with brownish, turbid fluid are also found as a result of the disintegration of the tissue.

Such tumors grow by new formation of tissue from within, expanding and compressing adjacent structures, but showing no tendency to invade or to set up, by metastasis, similar growths in distant organs. Never-

theless, they may cause great distortions in the uterus and interfere seriously with its function. Although childbirth may be possible when the tumor is not too large, or when it is situated in the fundus of the uterus, it may readily be understood that a large tumor, especially when situated low in the uterus, can effectively obstruct parturition. Submucous myomata tend also to interfere with pregnancy and may, in case pregnancy does occur, offer a serious obstacle to the birth of the child.

The submucous myomata are especially productive of serious symptoms at all times, since the uterus tends to expel them into the vagina, exposing the surface to infection. Circulatory disturbances aid in causing the mass to soften and disintegrate, and from the putrefying tissue absorption of poisonous substances soon leads to a cachectic condition in the woman who bears such a tumor. In addition, these growths usually cause frequent haemorrhages from the uterus, which may bring about extreme anaemia. Their presence seems to cause in some general way a disturbance in the circulation which leads to cardiac hypertrophy, and a risk of cardiac failure and collapse. The nature of this remains obscure.

The many other details in the biology of these tumors may be read in the book of Kelly and Cullen on Myomata of the Uterus, in which a great wealth of material is described. One of the most interesting phenomena is the formation of vascular adhesions between large subperitoneal uterine myomata and the omentum or intestine, or other abdominal organ, after which the tumor becomes dependent upon that organ for its blood-supply and may even be separated finally from all connection with the uterus (parasitic myoma).

Microscopically, fibromyomata are found to be composed of smooth muscle-fibres arranged in parallel rows in bundles which interlace in every direction. These are embedded in an abundant stroma of connective tissue which bears the blood-vessels. According to the proportion of muscle to fibrous stroma, the consistence of the tumor varies, increase in the fibrous tissue adding to its hardness. The muscle-fibres are recognizable by their rod-shaped nuclei and by their relatively plump cell body, which takes a greenish color with Van Gieson's stain, in contrast with the bright red fibrous stroma. Of course, the actual bodies of the connective-tissue cells stain greenish yellow also, but they are rather sparsely scattered in the stroma.

Several theories as to the origin of these tumors have been advanced, but none are as yet firmly established. While it seems probable that they arise from abnormal portions of the uterine musculature itself, there are those who assert their origin from the musculature of the walls of the blood-vessels. The fact that myomata relax and soften during pregnancy, recovering their hardness afterward, seems to point to their relation to the uterine musculature.

*Adenomyomata.*—The greatest interest has been roused by certain rather diffuse myomatous tumors which occur in the uterine wall, especially at the angle where the Fallopian tube enters, and also in the tube itself and in the round ligament. These are peculiar in containing

epithelium-lined, gland-like cavities scattered in the mass of smooth muscle. They were called adenomyomata by von Recklinghausen, who ascribed them to misplaced rudiments derived from the mesonephros or Wolffian body. This view has been widely accepted. The proof is not complete, however, and R. Meyer, Lockstaedt, and others bring forward arguments against it showing that it is quite possible that such glandular tumors might arise from inclusion of uterine glands in a muscular mass. Cullen, in his volume on the subject, has shown, by careful study of 73



Fig. 573.—Subperitoneal, submucous, and intramural myomata of the uterus (Kelly-Cullen).

cases, that in 56 it was possible to trace the uterine mucosa directly into continuity with the glands of the tumor, a finding which seems to decide the matter definitely.

These nodules occur also in the ovary and on the peritoneal surfaces even quite away from the pelvic organs in the region of the appendix and elsewhere, and are peculiar in that they take part in the phenomena of menstruation and swell and are filled with blood. The so-called chocolate cysts found in the ovary and sometimes on the surface of the uterus are thought to be the result of such menstrual changes with

retention of the disintegrated blood. Sampson has studied them for a long time and thinks them implantations of uterine epithelium resulting from retrograde transportation during menstruation, but Walz opposes Sampson's ideas and thinks that the cœlomic epithelium has retained in places the power of forming such tissue as produced the Müllerian duct. He agrees in essentials with Cullen, and this seems to us the best conclusion. Discussion of this doubtful question is found in the papers referred to.

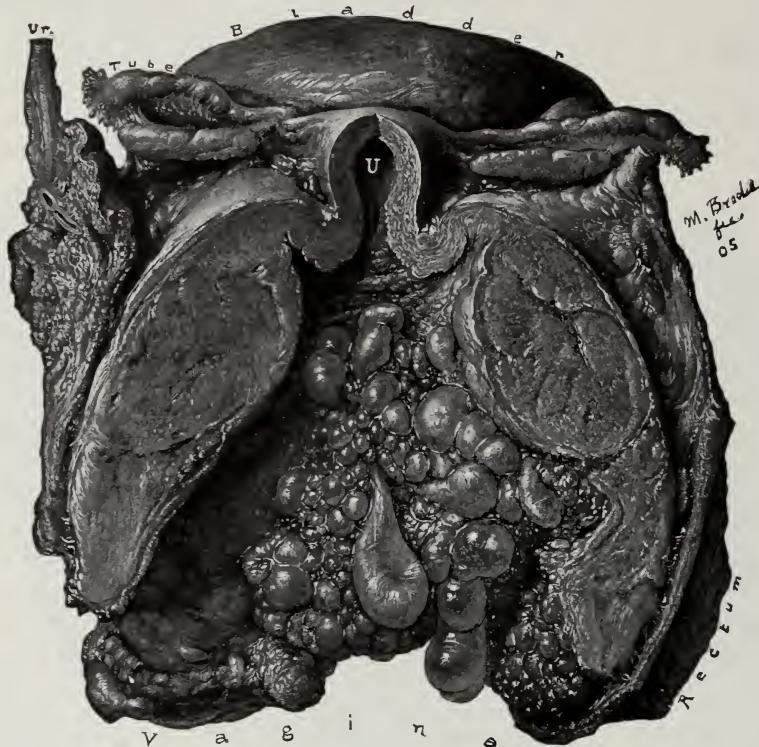


Fig. 574.—Rhabdomyoma beginning in the vaginal wall in a child, and extending into the bladder. Grape-like polyloid masses hang from the infiltrated vaginal walls (Dr. C. Cone's case, from Kelly-Noble).

Myomata of the stomach and intestine are usually small nodules lying beneath the mucosa or projecting on the peritoneal surface. They show no degenerative changes, and are, as a rule, too small to cause any symptoms. Those in the vagina and in the urinary bladder are sometimes much larger, while nodules of smooth muscle in the kidneys are usually quite small. In the skin, myomata develop as subcutaneous or intracutaneous nodules arising probably from the tissue of the arrectores pilorum, although other explanations have been given.

Malignant tumors composed of smooth muscle occur. Ghon and Hintz described one which arose from the intestinal tract with secondary growths in pancreas, liver, heart, etc., and give references to the literature

which show that many cases have been observed. The development of such malignant characters is most important in the case of the common uterine myomata. In those tumors there are observed changes in the microscopical appearance of the cells, leading to their extreme irregularity in size and form. Corresponding with these peculiar appearances it has been found that the tumors assume a rapid and irregular growth and give rise to secondary growths or colonies in other organs or in adjacent tissues. It seems clear that malignant tumors spring out of benign myomata which have already existed for a long time, but the question remains as to their exact origin. They may be due to the acquisition of malignant powers of growth by the smooth muscle-cells, in which case we should speak of them as malignant myomata, or the invasive tumor may be the offspring of the stroma of the myoma, and then it would be justifiable to call the tumor a sarcoma. It is only in the latter case, in which there is a true sarcoma mixed with the muscle tissue of the myoma, that such a term as myosarcoma is justifiable. A sarcoma is not a tumor derived from muscle, but rather one arising from connective tissue.

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Tobler: Frankf. Ztschr. f. Pathol., 1923, xxix, 558.  
Walz: Ctbl. f. allg. Path., 1926, xxvii, Nr. 7.

#### RHABDOMYOMA

In these tumors, which are found usually in young persons or children in such positions as the heart-wall, bladder and vagina, kidney, oesophagus, etc., the tissue frequently contains cells of various kinds, among which there are found striated muscle-fibres. It seems to be rare to find a whole tumor made up of muscle-fibres, and the admixture is often with such elements as cartilage, loose cellular connective tissue, and even epithelial structures. The suspicion is, therefore, aroused that rhabdomyomata are closely related to the mixed tumors or teratomata.

These are usually benign tumors, but in many cases they develop invasive characters and may metastasize widely. Those in the heart-wall form single or multiple nodules which often project into the cavity of the heart. Those in the bladder, of which we were able to study one case, hang in polypoid masses which often appear in the vagina as well and protrude from its orifice (Fig. 574).

Microscopically, these are soft, often edematous tumors, which show numerous small, irregular, and spindle-shaped cells which make up a considerable part of their bulk, but scattered among these, and sometimes in compact masses, are larger elements in whose protoplasm a delicate striation is visible (Fig. 575). These do not resemble muscle-fibres closely, but show transitions to other greatly elongated cells which do resemble the earlier developmental stages of striated muscle. These

are narrow, ribbon-like cells with a central space which may contain many nuclei. The protoplasm is not only longitudinally striated, but shows distinct transverse striations. The rhabdomyomata usually have an abundant content of glycogen. They are regarded by most writers

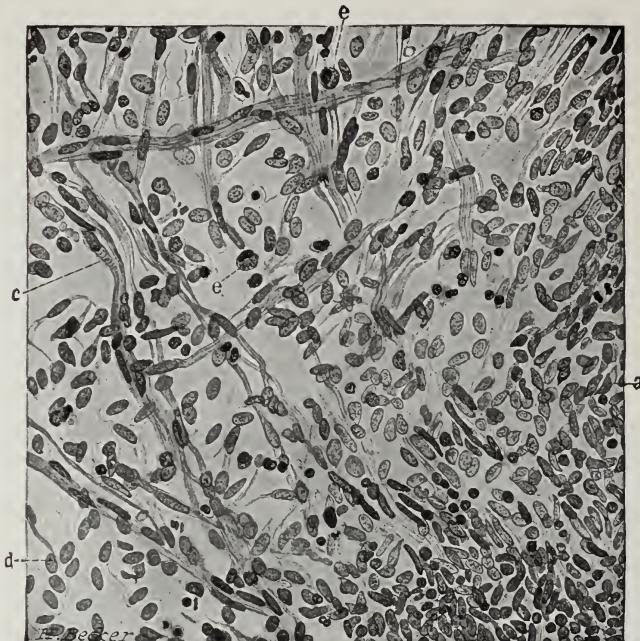


Fig. 575.—Rhabdomyoma, from same case as Fig. 574, long, ribbon-like, striated fibres (*c*) are mingled with round- and spindle-shaped cells (*a*, *d*). There are some wandering eosinophiles (*e*) (from Kelly-Noble).

as arising from a rudiment derived from an early embryonic stage, which, displaced in the course of development, has grown in its unusual situation.

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## CHAPTER LXIV

### TUMORS (Continued).—TUMORS DERIVED FROM ELEMENTS OF THE NERVOUS SYSTEM

*General relations to stages in development. Neuroblastoma; neurinoma, ganglio-neuroma, paraganglioma. Tumors of the brain, of the glioma type, medulloblastomas, spongioblastomas, astrocytomas.*

RECENT studies have made more clear than before the various steps in the development of the nervous system and have revealed the relation of the tumors which arise in connection with it to one or other of these developmental stages. It is an extremely complex subject, and the precise recognition of the nature of the tumors requires such familiarity with the embryonic stages and such skilful histological technic that it seems reserved for very few, who devote themselves to this study, to feel complete confidence in their decision as to the status of any particular tumor.

Every part of the nervous system and its appendages may give origin to tumors and their characteristics are rather closely related with their position, their time of origin and, of course, primarily with the cell type and the stage of its development from which they arise.

Before undertaking any description of these tumors we may well give the briefest possible outline of the development of the whole nervous system, although the student must be referred to the literature and perhaps most satisfactorily to the papers of Bailey and Cushing for a more detailed and coherent account not only of this, but of the tumors that occur in the brain.

In the medullary tube there arise, first, germinal cells which proceed through the stages of neuroblast of various types to the neurone; second, spongioblasts which proceed through several stages toward the production of the supporting neuroglia, the ependyma, etc.; and, third, undifferentiated cells or medulloblasts which retain the power, as admitted with faint protests, of developing in either direction. Special relations are found in the growth of the retina, olfactory lobes, pineal gland, etc. From the dorsal part of the medullary groove spring cells which wander ventrally and form ultimately the sympathetic system and the chromaffine system. In the course of their development there appear relatively undifferentiated cells which may be called sympatheticoblasts—probably comparable with medulloblasts—and from these, tumors commonly spoken of as neuroblastomas may arise. From later stages in their development there arise capsule or sheath cells, neurones, and a quite different tissue, the chromaffine or paraganglionic tissue.

This extremely sketchy outline will be sufficient to indicate the general idea of the origin of the tumors, but only if the student supplements it by reference to the papers given at the end of this section.

Tumors arising outside of the brain are seen to be derived from the migrated elements originating in the primitive medullary tube, and of these some may be represented also among the tumors which grow in the brain. Thus there is difference of opinion about the precise origin of that which since Wright's paper we have known as neuroblastoma, but it evidently corresponds closely with what Bailey recognizes in the brain as a medulloblastoma. He himself uses the term sympathico-blastoma for these tumors of adrenal and other situations. Recognizing the correctness of this position and also the correctness of his reservation of the term neuroblastoma for a tumor composed of neuroblasts, we shall still for a time retain the old name because it is so well established.

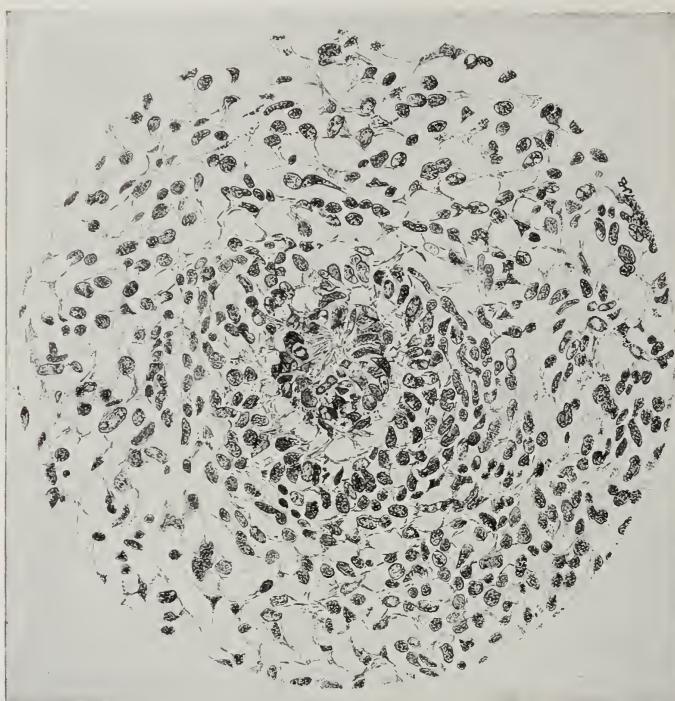


Fig. 576.—“Neuroblastoma” showing typical rosette.

**Neuroblastoma.**—Tumors have been described throughout many years usually arising from the adrenal in young children and metastasizing profusely to the liver and often to bones and other organs, which were found to be composed of rather small, indifferent looking cells often with peculiar balls or rosettes (Fig. 576), with the nuclei ranged around the periphery and the centre filled with fibrils. J. H. Wright recognized these as similar to cells peculiarly arranged among the foetal sympathetic formative cells and gave the name neuroblastoma, which has been widely accepted.

We have seen several of these cases in children beginning with a tumor mass replacing or involving the adrenal, but not in all cases were

the rosettes to be found. Several cases with typical structure have been described as arising from the scapular region. Closely allied are those extraordinary tumors which arise in the retina and spread with great destruction and metastasis. They often involve the opposite eye also and extend into the skull, lifting up the dura. They are peculiar in being congenital and hereditary, many families having been described in which several members were affected in succeeding generations. Flexner described such a case as neuro-epithelioma retinæ and Wintersteiner has accepted this name. The term retinoblastoma has been suggested recently by Verhoeff (see Jackson). It seems probable from the structure which shows rosettes with central space that they are derived from primitive spongioblastic elements.

Certain tumors seem to be derived from later developmental stages in the growth of the sympathetic and peripheral nervous system, and among these should be included the neurinomata, the ganglioneuromata, and the chromaffin tumors or paragangliomata.

**Neurinomata.**—Under many names tumors associated with nerves have long been known. These are multiple tumors, usually of small size, associated with the spinal nerves at their roots, usually affecting especially the dorsal roots, sometimes laterally placed, sometimes in the centre of the root so that the fibres are stretched over the tumor or included in it. The function of the nerve may be greatly impaired. Such tumors are composed partly of closely placed parallel fibrils with elongated nuclei, often closely placed side by side in adjacent cells so as to form ribbon-like ranks of nuclei, partly of a loose reticulated tissue. It is generally agreed since the work of Verocay that such tumors are derived from the sheath cells of Schwann which are of ectodermal origin, and not from connective tissue, although the neighboring connective tissue may be stirred to some growth too. It is thought that this must affect an embryonic stage in the development of the cells of Schwann, since they proceed to such excessive growth with only passively included nerve-fibers. The reticulated tissue is thought to be secondarily changed into that form, and frequently undergoes further change with hyaline metamorphosis, cyst formation, etc. Such neurinomata occur only in peripheral nerves in which there are the sheath cells of Schwann. Of this character is the so-called acousticus tumor which is a neurinoma (formerly called neurofibroma) of the more peripheral part of the eighth cranial nerve, perhaps beginning with the porus acusticus, that is, beyond the point at which the nerve loses its neuroglial constituents.

Such tumors, often called cerebellopontine tumors, are usually on one side, and grow to a considerable size, so as to distort the cerebellum and pons and stretch and destroy the eighth and, finally, the seventh nerve, also encroaching on the fifth. They produce deafness, symptoms of vertigo and nystagmus, and incoördination, and, finally, blindness and convulsions. For admirable descriptions of such cases the reader is referred to Cushing's monograph. These tumors show particularly brilliantly the combination of tissue with parallel fibres and ranked nuclei and degenerating tissue of reticular form.

In the peripheral nerves "neurofibromata" have been described by many and the case of Dr. Prudden is always referred to. The so-called *von Recklinghausen's disease* is a curious condition in which the occurrence of multiple peripheral neurinomata of characteristic type, but usually with associated fibrous tissue, is the underlying feature. This is a disease hereditary and associated often with imbecility or at least



Fig. 577.—Multiple neurofibromatosis (*von Recklinghausen's disease*). Observe the great relaxed mass of skin which hangs from the side of the head.

with some mental deficiency in which very numerous soft tumors appear all over the skin (Fig. 577), sometimes small, but sometimes so large and relaxing so much skin as to hang far down from the place where they start. Areas of pigmentation of the skin accompany them, and the soft tumor masses are developed around nerves in the course of which the denser neurinomata are found.

**Ganglioneuroma.**—Many tumors containing ganglion-cells have been described from all parts of the body, but most often from some situation such as the retroperitoneal or pelvic or retrocervical regions, where they might have arisen in connection with the sympathetic system. These contain nerve-fibres also, though chiefly those of the non-medullated sort. The ganglion-cells are usually imperfectly developed and irregular in form, and the fibres are twisted and irregular in appearance, with, of course, no proper connection with any end-organ. While most ganglioneuromata are now thought to be derived from the later developmental stages of the sympathetic system, there are some which arise in the same way in connection with the ganglia of the cerebrospinal system (Risel) or even in the brain itself. They are usually benign tumors, but a few, such as the second of Beneke's cases, show numerous metastases which seem to be derived from the smaller and less differentiated cells.

In connection with these there is sometimes a marked new formation of neuroglial elements which spring from the peripheral glial-cells, and such tumors have been called ganglioganglioneuromata.

**Chromaffine Tumors, Paragangliomata.**—Benign and solitary tumors have been found in old people, arising usually in the adrenal medulla and containing, as a rule, sympathetic formative cells. These are composed largely of masses of cells which are sufficiently developed to give the brown staining reaction with chromic salts. No one has yet discovered a tumor which could be assigned to the earlier stage in the development of these cells (pheochromoblasts).

It is seen that practically all these active tumors are derived from some stage in the development of the sympathetic system and its allied tissues, only rare examples of ganglioneuromata derived from developmental stages of the cerebrospinal system being mentioned. In contrast with this the tumors arising from the neuroglia of the cerebrospinal system are relatively common and occupy an important place in the surgery of the nervous system.

**Tumors of the Brain.**—Although we have always had the greatest difficulty in reaching any certain conclusions as to the nature of the numerous tumors found in the brain and have called them (helplessly) gliomata, the recent studies of various men, and especially of Bailey and Cushing, shed a new light.

We have long been aware that there are marked differences among them and have, of course, recognized those springing from the pineal gland or the hypophysis as well as the neurinomata and the meningeal tumors, but the other intracerebral and cerebellar tumors have offered difficulties only to be overcome by the aid of specific technical methods and especially by a knowledge of the development of the brain. For details the student is referred to the monograph of Bailey and Cushing and the other references cited, and here only the main types will be mentioned, largely on the basis of what Bailey and Cushing have written.

In accord with the embryological studies these authors recognize forms which show cells almost exactly corresponding with each of the stages in development in each branch of the genealogical tree of the

constituent elements, but this correspondence is seldom perfectly accurate, and the type is seldom quite pure, since some of the cells show a further differentiation with the appearance of their later characteristics.

Thereupon, although they were unable to classify a great many of their tumors, more than 250 were definitely determined according to the embryonic relations. Among these there stand out as tumors which occur commonly, medulloblastomas, spongioblastomas, astroblastomas, and astrocytomas, that is, tumors developing from various stages which lead toward the formation of neuroglia. In this sense there was justification for the old term glioma. Tumors arising from the series of stages leading through neuroblasts to neurone formation were extremely rare and only three were found by them of the type to which they give the name neuroblastoma—that is, a tumor definitely composed of neuro-

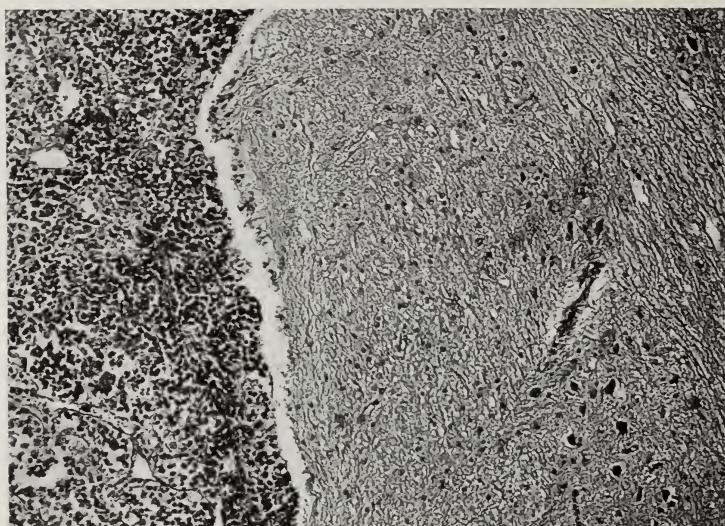


Fig. 578.—Medulloblastoma extension into meninges.

blasts which is a significance quite different from that in which the term neuroblastoma is commonly employed to mean a tumor derived from undifferentiated forerunners of the sympathetic system or other part of the nervous system, which they would then call sympatheticoblastomas. There were, however, several derived from the pineal and some from the ependyma or their forerunners. *Medulloblastomas* are soft, rapidly growing, malignant tumors, generally found in the cerebellum in children and capable of spreading into the meninges. The cells are not in any definite arrangement, although they tend to form such balls or rosettes as have been mentioned in the tumors arising from the adrenal. The cells of the extensions into the meninges are completely undifferentiated, although those in the original tumor may show evidence of differentiation into spongioblasts. Evidently this tumor is related to the retinoblastomas, too, if not quite identical with them.

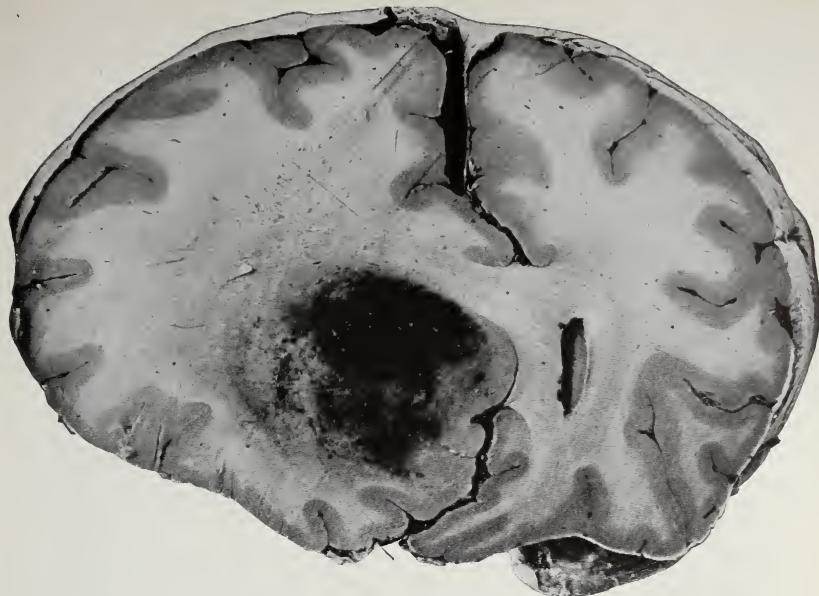


Fig. 579.—Spongioblastoma of brain with haemorrhage.

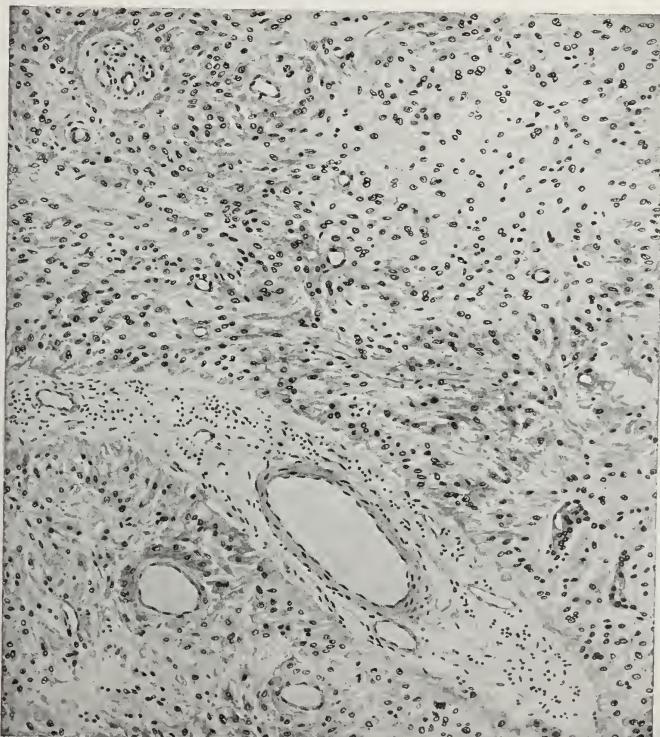


Fig. 580.—Spongioblastoma multiforme.

*Spongioblastomas* are perhaps the commonest of the cerebral tumors especially in the form known as *spongioblastoma multiforme*, while that

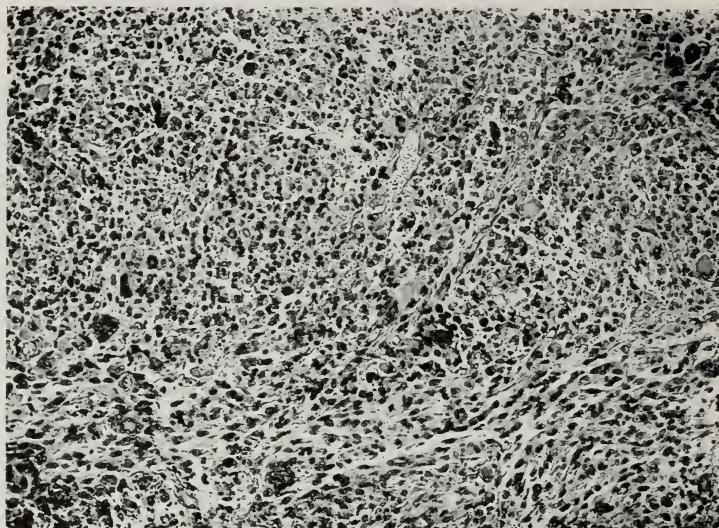


Fig. 581.—Spongioblastoma multiforme.

known as *unipolare* is less frequent. They are infiltrating invading tumors, hard to outline against the surrounding tissue, but they do not

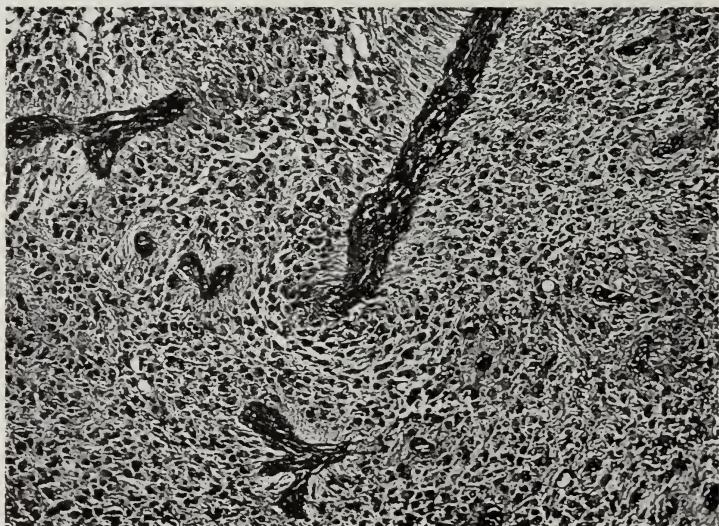


Fig. 582.—Astroblastoma.

metastasize or invade the meninges. They are soft tumors which show very commonly degenerative changes with necrosis and haemorrhage, so

that nearly every section shows hyaline vessels, pyknotic cells, and areas of necrosis (Figs. 579-581). The well-preserved cells vary greatly



Fig. 583.—Astrocytoma.

in form and size, being rounded or elongated or branched, with great differences in nuclear staining and in cytoplasm. There are sometimes

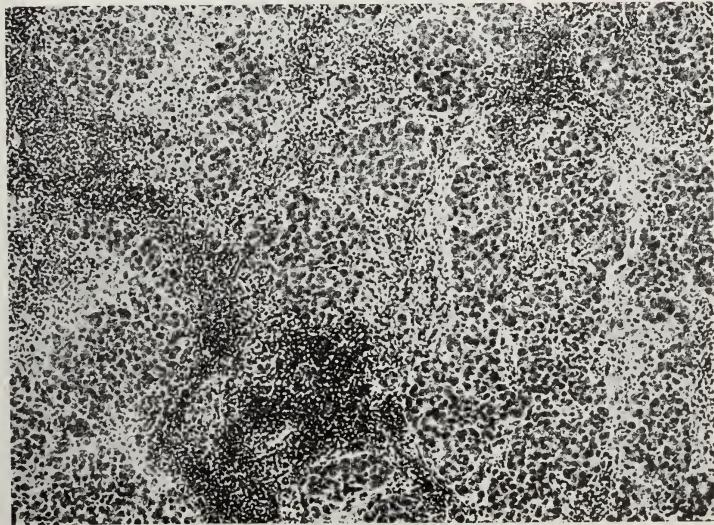


Fig. 584.—Pinealoma.

even multinucleated giant-cells. Cysts may arise from liquefaction of the tissue.

The *spongioblastoma unipolare*, which is far less common, is composed of elongated cells with one prolongation. These are usually much better preserved and the cells are much more uniform in character. They, too, occur in the cerebrum and often in the cerebellum.

*Astroblastoma*.—These, derived from cells of the next stage after the unipolar spongioblast, are infiltrating tumors of the cerebrum which usually appear in middle-aged people. They are made up of rather large cells with a few cytoplasmic branches, often with two or three nuclei, and a thick, foot-like process which is planted on a blood-vessel (Fig. 582). Although these cells have often been mistaken for ganglion cells, they are really not related.

*Astrocytomas* (Fig. 583) are very common tumors made up of astrocytes which may be either protoplasmic or fibrillary. The protoplasmic type of tumors in rather young people occurs generally in the cerebrum, although in very young people they may be in the cerebellum. They are very prone to degeneration and often form cysts with clear fluid content and little remains of the actual tumor. They are soft, pale



Fig. 585.—Choked disc with small haemorrhages, from a case in which a glioma of the cerebellum produced hydrocephalus and increased intracranial pressure.

tumors composed of star-shaped astrocytes without any neuroglial fibrillæ.

The fibrillary type is slow of growth and benign. They occur in relatively young people, and are found in the cerebrum or cerebellum. They tend to become cystic, perhaps especially when located in the cerebellum. The fibrillary astrocytes which make up this tumor are widely separated by a network of neuroglia fibres, and it is perhaps because of the inadequate blood-supply that they become cystic so often. Stroebel shows good histological pictures of such a tumor in his paper on Gliomata.

Of the other tumors, those arising from the pineal gland or the fore-runners of its cells are peculiar and easily recognized histologically because there is a characteristic arrangement of large cells with a connective-tissue reticulum in the meshes of which there are quantities of lymphoid cells. For discussion of ependymomas, oligodendroglomas, etc., the reader is referred to Bailey and Cushing's monograph.

Penfield, in a recent paper, has somewhat simplified the classification

of Bailey and Cushing and emphasizes the fact that in most of these tumors different stages in the embryonic differentiation may be recognized so that the tumor must be classified according to the general level of differentiation. He recognizes as derivatives of the neuro-epithelium besides the ependyma and the neuroblasts with their outcome in neurons, the various steps in the neuroglial series, polar spongioblasts, astroblasts and astrocytes, on the one hand, and apolar spongioblasts, oligodendroblasts, and oligo-dendrocytes on the other. As to the medulloblast, he finds no real support for the idea of their existence as cells from which either neuroblast or spongioblast might develop, and although the medulloblastoma is now a well-recognized tumor, it might have been called an apolar spongioblastoma. The spongioblastoma multiforme must be considered apart from the other tumors on account of the abundant growth of blood-vessels and the variations in their permeability which may produce changes in the appearance of the cells which show such great variety of forms. He feels that the practical value of a classification lies in the information it may give for prognosis and treatment.

The mechanical disturbances produced by such intracranial tumors are complex and depend not only upon their encroachment upon important structures which they destroy, but upon disturbances in the circulation of the blood arising from the increased intracranial pressure and upon obstruction to the outflow of the cerebrospinal fluid which so frequently results in hydrocephalus. Choked disc (Fig. 585), easily recognizable by ophthalmoscopic examination, is one of the early results of these pressure changes.

While none of these brain tumors actually metastasize in the way malignant tumors elsewhere are found to do, their bulk within the confined space of the cranium and their encroachment upon neighboring tissues make them equally incompatible with life.

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## CHAPTER LXV

### TUMORS (Continued).—ANGIOMATA. SARCOMATA

*Angiomata, hæmangioma, lymphangioma. Sarcomata. General characters: Spindle-cell, mixed, and round-cell and alveolar sarcomata. Giant-cell and osteosarcomata. Myxomata.*

#### ANGIOMATA

**Hæmangioma.**—A hæmangioma is a tumor composed essentially of blood-channels, in contradistinction to a lymphangioma, whose cavities contain lymph instead of blood. A true hæmangioma is distinguished from a mere dilatation of capillaries or venules belonging to the general circulation by the fact that its blood-channels grow independently, without regard to the laws which govern the distribution of such vessels. It thereby forms a mass which is somewhat withdrawn from the general circulation, and although supplied with artery and vein, does not stand in any intimate anastomotic relations with the adjacent circulation. Ribbert lays great stress upon this lack of communication between the capillaries of an angioma and those of the contiguous tissue, and has proved his point by injections. Further, he insists that such tumors grow from their own vascular substance and not through the widening and assimilation of adjacent vessels. There are some border-line forms in which it is difficult to say whether one is dealing with a tumor or not, such as the plexiform or cirsoid angioma of the scalp, which are made up of tangled masses of pulsating arteries, and others of even less tumor-like nature, such as the bluish vascular flecks seen in the skin of old people. True hæmangioma are most commonly divided into a simple or telangiectatic form, in which the abundant capillaries, though widened, maintain fairly well their form as tubes with parallel walls, and the cavernous form, in which the character of erectile tissue is approached, with large, irregular blood-spaces opening abundantly into one another. It is not very apparent, however, where the line of division can be sharply drawn between these groups. Certainly it is difficult to determine from sections in some cases whether one should regard the tumor as verging on the cavernous or not. Doubtless if the channels were injected and a slice of the tumor rendered transparent, a most beautiful proof of this distinction might be obtained.

These tumors occur most commonly in the skin, especially on the face and scalp, but also in all other parts of the body. The more definitely simple forms through which blood runs fairly rapidly present themselves as flat or slightly elevated, bright-red patches from which the blood may be squeezed out (*nævus flammeus*). Many of these are found in the neighborhood of angles or fissures about the face and neck so that they have been thought to be congenital displacements. Hanes has recently reviewed the history of a peculiar hereditary form of

multiple telangiectasis with numerous bluish nodules in the skin and nose from which any trifling injury would serve to start a profuse haemorrhage. In these, the irregularly widened capillaries lay just under the thin smooth skin. Other examples of simple angioma are found in the muscles, where they reach a considerable size. In the tongue, nose (Fig. 586), and lips they are also found, but in all these latter situations the tumors are likely to have more of the cavernous character.



Fig. 586.—Angioma from the nose. The blood-channels are of fairly uniform calibre.

Angiomata composed of very wide tortuous venous channels are found in the meningeal covering of the brain and especially over the spinal cord. These offer great difficulties to surgeons, since it is impossible to extirpate them or ligate the vascular connections without endangering the blood-supply of the nervous tissues. They are further destructive through the accompanying haemorrhages and, as we have seen, this occurs especially from those vascular channels which extend into the substance of the brain.

Cavernous angioma are also common in the skin, where they form most of the so-called birthmarks which are so frequently seen on the face. These are usually dark purple, and are often covered with rough, nodular skin (*nævus vinosus*). They are, as a rule, distributed over the region of one or more divisions of the fifth cranial nerve and seldom cross the midline of the face. It is said that they sometimes appear in the meninges in a corresponding distribution, and that they may give



Fig. 587.—Cavernous haemangioma of the small intestine.

rise to haemorrhage there (Cushing). In the lips or tongue they form large, nodular, purple masses very prone to injury and haemorrhage and very distorting. I have seen one or two cases of multiple cavernous haemangioma in the walls of the intestine (Fig. 587). Haemorrhage may occur from these, although it had not done so in our cases. In the muscles masses of spongy vascular tissue are found, extending between the fibres and into the intermuscular spaces. In these, too, the blood-channels are frequently irregular in form, with wide communications.

The cavernous angioma of the liver constitute perhaps the best studied type (Fig. 588). They are found, as a rule, at autopsy, without having given rise to any symptoms, and may be very small or reach a diameter of several centimetres. Frequently there are four or five in the same liver, of which some may be visible through the capsule, while others are buried deep in the substance. On section, they appear as deep, purplish-red, sharply outlined areas, from which dark blood can be squeezed or washed out, leaving a grayish-white, spongy framework. We have in one case seen at autopsy a huge angioma of the liver which was only partly surrounded by liver tissue, and hung as by a stalk from the right lobe. It measured 24 cm. in diameter, and corresponded in structure with the smaller ones. Microscopically, this framework is seen to enclose quite large spaces which open into one another, and which are evidently interposed between artery and vein (Fig. 589). They are lined with endothelium and do not seem to communicate with the adjacent capillaries, although some of them occasionally extend into the adjacent liver substance as though forming an outpost of growth. Liver-cell strands are often found to lie in the connective tissue of the angioma, practically surrounded by it. Never-



Fig. 588.—Cavernous haemangioma of the liver.

theless, as Ribbert points out, an injection of the angioma passes very little, if at all, into the circulation of the liver.

In all these angioma circulatory disturbances may occur. Infection may cause an inflammatory reaction in their substance, thrombosis of the blood-channels is common, and phleboliths may be formed. It is not infrequent to find parts of them scarred and obliterated by such processes with abundant pigmentation.

Ribbert's idea of their origin from a rudiment which is destined to form blood-vessels, from which they grow independently, is generally accepted, and the ideas as to their being due to mere dilatation of capillaries, or to the organization of hemorrhages, should be abandoned. That they may be the result of foetal displacement of tissue is, of course, prominent in all discussions, and applies here just as it does in the case of most other tumors; these are among the displacements or perverted formations of tissue which Albrecht separates as "Hamartomata."

In the edges of the heart-valves of infants there are frequently seen minute, tense, deep red nodules which project like tiny red berries. On section they look like cavernous hemangioma, but they persist only a short time, and are probably not to be regarded as tumors.

**Lymphangioma.**—Quite analogous tumors, except that they are composed of spaces and channels containing lymph, are the lymphangiomata. They are telangiectatic or simple, cavernous, and cystic. Of these, the first type is especially common in the skin, lips, tongue, and subcutaneous or intermuscular tissue. They form nodular masses or diffuse enlargements which, on injury, may allow the escape of lymph. In the case of the tongue they cause an enlargement which constitutes one of the forms of macroglossia, and in the extremities the diffuse distribution of such a cutaneous and subcutaneous tumor may give rise to a great enlargement which constitutes one of the numerous divergent forms of elephantiasis. In section such tumors are found to be made up of anastomosing channels or spaces lined with thin endothelium and filled with clear fluid with a few lymphoid cells. Naturally haemorrhages into these spaces may confuse the picture and suggest the exist-



Fig. 589.—Cavernous haemangioma of liver.

ence of a haemangioma, but the history of the case will prevent such an error in diagnosis. In these tumors, as in the haemangiomata, the interstitial connective tissue grows, together with the lymph-channels, to produce the tumor which again is more or less independent of communication with adjacent lymphatics. In the intestinal wall one may observe nodules of considerable size filled with clear or with milk-white fluid, and composed of cavernous arrangements of lymph-channels. It is important here to distinguish between true cavernous lymphangiomata and mere dilatations of the chyle-ducts.

The cystic lymphangiomata are, as a rule, still more circumscribed, and are composed of masses of rounded or irregular cystic structures with the same thin endothelial lining. They occur sometimes in the internal organs, as in the liver, spleen, adrenals, etc., where they are

usually pretty sharply marked out from the organ itself. In the neck and sacral regions the so-called cystic hygromata are found, and are especially easily recognized as the results of developmental disarrangements of tissues. They are cystic lymphangioma which are less circumscribed, and in the neck form large, ramifying masses which extend far up behind the ear and down between the muscles of the thorax and in the soft tissues of the shoulder. One, which we saw recently in a child, had become infected, so that all the cavities were filled with a purulent exudate which infiltrated the tissue between them. Another showed, in addition to the large tumor in the neck, a mass as large as an apple projecting into the pleural cavity. When, as in the so-called lymphangioma tuberosum multiplex of Kaposi, there are more complex strands of endothelial cells in the place of simple, endothelial-lined channels, it is perhaps better to speak of the tumor as an endothelioma.

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#### SARCOMATA

A sarcoma is a tumor arising from connective tissue and retaining most of the general characteristics of connective tissue, but endowed with the new power of invading and actively destroying adjacent structures and of forming colonies of its own tissue in distant organs. In this respect sarcomata are typically malignant tumors.

It has been shown that benign tumors may be derived from any of the various forms of connective tissue which make up the framework of the body, and that they depart somewhat, in each instance, in the character of their cells, from the normal standard. All this is equally true of the sarcomata, and while they, too, may originate in any kind of connective tissue, their cells are far more unlike those of the normal tissue in appearance and totally unlike them in their biological characters.

It is scarcely possible to decide from the study of a microscopical preparation as to the point of origin of any sarcoma, since almost any region may be the starting-point for any type of tumor. When the tumor contains bone or cartilage, it is fairly safe to say that it sprang from some part of the skeleton, although this, too, would be indiscreet, since such tumors occasionally arise elsewhere.

The sarcomata are tumors preëminently characterized by the energy and rapidity of growth of their cells, and this in itself brings about the striking morphological differences between them and the corresponding

benign tumors arising from similar situations in the connective tissue. It would doubtless be quite misleading to describe the lack of a capsule or of a dense stroma as mechanical factors favoring their rapid growth. On the contrary, they grow so quickly and irresistibly that there is no time for the formation of a dense stroma nor any opportunity for their encapsulation. There may be differences between these cells and those of a fibroma with regard to the process of mitosis. It is possible that irregularities in mitosis are associated with their precipitate growth, and that this explains the irregularities in the form of the cells sometimes met with, but in general they grow and develop in much the same way. Cultures *in vitro* from normal connective tissue and sarcoma tissue are almost indistinguishable from one another, except by most careful comparison of such things as the mitotic figures just mentioned. In both cases the cells grow out in scattered strands or isolated groups, quite unlike epithelial cells, and through their power of stretching themselves along a support and responding to tactile stimuli make considerable progress away from the point of origin. In the tumors, as they occur in the body, the impression is given in many cases that such cells form the whole compact mass, but in every case it is found that in addition there is a distinct framework of ordinary connective tissue with very abundant blood-vessels and some nerve-fibrils. Just as in all other tumors, the sarcoma elements demand this service of the normal tissues, and force the development of a mechanism for support and blood-supply. Sometimes the framework is extremely delicate and seems to consist of little beside thin-walled blood-vessels (Fig. 590, *c*). In other cases it is very abundant and dense, so that the tumor-cells are separated into strands and compact masses which anastomose with one another, but appear in sections as the contents of alveolar spaces (Fig. 590, *b*). There are also types of sarcoma in which the tumor cells themselves have the power of producing abundant intercellular fibres.

The malignant character of the tumor is evident in the infiltrating, destructive manner of its growth when it is well established, but in the beginning it may be difficult to recognize this. Nevertheless, unless the tumor is extirpated it soon reveals its true nature, and even if it is removed at operation, the tendency to recur in the same place from traces of the tissue left behind is associated with other evidence of its malignancy. Above all, the appearance of colonies of the same tissue elsewhere in the body leaves no room for doubt. It appears, then, that in order to decide upon the nature of a connective-tissue tumor which, so far as its microscopical morphology is concerned, might be a benign fibroma or a malignant sarcoma, it is necessary to know the history of the growth and its gross relations to the adjacent tissues. Even then it may be impossible to be completely sure until recurrence or metastases have appeared. It is at this point that the greatest uncertainty may exist, but ordinarily, as will be explained, the morphology of the tumors has become sufficiently well known in connection with the history of their growth to allow one to foretell the progress of the growth and to decide upon its nature.

There are great difficulties in outlining this group of tumors, since

there are so many malignant growths composed of ill-characterized cells upon whose origin it is almost impossible to decide exactly. Many authors are willing to speak of malignant tumors arising from muscle, neuroglia, etc., by such names as myosarcoma and gliosarcoma. Ribbert is among those who prefer, as it seems to me correctly, to call them malignant myomata and malignant gliomata, reserving the term sar-

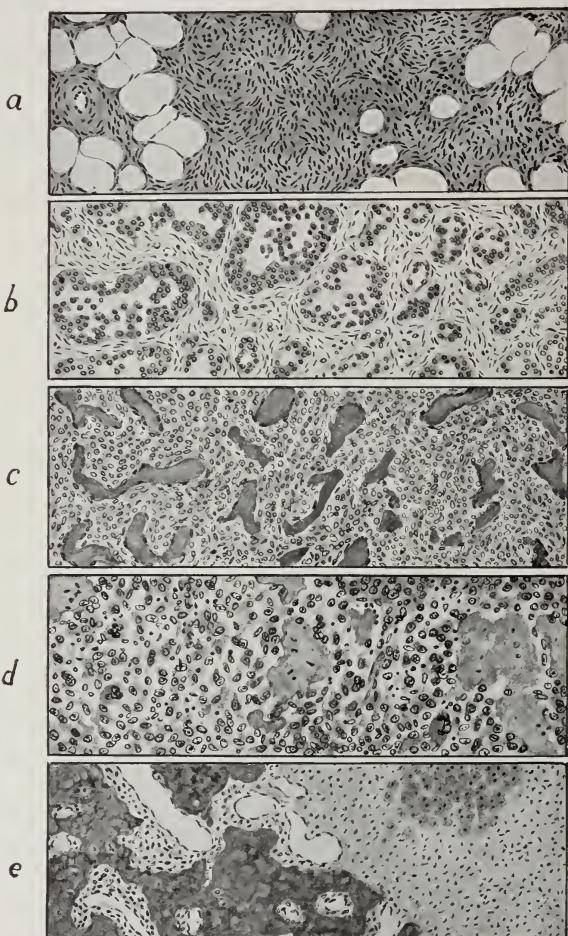


Fig. 590.—Several types of sarcoma: *a*, Spindle-cell sarcoma from chest wall; *b*, alveolar sarcoma of mesentery; *c*, spindle-cell sarcoma; the blood-vessels are injected and are seen to be very numerous; *d*, mixed-cell sarcoma of leg metasatizing to the mediastinum; *e*, osteosarcoma with calcified areas and cartilage.

coma for malignant tumors clearly of connective-tissue nature. Such names can be used, however, to indicate a sarcoma in which the type of connective tissue from which it originated is still evident, as osteosarcoma, chondrosarcoma. Recently, too, there has been a tendency to treat separately, on account of their peculiar character, tumors

thought to be derived from endothelium, and that group of pigmented tumors long known and still generally spoken of as melanosarcomata. In addition to these there are numerous tumors which arise from somewhat specialized cells belonging to the blood-forming apparatus and which, under various names (lymphosarcoma, leucosarcoma, myeloma, etc.), have, rightly or wrongly, been considered in connection with the

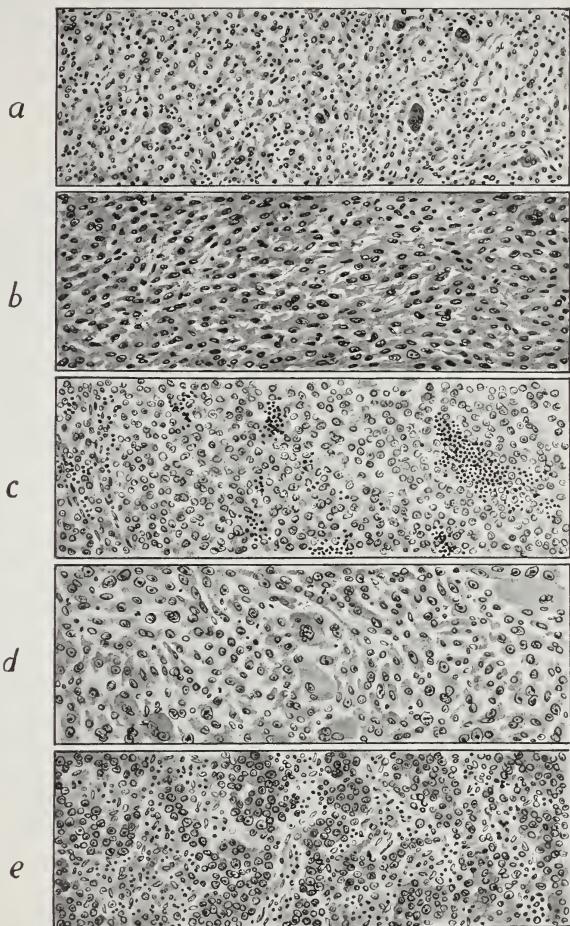


Fig. 591.—Several types of sarcoma: *a*, Mixed-cell sarcoma; *b*, coarse spindle-cell sarcoma; *c*, metastatic round-cell sarcoma; *d*, sarcoma of thyroid with giant-cells; *e*, sarcoma of ovary.

diseases of that apparatus, since it is by no means quite clear that they are tumors at all. Finally, there are tumors, usually of rather complicated structure and often occurring at birth or in the very young, which have long been designated sarcomata, but which appear to be rather of the nature of the so-called teratomata, which are referable to the aberrant growth of tissue displaced in the course of embryonic

development. In this group there may be mentioned especially many of the malignant tumors of the testicle and the sarcomata of the kidney which grow during infancy and childhood.

Nevertheless, in spite of the nebulous state of our knowledge as to the real relations of these questionable growths, there remain many well-defined sarcomata which, in any series of cases, stand out sharply as easily recognized representatives of certain groups. They are distinguished from one another chiefly by the form of their cells and by

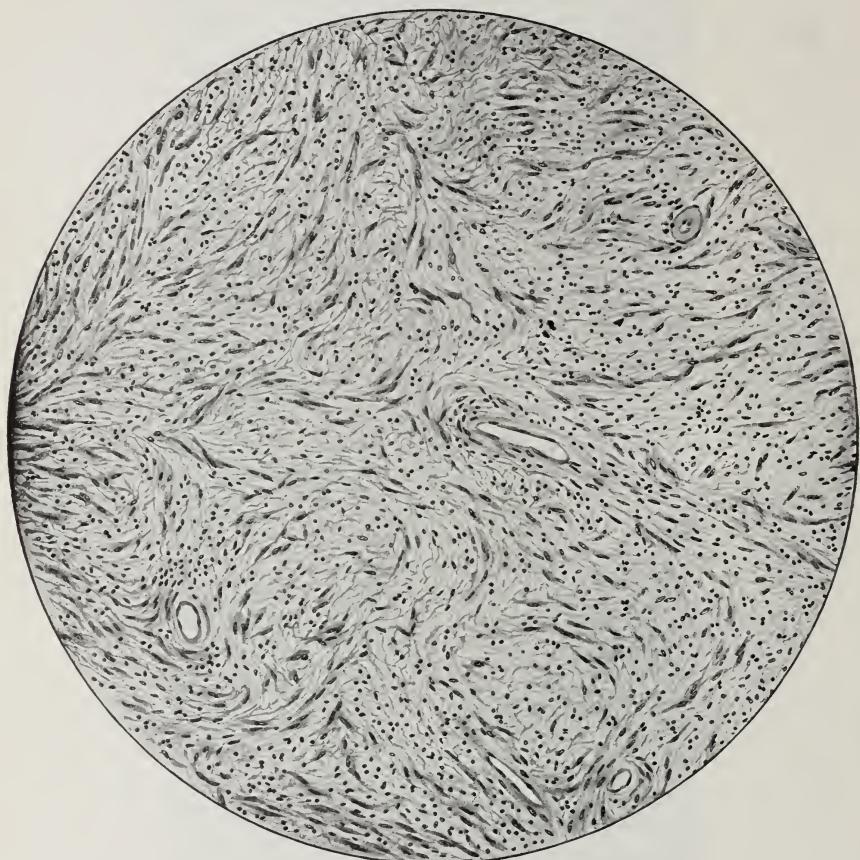


Fig. 592.—Sarcoma of tissues of the axillary plexus. The cells of the tumor are long and fusiform, and there are many wandering cells.

the character of their intercellular substance, as well as their energy of growth, but there are so many transitional forms and combinations that I do not wish to draw very sharp lines between them (Fig. 591).

Of these, the commonest are the **spindle-cell sarcomata**, which originate in almost any situation. In the series which I have for study spindle-cell sarcomata arose in the breast, hand, mesosalpinx, vulva, wall of ovarian cyst, leg, liver, etc., but any connective tissue, such as

fasciae, subcutaneous tissue, or the framework of organs, may be their starting-point. They are white or grayish-white, rather firm, shining, and somewhat circumscribed masses which have perhaps less tendency to metastasize widely than some of the other forms. Microscopically, they are found to be composed of smoothly arranged, elongated or spindle-shaped cells, very uniform in size and general appearance, and supported in bundles or whorls by the most delicate stroma, with wide and very thin-walled blood-vessels. The intercellular substance of the tumor itself is usually extremely scanty, so that the cells lie close to-



Fig. 593.—Spindle-cell sarcoma. Secondary nodules in the lung, of which one in the lower lobe is stained by haemorrhage.

gether. In some cases, however, there is a good deal of fibrillar intercellular substance, the cells are less uniformly arranged, and tend rather to a branched form (Fig. 592). To such tumors the name fibrosarcoma may be fittingly applied. The secondary growths or metastases may occur in the lymph-glands, which drain the area of the tumor, but they are more frequently found in the lungs (Fig. 593) and later in other internal organs, which would indicate that the cells of the tumor were transported by way of the venous blood-stream (*cf.* Fig. 34). Borst emphasizes the idea that such spindle-cells are especially immature, approaching in this respect embryonic cells. It seems to me, however,

that this is based merely upon the general resemblance in form to the cells of embryonic connective tissue. Their biological characters, which should be of greater weight in deciding such a question, are totally abnormal, and they have acquired powers which might distinguish them very sharply from even the most immature of embryonic cells, since they are such as to enable them to grow indefinitely without at any time differentiating themselves into any finite tissue which obeys the normal laws of growth. The resemblance to embryonic tissue is, therefore, most superficial, and they are rather cells which have no true analogue in the body at any stage of its development.

Nearly as common as the spindle-cell sarcomata are those in which cells of many forms and sizes occur, with many bizarre modifications of their nuclei. For want of any better term, these may be called **mixed-cell sarcomata** (Fig. 591, *a*). They arise anywhere, too, but perhaps most commonly in connection with the internal organs. I have seen them especially in the retroperitoneal region, apparently springing from the lymph-glands there, and forming huge masses, but there are before me examples from the thyroid, from the ovary, periosteum, etc. The cells are in general fusiform, but are somewhat irregularly arranged and form by no means so compact and orderly a tissue as in the pure spindle-cell type. Among these are many of much larger size, with several nuclei or one very large and deeply stained nuclear mass.

**Round-cell sarcomata** are, in our experience, relatively rare as long as we separate from them the lymphosarcomata and leucosarcomata, which have distinctive features, as already mentioned. They are tumors composed of small round cells held in a most delicate vascular stroma which in any single microscopical preparation might be difficult to distinguish from lymphosarcomata. They arise, however, as single, rather circumscribed masses springing from the connective tissue of the skin or fasciae or intermuscular septa or elsewhere, and, aside from the local invasion and destructive growth spread, not in a regional way, as lymphosarcomata do, but exactly as other sarcomata, by the transportation of their cells, usually by the blood-stream to the distant lungs, where they form once more circumscribed and solid nodules (Fig. 594). When a regional lymph-gland is involved, it usually presents a more or less definitely outlined tumor mass embedded in its substance, and is not itself at first completely replaced by the new tissue. These round-cell sarcomata are extremely malignant, and give rise to wide-spread metastases, often passing through the lungs into the general circulation. There are some with small and some with relatively large cells.

It is rather difficult to find good examples of typical round-cell sarcomata, and it really seems that those which fit best the description usually given are those from the testicle (Fig. 594), which are almost surely teratomatous in nature and should be classed with those tumors.

Other distinctly sarcomatous tumors of equally cosmopolitan origin are composed of cells uniform in type, but not definitely round or spindle-shaped. They are rather polygonal or plump cells, which form a compact tissue with abundant ramifying blood-vessels.

In these especially, but also in the other forms already described, there often occurs what seems to me to be a local necrosis of the tumor cells from lack of sufficient blood-supply. This leads to a curious condition in which only those cells which are close to the blood-vessels remain alive and the rest fade into a pale pink-staining débris (Fig. 595). Consequently, the tumor appears to be made up of blood-vessels each with a thick mantle of cells, and such tumors have been described

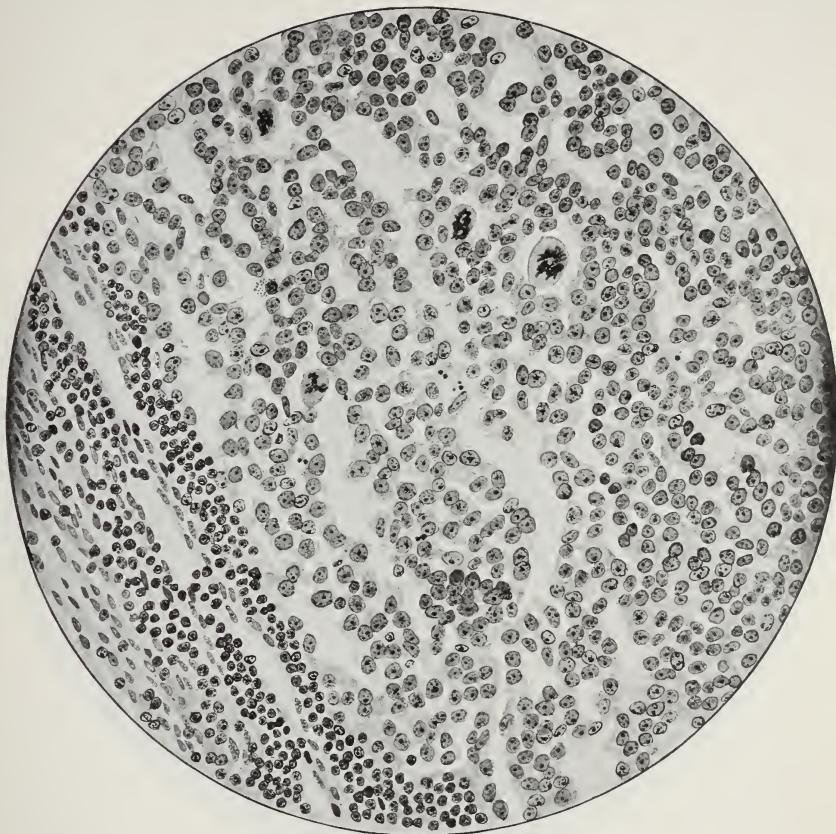


Fig. 594.—Round-cell sarcoma primary in the testicle. There are several large cells which show irregular mitotic figures. This is probably really from a teratoma of the testicle.

as a separate type under the name angiosarcoma. The cells about the blood-vessels have been regarded as arising from a hypothetical tissue spoken of as perithelium, and the tumor, therefore, called a perithelial angiosarcoma. It is possible that tumors with this structure really exist to which the explanation just given will not apply, but I have not seen them. The appearance is common enough, but in itself does not seem sufficient to warrant the use of a special name.

**Alveolar sarcomata** are those in which the tumor-cells are rounded or polygonal, rarely fusiform, and grow in groups or strands which lie in the meshes of a fairly dense stroma (Fig. 590, *c*). In a single section the cells appear to be inclosed in alveolar spaces and, indeed, they then resemble very closely some kinds of carcinoma. At times it is difficult if not impossible to distinguish between them from a single section, although the distribution of the tumors and the history of the case will usually decide. Efforts have been made to state histological

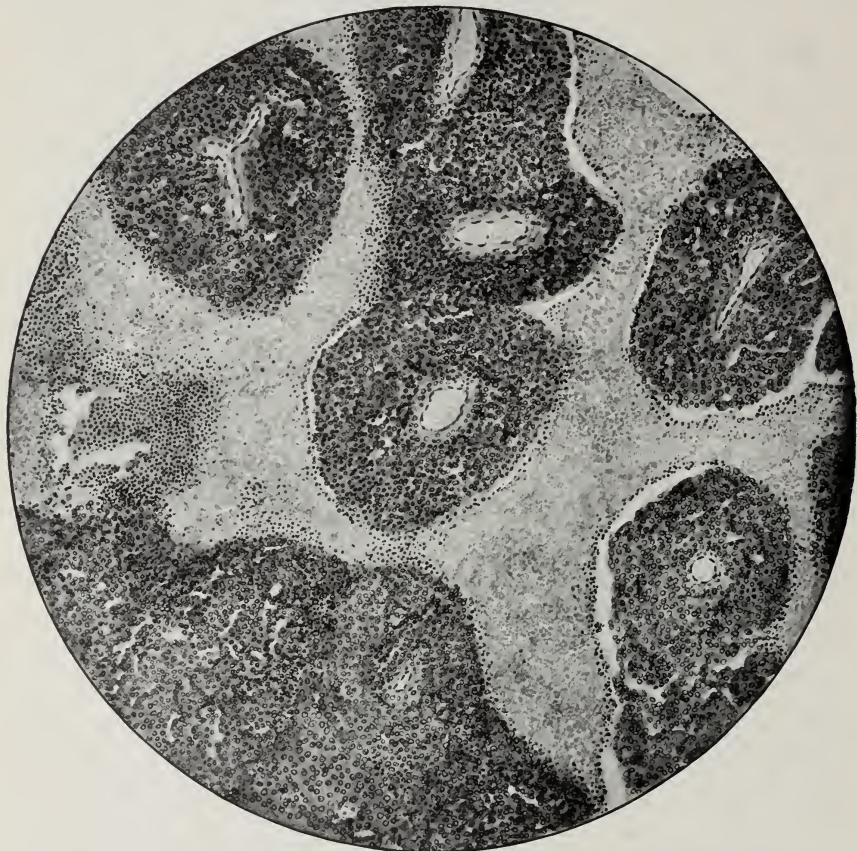


Fig. 595.—Sarcoma springing from the pelvis and showing disintegration of the cells, except in the neighborhood of the blood-vessels.

criteria, by which it is made to appear that the cells of the sarcoma are in more intimate relation with the stroma and often pervaded by fine fibrillæ of stroma, while the carcinoma cells lie isolated in spaces lined by endothelium. I am sure that this is all based on hypothesis made to suit the case, for the relation of the epithelial cells of the cancer to the connective tissue may in point of space be just as close as that of the sarcoma cells; moreover, the fibrillæ of stroma are not evident, and the cancer cells do not restrict themselves to endothelial-lined

channels, but push into any cranny or crevice of the fibrous tissue. The form of the tumor cells is of no help because sarcoma cells and epithelial cells may look exactly alike. But an epithelial origin is soon found for the cancer in one or other characteristic site, whereas the alveolar sarcoma begins its growth not in an epithelial organ, but in some such place as the dermis or the fascia or the skeletal tissues. It is quite common to find very numerous subcutaneous or intracutaneous nodules scattered over the body which reveal themselves as alveolar sarcomata,

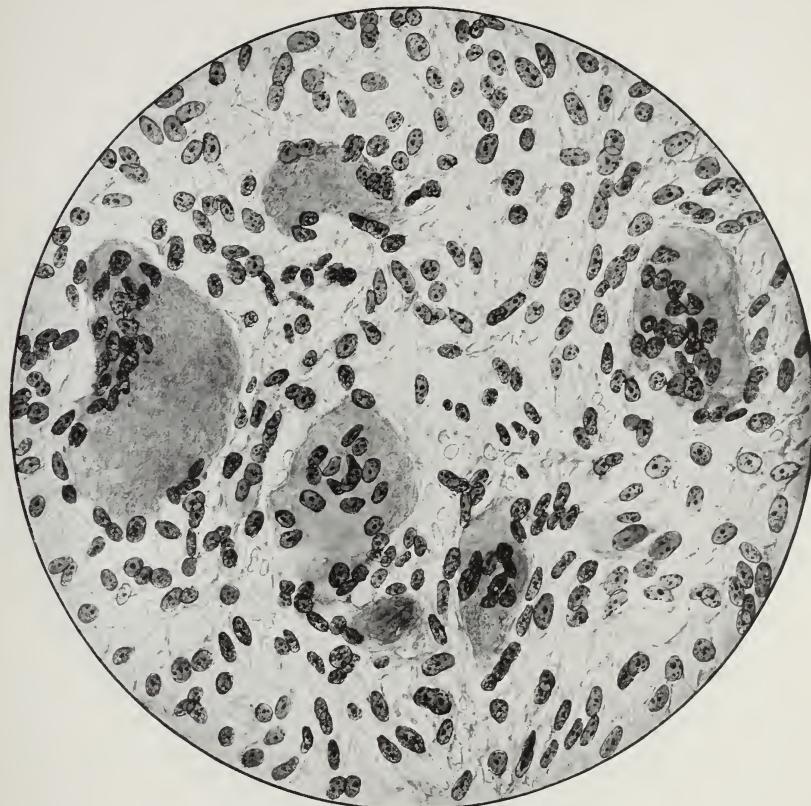


Fig. 596.—Giant-cell sarcoma springing from a bone.

and appear to grow simultaneously. They are usually secondary to some original growth of earlier formation.

**Giant-cell Sarcomata.**—Although large irregular protoplasmic masses with several nuclei occur at times in many of the mixed-cell sarcomata, there is a group of tumors in which typical multinucleated giant-cells form so constant and characteristic a feature that they are classed by themselves under this name.

They arise usually in connection with bone, and although many of them are otherwise composed of spindle-shaped cells showing no tendency to cartilage or bone formation (Fig. 596), there are also tumors

containing such giant-cells which definitely belong to the group of osteosarcomata. For this reason the idea has been suggested that the giant-cells may be identical with the osteoclasts of the bone which are endosteal or periosteal cells modified by their phagocytic function. Others have thought that since giant-cell sarcomata occur also in other places, such as the breast, far from any connection with bone, the giant-cells might be regarded as comparable to the ordinary foreign body giant-cells. There is perhaps no fundamental difference between the

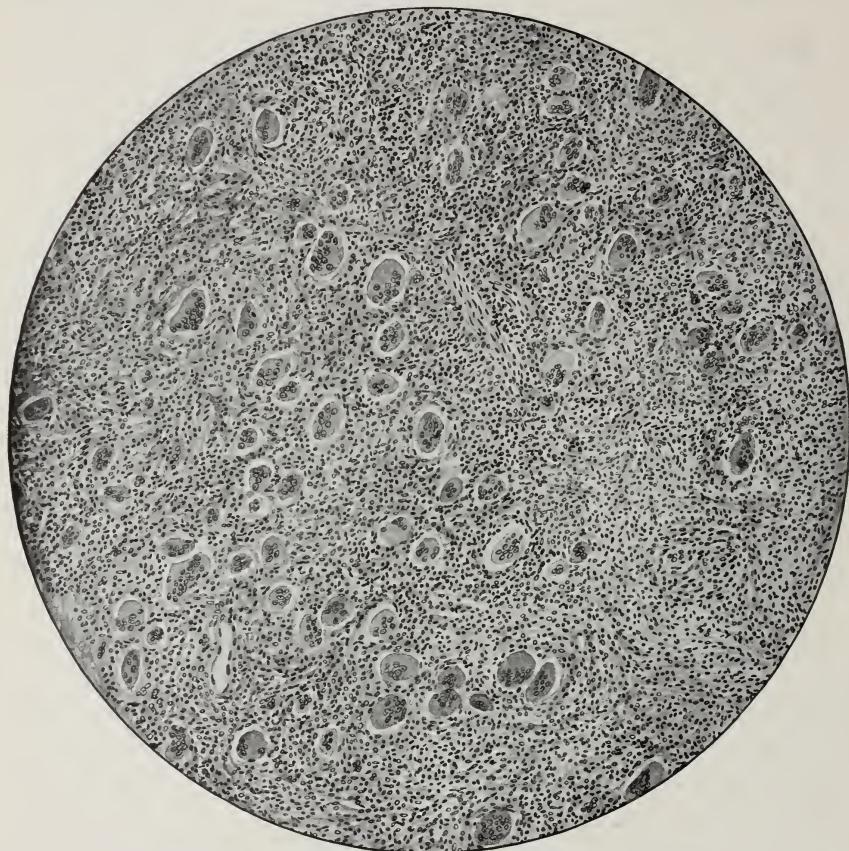


Fig. 597.—Giant-cell sarcoma (epulis) from the jaw.

giant-cell character of osteoclasts and that of foreign-body giant-cells, and in both cases it seems to be a morphological modification dependent upon the function of the cells and perhaps only temporary. It is, therefore, difficult to decide upon the relation of the cells of the tumor to such cells, and probably dangerous to assume that any of these types of giant-cells could transmit their giant-cell character to their offspring.

The most common giant-cell sarcomata are those which grow from the alveolar process of the jaw and hang as pedunculated tumors in the cavity of the mouth. These growths, which are known by the name

*epulis*, are covered for a time with the mucosa of the mouth, but tend to become ulcerated. They are usually rather small, but occasionally, as in one case which I saw, reach such a size as practically to fill the mouth. When removed, they show little tendency to recur and there are no metastases. Microscopically the dense, hard tumor is found to be composed of interlaced spindle-cells with numerous large multi-nucleated giant-cells (Fig. 597).

Other giant-cell sarcomata, closely related to these, spring from the periosteum of long bones, or, still more commonly, from their endosteal lining. Expanding and eroding the cortex of the bone, they form large masses which are kept covered by a constantly new formed shell of periosteal bone. The central part may, through haemorrhage or other disturbances of circulation, become necrotic and softened, and there may be formed a cyst-like swelling in or about the bone, in the walls of which little or no tumor tissue is left. These sluggishly growing bone cysts with ragged lining, fluid or hemorrhagic content, and abundant large giant-cells, never metastasize, and the surgeons, especially those who have studied a great series in connection with Dr. Codman's registry of bone tumors, are convinced that they are not tumors at all (Bloodgood), but that the giant-cells have rather the character of foreign body phagocytes associated with a granulation tissue which encapsulates the central haemorrhage and necrosis.

**Osteosarcoma, Osteochondrosarcoma.**—There are other sarcomata, usually forming large nodular masses about the bones, which are developed from the periosteum or from the endosteum. These, while showing to some degree the capacity of sarcomata to metastasize, have retained the power of the bone-forming cells to elaborate all the types of connective tissue concerned in the formation of bone. Hence the tumors are found to contain cartilage, osteoid tissue, and definite bone, as well as the less specialized cellular or fibrous tissue.

Those which arise from the periosteum form spindle-shaped or irregular nodular masses around the bone (Fig. 598), often with beautiful, glistening, radially arranged spicules of bone which give the tumor great rigidity. Those which start in the endosteum fill the marrow cavity, erode through the cortex of the shaft of the bone, and finally spread outside as expanding nodular tumors (Fig. 599). In either case there may be great irregularity in the form of the growth and in the character of the tissue of which it is composed. In all these tumors which arise from bone-forming cells the newly formed tissue usually presents a ground-substance of irregular or spindle-shaped cells, among which certain groups give rise to areas of cartilage or cartilage-like tissue. This becomes calcified, and, by a process resembling that of normal ossification, lamellæ of bone are formed, usually in the most irregular arrangement. In other cases, or even in the same tumors, osteoid tissue is usually formed without the intervention of cartilage, and later becomes calcified into true bone. Many tumors, however, remain as osteoid sarcomata, composed largely of osteoid tissue with relatively little bone formation. The cortex of the original bone may remain

visible in the midst of such tumors, but usually shows much erosion and one or more fractures. In other cases, with the growth from inside, the dense cortex is eroded away and replaced on the outer surface of the advancing tumor. Since the replacement is less rapid than the erosion, a thin-walled dilatation of the cortex is produced and finally broken through.

Osteosarcomata and the allied chondrosarcomata form metastases in distant organs, such as the lungs, and in those new situations the

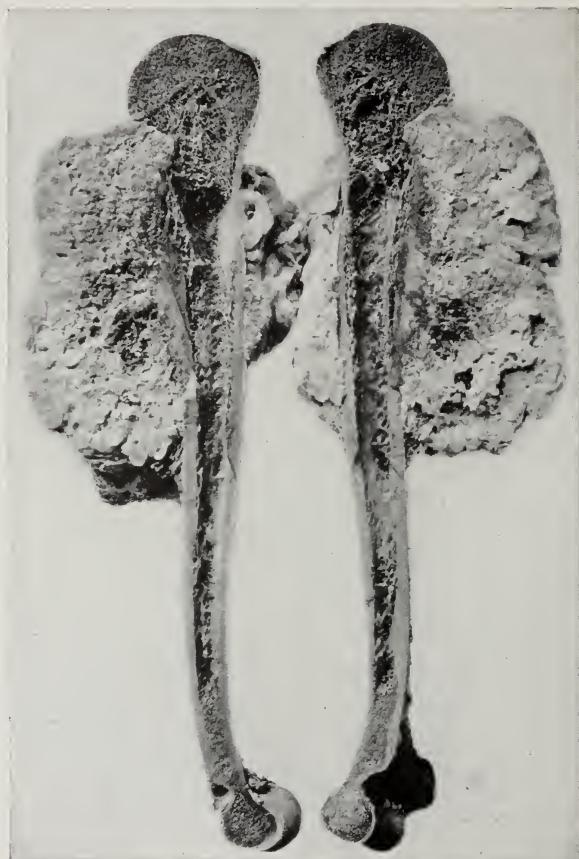


Fig. 598.—Periosteal osteosarcoma of the humerus. The marrow cavity is not invaded.

secondary nodules usually show the same atypical cartilage and bone formation. They are, in general, less malignant than other sarcomata, but are by no means entirely innocent.

Sarcomata of other types may also arise in the interior of the bones, and, having eroded their way through the cortex and spread outside into a large tumor, they metastasize extensively elsewhere. These appear not to grow from the active bone-forming endosteum, since they form little or no bone or cartilage, but are composed of soft cellular tissue.

In one which we studied recently there had been a tumor springing from the femur for which the leg had been amputated several months before death. At autopsy enormous, soft, partly necrotic tumor masses were found in the lungs and mediastinum. These were composed of variegated cells without the least evidence of any tendency to bone formation (Fig. 590, *d*).

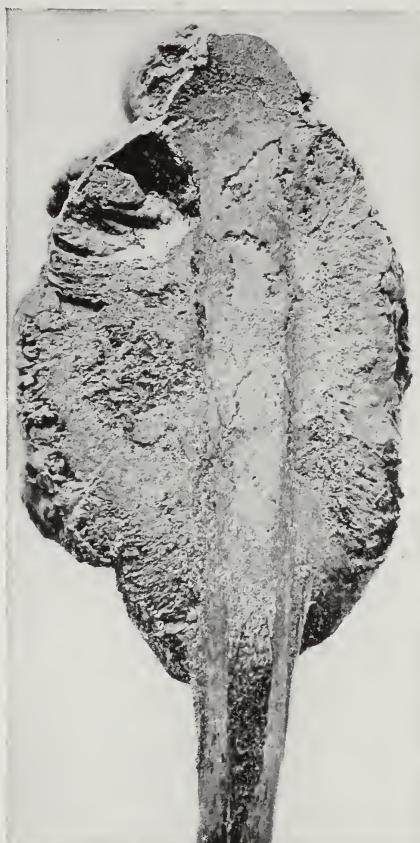


Fig. 599.—Osteosarcoma involving the marrow of the humerus, piercing the cortex in many places, and growing out radially under the periosteum.

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Borst: XV. Congr. Internat. di Med., Lisbonne, 1906, Section iii.  
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#### MYXOMATA

This term is used to indicate tumors which are composed of a loose connective tissue with branched cells widely separated by a viscid, opalescent, mucoid fluid, which actually contains mucin. While such tissue is not found in the adult body, it does exist in the Wharton's jelly

of the umbilical cord, which tissue, therefore, stands as the prototype of the myxoma.

These tumors are found in various situations in the subcutaneous and intermuscular tissues in connection with tendons, periosteum, and joints, and especially in the heart.

Ribbert makes a point of declaring that in those frequent cases in which a complex or teratomatous tumor presents patches of mucoid tissue here and there, the myxomatous part is not to be regarded as a secondary degeneration of some other part of the tumor. In other



Fig. 600.—Myxoma from retroperitoneal region.

words, he maintains the independence of the myxoma as a distinct tumor which may be combined with cartilage or with bone, etc., to form a myxochondroma or myxo-osteoma.

In the heart the soft tumor is in most cases found to hang in polypoid form from the wall of the left auricle, more rarely arising from the septum or other situation. It is covered with endothelium and composed, as in other cases, of the mucin-containing loose tissue.

In most instances myxomata are benign and well-outlined tumors, but occasionally they evince signs of malignancy and invade widely and metastasize to other organs. On the whole, they are rare tumors.

There is a form of myxomatous tumor which grows in great nodular masses in the retroperitoneal region at the root of the mesentery, and pushes aside the abdominal organs, although it does not become closely adherent to them. The nodules are encapsulated, and may be as large as a cocoanut. On removal they tend to recur, and even to produce metastases in the liver and other organs. Such tumors are not rare, and we have had an opportunity to study one of them from the Mount Sinai Hospital material, where Dr. Mandlebaum has seen four. In this case there were five large masses, one of which seemed almost entirely composed of fat. The others were elastic, translucent, and gelatinous, with little admixture of fat. Microscopically the lipoma-like tumor showed some areas of the same translucent tissue. The larger gelatinous tumors were composed of an extremely loose vascular tissue in which the cells were rather small, provided with a rounded or oval vesicular nucleus, and long branching protoplasmic processes by which they held together (Fig. 600). The intercellular fluid was extremely abundant, and it was necessary to examine frozen sections, since any attempt to make a paraffin section resulted in great shriveling of the tissue. With haematoxylin the fluid assumes a bluish stain.

#### LITERATURE

Ribbert: Frankfurter Ztschr. f. Path., 1910, iv, 30.

## CHAPTER LXVI

### TUMORS (Continued)

*Pigmented tumors: Nævi. Their relation to epithelium and connective tissue. Melanomata or melanotic sarcomata. Tumors of adrenal origin: Hypernephromata. Relation to aberrant adrenal tissue. Endotheliomata: difficulty of establishing their relation to endothelium. Endotheliomata from lymphatic endothelium; cylindromata. Pleural and peritoneal tumors. Endotheliomata of the meninges. Tumors derived from endothelium of the blood-vessels.*

TUMORS which show the presence of brown or black pigment, and which in some cases develop an extreme malignancy, form a group whose position in the general scheme of tumors is still extremely debatable, because it is impossible to decide as to the nature of the cells from which they arise. Since they behave more in the manner of sarcomata than in that of other tumors, they may be described here, although it must be borne in mind that there is no good proof of their right to this place.

#### NÆVI

The simplest of these are the pigmented moles or nævi, which are flat or slightly elevated, gray or brown or almost black patches in the skin. Sometimes they are quite prominent, roughened, and irregular, and may be marked by the growth of coarse hairs (Fig. 601). There are many varieties in so far as the intensity of pigmentation and the bulk of the tumor tissue are concerned, but the structure is, in its essentials, similar in all. Occasionally, however, the tumors are exceedingly rich in blood-vessels, so that they have then the character of superficial angioma. The overlying skin is slightly irregular in thickness and sends down quite long interpapillary processes of epithelium. The papillæ of the corium are enlarged by the presence of compact or loose masses of cells, commonly called nævus cells, which are sometimes quite colorless (Fig. 602) and sometimes deeply pigmented. It is with regard to the nature of these cells that discussion has been carried on for years, since it is most desirable that we should know whether they are derived from the epithelium or not. The following table from Dalla Favera shows fairly well the position taken by various authors on this point.

1. They arise from epidermis (Unna, Kromayer, Marchand, Gilchrist, and many others).
2. They are of mesodermal origin, and are—
  - (a) Young connective-tissue cells (Simon, Virchow, Riecke).
  - (b) They arise from proliferation of the lymphatics (v. Recklinghausen, Lubarsch, Herxheimer, and others).

- (c) They spring from the endothelium and perithelium of blood-vessels (Pick, Jadassohn).
  - (d) They originate in the sheaths of nerve-fibres (Soldan).
3. They are specially characterized cells of mesodermal origin—chromatophores (Ribbert).

From this it will be seen what divergent views have been held by the best observers. Dalla Favera, in a paper from Marchand's institute, presents the study of 30 nævi, and brings very convincing histological pictures to prove that nævus cells originate in direct continuity with the epithelial cells, forming in little nests in cavities among those cells,



Fig. 601.—Small pedunculated nævus of skin showing the relation of the nævus cell strands to the epidermis.

and later becoming loosened and separated. Ribbert is quite as emphatic in his claim that these cells are *not* epithelial cells, since the character of their nuclei and protoplasm, and especially the possession of numerous long processes, makes that practically impossible. As chromatophores they are mesodermal cells whose duty it is to carry pigment. Similar cells are found in many lower animals, where they lie in the skin, and by changes in their form are instrumental in producing changes in its color.

Recently much study has been concentrated on the nature of these tumors, and the question is extremely complex because of the obscure nature of the normal elements involved and the difficult technic required

in their investigation. The student should read the illuminating papers of Masson who has progressively changed his views as further comprehension of the condition evolved itself. He recognized in the skin, among the basal cells of the Malpighian layer, those peculiar branched cells first described by Langerhans which seem to be essentially melanoblasts, that is, they produce an oxydase ferment and, receiving chromogenic material from the underlying dermis from the capillaries of the papillæ, convert it by oxidation into pigment some of which may be transferred to the deeper cells of the connective tissue, which are thus

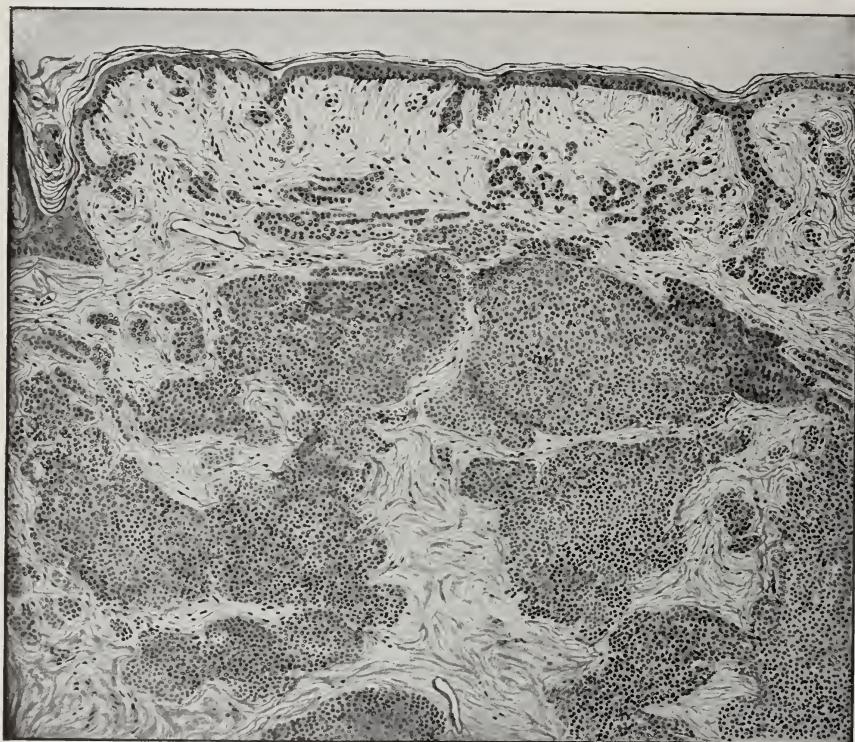


Fig. 602.—Non-pigmented nævus of skin of the shoulder. The papillæ of the corium are hypertrophied. Large masses of “nævus cells” lie in its deeper parts.

melanophores, but not melanoblasts. It is largely from these cells of Langerhans with their melanoblastic powers that there are derived the cells of the nævus and in other cases of the melanoma.

But in another paper he recognizes the extremely intimate relation of these cells with fibrils of the nerves which run in the skin, and with the tactile corpuscles of Wagner-Meissner. It seems that the nævus cells arising from the ramifying Langerhans' cells intercalated, as we have said, among the basal cells of the Malpighian layer, are, therefore, of the same race as the peripheral neuroglial cells, or cells of Schwann, because their relations to the tactile nerve endings are the

same. In this way the pigmented nævi are in some degree related to the peripheral neurinomata with pigmentation of v. Recklinghausen's disease. The application of these discoveries, which confirm the original statements of Soldan, to the metastasizing melanomata will be interesting.

Such pigmented and colorless nævi may remain for many years without much increase in size and without producing any ill effects. Through traumatism or for some other more obscure reason they may, however, begin to grow and produce a definite tumor. The pigmented tumor thus formed is a melanoma or melanotic sarcoma.

#### MELANOMATA

These tumors cannot always be shown to have originated in a well-defined mole, and there are many cases in which the cutaneous manifestations remain inconspicuous while large internal metastases develop. Doubtless it could be said that the origin was really from some small mole in such cases, but in one which was seen in the Presbyterian Hospital there was only a bluish stain above the knee which could not be felt with the finger, and yet the adjacent inguinal lymph-nodes were greatly enlarged, and the man actually coughed or spat up a piece of tissue, which on section showed the typical structure of a melanosarcoma. No autopsy was obtainable to reveal the position of the growth from which that piece came. Another case may be recalled in which a melanosarcoma apparently arose in a healing haematoma under the thumb-nail and caused death from numerous metastases some months after the first injury.

It is a curious and interesting fact that these tumors, which occur also in horses, are practically never found in any but white and gray horses. In response to an inquiry we were surprised to find that all of the 10 cases of melanoma that were observed at autopsy here were in white persons, although in the course of the 12,000 autopsies in which these occurred, the proportion of negroes is high.

Usually it is possible to trace the black tumor mass which develops in the skin to a preexisting nævus at the same spot. That nævi are not essential is shown, however, by the growth of quite similar tumors from the choroid of the eye, from the brain and meninges, from the conjunctiva, the nasal mucosa, the adrenal, ovary, intestine (ampulla of Vater), the rectum, urethra, etc.

For those who hold to the ectodermal or epithelial origin of the tumors, it would seem that some of these sites could hardly be explained. Nevertheless, the invasion of ectodermal sympathetic cells in the adrenal is adduced to explain the tumors of adrenal origin, while in other cases the participation of displaced embryonic remains in the form of teratomata may afford a source of epithelial cells. It is not possible to form a definite opinion as to the true nature of the pigmented cells from the evidence now available. Naturally, there is no fundamental reason why mesodermal cells should not form pigment from materials supplied by the blood, although in general we are more ac-

customed to find the pigments of the body produced by cells of epithelial origin. Whatever is ultimately determined to be their true relation, it is clear that these cells do not merely receive pigment transferred to them from other cells, but maintain throughout their existence the ability to form pigment and transmit that ability to their offspring.

The melanomata of the skin are composed of compact masses of cells which in section have an irregular polygonal form or are more often fusiform (*cf.* Fig. 57), although Ribbert shows that in fresh teased specimens they possess numerous long processes which are pigmented to their ends. The pigment is in fine granules and clumps and is yel-

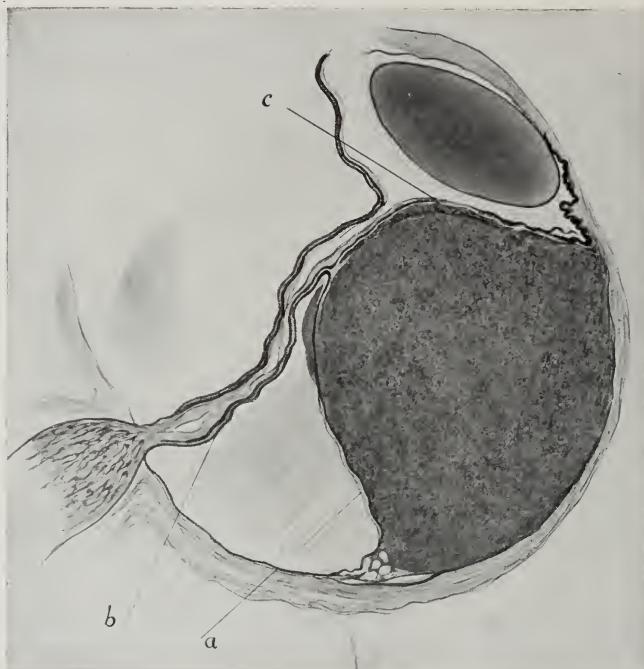


Fig. 603.—Primary melanoma of the choroid. There was relatively little pigment in this tumor. The retina is dislodged and stretches through the middle of the vitreous humor at *b*. The outer layer of the retina passes over the tumor at *a*.

lowish-brown or dark brown in color. Much of it is scattered free in the crevices of the tissue and is taken up by various phagocytic cells. The stroma is sometimes very delicate, but often coarse enough to divide the tumor into an alveolar arrangement.

In the eye these tumors spring from the choroid either as a flat, lamellar plate, or as a nodule which may be distinctly pedunculated. They grow up into the vitreous humor, pushing the layers of the retina before them, and finally filling the whole eye or bursting outward to invade the orbit (Fig. 603).

In the other sites in which primary melanomata occur their mode of growth and histological structure are similar. Melanomata grow with

great rapidity and spread their metastases by way of the blood-stream with extraordinary effect, producing secondary growths in great numbers in all the organs (*cf.* Fig. 56). These vary in size from minute groups of cells so small as to be visible only when they stand out by their black color against such a tissue as the white matter of the brain, up to enormous masses which occupy a great part of the liver. There are usually many nodules scattered in each organ, and in the case of the liver it is common to find hundreds of rounded tumors which are embedded everywhere in the tissue (Fig. 604). Most of these are very deeply colored, but some of them may be perfectly unpigmented. Frequently a single nodule shows both black and white portions. In the heart wall one may find several coal-black nodules or a whole sprinkling of small black points.



Fig. 604.—Melanoma. Multiple small metastatic nodules in the liver. The primary tumor was in the choroid of the eye.

In all these positions necrosis and disintegration of the tumor occur, and much of the pigment thus released is taken up by the wandering phagocytes or remains scattered free in the crevices of the tissue. It seems to be carried in the blood-stream to the kidneys, and is decolorized in this transit, but appears again in its black form in the urine, especially after exposure to air. The pigment itself is one of the melanins, and contains sulphur, but no iron.

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#### TUMORS OF ADRENAL ORIGIN (HYPERNEPHROMATA)

This is a group of tumors of such common occurrence as to be familiar to all pathologists, but yet so peculiar in their histological characters and location as to have given rise to differences of opinion with regard to their origin, which are even yet unsettled.

They are nodules of soft, opaque, yellow tissue, sometimes very small, sometimes growing to a great size, and situated in the adrenal gland, in the kidney, or just beneath its capsule, or in any one of many other positions, such as the liver, pancreas, retroperitoneal tissue, spermatic cord, epididymis, etc. The tumors may be multiple, and while the small multiple nodules appear to remain localized, the larger ones may exhibit an extreme malignancy, forming metastases in the lung, bones, and other distant organs.

Attention was directed to the probability of their origin from the adrenal by Grawitz, who referred those occurring in the kidney to the overgrowth of small misplaced masses of adrenal tissue embedded in the substance of that organ. It is found that accessory nodules of adrenal tissue are actually distributed quite widely in the body, and are found not only in the immediate neighborhood of the adrenal itself, or embedded in its cortex, but also in the liver, kidney, and in the other situations mentioned, broad ligament, spermatic cord, epididymis, etc. These are often of microscopic dimensions, may be present in considerable numbers, and are usually composed of tissue identical with that of the cortex of the adrenal. There are found occasionally accessory adrenals which contain medullary elements also, and a few have been described which were said to be composed entirely of medullary tissue. The most common are those in which cortical cells are arranged radially to form a small rounded nodule.

Such nodules appear not to grow to any great size. They contain the same abundant lipoids as the adrenal cortex, but do not produce adrenaline, since that is, of course, a function of the medulla.

The larger tumors are most commonly found embedded in the kidney, the tissue of which they push aside or destroy (Fig. 605). They usually grow in the cortex; bulging under the capsule, which they may perforate, but in many cases they extend through the pyramidal region so as to approach the pelvis. The best preserved part of the tumor is yellow or reddish yellow, often interspersed with gray, translucent areas, but in practically every case there are found extensive areas of necrosis with wide-spread hemorrhage, which gives the cut surface an extremely variegated appearance.

In the further course of their development these tumors metastasize sometimes by way of the lymphatic channels, but more often through the venous blood-stream. I have seen one case in which the lymphatics in the walls of the blood-vessels in the lungs were filled with the yellow

tumor mass, in such a way that all these vessels stood out prominently as thick-walled tubes composed of a soft yellow material. In this case the primary transportation may well have taken place by way of the circulating blood, the filling of the pulmonary lymphatics being a secondary phenomenon. On the other hand, Oberndorfer, Ribbert, and others describe extraordinary invasions of the branches of the renal vein, with continuous extension of the tumor through the vena cava into the heart. We saw such a case at autopsy in which the main tumor was situated in the left kidney. The veins draining it were completely oc-

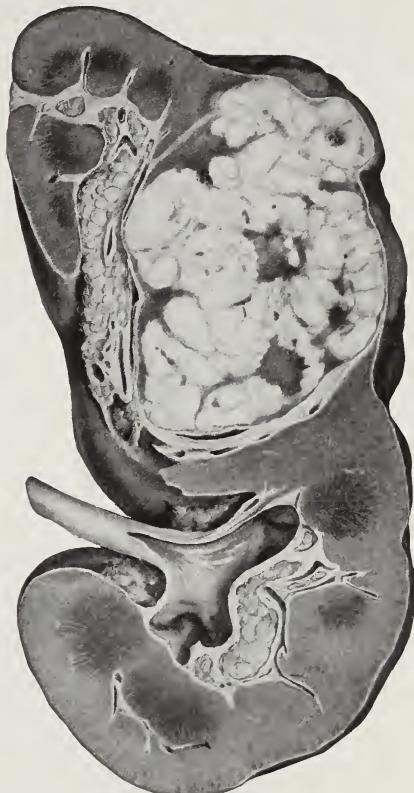


Fig. 605.—Hypernephroma embedded in the substance of the kidney.

cluded by moulds of tumor tissue which extended to fill the left renal vein, and reached across to ramify in the right renal vein far into the right kidney. In the vena cava it proceeded upward, forming a cylindrical mass 3 cm. in diameter, which completely blocked and distended the vein up to a point just below the entrance of the hepatic veins. On looking down into the vena cava it could be seen as a rounded mass partly covered with fresh thrombi. Metastases were found in the lungs and in various bones, those in the skull being especially striking since their growth from the diploë was accompanied by the formation of sharp spicules of bone which projected about each nodule.

When studied microscopically, these tumors are found to present a great variation in structure, but those arising from the kidney resemble closely those derived from the adrenal itself. The most common microscopical picture is that in which wide strands of cells anastomose freely with one another and are cut at various angles (Fig. 606). These are supported by a delicate stroma with thin-walled blood-vessels. The cells are large, cylindrical, or cubical, and extremely pale and transparent, recalling in their appearance the cells of a growing plant tissue.



Fig. 606.—Hypernephroma showing characteristic large clear cells.

Glycogen is found in these cells, together with abundant droplets of cholesterine esters and other lipoids, such as are normally found in the adrenal cortex. The resemblance of the tumor-cells to those of the adrenal cortex has always been emphasized, but it must be admitted that they are far more transparent than the cells of the gland. In many cases the tumor-cells are arranged not in strands, but as the lining elements of tubular spaces. These canals may anastomose widely or become distended into spaces of considerable size. Frequently they are filled with blood, which appears to be in a good state of preservation,

so that the idea has arisen that these may be tumors in which the typical cells are really endothelial cells lining blood-channels, and that they should be regarded rather as endotheliomata. In other cases still the necrosis of the tumor tissue leaves nothing but mantles of cells about the blood-vessels, and these have been looked upon by some authors as peritheliomata. This peculiar condition has been mentioned elsewhere in connection with other tumors, and it was said that it seems quite wrong to assign to these remnants of tissue a name which suggests that they, as "perithelial" cells, had given rise to the tumor.

Not all these tumors are even as simple as this, for there are some in which large cavities occur, and others in which the epithelial cells are thrown up into most complicated papillary folds which may almost fill the cavities. In these cases the cells are usually more granular and less like vegetable cells.



Fig. 607.—Tumor of renal cortex with lipoid-holding cells.

Since the assertion of Grawitz that such tumors, even when they occur in the kidney, arise from misplaced bits of adrenal tissue, there has been a great deal of discussion of their origin and true relations. Sudeck, Stoerk, and others contest their relation to the adrenal, and claim that there is strong evidence that they are really derived from the tissue of the kidney, and that they are renal rather than adrenal tumors. In the lack of any perfectly decisive proof it seems to me that their arguments are not entirely convincing, and that the evidence which Grawitz himself brought forward to show their relation to the adrenals is stronger. These arguments, which deal with the lipoid and glycogen content, with the formation of spaces or lumina in the tumors, etc., may be read in the papers of Stoerk, Sisson, Sabolotnow, and others.

Wells has analyzed the lipoid content, and has found that it ap-

proaches that of the normal adrenal cortex and far exceeds that of other tumors. He could demonstrate no adrenaline-like substance in any of the tumors.

There is another peculiar type of tumor found in the kidney of which we have encountered two examples almost precisely alike. The complex papillary structures which make up these tumors have central blood-vessels surrounded by a thick layer of large cells distended with globules of lipoid material and covered by a single layer of cuboidal cells of different character. Free blood may be found in the inter-papillary spaces, and where disintegration has occurred there are seen crystals, probably of cholesterine.

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#### ENDOTHELIOMATA

The tumors so far discussed have been described as though they were composed of elements whose relationship to some tissue which gave them origin is so readily recognizable as to rouse no doubts. Further, they have been spoken of as though in every part they presented the same characteristic appearance. In many cases these things are true, and we have no hesitation in assigning a definite source for a tumor which is quite uniform in structure throughout, and whose cells are, as in the case of a fibroma or chondroma, obviously of the same general character as those of the tissue in which they develop. More emphasis should have been laid, however, upon the frequent admixture of other tissues, and especially upon the modifications which the essential tissue of the tumor undergoes. Thus nothing is commoner than to find, instead of a pure chondroma, an osteochondroma or a myxochondroma or a myxochondrosarcoma. In these cases it must be decided whether the tissues are of equal dignity in the tumor growth, or whether one or two of them represent metaplasia or degenerative changes in the other. In most of the cases already considered we have dealt with tissues so closely related that, as in the case of cartilage, bone, and connective tissue, we are not surprised to find one assuming the character of the other or giving rise to the other in its further growth. We realize that many of these changes are due to the infiltration of fluid or of mucin or to some other mechanical or chemical change which can produce an alteration in the appearance of the interstitial substance or of the cells themselves.

In spite of some difficult feats of tracing the cells to unfamiliar stages in the embryonic development of their parent cells, we have found it

possible to feel pretty sure of the point of departure of the tumor elements. Of course, a rigid criticism might show that we are by no means possessed of proofs of these histogenetic relations, but, on the whole, there is so much evidence that the tracing seems safe enough.

There are, however, many tumors whose origin and histogenetic relations it is difficult, if not impossible, to trace. They are never the familiar tumors which occur in dozens of cases in practically the same form and situation, but odd growths which appear in some unusual site or in tissues where any one of several origins might be assigned to them. In structure they are unlike any known tissue, and offer no suggestion as to their nature from the non-committal arrangement of their cells. Of course, it must occur to every one that in time these tumors will be recognized in spite of their lack of resemblance to known mature tissues, just as the neuroblastomata were finally recognized, although they had long been contemplated without understanding. But the stumbling-block is that a name has been discovered under which all these difficult tumors can be conveniently classed, and thus pigeonholed and withdrawn from further study. Every unusual tumor which lacks characters that will permit its ready recognition stands an excellent chance of being labeled endothelioma and relegated to oblivion. Still more disturbing is the fact that certain well-known groups of tumors, such as the mixed tumors of the salivary glands, have been declared by some one to be endotheliomata, and have, therefore, been classed in that capacious group by every one. Happily, in that particular type of tumor there has been sufficient interest to bring forth further study with more accurate results.

In practically no case has the origin of a tumor from endothelium been proven. As Ribbert points out, the mere continuity of the tumor-cells with endothelium at the margin of the tumor is no proof of their identity. Borst has shown that tumor-cells may grow into lymphatic channels and cause the endothelial cells to proliferate, but that even when the proliferation is sufficient to close the channel, it is only a normal reaction to the presence of a foreign tissue and not a participation by the endothelial cells in the tumor growth. Ribbert thinks that proof of the endothelial nature of a tumor will require the study of that tumor at its inception, which is impossible.

Much confusion has arisen because of the uncertainty as to what should be called endothelium, and many different standpoints have been taken. All agree that the lining cells of blood- and lymph-vessels and the lining of the cerebrospinal spaces must be accepted as endothelium. Disputed tissues are the lining-cell layers of pleura, peritoneum, etc. According to the *cœlom* theory, these cells must be epithelial (*hypoblastic* and *epiblastic*) in origin. Some other characteristics, such as the possession of cilia, etc., make them seem more allied to epithelium, and indeed there are many now, including Ribbert, who regard the serosa cells as epithelial in nature and the tumors derived from them as epithelial tumors.

Even yet, in spite of all the work on the relation of the lymphatics to

the connective tissue, much is written of the endothelial cells which line or partly line the indefinite lymph-spaces or crevices in the tissue, and what is written is used as a complete explanation of the origin of certain obscure tumors. Since it appears that the lymphatics are complete blind-ending tubes lined with endothelium, such tumors would have to be derived from their walls.

There is no reason that endothelial tumors should not arise from the endothelium of the lymphatics or blood-capillaries. No doubt they do



Fig. 608.—Cylindromatous tumor.

and possibly some of the tumors described as endotheliomata really have this origin, but it is far from proven or even plausible in most cases, and in many the essential cells of the tumor, though flattened and stretched out, are easily shown to be epithelial cells. Indeed, in most of these tumors which arise in the skin, in the mouth, or nasal sinuses, in connection with bones, or in less characteristic situations, it is found that the tumor-cells are flattened, rather deeply staining cells, arranged in strands which anastomose and give off long-pointed processes which extend into crevices of the connective tissue. The cells do not resemble any normal

type closely, and since no primary growth is found in any of the usual epithelial organs, and since further the cells stand out too distinctly from the stroma to be accepted as connective-tissue cells, it is rather feebly assumed that they must be endothelial cells. The proof is not much stronger than that, and is rather a process of exclusion than a positive tracing of a relation to endothelium. Even though every one must admit the possibility and even the probability of the existence of tumors derived from endothelium of the lymphatics, this kind of reasoning is most unsatisfactory.

In the following, the type of tumors which have been looked upon as derived from endothelium may be given briefly and discussed. It will be found that the evidence of their relation to endothelium is thought to be satisfactory in the cases of endothelioma of the dura, and in a very small number of tumors derived from capillary blood-vessels, but that in the others it is either disproven or very doubtful. New tumors are constantly being described in which an attempt is made to establish an endothelial origin, and the matter may soon reach a state of greater clearness.

**Endotheliomata Derived from Lymphatic Endothelium.**—Tumors of the skin are described by Borst and others as composed of nodular masses of rather dense tissue in which anastomosing strands of flattened smooth cells, sending off pointed processes, are embedded in connective tissue. Similar tissues are found elsewhere, and may be really endotheliomata or derived from much altered epithelium.

**Cylindromata**, or tumors in which hyaline cylindrical strands or balls are interspersed with strands of flattened cells, were described by Billroth, and have been much discussed in later years. They are usually tumors which occur in the mouth, near the salivary glands, or in the nasal sinuses, but may be found elsewhere. They are generally benign, but may metastasize. Histologically the cylindrical hyaline structures (which are not peculiar to these tumors, but may occur in sarcomata and carcinomata) are seen to be formed by modification of the connective-tissue stroma or of the walls of the blood-vessels (Fig. 608), although in some cases such hyaline masses appear to be formed in the middle of a strand of tumor-cells. The name is given on account of this anatomical peculiarity, and should not distinguish a special type of tumor. While it is difficult to decide upon the actual origin of the tumor-cells, Ribbert has brought strong evidence that they are *epithelial* and that they arise from the glands or surface epithelium of the mouth and nasopharynx.

**Pleural or peritoneal tumors** have given rise to much difference of opinion. They are apparently primary in the lining cells of the pleura or peritoneum, and can be distinguished from those which occur as metastases from primary tumors situated elsewhere. The latter are usually in the form of small lenticular or rounded nodules, which extend into the underlying lymphatic channels, while the primary tumors of the pleura are most commonly seen as thick white layers of dense tissue covering the lung and containing in the meshes of the connective tissue simple or very complicated arrangement of cells whose nature cannot be positively stated from a study of their morphology. There are some investigators

who insist that they are derived from the endothelium of the underlying lymphatic channels, but the majority, including Ribbert, refer them to the serosa cells and consider them epithelial tumors. They may metastasize to lymph-glands or extend into the lung. Those arising in the peritoneal cavity are more likely to occur in nodular form. They too may invade, and, penetrating the diaphragm, spread over the pleura.

**Meningioma ("Dural Endothelioma").**—There are certain tumors, sometimes of large size, which apparently spring up by a stalk from the dura mater and lie deeply embedded in the brain (Fig. 609), although still sharply outlined and not invading the brain substance, but separated from it by the pia arachnoid. They are not malignant and do not recur when removed. Such tumors occur most often in the frontal region, al-



Fig. 609.—Meningioma lying in a deep depression in the surface of the cerebral hemisphere.

though they are common enough in many other positions, and are composed of elongated cells with a whorled arrangement (Fig. 610), often with clusters of plumper cells and with psammoma bodies which are tiny concretions or rounded grains of calcified material enwrapped in concentric layers of cells. Such psammoma grains are by no means peculiar to these tumors, but occur in the choroid plexus, pineal gland, and elsewhere.

There has been much doubt as to the origin of these tumors, and the old idea conveyed by the name given above, which is in common use, is relegated to the past by Cushing, who shows that they are really derived from the crests of cells which cover the arachnoid villi in the Pacchian granulations. These Pacchian granulations with their arachnoidal

villi pressing into venous sinuses or veins in the dura and thereby affording passage for the cerebrospinal fluid into the blood-stream are very widely scattered and by no means limited to the longitudinal sinus. It is clear from the appearance of the covering cells which often form whorls, as well as from the attachment of the stalk of the tumor in some cases, that this is a far more plausible explanation of the origin of the tumor than to say that they arise from the lining cells of the dura. Cushing

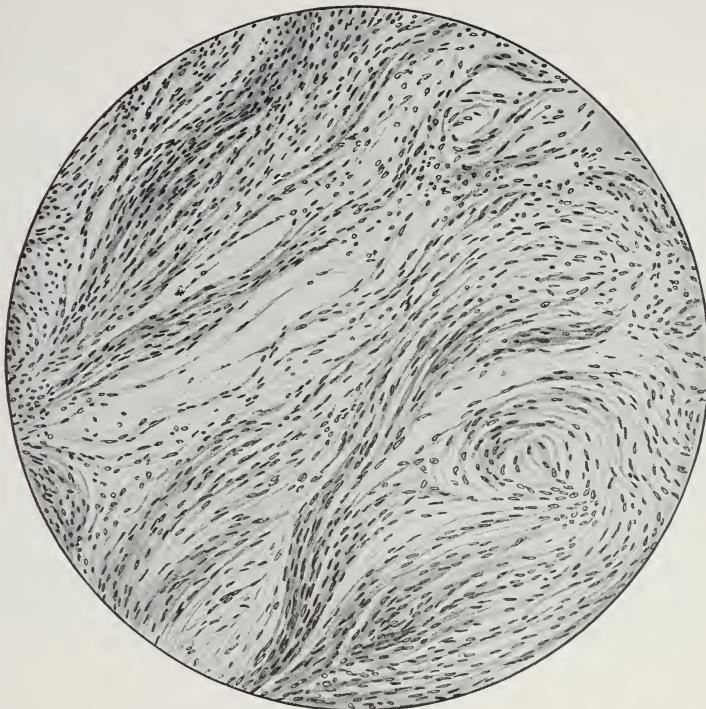


Fig. 610.—Meningioma. The tumor is made up of long, fusiform cells arranged in whorls.

proposes the name meningioma for such tumors, and describes their peculiar effect on the overlying skull which is either greatly thickened both internally and externally over the site of the tumor or eroded and entered by the tumor itself.

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**Tumors Derived from the Endothelium of the Blood-vessels.**—A few tumors have been described which appear to represent this group, but they seem to be very rare. Borrmann for example, has described two tumors composed of long strands and channels composed entirely of endothelium and connected with the blood-capillaries. These he calls tubular capillary

endotheliomata, and, in so far as the relation to the capillary endothelium can be proved, the name is well chosen. Colmers has also described a tumor of the penis, metastasizing into the internal organs, which was composed of blood-channels lined by tumor-cells, which he regarded as endothelial cells. The endothelial cells were much changed in form, and greatly enlarged, and sometimes occluded the wide blood-channels of the corpora cavernosa into which they grew. B. Fischer describes another peculiar tumor situated in the liver, most of which it occupied. In the outlying parts of the many nodules this was seen to be a mere widening of the capillaries with thickening of the endothelium, but in the centre of each nodule the change in the endothelium became more striking, pro-

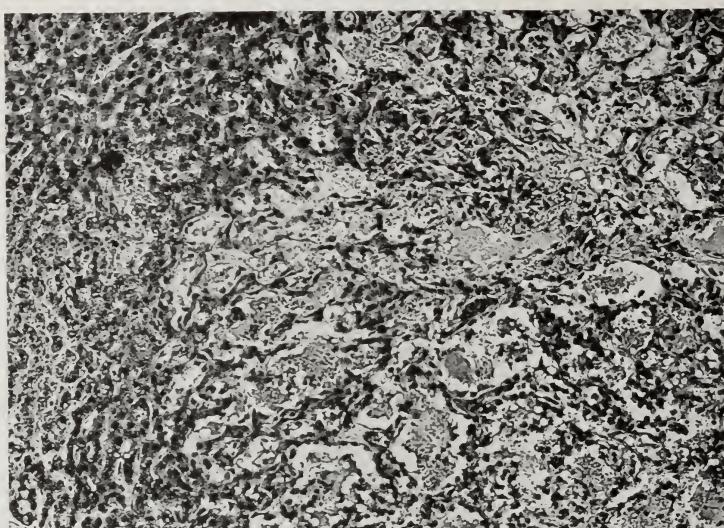


Fig. 611.—Hämangio-endothelioma, metastasis in liver.

ducing great widening of the capillary, often with occlusion and disappearance of the liver-cells. Most active blood formation was found to be going on in the capillaries of these areas, and one is led to speculate as to whether this may have been an exaggerated myeloid alteration rather than a tumor. We have, however, recently met with an exactly similar tumor arising in the small intestine where it was constantly injured and bled a great deal. It produced hundreds of metastases in the liver, and these were found to be made up of wide blood-channels the lining cells of which are the tumor cells (Fig. 611).

One tumor which I studied microscopically seemed to fall into this group. It was a pulsating mass in the region of the left scapula in a boy, and was incompletely removed at an operation, which had to be stopped because of the excessive haemorrhage from the tumor. There was a recurrence which grew rapidly until the boy's death, when metastases were found in the lungs. In the metastases, as well as in the primary growth, the whole tumor was composed of delicate canals lined with high swollen

cubical cells with very clear protoplasm, quite like those in a hypernephroma. Each canal was filled with blood, which seems to have been in circulation and to have given rise to the extensive haemorrhages at operation. This tumor reminded us of a hypernephroma, and it is possible that it may have been a secondary growth, although no tumor was found in the adrenals or kidneys or elsewhere, except the pulmonary nodules, which were numerous and all about the size of peas.

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## CHAPTER LXVII

### TUMORS OF EPITHELIAL ORIGIN

*Relation of epithelium to stroma.* Papillomata: Origin from skin and mucosæ. Papillomata of bladder and ovary. Adenomata: Origin from skin, salivary glands, gastric and intestinal mucosæ, kidney, liver, adrenal, hypophysis, and prostate. Adamantinomata. Adenomata of the breast. Intracanicular forms. Cystadenomata of ovary: Their origin and form; papillomatous types. Adenomata of the uterus.

In the tumors hitherto discussed cells evidently derived from the connective tissue or some other mesoblastic structure have in most cases formed the essential feature of the growth, although in every instance these have been supported and supplied with nutrition by a vascular connective-tissue stroma. It has been made clear that in these tumors, as in the growth of organs in the embryo or in the new formation of tissue in the healing of a wound, the supporting framework and the vascular supply are called for and made to serve the ends of the more important specific tissue. This becomes even more apparent in the case of the great group of tumors in which epithelial cells play the leading part in the constitution of the growth. Although there are some authors, such as Ribbert, who hold to the idea, expressed by Virchow, that the new-growth of epithelium is initiated by an atypical growth of the underlying connective tissue, the opposite view is maintained by the majority, and seems to me to be supported by far greater weight of evidence. Nevertheless it will be necessary to weigh this matter in each case, and in some it may be found difficult to decide.

Very convincing proof of the mastery of the epithelium seems to be furnished by those papillary epithelial tumors of the ovary which grow both from the inside and the outside of cysts in that organ. If minute clusters of the epithelial cells which cover the branches of these growths as they project into the peritoneal cavity are broken off and scattered over the loops of the intestine and on the surface of the other abdominal organs, they take root and grow, not merely into masses of epithelium, but into new branched formations which are supported by connective tissue springing from the peritoneal tissue, and supplied by branches of the blood-vessels of the organ on which they grow. Even if a bit of connective tissue be implanted with the group of epithelial cells, we must admit that the new blood-vessels and probably the new stroma are commandeered from the underlying tissues.

Although we may agree that epithelium growing so abundantly on a surface as to be forced up into folds demands a vascular stroma for each fold, and that epithelium growing in the form of gland demands the formation of vascular connective tissue enough to surround it, there are instances in which the epithelium assumes a growth so rapid that it far outstrips the connective-tissue formation, and abandons the ordinary relation which it regularly bears to that tissue, in the formation of an organ or in the normal covering of a surface. Then the epithelial cells in

solid strands push their way lawlessly into any crevice in the tissue. Even then, however, when muscle, organ tissue, or bone is destroyed by the advance of these cells, there is never formed any considerable mass of epithelium alone, but the connective tissue follows with its blood-vessels, though often in an irregular and inadequate way, and forms a support for the epithelium in its new position. Should the epithelial cells be set free in the lymph- or blood-stream and lodge in the capillaries of a distant organ, their multiplication in that new site is at once assisted by the ingrowth of fibroblasts and capillaries which quickly organize a stroma. These are the malignant epithelial tumors, and it is seen that the difference which exists between their structure and the more orderly form of the benign ones depends upon the headlong irregularity of their growth, with which the stroma can scarcely keep pace.

We may consider first the benign epithelial tumors, in which the relation between the epithelium and its stroma or supporting framework is maintained nearly as it is in normal tissues, and afterward the malignant or cancerous form, in which this relation is disturbed. It must be remembered, however, that the difference between a malignant and a benign tumor consists not merely in this morphological manifestation, but in the overwhelming energy of growth of the epithelial cells of the cancer against which the normal tissues can set up no effective barrier.

**Benign Epithelial Tumors.**—Those epithelial growths which maintain, at least in principle, the normal relations between epithelium and stroma fall into several groups, according to their general form, although these groups overlap in the sense that combinations or transitions from one form to another are found. The types are as follows:

A *papilloma* is a tumor of lobulated, branched, or papillary form, in which each fold or offshoot of the epithelial layer has a central core of connective tissue with blood-vessels.

An *adenoma* is a tumor composed of glands of tubular, acinous, or other form, embedded in a vascular stroma. Such a tumor may exist as a nodule in the substance of a solid organ, or it may project as a polypoid growth on a mucous surface. Since the glands are often without connection with the efferent ducts, many of them may become cyst-like. Indeed, there is no sharp line between these tumors and *cysts*, which may be multilocular or unilocular. Within such cysts the epithelium may be thrown up into papillary growths, so that a combination of cystoma or cystadenoma with papilloma occurs.

#### PAPILLOMATA

The term is applied on the basis of their form to tumors composed of branching, cauliflower-like, or finely lobulated growths of epithelium, with a stroma which branches to carry blood-vessels into each prolongation. Sometimes these branches are so small that only single capillary loops supply them with blood. Although this general principle of formation is carried out throughout the group, there are great differences in their form and consistence, which depend upon the character of the epithelium from which they rise, since those which occur upon the skin are usually

rough and hard, while those growing from the mucous membranes in the interior of the body are more commonly very soft, with loose, cedematous stroma. In the skin, papillomata may appear anywhere on the surface of the body, but are somewhat more common on the face and in the anal and genital region, than elsewhere. They are often mulberry-shaped on a short stalk, and rather soft, often more deeply indented, rough, and horny. These, especially in some cases in which they are situated on the penis or labia, may grow to a considerable size. Being exposed to constant traumatism, they are frequently inflamed or ulcerated. Figure 612 shows the structure of such a tumor which was found growing on the cheek, and corresponds almost exactly with the appearance of others found on the lips, margin of the anus, and elsewhere.



Fig. 612.—Papilloma of cheek.

Less complex are the common warts, which are small papillomata, most frequently seen on the hands and composed of elongated papillæ covered with thick epithelium. In many of them the skin is merely thickened and deformed, although continuous, while in others the main mass of the wart seems to break through the surrounding skin, to protrude as a brush of fine, stiff, epithelium-covered papillæ. Section shows the continuity of the deeper layers of the epidermis with this papillary growth. Wile states that these warts are infectious in character and may be produced by inoculation of a cell-free extract from other warts. In other cases the keratinization of the thick epithelial covering is so extensive that an actual horn-like outgrowth may be formed, and such horns, growing usually on the face or scalp, may reach a length of several centimetres.

Many pedunculated papillary tumors are pigmented or bear long hairs, and these on section are found to be made up largely of the peculiar cells described as characteristic of pigmented moles. They are, in fact, nævi which have assumed a papillary form, and although to this degree they are papillomata, the fact that they are only thinly covered with stretched-out epidermis and that the cells which take the initiative are nævus cells, and not epithelium proper, justifies the distinction. They are extremely common, and when not deeply pigmented, may resemble the ordinary papillomata very closely.

Besides these, there are many small, pedunculated fibromata which impose themselves as tumors resembling papillomata. They have been referred to in an earlier section, where their relation to the nerves was discussed. The fact that they are essentially new growths of connective



Fig. 613.—Papilloma of antrum of Highmore. This was accompanied by polyps.

tissue with only a thin covering of normal epidermis serves to distinguish them from the present group.

In the stratified epithelium which lines the mouth and nasopharynx papillomata spring up from the tongue, the nose, and elsewhere, which resemble those of the skin. Irritation and trauma may cause modification in the epithelium, so that the more exposed parts are denuded. Similar tumors are found in the larynx and trachea, often attached by stalks to the vocal cords, where, of course, they interfere greatly with phonation. These are fairly hard, and although in the trachea rising from cylindrical epithelium, may be covered with stratified epithelium.

In rare instances there has been found a papillomatous growth in the antrum, ethmoid, or frontal sinuses, conforming in general type with those just described by growing into large, cauliflower-like masses which are accompanied by polyps such as are found in chronic infections of the

sinuses. It may fill the antrum or ethmoid and cause destruction of the bony walls by pressure. We have recently studied such a case, the tissue removed at operation presenting the appearance shown in the photograph (Fig. 613). The superficial epithelium forms a very thick layer and in the depths between the papillary projections appears to lie embedded in the stroma but everywhere, although it is rich in mitotic figures, it is seen to be sharply outlined from the connective tissue, and in this case an exploratory operation four months after the apparently complete removal of the tumor, showed no recurrence. Four years later the patient is well.

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In the urethra, vulva, and vagina similar growths occur. In these regions care must be taken to distinguish from true papillomata the flat and pointed condylomata, which are not tumors, but peculiar hyperplastic growths of epithelium caused by infection, with inflammatory reaction. The flat condylomata are of syphilitic origin, while the pointed or irregular ones are formed in the course of chronic gonorrhœa, chancroids, or other long-standing infectious processes about the genitalia. They even occur in pregnancy, and disappear after childbirth, although here the participation of an infection is not to be excluded. Apparently the gonococcus is not directly responsible for them. Such condylomata show on section (Fig. 614) an intensely inflamed tissue with distinct papillary new-formation of epithelium, so that without the clinical history it might be rather difficult to draw a sharp line between them and papillomata.

In the stomach and intestine papillomata occur, but they are by no means so frequent as the more polypoid glandular tumors, which will be referred to under Adenomata. This is probably because of the tendency of the cylindrical epithelium of the digestive tract to form tubular glands, rather than to throw itself up into papillary processes. Nevertheless, there are some such tumors which hang like great tassels in the cavity of the stomach, or less commonly in the colon. Those which I have seen in the stomach were associated with other tumors of a cancerous nature, but this is probably a coincidence. They are so soft and fragile that losses of substance frequently occur with haemorrhage from the remaining surface.

The papillomata of the bladder are very similar in appearance, being extremely soft, tassel-like, stalked masses of thread-like papillæ which float about in water. They show in section a delicate stroma covered by thick, stratified epithelium, the surface layers of which are usually lost. From being caught in the urethral orifice in the contraction of the bladder the papillæ are often torn and portions are discharged in the urine, together with blood. These tumors tend to recur when they have been removed by operation, and in most cases, whether interfered with by operation or not, they finally invade and destroy the bladder-wall, re-

vealing themselves as carcinomata. They should doubtless be regarded from the first as papillary carcinomata of the bladder.

From the surface of the ovary, and usually simultaneously from both ovaries, richly branching papillomatous tumors are found to grow, extending into the peritoneal cavity. They appear to arise from the epithelial covering of the organ, and are supported by the usual vascular stroma derived from the ovary. In their biological characters they resemble those which occur in the walls of ovarian cystadenomata.

In all these tumors the extensive growth of the epithelium, which casts it into folds and projecting papillæ, is, nevertheless, governed by a certain obedience to the normal laws of growth, which maintains a smooth line of demarcation between the epithelium and the underlying stroma. The whole tumor may become infiltrated with leucocytes during inflam-



Fig. 614.—Acuminate condyloma from a case of chronic gonorrhea.

mation, and these cells wander readily from the stroma into the epithelium, but it is possible to trace round every projection and into each bay and indentation the distinct, regular line of separation between epithelium and stroma. The usefulness of a recognition of this line in diagnosis is realized daily. In one case there was a mass extending from the tonsil and pillars of the fauces downward on the epiglottis, in a man of middle age. Sections of an excised portion showed everywhere a typical papilloma with perfectly even, thick, stratified epithelial covering, uniformly marked off from the stroma. Doubts as to the nature of a tumor in that situation prompted the excision of another fragment, which in general showed the same structure, but at several points it was possible to see that an excessive and lawless growth of epithelium had burst the barrier, and had invaded the stroma in the form of long strands of

cells. The malignant nature of the tumor was at once clear, and the diagnosis was substantiated by the clinical course of the growth.

### ADENOMATA

Epithelial tumors of glandular origin and retaining in general a gland-like structure are extremely common, and occur in practically every situation where there are glands. They may present themselves as nodules embedded in the substance of solid glandular organs, or as polypoid masses projecting on the surface of a mucosa. The stroma is sometimes dense and hard, often soft and gelatinous, so as to give the tumor a polypoid character. The epithelium-lined spaces may become enlarged to form cysts, and these may be partly occupied by papillary ingrowths of the same epithelium. It is as well to consider the cysts with the adenomata, since those cysts which are not modifications of these tumors are of a quite different nature, and are due either to obstruction and dilatation of the ducts or glands or to the congenital misplacement of embryonic tissues, under which headings they may be discussed.

Adenomata of the skin may arise from the sweat-glands or from the sebaceous glands. Such tumors are rare and must be distinguished from the vesicles which result from obstruction of the ducts of the sweat-glands and the so-called milia or comedones, which are due to the accumulation of sebaceous material in obstructed sebaceous glands.

In the digestive tract small adenomata may spring from the mucus-secreting glands, or occasionally appear in the salivary glands. The so-called *ranula* is a cystic tumor which forms in the frenulum of the tongue, and is derived from the sublingual ducts, especially from Nuhn's glands. In the salivary glands themselves there occurs not only a form of "cylindroma," but also and more frequently composite tumors containing several types of tissue. These may be discussed later.

In the stomach and intestine adenomata usually project or hang by a stalk as soft, polypoid tumors made up of abundant, irregular, and partly cystic glands, of much greater length than the normal glands, and embedded in a loose stroma which, on account of the traumatism to which it is exposed, is constantly inflamed. Sometimes these polyps reach a considerable size, and may offer a certain obstruction, or be seized by the intestinal wall in its peristaltic contraction and dragged on into a lower part of the gut. In this process the wall of the intestine may be invaginated by the tension on the stalk of the tumor, and an intussusception started.

Microscopically, such adenomata are in continuity with the rest of the mucosa, but there is a sudden transition from the normal into the large distorted glands, lined with cylindrical epithelium, which stain more deeply than the normal cells. The muscularis is not affected, but the submucosa is greatly thickened at this point and extends upward into the tumor (Fig. 615).

Polypoid adenomata are often multiple, and sometimes so numerous and so small as to give the intestinal mucosa a shaggy appearance. When they are larger (Fig. 616) they project into its lumen at every level as

rounded, soft, velvety masses, varying in diameter up to one centimetre or more. They must be distinguished from the irregular, polypoid masses of mucosa which are often formed at the margins of ulcers in the process

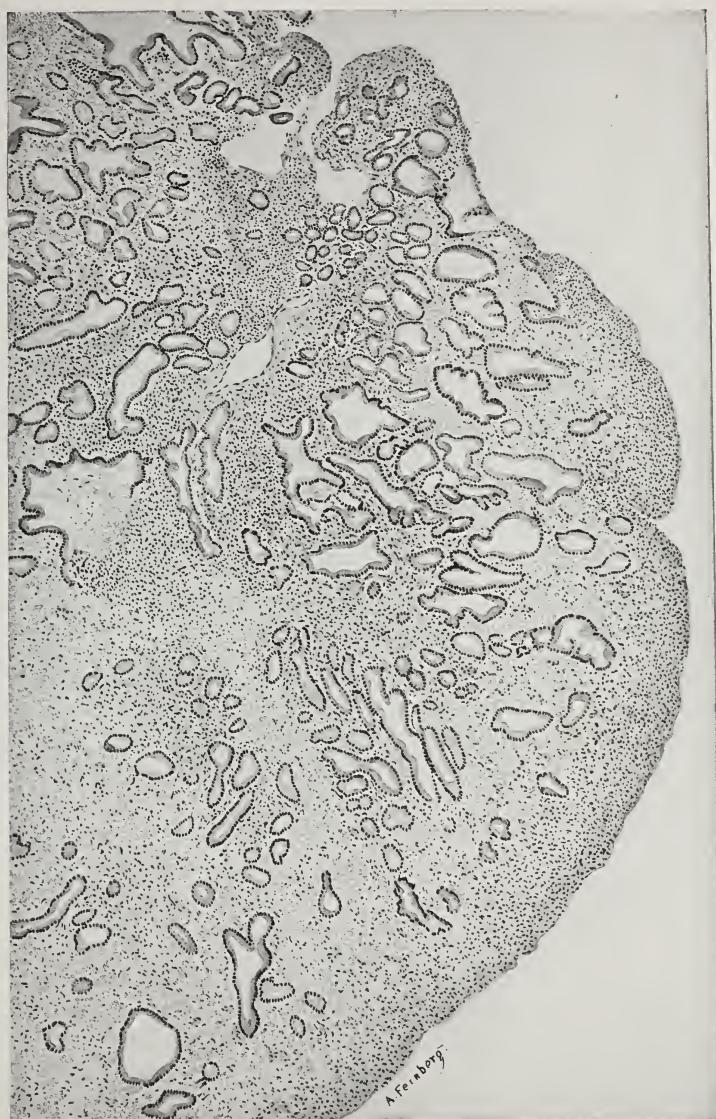


Fig. 615.—Tip of polypoid adenoma of the intestine.

of healing, or by the undermining of part of the mucosa in old dysentery. In the latter case the isolated mucosa breaks free at one end and hangs in the intestine as a polypoid mass.

Adenomata in the kidney are grayish-red nodules lodged in the cortex, usually small, but sometimes attaining a great size. They are composed of ramifying or twisted glandular or tubular epithelial structures in which the cells are much smaller than those of the convoluted tubules (Fig. 617). It seems probable that the tumor-cells are the offspring of cells destined to form kidney substance, but diverted to the formation of a tumor at a relatively early stage of development.

In the liver, as in other solid glandular organs, it is sometimes difficult to determine whether the nodular growths of the parenchyma of the organ should be looked upon as tumor formations, or as the result of a compensatory hyperplasia. It has been made clear in discussing cirrhosis of the liver that the destruction of a portion of the liver tissue causes the great overgrowth of the remaining fragments, so that the organ assumes a rough, nodular arrangement, in which the nodules are sometimes quite



Fig. 616.—Multiple polypoid adenomata of the mucosa of the colon.

large. Microscopical study shows, however, that the strands of cells which make up these nodules, though disarranged from the normal order, are still in connection with the bile-duets and actively functioning. It is probable that this is the nature of the circumcribed and irregularly arranged nodules of liver tissue which are sometimes found embedded in a liver which is otherwise almost normal looking. At least this explanation seems safest so long as the cells of the nodule closely resemble the normal liver-cells. Occasionally, however, there are seen nodules composed of irregular strands or tubules of cells which no longer stain as do the normal cells, and these must be regarded as adenomata representing less highly differentiated liver-cells or derivatives of the bile-duct epithelium.

The adenoma-like nodules of the cortex of the adrenal have been described elsewhere, and mention has been made of the thyroid. The thyroid adenomata are extremely common, and here again it is difficult to feel

sure that we are dealing with actual tumors, and not with hyperplasia of the functioning gland. The occurrence of sharply outlined nodules growing and compressing the surrounding tissue is an extremely common feature in almost every form of goitre, including the exophthalmic goitre, but there is little about this which compels us to regard it as an actual tumor growth, and it seems more plausible to regard it as a phenomenon associated with disturbances in the normal functioning of the remainder of the gland, perhaps in some sense as a compensatory



Fig. 617.—Adenoma of the kidney.

growth, perhaps, as Rienhoff will have it, as the perverted result of return to the normal state of function of an area which has been hyperplastic and overactive.

Tumors of the *hypophysis*, composed of a gland-like growth of one or other of the elements of the organ, have been much studied of late, and have been mentioned in connection with acromegaly. They are most commonly composed of the chromophobe cells, which are arranged in

solid strands or alveoli. Adenomata of the eosinophile cells have also been observed.

**Adamantine Epitheliomata or Adamantinomata.**—These are tumors which develop in the substance of the jaw bone at the base of a tooth, and push their way out, displacing the tooth and causing the wasting away of the bone until they emerge as nodular, hard masses which may reach the size of a grape-fruit. The tumors, which are usually quite small, are derived, according to the general opinion, from the enamel



Fig. 618.—Adamantinoma. Each mass of cells presents a central cavity filled with fluid.

organ which is an epithelial structure at the base of the tooth concerned in the formation of enamel. Malassez regards them as derived from certain paradental remnants of epithelium, but the evidence for the other origin seems stronger.

The strands of epithelium are broad and anastomose irregularly (Fig. 618). They are hollowed out centrally into cavities which are seen to be due to the gradual separation of the cells and the accumulation of fluid. The cells ramify somewhat, and are connected by very distinct inter-

cellular bridges. The most peripheral cells abutting on the connective tissue are almost cylindrical in form. A characteristic appearance is produced by this arrangement, and it is very easy to recognize these tumors. The stroma is dense and fibrous and sometimes contains bone.

Tumors arising from the remaining rudiment of the connection of the infundibulum with the roof of the pharynx (hypophyseal duct) have been described by Erdheim, Haberfeld, Duffy, and others. They are by no means uncommon benign tumors, behaving as destructive growths largely from the position they occupy in the sphenoid or in the sella turcica, which allows them to encroach upon the hypophysis, and further, upon the brain. Their structure is almost identical with that of the adamantinoma (Fig. 619), although the epithelial cells form, as a rule, smaller strands with less extensive rarefaction in the centre.

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There remain the most common and important adenomatous growths, namely, those of the breast and the ovary. The adenomata of the prostate have been discussed elsewhere.

The *adenomata of the breast*, often called adenofibromata on account of their dense stroma, are very common, and assume a great many different forms. They are benign tumors, limited in their outline, and growing expansively so that they can sometimes be shelled out of the remaining breast tissue. This is not always the case, and if they are examined in a section through the breast, they are found to appear as grayish-white rather translucent nodules, or indistinctly localized areas of dense consistence. There is one group which in such a cut surface shows a peculiar structure, as though many small papillary or cauliflower-like masses were inclosed in cysts. These can indeed be partly turned out of such cavities, but are attached at some point by a stalk. They are the intracanalicular fibroadenomata, and their peculiar appearance will be recognized by the description of their microscopical structure.

The more homogeneous adenomata of the breast show on section many epithelial structures in the form of acini, canals, or small cysts surrounded by an abundant stroma which is usually rather lax immediately about the glands and denser in the broad intervening strands (Fig. 619). In some cases the whole stroma is cellular and rather oedematous, without any dense bands or areas of fibrous tissue. This is so, especially in the cases in which the epithelium-lined spaces have the character of long tubules (Fig. 620). In every case, whether the epithelial structures have the arrangement of acini or tubules or are in the form of cysts, the lining epithelium, which may be in two layers, is sharply bounded by a hyaline basement membrane. In some tumors this membrane is very broad and

thick. When the cells are able to disregard the barrier and burst through to grow at large in the crevices of the stroma, the tumor must be recognized as a cancer. While it is not easy to show histologically that an adenoma can change its character and assume that of a carcinoma, the clinical history of these tumors gives much support to the idea that this change may occur.

The formation of cysts is of very frequent occurrence (Fig. 621), and although in most instances they never reach any great size, there are oc-



Fig. 619.—Adenofibroma of breast. The acini are very uniform in size, and are often lined with two layers of epithelial cells.

casionally seen adenomata in which nearly the whole tumor is occupied by a cyst. Distinction must be drawn between the cyst formation in actual adenomata and the development of many minute cysts scattered diffusely through the breast in the so-called chronic mastitis, which will be described later. In the adenomata the cysts are found to contain clear fluid, or fluid rendered turbid by the presence of many desquamated cells,

or blood-stained fluid which may become thick and deeply pigmented with blood-pigments. In some cases the cysts contain a butter-like material produced by the epithelium. The epithelium may be reduced to a thin layer of flattened cells, or it may be lost entirely. On the other hand, it is frequently proliferated and thrown up into folds and papillæ (*cf.* Fig. 621). Distinct papillomatous outgrowths may press into the cyst so as to fill it completely. Such intracystic papillomata are of quite frequent occurrence.



Fig. 620.—Adenofibroma of the breast. The epithelial structures resemble ducts in many places.

**Intracanalicular Adenomata.**—Closely related to these are the intracanalicular forms described above. In microscopic sections even the smaller epithelial structures may show the curious appearance in which isolated masses of connective tissue covered with epithelium lie packed together inside an irregular, epithelium-lined cavity or canal, as though they were really free within the canal. The canal itself is thus reduced to a series of branching slits (Fig. 622). In truth, these are sections of polypoid ingrowths which press into the cyst or canal and are cut at a point away from their stalks. Sections in another direction would show

them as stalked polypoid masses. The question once more arises as to whether they are initiated by the growth of epithelium or by an excessive growth of connective tissue which pushes the epithelium into the cavity. In all probability it must be answered, as in the case of the papillomata, that the evidence is in favor of the primary activity of the epithelium. Such intracanalicular growths have a stroma which is loose and mucoid in the neighborhood of the glands; dense and firm in the intervening



Fig. 621.—Adenoma of breast. Some of the acini are lined with high cubical or cylindrical epithelium, and such acini are sometimes dilated into cysts.

areas. The denser fibrous tissue stains red with eosin, while the mucoid tissue assumes a blue stain. On this account they are often called intra-canicular myxofibromata.

McFarland, in his recent study, would simplify the nomenclature and recognizes most of these tumors as varieties of periductal fibroma. In his large post-operative material he finds a great number of cases in which the tissue removed showed no tumor at all, but only normal tissue or

some stage in the physiological involution of the breast, and assumes that the diagnosis of adenofibroma of some sort was due to the desire of the pathologist to coöperate amicably with the surgeons.

**Cystadenomata of the Ovary.**—In the *ovary* the epithelial growths are very commonly cystic. It is true that there are rare instances in which a papillomatous tumor springs from the surface of the ovary, and we shall see later that there are other solid ovarian tumors of a malignant character. The common adenomatous ovarian tumors are, however, cystic and are spoken of as *cystadenomata*. There are several varieties:

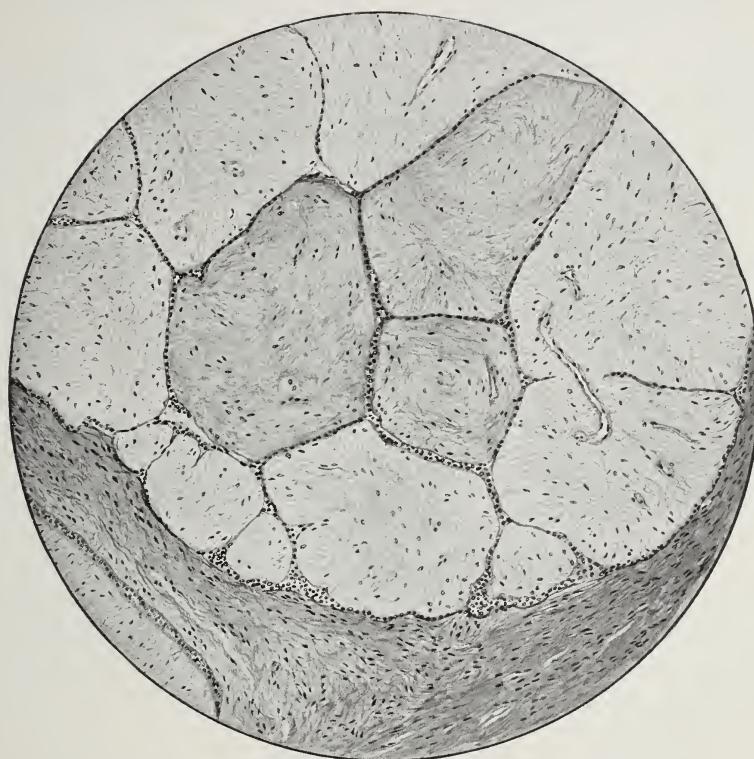


Fig. 622.—Intracanalicular adenofibroma of breast, showing numerous apparently free epithelium-covered masses packed together.

1. Simple ovarian cysts—the so-called hydrops folliculi.
2. Pseudomucinous cystadenomata.
3. Serous cystadenomata.

The division is not important, as it is evident that it is based on no essential difference. The first type has long been supposed to arise from the Graafian follicles through mere accumulation of fluid in their cavities, and this view was supported by the finding of ova in the walls of the cysts (Rokitansky and others). Although rigorously upheld by Pfannenstiel, it has been practically abandoned by most writers since the work of

Nagel, v. Kahlden, and others, who have shown that these cysts are not derived from Graafian follicles, but from ingrowths of the germinal epithelium of the surface of the ovary. v. Kahlden traced this clearly in many cases and showed that the ova seen by several investigators were really protoplasmic masses somewhat resembling ova, but produced by the epithelial cells, perhaps as a futile effort on the part of those cells to carry out the function for which they were originally intended.

The cystadenomata are also derived from solid or tubular ingrowths of the superficial germinal epithelium, and not from the Graafian follicles or from the so-called Pflüger's cords, which are groups of ova and epithelial cells. They are frequently single, but often arise from both ovaries

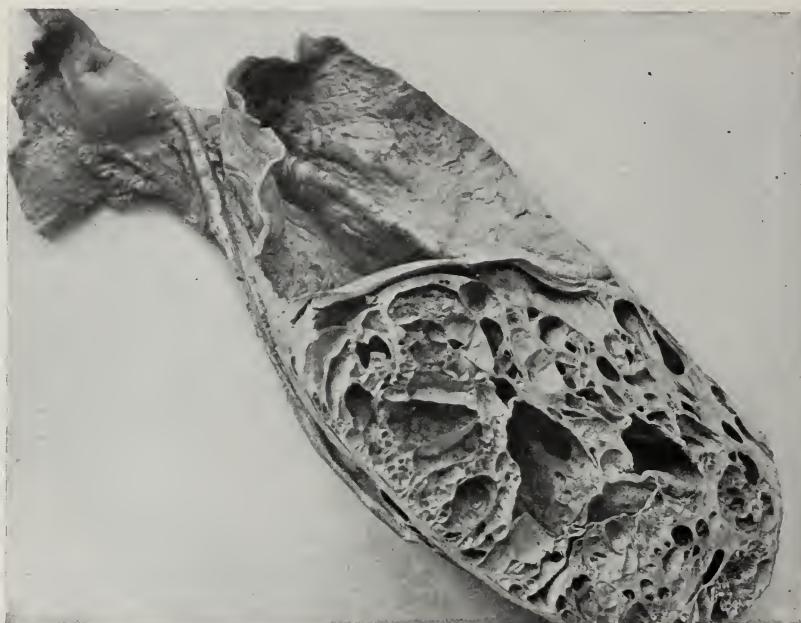


Fig. 623.—Large multilocular cystadenoma of the ovary. The Fallopian tube on that side is greatly elongated and stretched out over the tumor.

simultaneously and are formed of one large cyst or of a great number of smaller ones (simple and multilocular cystomata). At one time much attention was devoted to the chemical study of the contents of these cysts, and they were grouped on this basis, although it is not a distinction of great importance. There are some which contain pseudomucin, a substance allied to mucin, but easily split by boiling with acids so as to produce a carbohydrate which will reduce copper. This fluid may be slightly viscid or thick and gelatinous, sometimes dense enough to cut. I remember well one such cyst of enormous size, from which, at operation, a whole tubful of yellowish-brown, gelatinous, semifluid material was evacuated. The others, which may be called serous cysts, contain a fluid rich in albumin, but not gelatinous and containing no glycoproteid.

The cystadenomata are sometimes quite small, and may at times push their way into the substance of the ovarian and broad ligament. Usually they occupy most of the substance of the ovary, which is spread out on the surface, and press up into the peritoneal cavity attached only by the stalk which contains the ovarian blood-vessels. In this way they may reach the most enormous size, producing a colossal distention of the abdomen where they are carried like a tremendous burden held in front. Their operative removal after the fluid is withdrawn through a cannula is



Fig. 624.—Multilocular cystadenoma of the ovary. The cysts are lined with high columnar epithelium.

often an extremely easy feat, since it consists merely in cutting through the stalk of the vessels.

The pseudomucinous cysts frequently develop many daughter cysts in their walls, or they may be definitely multilocular or composed of a great mass of small cysts (Fig. 623). These are lined with columnar or high cuboidal epithelium, which produces the fluid contents. They are by far the commonest of the cystadenomata (Fig. 624).



Fig. 625.—Multilocular papillomatous cystadenoma of ovary.



Fig. 626.—One of thousands of stalked peritoneal implantations from an ovarian tumor, associated with great collections of fluid in the abdominal cavity.

The serous cysts are also usually unilateral, but are very often multilocular, each small cyst being lined with high columnar epithelium which is often ciliated. We have recently observed, in two cases, bilateral multilocular ovarian cystadenomata composed of such small cysts that the very large tumors appeared to be almost solid. In such cases there is frequently a great accumulation of fluid in the peritoneal cavity.

Both pseudomucinous and serous cystadenomata may thus be multilocular, or in the form of a single cyst, although even then the remnants

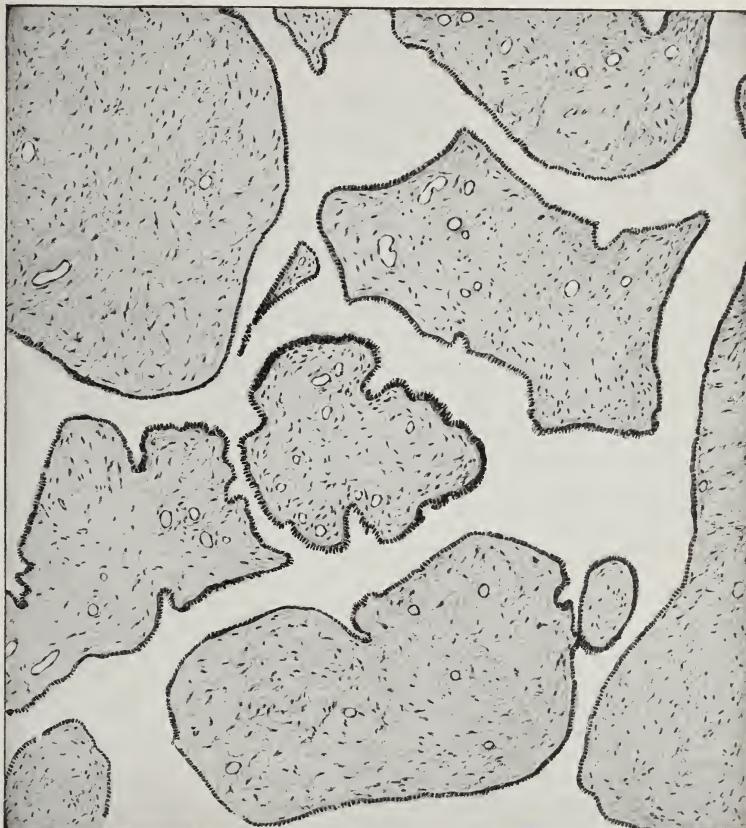


Fig. 627.—Portion of a papillomatous growth springing from the wall of an ovarian cystadenoma.

of broken partitions are usually evident. Both types show, as a rule, some infolding or papillary growth of their epithelium, and this may proceed to the formation of highly complex papillomatous ingrowths (Fig. 627). These are sometimes small and uniformly scattered over the wall; more often they arise from the wall in branching masses, leaving much of the lining smooth (Fig. 625). Such masses may completely fill the cyst. The papillomatous growths may also appear on the outside of the cyst, so as to hang in the peritoneal cavity, and then they resemble the papil-

loma of the ovary already described. Fragments are broken off and swept into all parts of the peritoneum, where they adhere and grow, forming new papillomata wherever they lodge. This may take place, also, in the edges of an operative wound in the abdomen. In this sense the papillomatous cystoma partakes of the character of malignancy, but it goes no further, and there are no metastases outside of the peritoneal cavity, nor is there any destructive invasion of the underlying tissue. Nevertheless, these stalked, papillary growths scattered over the peritoneal surfaces keep up an extreme ascites and end fatally after a tedious illness. A somewhat analogous process follows the rupture of a pseudomucinous cyst, with extravasation of the contents into the peritoneum. The gelatinous material is spread everywhere over the wall and becomes partly organized by the upgrowth of granulation tissue. Some writers have thought that epithelial cells are implanted and continue the production of the pseudomucin, but the evidence for this is insufficient. The result is that the whole peritoneal cavity is lined with a thick translucent layer, often spoken of as *pseudomyxoma peritonei*. A similar process may take place in connection with certain epithelial tumor growths of the appendix vermiciformis.

Cysts of the *parovarium* are generally unilocular, thin walled, and filled with clear fluid. They are derived from the parovarian remnants which lie in the mesosalpinx, and the cyst is found in that situation.

**Adenomata of the Uterus.**—From the uterine mucosa there are formed polypoid adenomatous growths comparable to those of the intestine. They are soft, broad masses, sessile on the mucosa of the uterus, and usually situated in or near one of the cornua, although they sometimes occur in the cervix and may contain small cysts. On section they are found to be composed of enlarged and distorted glands embedded in a cellular stroma.

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## CHAPTER LXVIII

### CARCINOMATA

*General characters, grouping. Flat-cell carcinomata. Epitheliomata of lip, skin, etc. Mode of growth and metastasis. Epitheliomata of tongue, tonsils, bronchi, œsophagus, gall-bladder, urinary bladder. Epitheliomata of the vaginal portion of the cervix uteri. Their frequency and importance. Basal-cell carcinomata. Their relatively benign character. Distribution, peculiar morphology. Relation to nævi. Argentaffine tumors.*

**General Characters.**—The carcinomata or cancers are tumors composed essentially of epithelium, although they, like other tumors, are supported or surrounded by a vascular stroma, which they exact from the neighboring tissue. They are quite analogous to the papillomata and adenomata except in the fact that their epithelial cells are possessed of the enormous vigor of growth, which breaks through every barrier, and enables them to grow into new colonies when they are transported by the lymph- and blood-streams and lodged in distant organs. It is this character of malignancy which marks them out from other epithelial tumors, and even in the earliest stages gives them an anatomical form different from that of the benign growths. It is not possible with the means now at our command to distinguish with certainty a cell of the epithelium which has this exaggerated power of growth from a cell of the epithelium of a benign tumor or even a normal cell. But it is quite possible to distinguish these cells by their behavior, not only in the distribution of the tumor throughout the body, but in the minuter relations which, in microscopical section, the epithelial cells are seen to bear to the surrounding tissues. It is true that the cells themselves are usually different from normal cells, and in some cases extremely different. No doubt, in time we shall have a reliable morphological criterion by which we may say definitely that an isolated cell is a cancer-cell or a normal cell, but at present no such criterion exists, and we rely upon the arrangement of the cells and their relation, in their growth, to the surrounding tissues, because there are many instances in which the individual tumor-cells look so precisely like the normal cells.

Practically the same distribution and architectural plan found in the papillomata and adenomata is repeated in distorted fashion in the carcinomata. We may, therefore, expect to find a great variety of cancerous tumors; nevertheless, by divergence from the original form, epithelial cells from the most widely different sources often approach a common nondescript type so that the tumors which they produce finally resemble each other.

We may distinguish the following groups of carcinomata:

1. *Squamous- or Flat-cell Cancers.*—These arise in the skin, œsophagus, etc., or wherever there is stratified epithelium, and are commonly known as epitheliomata.

2. *Basal-cell Cancers.*—These arise chiefly in the skin, but analogous tumors are found elsewhere. They are relatively non-malignant and are the basis of the so-called *rodent ulcers*.

3. *Cylindrical-cell Cancers.*—These are analogous to the polyps or polypoid adenomata of mucosa which have glands lined with columnar epithelium. They retain the tendency to form gland-like structures lined with cylindrical epithelium and are hence called *adenocarcinomata*.

4. *Cancers Derived from Acinous Glands.*—These are analogous to the solid adenomata and are the commonest cancers, since they include the cancers of the breast. In them the epithelium usually grows in solid strands. No very appropriate name has been given them and none is in common use. They are gland-cell cancers so non-committal in appearance as not to suggest a definite morphologically descriptive name. The term carcinoma simplex which was at one time applied to them is misleading and useless since they are in no sense more simple than the others. Of the various metamorphoses of these tumors which change their consistence or give them peculiar characters, almost constant enough to stamp some of them as another type of carcinoma, we shall speak later. The most striking of these is the formation of a gelatinous or colloid material either in the cells themselves, in cystic spaces lined by columnar cells, or in the stroma. Such *colloid cancers* fall readily enough into the different groups already given, but on account of this common peculiarity it might be tempting to class them together as a distinct type.

#### FLAT- OR SQUAMOUS-CELL CARCINOMATA

There is extraordinary similarity among these tumors from whatever point in stratified epithelium they arise. Those which spring from the skin show as a rule a greater tendency to keratinization than those derived from such epithelium as that of the oesophagus, but this is not invariably so and does not constitute a reliable distinction between the two.

Epitheliomata of the lip (Fig. 628) begin in persons of rather advanced age, most commonly in men, in the form of a slight scaly roughness with little or no underlying induration. After some slight traumatism which may cause the place to bleed, a crust forms, but there is no healing, and if it is pulled off, an ulcer is left upon which another crust forms. By this time thickening of the skin in that area is palpable. The growth of this thickened area proceeds until there is a considerable mass, which extends quite far into the substance of the lip. Usually there is repeated uncovering of a superficial ulceration, which quickly becomes overlaid with a dry crust, but it sometimes happens that this destruction of the surface is very slight indeed. On the other hand, the ulceration may go very deep and cause great distortion of the lip, hollowing out a great cavity which exposes the teeth. A firm nodule may be felt by this time in the position of the submental lymph-gland, and there may even be similar firm masses replacing the cervical lymph-glands. If operative extirpation of the primary tumor, together with the glands which may be involved, be delayed beyond the early stages,

death follows after long delay, from the development of metastases in more distant organs, among which the liver is most prominent. As a rule, however, in all such neglected cancers which are allowed to metastasize, death is actually the immediate result of lobular pneumonia or other similar terminal infection.

When cut through, the tumor and its metastatic growths appear as grayish, translucent masses of tissue closely flecked with opaque yellow spots. These become more conspicuous as the tumor grows older and are scarcely to be found in the perfectly fresh margins where growth is proceeding. Slight pressure will express little masses or cylinders from the cut surface, and these are found to be composed of necrotic and keratinized cells.



Fig. 628.—Epithelioma of lip with beginning ulceration.

Microscopical study of a section through an epithelioma of the skin (Fig. 629) reveals the existence of a mass of growing strands of epithelium which extend far down into the thickened dermis and subcutaneous tissue. These are solid columns of epithelial cells which frequently anastomose with one another and branch. They are several cells broad or may expand into much wider or bulbous masses in which there is evident a tendency to a concentric arrangement of the cells, which become more and more keratinized toward the centre. Sometimes these concentric horny masses are relatively large, and are often spoken of as *cancroid pearls*, *cancroid* being an old name for this type of epithelioma. All the stages in keratinization are seen plainly in passing from the outer layer of cells which lies next the connective tissue in

toward the centre of such a pearl. The cells become thickly studded with black-staining droplets of eleidin, which in turn fade as the nucleus and cell-body shrink into the horny scale of the innermost layers. The most extraordinary enlargement and deformities of the epithelial cells appear in such areas and all semblance of the regularity with which the process goes on in the normal skin may be lost.

The margin of the tumor is usually continuous with the normal skin—occasionally there is a break between the epithelial masses of the tumor and the edge of the normal epidermis, as though the tumor had burst up through the skin. When the two are continuous, there is not a perfectly abrupt transition, for the epidermis becomes thickened and sends down some rather irregular prolongations just before it joins the tumor. Even then it is quite possible that the epithelium of the tumor has healed to the epidermis after having burst up through it. It is not be-



Fig. 629.—Epithelioma of penis showing atypical hyperplasia of adjacent epithelium and downgrowth of the tumor-cell strands.

lieved that the epidermis is converted into tumor tissue as the tumor spreads, but that all tumor epithelium arises from that which first began to grow. Therefore, the epidermis must be pushed aside or burst through in order to allow the tumor to grow. In the first case it might retain its continuity with the tumor throughout; in the second there must be a secondary healing together.

The stroma runs everywhere among the strands of cells, carrying blood-vessels. It is new tissue, of course, different in arrangement from the surrounding dermis and subcutaneous tissue, but in itself there is nothing peculiar to be seen. It has no recognizable tumor character, but is rather thickly infiltrated with polynuclears and especially mononuclear leucocytes or lymphocytes. It is encroached upon by the epithelial cells at every point, and if we follow the coarse strands downward, we find that at their termination they frequently narrow themselves to

single rows of cells or even isolated groups of cells with advancing prolongations which are obviously insinuating themselves into crevices of the tissue (Fig. 630). In this way they invade not only the stroma, whose formation they have enforced, but also the deeper connective tissue and muscle. Any crevice or intercellular space is seized upon for their invasion, and they are by no means limited to the endothelium-lined lymphatic channels, although they also enter these. At the sur-



Fig. 630.—Portion from tumor (Fig. 629) more highly magnified, showing extensive keratinization, invasive growth of epithelium, and inflammatory reaction.

face, where ulceration has taken place, the epithelial strands are interrupted, and their broken ends exposed in the base of the ulcer or covered by an ordinary granulation tissue. Where the strands are intact there may be excessively thick layers of keratinized or horny cells. In the deeper strands, too, instead of compact pearls, there are often found cavities lined with keratinized cells and filled with a soft débris of desquamated scales (Fig. 629).

The living cells of these strands are obviously unlike the cells of the normal epidermis in many respects, although since other conditions may produce similar morphological alterations, it is not possible to recognize them by these abnormalities as definitely cancerous cells. They are usually rather enlarged and polygonal, or irregular in outline, and are irregularly arranged with regard to one another. Their protoplasm takes a rather deep pink stain with eosin in many cases, and their nuclei seem especially rich in chromatin and consequently deep stained. There may be two or more nuclei in a single cell and the mitotic figures which are abundant may be irregular or multipolar. The cell strands are often invaded by leucocytes, and fragments of these cells may even be found embedded within the cancer cells. Other cell inclusions of various forms occur, and have been studied with great care, because it was thought that they might be parasites causing the growth of the tumor. These must be discussed later.

The most important point for consideration, however, is the relation of the tumor-cells to the adjacent tissue. They are not definitely and smoothly bounded by a line of demarcation from the connective tissue. Instead, it is constantly to be observed that the cells grow out irregularly at any point in the course of the strand, and push their way into that tissue in a way totally foreign to the normal epidermis. This process, which, as we have said, is most striking along the advancing margin of the tumor where it encroaches upon the underlying tissue, is the visible sign of the malignancy of growth which gives the tumor its peculiar character.

It has been said that the tumor-cells sometimes push their way into the lymph-channels, and it is probable that in doing this they are aided by a certain degree of amoeboid activity, which they have been shown to possess in tissue cultures (Hanes and Lambert). In those channels they are swept along with the stream whenever they break loose, and lodge in the next lymph-gland, which acts as a sieve. There, instead of disintegrating and being devoured by phagocytes as other cells would be, they are often able to establish themselves in the lymph-sinus and grow rapidly, filling up all the sinuses between the lymph-cords and beneath the capsule of the gland with a solid injection of epithelial cells, or else spreading from the sinus in which they lodge to produce a nodule of tumor tissue which extends radially to occupy a large part of the gland. In this process the epithelium at once causes the formation of a new vascular stroma for its cells at the expense of the gland, and in its growth separates and destroys the normal tissue of the gland which it replaces. The structure of this new nodule is finally in every respect similar to that of the original tumor and all the processes of keratinization and other changes described for that situation are repeated here. This is true, too, for further metastases even when the renewed transportation of cells from the first metastasis gives rise to secondary or tertiary colonies in distant organs.

Epitheliomata may occur in many situations in the skin, although it seems that places at which two types of epithelium come together

are rather predisposed to the development of these tumors. The lip, the edges of the nostrils, the eyelid, the penis and vulva, the margin of the anus are places where they most frequently occur. In the margins of old varicose ulcers they may develop, apparently stimulated or possibly even caused to grow by the long-continued irritation to which the skin is exposed in a site where it is continually endeavoring to grow and being as constantly frustrated.

Epitheliomata are by no means limited to the skin, but occur very frequently in mucosæ which are covered with stratified epithelium.

Thus such tumors may originate at almost any point in the interior of the mouth. Although they sometimes occur in the cheek or gums, epitheliomata of the tongue are far more common. They may occupy any situation from the tip to the extreme base of the tongue, and grow



Fig. 631.—Epithelioma of tongue with ragged ulceration.

in such a way as to form a dense mass extending far into its substance and becoming deeply ulcerated (Fig. 631). There is little or no keratinization, and the superficial layers readily become macerated. Metastases may appear in the regional lymph-glands and internal organs. In one case in which we found a great solid mass embedded in the root of the tongue, with only slight superficial ulceration, there were enormous nodular masses in the cervical lymph-glands throughout the whole chain, and other nodules in the liver. In another case in which the deeply ulcerated tumor had extended so as to approach the internal carotid artery, it finally eroded that vessel some weeks after a partial extirpation of the tumor tissue. A formidable haemorrhage was stopped by ligature of the artery, but the man died ten days later. There were no metastases, but there was a large abscess in the cerebral hemisphere of that side. This case is cited merely as an example of the unexpected sequelæ which may complicate the course of a tumor of this kind, developed in the immediate neighborhood of important structures.

Epitheliomata may develop from the surface epithelium or crypts of the tonsils, and are often particularly destructive. Laryngologists meet with similar tumors involving the vocal cords, the arytenoid folds, or the epiglottis. They are quickly ulcerated, and lay bare the cartilages



Fig. 632.—Carcinoma primary in the lung. Extension toward apex by way of lymphatics.

of the larynx after having destroyed the soft tissues. One case has already been mentioned in which a tumor assumed the form of a papilloma, although spreading over the arytenoid folds and epiglottis on both sides and extending to the pillars of the fauces. In most cases, how-

ever, the tumors are not elevated, but appear as flattened, rough thickenings of the tissue, soon hollowed out into ragged ulcers.

Tumors of the trachea and large bronchi are rare, and not ordinarily of the type of flat-cell epithelioma, as is natural from the fact that those canals are lined with cylindrical ciliated epithelium. Nevertheless in the substance of the lung, tumors which are definitely squamous epitheliomata do arise from the branches of the bronchi. We have recently observed a whole series of these tumors of the lung, among which there were several instances in which a great cavity in the upper part of the lung was found on incision to be lined with opaque, yellowish-white, friable, crumbling tissue. In some of these the bronchus could be traced directly into the cavity, its walls becoming thickened by a great new-growth of the mucosa, which became continuous with the margins of the lining of the cavity. Microscopical sections show in these cases that most of the tumor is made up of strands of atypical stratified epithelium showing all the characters of those seen in the cutaneous cancers. The cells are held together by very distinct intercellular bridges (prickle cells) and undergo keratinization. In the bronchus one may trace the transition of cylindrical into squamous epithelium which is perhaps an example of metaplasia which converts one kind of epithelium into another.

There are various other types of carcinoma to be found in the lung, some apparently arising from less modified epithelium of the bronchi which may retain its columnar form or become packed in solid masses which fill the adjacent alveoli and extend by way of the lymphatics to the pleura and to the lymph-nodes at the hilum. In other cases there is a suggestion that the alveolar lining epithelium may give rise to the tumor which then produces a consolidation almost like pneumonia. Still other tumors seem to arise from the mucous glands of the bronchi.

There has been much discussion in recent years of an apparent increase in the number of cases of cancer of the lung and it is even suggested that the inhalation of dust from tarred roads is responsible, but the evidence for all of this is not very convincing.

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To return to the digestive tract, epitheliomata are common in the *œsophagus*, where they occur at almost any level, but most frequently opposite the cricoid cartilage, the bifurcation of the bronchi, and at the cardiac orifice of the stomach. Whether the explanations given for these traditional sites are satisfactory must be left to the future to determine. It has been thought that the œsophageal mucosa at these points is irritated by passing food, since a certain projection into the lumen is caused by the firm structures which touch the outside.

The epitheliomata are usually broad, flattened masses which nearly encircle the œsophagus, and, by encroaching upon its lumen, obstruct

it greatly. The starvation caused by this obstruction hastens the decline in health of the affected person. We have been repeatedly struck by the fact that the tumor may not extend all the way around the wall of the oesophagus, but leaves intact a narrow band of normal mucosa

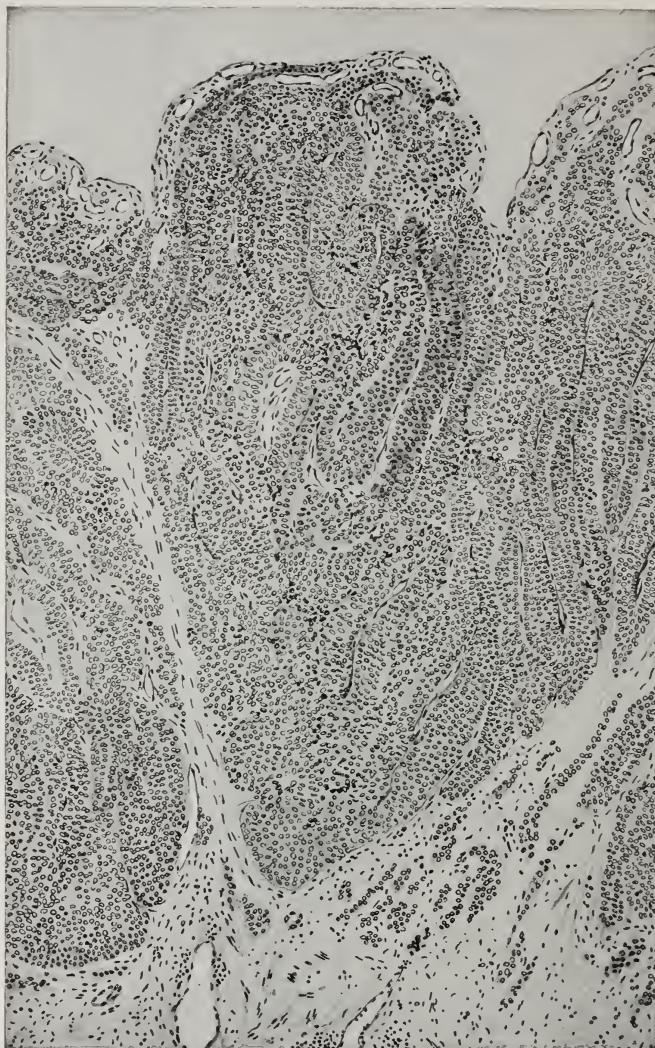


Fig. 633.—Papillomatous tumor of bladder, showing invasive growth of some strands of epithelial cells.

which joins the unaffected mucosa above and below the tumor. On section, the cut surface of the tumor is quite like that of other epitheliomata, except that it is perhaps less closely flecked with necroses. Nevertheless, ulceration does occur rapidly and at the same time the tumor extends through the muscular and connective-tissue coats. Usu-

ally adhesions of dense fibrous tissue form between the diseased œsophagus and neighboring structures, so that further growth of the tumor extends through the adhesions into those organs. Thus a main bronchus or the trachea may be invaded and perforated so that there is formed a definite fistula between the bronchus and œsophagus. In that case bronchopneumonia rapidly follows the leakage of œsophageal contents into the bronchus. The lung may be invaded directly, or an opening be formed into the pleural cavity. In rare cases the aorta or inferior vena cava are eroded and death may follow from haemorrhage. Occasionally the tumor recedes in its growth and undergoes a partial healing, with the formation of scar tissue which contracts about the œsophagus, forming a narrow stricture. Metastases are found in a rather small proportion of the cases and are then in the perœsophageal lymph-glands, in the lungs, in the liver, or in other more distant situations. I saw a



Fig. 634.—Partially papillomatous cancer of bladder.

case in which the tumor had invaded a pulmonary vein, producing infarcts in the kidneys and intestines and emboli surrounded by haemorrhages in the liver and meninges. Another projected, in the form of nodules, into the lumen of the trachea, while there were secondary nodular growths in the parietal pleura. Microscopically these tumors, like those of the skin, grow in the form of solid branching strands of cells which readily invade the muscularis. They are rather less regular in form, and in the character of their nuclei, than the cells of the skin cancers and do not become keratinized. Nevertheless, the same concentric arrangements may be found with flattening and degeneration of the central cells.

The tumors of the *gall-bladder* are usually of the cylindrical-cell type, but they may sometimes, as in the case of the lung, show themselves to be composed of squamous epithelium, a character which is maintained in all the metastatic nodules.



Fig. 635.—Epithelioma of vaginal portion of cervix uteri, invading uterine and vaginal wall. There is great ulceration, which approaches bladder and rectum without actually perforating them.



Fig. 636.—Epithelioma of vaginal portion of cervix uteri.

In the *urinary bladder* there appear papillomatous tumors which have already been described, and these, as it was then said, are probably from the beginning malignant in character and merely impose themselves for a time as benign growths. At the bases of the tassel-like papillomatous growths the thick stratified epithelium is found to invade the underlying tissue in the form of solid strands (Fig. 633). Usually after a time ulceration may destroy most of the papillomatous growth, leaving only a ragged area in the bladder wall lined by rough masses of growing epithelium (Fig. 634). Another type of carcinoma of the bladder does occur, however, in which the wall is infiltrated and invaded widely without having lodged at any time a papillomatous growth. I saw one case, however, in which there were many small polypoid tumors scattered over the bladder wall and concentrated especially about one ureteral orifice. That ureter was greatly dilated and was lined with similar tiny papillomata which extended up into the pelvis of the kidney. It was difficult to be sure whether the primary growth was in the ureter or bladder. Single carcinomatous nodules sometimes occur in the *ureter*, causing its great obstruction, and giving rise to metastases in neighboring lymph-glands. In these one finds very delicate narrow strands of epithelial cells which no longer resemble closely the large cells of the typical epitheliomata.

The epitheliomata of the *cervix uteri* and adjacent vaginal wall are perhaps the most important of all, on account of their frequency, their malignancy and rapid growth, and their fatal effects.

Another type of carcinoma of the uterus derived from the tubular glands of the body of the organ, and maintaining the character of an adenocarcinoma, will be described later, but it is of much less importance, since it is relatively rare and by no means so malignant.

These tumors (Fig. 636) develop in the portio vaginalis of the cervix uteri, near the line of transition of the stratified epithelium into the cylindrical mucosa, and appear at first as rough erosions with a surface which bleeds easily and is almost papillary in form. Growing into the substance of the cervix the tumor may surround the external os with a dense ring of friable epithelium. The further growth is usually accompanied by ulceration, which hollows out a funnel-shaped or irregular aperture. A longitudinal section of the uterus at this stage shows that much of the cervical wall is occupied by a gray, solid tissue with numerous opaque flecks of white (Fig. 635). The growth extends irregularly into the muscle above, and extension outside on the vaginal portion of the cervix and over the vault of the vagina is common; later more of the vagina may be involved in the continuous growth. Metastases to the inguinal lymph-glands and later to those of the retroperitoneal region may occur at this stage, and there may even be nodules in the liver or lungs. The further growth of the tumor extends into the parametrium, forward into the wall of the bladder, and backward to involve the wall of the rectum. Ulceration takes place rapidly, and it is not uncommon to find a great, ragged perforation between the vagina and bladder or

between vagina and rectum. I have seen one case in which, from such ulceration, bladder, uterus, and rectum all opened in common into a great ragged cavity. Infection of the bladder and ureters is sure to follow, and death may be immediately due to an ascending suppurative nephritis. The tumor is composed of thick, irregular strands of stratified epithelium, which is not keratinized, but in which the most extreme irregularities in the form of the cells may be observed. In one such case



Fig. 637.—Epithelioma of cervix uteri with many multinucleated cells. In the centre there is an epithelial cell showing multipolar mitosis.

(Fig. 637) there were cells of all sizes, even including huge protoplasmic masses containing as many as 12 nuclei irregularly placed throughout the cell body. Multipolar mitotic figures, in which several centrosomes and achromatic spindles could be seen in relation to a very much branched arrangement of chromosomes, gave the explanation of the formation of these multinucleated cells. Other tumors of this type are less atypical and merely present irregularly branching cords of cells, which ramify and spread freely in any direction to invade the uterine muscle. Necroses are frequent in such tissue, involving the broader

bands of epithelial cells. The stroma which is formed in association with them is much infiltrated with wandering cells, and it may happen that, at the surface of the tumor, only those epithelial cells which are immediately around the blood-vessels remain alive and project as papillary remnants.

The remote metastases which may be in the peritoneum or omentum, in the liver, kidneys, etc., as well as in the regional lymph-glands, often reach a considerable size, although in the cases which I have seen they have been relatively small. They maintain the type of tumor tissue seen in the original growth.

Tumors which belong in this general class are the cancers of aniline workers, of chimney-sweeps, of betel chewers, and of those in whom *x*-ray burns have long persisted. It will be more useful to describe them in connection with the general discussion of carcinoma and other tumors.

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#### BASAL-CELL CARCINOMATA

Krompecher has pointed out the fact that many of the tumors which grow in the skin and are distinctly derived from the epithelium are quite different in structure from the epitheliomata just described and quite as different in their biological characters. These comprise, in addition to many flattened irregular nodular masses, the so-called *rodent ulcers*, which have been long known to differ from the ordinary epitheliomata in that they are relatively benign and rarely show any tendency to metastasize rapidly. Krompecher regards these tumors as growths derived from the lowermost or basal layers of the epidermis, for which reason they show no tendency to keratinization or to pearl formation. Indeed, he is willing to ascribe certain tumors to the cylindrical or Malpighian layer, others to the rete layer with cuboidal cells, and the highly malignant epitheliomata to the more superficial or spiny layer. This seems open to question, and it is conceivable that, while the more innocent basal-cell cancers may, in truth, be derived from these lower layers, the malignant epitheliomata may represent a different biological alteration of any or all cells of the epidermis, so that their malignancy is not merely the effect of their being derived from a somewhat more differentiated layer of the same cells.

The basal-cell cancers appear most frequently on the face, being especially common in the upper part, about the forehead, the cheek, the nose, and the eyelids (Fig. 638). They are also to be found on the back of the abdomen, or in any other region of the body, and it is to be observed that they do not, like the ordinary epitheliomata, arise at the margins of the skin and mucosæ, where complexities in development

occur. Krompecher gives diagrams which show how they grow from the lower layers of the epidermis, forming masses of solid strands or complicated formations of ramified epithelial structures in which the cells maintain themselves in single layers. In these cases the superficial layer of the epithelium persists as a smooth sheet of cells, although occasionally it may dip down into the middle of each downgrowth of the basal epithelium.

On section through such tumors (Fig. 639) one is impressed with the fact that, in spite of the complexity of the downward-growing strands,



Fig. 638.—Basal-cell epithelioma or rodent ulcer of eyelid.

all reach to about the same level. Further, it is seen that they are very sharply outlined against the stroma, and show little inclination to strew their cells into the irregular crevices of that tissue. Doubtless this morphological character is an expression of their benign type of growth. The cells are rather small and compact, with deeply staining nuclei and relatively scant protoplasm, which also takes a rather dark stain. There is little or nothing of the pallor, the inflation, and the nuclear irregularities which are so common in the cells of the more malignant epitheliomata. Necrosis and ulceration are common, however, and the tumors often present themselves as advancing ragged ulcers with only a

very thin wall of tumor tissue. Upon extirpation they show little tendency to recur, but even if there is a recurrence, it is exceptional to find metastases in the regional lymph-glands or in more distant situations.

It will at once suggest itself that the nævi bear a considerable resemblance to these tumors, since they are composed of small, compact

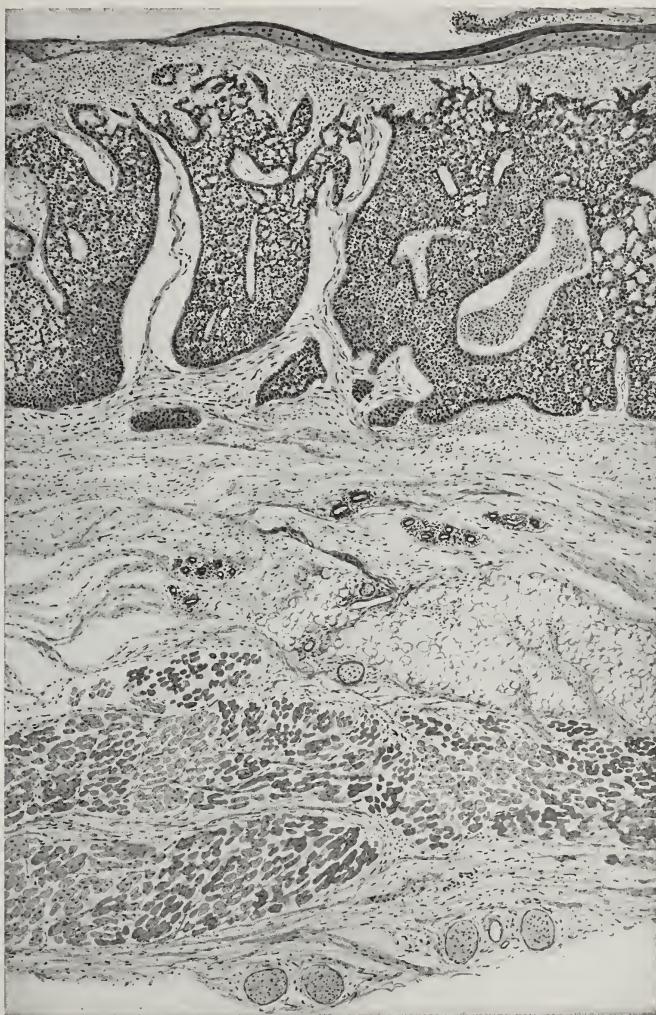


Fig. 639.—Basal-cell epithelioma of the skin, showing peculiar limitation of the downward growth.

cells which lie in the papillæ of the dermis, and are thought by many to be connected with the epidermis itself. It is true that, in nævi, the connection of the tumor-cells with the epithelium must be sought for with great care, and is frequently impossible to find, that the cells have little histological resemblance to those of the epithelium, and that their

great tendency to form or to accumulate pigment in their cell-body marks them out from those of the basal-cell tumors. Here the tumor-cell strands are everywhere continuous with the epithelium; they are not merely isolated groups of cells lying in the substance of the dermal papillæ: they are typically epithelial in character, and seldom contain any considerable amount of pigment. They have little energy of growth and rarely metastasize, while from the nævi there arise the most malignant of all tumors, the melanomata, which may scatter secondary nodules in thousands in every tissue of the body. Nevertheless, there are many who regard the nævi and the melanomata as tumors of epithelial origin, and Krompecher identifies them more or less closely with his basal-cell cancers. A decision is difficult in this matter, but it seems that there are sufficient points of distinction to warrant the separation of the groups. The tumors which were referred to as endotheliomata of the skin by Braun, and accepted as such by Borst, were mentioned under that heading as possibly derived from the endothelium of the lymphatic channels in the skin. Such tumors are, of course, possible, but Krompecher unhesitatingly ascribes to them an epithelial origin and regards them as identical with the basal-cell cancers. This identification he pushes further to include many tumors which arise from the glands which open upon surfaces of stratified epithelium, and even the mixed tumors of the salivary glands, which we shall discuss in the next chapter. He finds that basal-cell cancers arise in ovarian tumors, in dermoid cysts, and other tumors of teratomatous origin. This can, of course, never be contradicted, since those tumors have such manifold possibilities. Finally, the neuroepitheliomata of the retina described by Flexner, and later by Wintersteiner, seem to him to have similar characters.

**Argentaffine Tumors.**—Tumors somewhat resembling these basal-cell tumors of the skin have been described by many authors in the wall of the intestine and in the appendix, and Bunting and Burckhardt suggested a relation between them. While this may eventually prove to be true, the more recent studies have revealed such surprising facts about these nodules that there has been no further mention of that possibility. It is essentially due to the work of Masson that we now know that in the appendix and in the wall of the intestine there are cells, recognized by Kultschitzky and by Ciaccio, which have an affinity for chrome salts like those of the adrenal medulla, and that the tumors of these regions are composed of such cells, which he found were also able to reduce silver. For this latter reason Masson speaks of them as argentaffine cells and of the tumor nodules as argentaffine tumors. These cells lie in the basal level in the crypts of Lieberkühn and do not reach to the top of the epithelial cells. In these respects they recall the Langerhans cells in the skin. And now Masson finds that they are in most intimate conjunction with nerve fibrils which in obliterated appendices even grow into tangled masses or neuromata as long as the argentaffine cells are present, but not otherwise. He suggests, therefore, a neurogenic relation, but in general, without very cogent proof, looks upon

them as having an endocrine character and speaks of the tumors in the appendix as endocrine tumors. All this is very like what he has also described in connection with naevi in which the same intimate relation of the melanoblasts with nerve terminals is discovered. It must remain for further study to ascertain the exact status of all these tissues and whether or not there is any relation between the argentaffine neurophile tumors and naevi or the basal-cell cancers.

The actual tumors composed of these elements have hitherto been called carcinoids following the suggestion of Oberndorfer, but that seems a rather futile designation now that we know more about them.

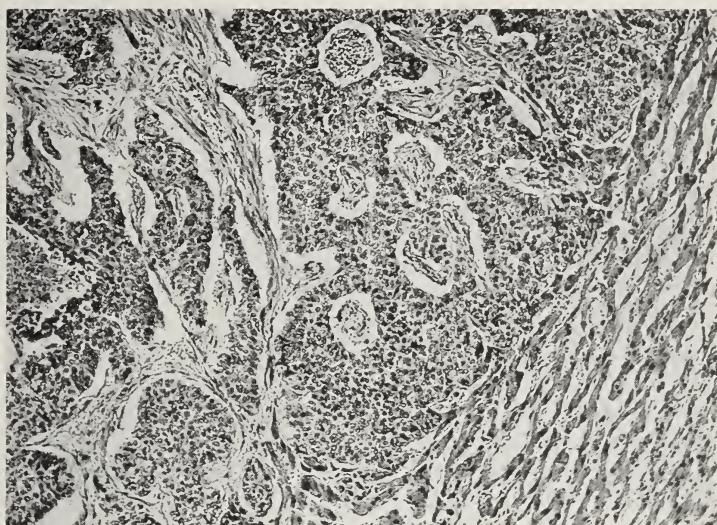


Fig. 640.—Argentaffine tumor, metastases in liver from intestinal nodule.

Argentaffine tumors occur most commonly in obliterated appendices after an old inflammatory process, but in many cases they have been found as flattened compact masses in the wall of the small intestine lying below the muscularis mucosæ and often extending deeper. They may be confusing sometimes, as in a case observed at autopsy a short time ago in which there was an adenocarcinoma of the lung with metastases. A nodule in the intestine was regarded as a metastasis as a matter of course, but it was found to be an argentaffine tumor, and the single metastatic nodule in the liver was found to be a metastasis not from the adenocarcinoma, but from the argentaffine tumor. This is the first instance we have found in which one of these tumors produced a metastasis, although they are commonly multiple in the intestine, but since the nodule in the liver was intensely argentaffine there could be no doubt.

Forbus has studied our material of such tumors of appendix and small intestine and reviewed the literature.

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## CHAPTER LXIX

### CARCINOMATA (Continued)

*Adenocarcinomata: General characters and distribution. Carcinomata of the stomach: polypoid, solid, and scirrhouss forms. Their histology and mode of growth; metastasis. Colloid forms, their somewhat different mode of growth. Carcinomata of the gall-bladder and ducts; carcinomata of the pancreas, of the colon, of the prostate. Metastasis into bones from prostatic tumors. Adenocarcinomata of the uterus and of the ovary.*

#### ADENOCARCINOMATA

FROM all mucosæ in which the epithelium is cylindrical in form, and from glands and ducts lined with cylindrical epithelium, there may be derived adenocarcinomata or cylindrical-celled cancers. These are malignant tumors which give rise to extensive metastases, often far larger than the primary growth. They maintain in irregular fashion the arrangement of tubular glands, transmitting this mode of growth to the primary metastases, but sometimes losing it in secondary metastases which arise from the transportation of cells from the primary ones. This modification of the architecture of tumors in secondary or tertiary metastases is not uncommon, and will be discussed later in a more general way.

While adenocarcinomata may thus appear in situations almost as numerous as those which form the point of origin of epitheliomata, there are certain sites which become important from the fact that they are so frequently the starting-point of these tumors—the stomach, the gall-bladder, and bile-ducks, the pancreas, the large intestine, the body of the uterus, and to a less extent the prostate and the bronchial mucosa. Of course, tumor tissue of this structure may also occur in teratomata, where there are abundant opportunities for its development. Except for the exaggerated energy of growth of their cells, they are quite comparable to the adenomata and polypoid glandular tumors.

**Carcinomata of the Stomach.**—The extreme prevalence of carcinomatous tumors of the stomach, their disabling effects, and fatal outcome cause them to occupy a very prominent place among tumors. There are many varieties, and many situations in the stomach may be occupied, so that the symptoms vary greatly. A cancer at the cardiac orifice, by obstructing the entrance of food into the stomach, may, like the epitheliomata of the œsophagus, result in starvation and extreme emaciation. A cancer in the fundus of the stomach or on any part of the wall away from the orifice may exist a long time without causing any symptoms, while such a tumor at the pylorus or encircling the pyloric ring is sure to cause stagnation of the gastric contents and dilatation of the stomach. Absorption of poisonous decomposition products must then occur, and the gastric juice loses its antiseptic qualities with the loss of its high content of hydrochloric acid, in place of which lactic acid often

appears. Bacteria or moulds may thrive in considerable quantities in the accumulated material, particularly the large Oppler-Boas bacillus. Vomiting is frequent, and gastric tetany may appear just as it does when the pylorus is obstructed by the scar of an old ulcer.

The following types of cancer of the stomach are met with and are sufficiently different morphologically to fall into groups, although doubtless in principle they are alike.

Carcinomata about the cardiac orifice may be derived from the prolongation of the stratified epithelium of the oesophagus and may therefore have the anatomical characters of the epitheliomata. The others derived from the cylindrical epithelium usually maintain that

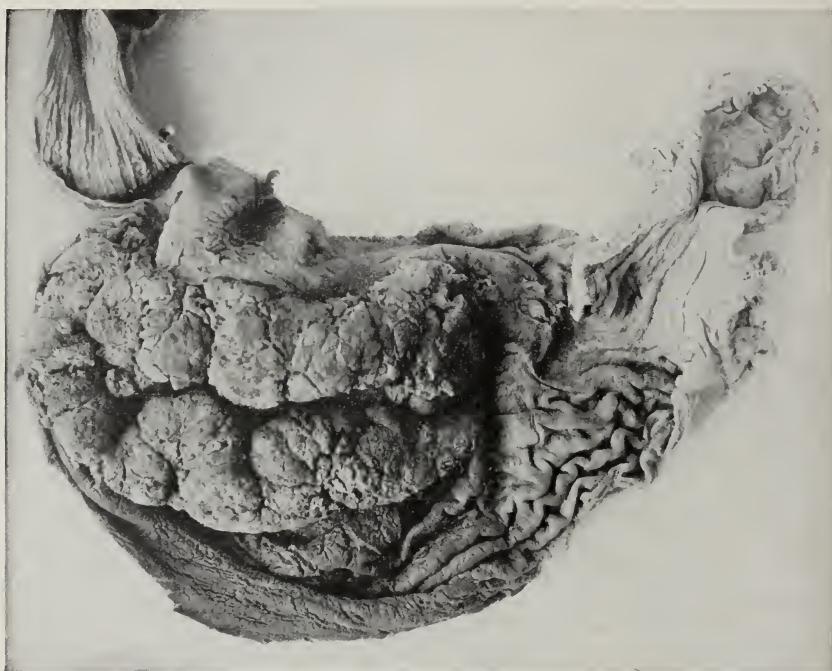


Fig. 641.—Large fungus-like carcinoma near fundus of stomach.

type of cell, although in many instances in which fine strands of cells are found scattered through the musculature, the cylindrical character is lost.

*Polypoid Carcinomata.*—These occur anywhere on the stomach-wall and project into the lumen as broad, pedunculated, fungus-like masses, which are rather soft and easily torn or broken apart. In Fig. 641 there is shown an example of this type, in which the tumor is situated very near the cardiac orifice, and doubtless projected in front of it, without, however, causing any marked obstruction. Quite similar tumors are found near the pylorus. In this case there were no discoverable metastases, and it is my impression that these tumors do not form metastases

as rapidly as do the other types. The normal mucosa passes upward to the overhanging edge and gives place to the most complex arrangement of gland-like structures lined with cylindrical epithelium. In places there appear to be papillomatous areas; in others through the whole depth of the tumor the tissue is made up of a delicate stroma, supporting wide and narrow ramifying tubular epithelial structures. There is surprisingly little downgrowth into the muscular wall in this case, but in others of the same type it is far reaching and destructive. Necrosis and sloughing of the exposed tumor is of almost regular occurrence.

*Solid carcinomata* of more sessile form are much denser than these fungating types. They, too, may grow anywhere in the stomach, but appear most frequently about the pylorus and the lesser curvature. Various stages may be found, from a beginning adenoma-like growth of small size to the huge, crater-like, excavated masses which occupy a great part of the wall of the stomach. I remember one such tumor as large as a child's head, composed of dense, elastic, yellowish-white



Fig. 642.—Carcinoma of stomach involving cardiac portion and fundus.

tissue, which projected into the stomach and was hollowed out so that the cavity extended far into the liver, to which the outer surface of the stomach had become densely adherent. Ordinarily, such tumors are found as rounded or irregular ulcers with thick, elevated, rounded edges which can be felt to project a short distance beneath the adjacent mucosa (Fig. 642). One may pick up and move the mucosa almost as far upward on this ridge as its crest—beyond that, although the mucosa looks smooth and velvety for a short distance further, it is adherent and immovable. There follow a roughening and irregularity of the surface which then drops precipitously into the ulcer. On cutting through the margin of the tumor the transition of the normal mucosa into the greatly thickened epithelial mass of the tumor can be seen. Here as in the epitheliomata of the skin, the significance of this continuity may be questioned and it seems probable that in spite of the intermediate

zone of modified mucosa, the unbroken epithelium may be maintained by repeated healing together. It is, however, possible that the normal mucosa is merely pushed back by the increase in size of the tumor. It does not seem probable that normal mucosa is converted into tumor as the growth advances.

It is rare to see a gastric carcinoma which is not ulcerated, although the tumor itself may be far larger than the area occupied by the ulceration. The cut surface reveals a white or grayish-white or yellowish tissue which interrupts the muscularis mucosæ, and passing through the submucosa, interrupts and penetrates the muscular coat of the stomach. At the margin the muscular coat may be traced for some distance into the tumor, and then it is found that the tumor has grown in thousands of fine strands between the fibres of the muscle, leaving it otherwise intact for a long time. In the subserous tissue it again becomes a solid mass. On the outer surface the site of the cancer is readily made out by the rigidity of the wall, and usually by the appearance of whitish, flattened nodules which cover the peritoneal surface. Dense adhesions to surrounding organs are very common, and the stomach is, in consequence, often kinked and distorted by being drawn up against the liver or pancreas. Metastatic nodules are usually found in the neighboring lymph-glands, which may be greatly enlarged. On section, they show a white tissue, usually with yellowish necrotic flecks in every way similar to that in the gastric wall. The omentum is studded thickly, in many cases, with minute nodules of the same tissue and is drawn up into a dense prismatic mass which lies transversely in the abdomen and can be felt through its wall. There may be more distant metastatic nodules in the peritoneum, but it is more common to find them rather limited to the region of the stomach. The occurrence of metastatic nodules in the liver is extremely frequent and these may reach a very great size and be very numerous. The most remarkable variation occurs in this respect, for while some large tumors show only a few small metastases, others of less extent are found to have given rise to enormous growths in the liver sufficient in number to occupy most of its substance. The occurrence of metastases in other situations will be referred to later.

It has long been thought that these tumors may develop in the edge of a round ulcer of the stomach, and there is much clinical and pathological evidence to support this view. The transformation of symptoms of long-standing gastric ulcer into those of a gastric carcinoma may not be very convincing, nor even the discovery of an ulceration in the middle of the tumor, with such induration of its base as to suggest the existence of a primary chronic gastric ulcer. But when the tumor develops on one side of a typical round ulcer, the conclusion is more difficult to escape. We have seen two typical round ulcers of the stomach, in the margins of which carcinomatous growth of epithelium of unmistakable character was found, although in neither case had the tumor developed sufficiently to disturb the characteristic appearance of the ulcer.

Other solid gastric cancers grow as in Fig. 643, without such extensive

ulceration and produce a great thickening of the mucosa and of the submucosa, infiltrating the muscle layer and the subserous tissue. Such

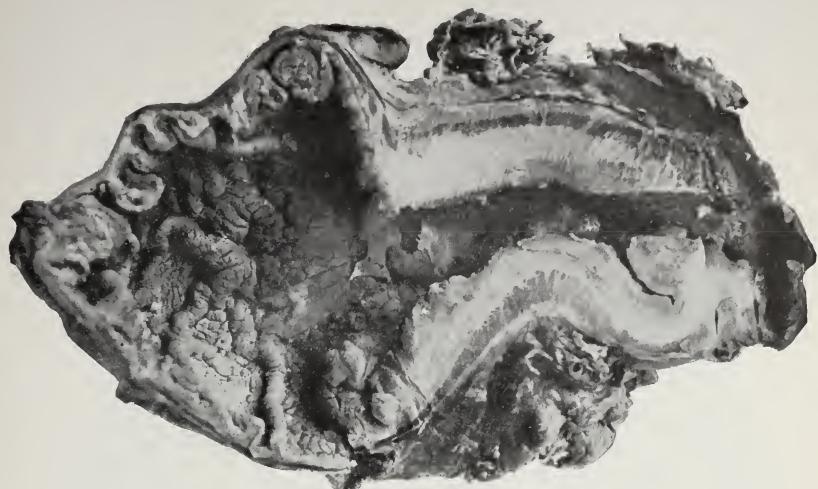


Fig. 643.—Dense carcinoma of stomach surrounding the whole pyloric region and narrowing the channel. There is diffuse infiltration of the whole thickness of the wall with the tumor-cells.



Fig. 644.—Scirrhous cancer with very slight ulceration occupying whole wall of stomach and causing its great contraction.

a tumor does become ulcerated, but its earlier growth forms an extremely dense, resistant mass, which may completely surround the pyloric portion and render it quite rigid.

Occasionally there is found a peculiar thickening and induration of the whole stomach-wall, which causes it to shrink to a small size. There may be no prominent tumor nodule and little ulceration, but the mucosa is roughened and wrinkled, and not readily movable upon the underlying tissue. A section shows that the whole wall is infiltrated with a tumor in which the epithelial cells are relatively sparsely scattered in



Fig. 645.—Carcinoma of stomach showing sudden transition of glands into the carcinomatous distortion.

an abundant and dense stroma. This is the so-called *diffuse scirrhous carcinoma* of the stomach (Fig. 644).

Microscopically, various appearances are met with in these forms of more solid carcinomata. In most cases the normal mucosa, in approaching the tumor, becomes infiltrated with lymphocytes and other wandering cells, and its glands are lengthened and become tortuous,

often with dilatation of the lowermost part. Nevertheless, they retain the smoothness of their outline. Suddenly as the surface layer of the epithelium reaches the crest of the marginal ridge of the tumor, the whole arrangement changes and the cells themselves assume a different character (Fig. 645). The glands become exceedingly irregular, with numerous branches, or are greatly enlarged and partly or completely filled with epithelial cells. It is now very difficult to determine just how much of the epithelial mass belongs to each gland, for their identity as glands is lost, and instead there are ramifying cavities lined with

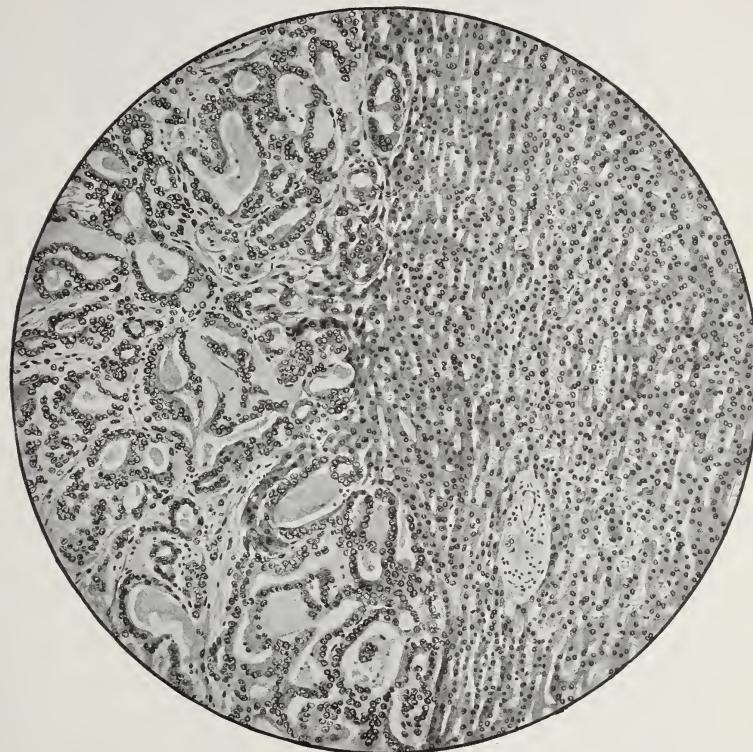


Fig. 646.—Margin of a secondary nodule in the liver derived from an adenocarcinoma of the stomach.

several rows of cells among which are other cavities, or there are solid groups of cells. The cells lose their regular arrangement and to a great extent their uniform cylindrical shape. They no longer range themselves on a smooth basement membrane, but grow at will in any direction into the stroma. The sudden change from the moderately infiltrated and loose stroma of the mucosa to the much denser stroma of the tumor which is thickly infiltrated with wandering cells is very striking. Still, in other cases, the disarrangement of the glands in passing over from the mucosa into the tumor is by no means so great, and the whole tumor is found to be made up, even in its distant extensions through

the muscle and into the subserous tissue, of long tubules which are coarse and deeply stained and variable in calibre, but which do not seem to fray out into the tissue or to grow into more solid masses. At these extreme ends there is generally an indication of the invasive freedom of their cells. Usually, however, even in those in which the glandular or tubular arrangement is best preserved, there are parts of



Fig. 647.—Metastatic cancerous nodule in the liver from a primary carcinoma of the stomach. The section shows the central necrosis and scarring of the tumor, with retraction and dell formation.

the tumor in which the tubules appear as solid strands with numerous spaces lined with cylindrical cells, which keep up the glandular appearance.

In the denser tumors, such as that shown in Fig. 643, it is common to find the glands of the mucosa, as one passes into the tumor, changing into extremely long narrow tubules which are lost in a dense and

greatly thickened submucosa. Between these glands the tissue is packed with cells, many of which are clearly wandering cells, while great numbers are loose epithelial cells. It is difficult to trace the exact source of these cells, although they may sometimes be obviously derived from the lowermost ends of the glands. Deeper in the submucosa and far into the muscle they assemble themselves into more definite groups, which arrangement they retain wherever they are found. This is practically the character of the growth in the scirrhouss cancers, in which very small solid groups of cells are set free from the ends of the glands, and

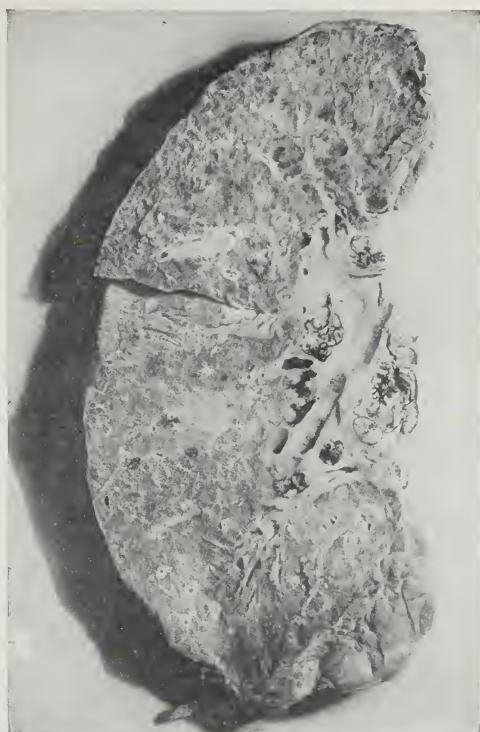


Fig. 648.—Metastatic carcinoma filling all the lymphatic channels in the lung and producing fine white ridges on the cut surface. Secondary to a carcinoma of the stomach.

grow into the submucosa. The extreme growth of connective tissue in response to this causes the mucosa, submucosa, and muscularis to become matted together into a leather-like mass, in which tumor-cell strands are sparsely scattered.

Occasionally there are observed several carcinomatous nodules projecting from the mucosa of the stomach, and the explanation is to be found in the fact that in these cases the network of lymphatic channels in the submucosa and in the subserous tissue is filled solidly with tumor-cells, which enter at the primary growth and grow along until they form

a sort of injection of the whole network. The accessory nodules appear to be eruptions of tumor growth from those underlying lymphatics. This mode of growth was studied by Borrman, whose illustrations correspond well with the condition found in several of our cases.

With regard to **metastasis** from the carcinomata of the stomach a brief statement was made above. It is true that the adjacent lymph-nodes and the adjacent peritoneum are usually primarily involved, and also that numerous nodules are frequently formed in the liver (Fig.



Fig. 649.—Invasion of lymphatics in the wall of a bronchus extending from pleural metastases.

646). These vary greatly in size and evidently in age, and while there are small, translucent, grayish-white nodules of smooth globular form, there are also very large masses of similar form, but showing the well-preserved tumor tissue only in their marginal portions. The whole central part of such nodules usually presents necroses, which may affect only small groups of cells here and there, so as to produce the familiar yellow flecks on a gray surface, or may be complete, so that nothing remains alive except the connective-tissue stroma. When the nodule

lies at the surface of the liver, it at first presents a convex or flattened face, but, with the liquefaction and absorption of this central necrotic part and the contraction of the stroma which remains behind, there comes a sinking of the centre. Every secondary cancer nodule of any age which projects from the surface of the liver shows this central depression, and on section the reason is plainly seen (Fig. 647). Doubtless insufficient blood-supply is the cause of such necrosis. The nodules press upon the blood-vessels and bile-ducts and cause local areas of anaemia and chronic passive congestion, and also jaundice. The jaundice may be extreme, but it must be remembered that there are often opportunities for its production by the compression of the large bile-ducts outside the liver by the main tumor or by its intraperitoneal metastases.

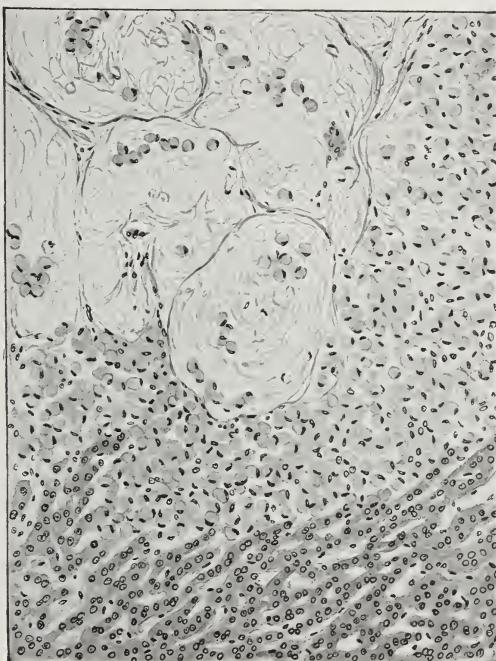


Fig. 650.—Colloid carcinoma of the stomach. Secondary nodule in the liver, showing the tumor-cells separated from one another, and each containing a globule of colloid.

The metastases are not confined to the abdominal organs, but are found in the pleural cavities on the costal pleura, or on the surface of the lung. There one observes peculiar minute, lenticular flecks of gray, translucent tissue, which look almost like tubercles. They are larger and flatter, however. On section, the lung is air containing, but is roughened by the projection of the interlobular septa, blood-vessels, and bronchi, all of which stand up a little from the cut surface as gray, translucent, rough ridges (Fig. 648). This is due to the filling up of the lymphatics in the walls of vessels and bronchi and in the inter-

lobular septa with an injection of epithelial cells (Fig. 649). Occasionally larger lymphatic trunks can be seen branching over the pleural surface, and made conspicuous by the grayish-white injection of tumor-cells. In other cases the secondary growths are in the form of button-like nodules on the pleura. In the lung itself the tumor may metastasize, with the formation of large, discrete nodules which push aside the tissue or, as in a case which we saw, with the production of a pneumonia-like process. Each alveolus over a large area of the lung was filled with tumor-cells, and since the alveolar walls and vessels were intact and undisturbed, the patch had almost exactly the appearance of a pneumonic consolidation.

Metastases in the brain, kidneys, spleen, and other organs occur, but are not especially common. Numerous metastases in the bones have



Fig. 651.—Colloid carcinoma of stomach. Secondary masses surrounding liver.

been found, and I have seen one case in which these growths produced rarefaction with fractures of the bones.

Another form of carcinoma of the stomach which is peculiar in many of its characters is the *colloid cancer*. There are at least two types in which the accumulation of a gelatinous colloid material is found; one in which the glands or tubules of the tumor are made up of spaces in which the epithelial cells lie quite loose, are rounded or spherical, and contain each a large globule of clear fluid (Fig. 650); the other, in which the tubules are distended into cyst-like cavities lined with a single layer of cylindrical epithelium and filled with glairy fluid (Fig. 652). The first of these appears as a diffuse thickening of the mucosa and of

the whole wall of the stomach, with a gelatinous, yellowish, translucent tissue, which accumulates in soft nodules over the outer surface of the stomach and spreads quickly into adjacent glands and over the peritoneal surface. The second usually causes a far greater thickening of the stomach wall, with a large ulcerated area in the mucosa and with great layers of new tissue on the outer surface (Fig. 653). The omentum is converted into a huge mass of friable gelatinous material, and the whole peritoneum may be lined with a thick layer of it. On cutting through any of this tissue the cavities filled with fluid are quite visible to the naked eye, so that this type was once called alveolar cancer.

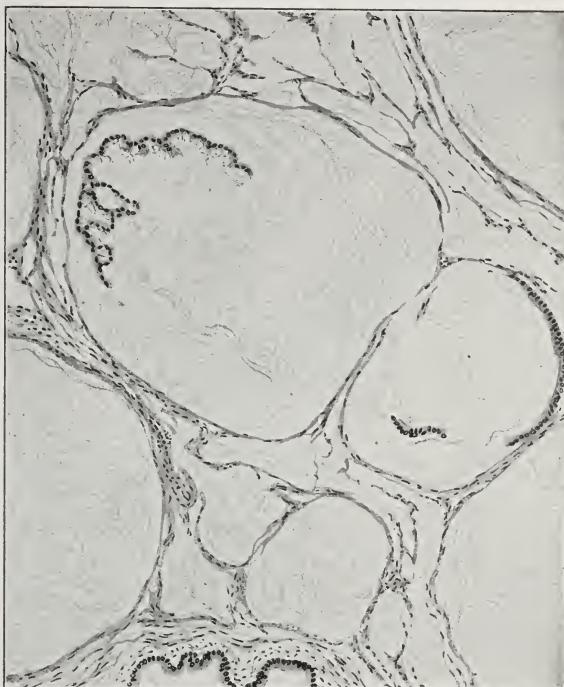


Fig. 652.—Colloid cancer of the stomach with large alveoli filled with colloid material and only partly lined with the remains of the epithelium.

It has the appearance of sago pudding, and one may scrape off a tenacious glutinous fluid from the surface. In one case which I saw at autopsy all the abdominal organs and the parietal peritoneum were covered with a layer more than a centimetre in thickness, which was quite brittle, although fairly firm. It was so transparent that one could see the blood-vessels in its depth. Metastases, if they occur, have the same structure, but while the tumor easily penetrates the stomach-wall and spreads implantations throughout the abdominal cavity, it is not strikingly capable of producing metastatic nodules in other organs.

**Carcinomata of the Gall-bladder and Ducts.**—These tumors may be described much more briefly, since their general behavior resembles that

of the adenocarcinomata of the stomach. It has been stated that epitheliomata may arise in the gall-bladder, especially when there are incarcerated gall-stones there which have long caused irritation. One sees them sometimes accurately moulded round the gall-stone, and extending only so far as it lies in contact with the mucosa. Adenocarcinomata may spring from the mucosa of the gall-bladder even in the absence of inciting gall-stones, and usually metastasize quickly to the liver. As a rule, the primary tumor is found to invade the liver in such a way as to bury the remnant of the gall-bladder in a dense mass of tumor tissue. Metastases resemble those from the carcinoma of the stomach, and usually cause jaundice, occasionally, as in Fig. 654, by obstructing one of the larger duets. Quite similar carcinomatous tumors may spring



Fig. 653.—Colloid cancer of the stomach. The wall is greatly thickened by the gelatinous mass which extends into the omentum.

from the bile-ducks at any point, from the ampulla of Vater to the branches high in the liver. They often appear to be multiple in origin, although that is by no means certain. They almost invariably produce jaundice, which may be very deep. These tumors form a large proportion of the primary cancers of the liver and may grow to enormous masses in one or other lobe of the liver (Fig. 655).

**Adenocarcinomata of the pancreas** are most frequently situated in the head of the gland, near the duodenum, and form large, irregular masses invading and compressing the adjacent structures, with various results. One or both of the pancreatic ducts may be compressed, and the pancreatic tissue drained by the obstructed duct becomes atrophic. The



Fig. 654.—Adenocarcinoma of the fundus of the gall-bladder with metastases in the liver compressing and obstructing a large bile-duct and producing jaundice.



Fig. 655.—Primary carcinoma of liver springing from bile-ducts. Numerous secondary nodules in the liver.

tumors have, as a rule, a complex tubular arrangement with high cylindrical epithelium. Metastases have the same distribution as in carcinoma of the stomach.

**Adenocarcinomata of the Intestine.**—In the small intestine adenocarcinomata are quite uncommon. On the other hand, those of the *colon* are especially common, and therefore important. They may occur at the ileoæcal region (Fig. 656), or anywhere in the course of the colon or in the rectum. In nearly all cases the tumor springs up from the mucosa as a projecting mass which encroaches upon the lumen of the colon and usually encircles it. Great obstruction may be produced in this way not only by the actual bulk of the mass, but more especially by the contraction of those tumors which, in their late stages, become extensively degenerated and scarred. In these cases the lumen of the in-



Fig. 656.—Adenocarcinoma of colon causing obstruction with hypertrophy and dilation above the tumor.

testine may be reduced to the diameter of a few millimetres, so that the contents stagnate above the obstruction, remain fluid, and escape continuously in small quantities. As stated in a previous chapter, muscular hypertrophy appears above the obstruction, often accompanied by ulceration of the mucosa.

The carcinomata of the colon are nearly always composed of irregular, tubular downgrowths of epithelium lined with high cylindrical cells (Fig. 657). In the deeper portions these may, of course, become more atypical in appearance and more confused in their order.

The intestinal wall is often penetrated by the growth, and extensive

adhesions and excavations into adjacent organs occur. Regional metastases into neighboring lymph-glands are common, peritoneal implantations occur, and there are metastatic nodules in the liver in many cases resembling closely those derived from tumors of the stomach. I recall one case in which there was a very small nodule of hard tumor tissue surrounding the colon and drawing it into an extremely narrow stricture. The whole mass was not more than 3 cm. in diameter, and yet there were many metastatic nodules in the liver, one of which reached the size of a man's head.

**Carcinoma of the prostate** is most commonly of the adenocarcinomatous type, although there are some cases in which the tumor-cells pre-

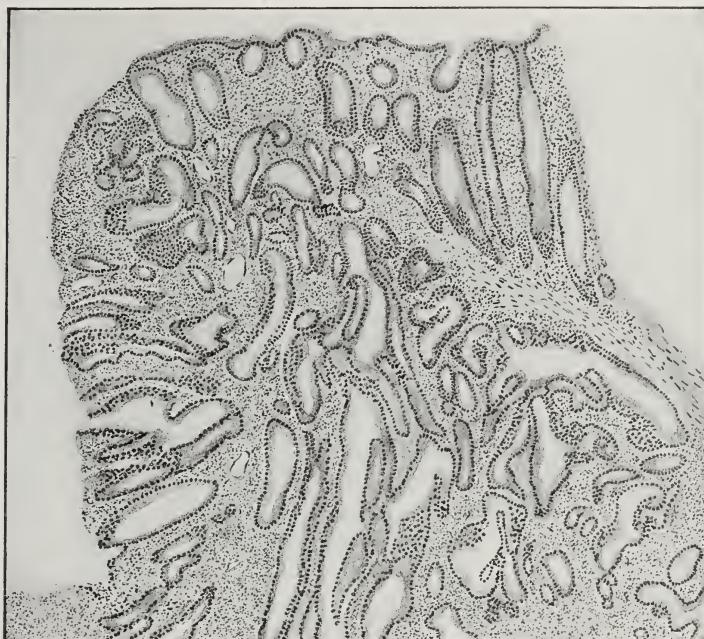


Fig. 657.—Margin of an adenocarcinoma of the rectum showing a transition from slightly modified mucosa to the tumor growth, which maintains a gland-like arrangement of the epithelium.

sent themselves in broad, solid strands. The tumors are capable of penetrating into the bladder or into the rectum, with resulting ulceration and infection. Metastases are usually abundant in the lymph-glands of the pelvis and retroperitoneal tissue, in the liver, lungs, and other organs, but particularly in the *bones*. In two of our cases in which the primary growth was inconspicuous and microscopically showed the complex glandular arrangement of an adenocarcinoma, there were a few internal metastases, but on examining the skeleton it was found that practically every bone was involved. The cancellous marrow of such bones as the vertebræ, sternum, ribs, and clavicles was completely replaced by the tumor, which had stimulated an excessive new formation of bone,

which was very dense and hard. In the long bones the marrow cavity was entirely filled with a yellowish, opaque, ivory-hard tissue, so that the bone seemed to be quite solid. It is so evident that much new bone is formed in such cases that these metastases are called osteoplastic. Microscopically it is found that every lamella of the cancellous bone is enormously thickened, and that the marrow spaces are correspondingly narrowed. All these spaces are filled with tumor tissue which completely excludes the marrow. The layer of osteoblasts is preserved in apposition to the bone, and it seems probable that the tumor exerts its osteoplastic effect by stimulating those cells to increased activity. Widespread necrosis, which involves a great part of such cancerous bone, seems to be of very frequent occurrence. The almost complete destruction of



Fig. 658.—Adenocarcinoma of the kidney.

the bone-marrow leads to an extreme anaemia and to efforts at blood formation in other organs, which have been referred to elsewhere in discussing osteosclerotic anaemia. The carcinomata of the prostate are well known for this peculiarity of metastasizing into the bones, a property which is shared to some extent by the carcinomata of the breast, stomach, and thyroid.

**Adenocarcinoma of the Kidney.**—An adenocarcinoma evidently arising from the epithelium of the kidney tubules has been described by Ewing and others, and Fig. 658 from one such case shows well the extreme delicacy of the epithelial cells which resemble closely those seen in the so-called hypernephroma.

**Adenocarcinomata of the Uterus.**—These tumors, already referred to in contrast with the epitheliomata of the cervix, are developed from the

tubular glands of the fundus uteri or the more complex glands of the cervix. In some cases their growth seems associated with the previous existence of an adenoma of the uterus, but this is by no means a regular occurrence. Since they appear to grow rather slowly, many cases have been observed in which extirpation of the uterus was performed at a time when the carcinoma was still small (Fig. 659). In such a case the mucosa is found thickened and rough, with many papillary projections. The growth extends into the musculature, but for some time is fairly evenly outlined against it. Nevertheless, it is not long before the invasion of the musculature occurs by the downgrowth of some of the glandular elements which may be found deep in the uterine wall. Ulceration may occur, and the cavity of the uterus becomes enlarged by the



Fig. 659.—Adenocarcinoma of the uterus. The tumor is a mere ragged thickening of the mucosa at the fundus. There is a fibromyoma lodged in the substance of the uterine wall.

excavation of the tumor in its wall. Even then the outer surface of the uterus may show no evidence of the presence of the tumor other than the enlargement.

Metastases are slow to form, and appear in the retroperitoneal lymph-glands. I have seen a few cases, however, in which the secondary growths were very widely disseminated, involving the peritoneum, liver, and other organs. Microscopically, the tumor is made up of tubular epithelial growths resembling in all their complex modifications those already described for other adenocarcinomata, although seldom showing any such orderly columnar cells with globules of mucus as are usually found in the rectal carcinomata.

The tumor is to be sharply distinguished from the squamous-cell epitheliomata of the cervix not only through its histological characters, but

through its original site, its mode and rate of growth, and its much slighter malignancy.

Adenocarcinomata in general, similar in character to these, develop in many other places, and mention may be made of the kidney, breast, ovary, and thyroid as points of origin.

**Adenocarcinomata of the ovary** are quite common, and assume many puzzling forms, sometimes appearing as solid tumors which may occupy



Fig. 660.—Adenocarcinoma of ovary. There are numerous mitoses in the epithelial cells and many multinucleated cells.

both ovaries, and metastasizing widely into distant organs. The gland-like spaces in such a tumor are lined with cells which are very unlike the epithelial cells derived from the skin or mucous surfaces (Fig. 660). In other cases the tumor develops in a cystadenoma of the ovary and causes great thickening of the wall of one or more of the cysts. These tumors are frequently colloid cancers, and even in their distant metastases maintain the power of forming blue-staining colloid material (Fig. 661). In one which we studied there was a huge cyst with thick walls which, on section, showed a sticky, gelatinous material in the substance of the walls. Metastases in the abdominal and retroperitoneal

lymph-glands showed the tumor to be composed of small cysts lined with cylindrical epithelium, which was frequently thrown up into folds. The content of these cysts was, however, not like the colloidal material mentioned above, but resembled the pseudomucinous content of some adenocystomata.



Fig. 661.—Metastasis in lymph-gland from colloid carcinoma of ovary. Many of the epithelial cells are seen to be isolated in the colloid material.

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## CHAPTER LXX

### CARCINOMATA (Continued)

*Gland-cell carcinomata. Carcinoma of the breast. Carcinoma of the ovary, of thyroid. Primary carcinoma of liver with cirrhosis. Ovarian tumors with endocrine character. Dysgerminoma, Brenner tumor, granulosa-cell tumor, arrhenoblastoma. Chorionic tumors. Hydatidiform mole. Chorionic epithelioma. Histogenesis, relation to corpus luteum.*

#### GLAND-CELL CARCINOMATA

THERE is probably little justification for the separation of cancers derived from the cuboidal or polygonal cells of the solid glands from the others which have just been described, because the division is made on a purely morphological basis, and it is not always easy to distinguish them in this way. Nevertheless, the division is convenient and serves a useful purpose. Such tumors are extremely common in the breast. Elsewhere they play a less important part, but they are to be found in the thyroid, the liver, the ovary, the prostate, and in some other glands.

**The Carcinomata of the Breast.**—There is so great a variety of these tumors that the experience of any one is scarcely sufficient to cover the whole range. They are extremely common and fatal in their effects, and the efforts to extirpate them completely and to understand and frustrate their extension affords much work to the surgeon. It is difficult to make any short classification, but there may be distinguished the following:

1. **Tumors of stratified epithelium**, which are either those beginning in an eczema-like alteration of the nipple and adjacent skin (Paget's disease), or those which arise in the substance of the breast and are, nevertheless, composed of squamous epithelium (Troell and others).

2. **Tumors Derived from the Cells of the Acini of the Gland.**—These may be made up of abundant ramifying masses of cuboidal cells, with relatively little stroma, so that great, soft, cellular masses are formed (medullary cancer), or there may be less abundant cell strands, with a relatively greater amount of stroma, so that the tumor area is composed of firm whitish tissue, or finally the epithelial structures may be greatly reduced, so that only small groups and thin strands of cells are formed, embedded in a dense, scar-like mass of fibrous tissue (scirrhoucancer).

3. **Tumors Derived from the Ducts and Their Branches.**—These approach more nearly the cylindrical-cell cancer, and are often in the form of tumor masses made up largely of tubular epithelial structures. There are usually cysts associated with this form, and these may have a thick lining of several layers of cells. There is another type, of relatively benign character, in which every section shows canals or cavities lined with a thick layer of many rows of irregular cells. These have been called adenocarcinomata by Halsted, and have also been referred to as comedo cancers, on account of the fact that cells can be squeezed out like the material from a comedo or blackhead in the skin.

4. **Colloid Tumors.**—Tumors derived from the epithelium of the acini, but presenting an extraordinary colloid or gelatinous metamorphosis of the stroma.

Of these, the most important by far are those derived from the cells of the acini. The tumor appears as a hard nodule in the substance of the breast, and later often forms adhesions with the skin or causes a retraction of the nipple (Fig. 662). The extension to the skin may be followed by ulceration. A wealth of detail has been worked out by surgeons as to the mode of growth and extension, and an interesting series of observations has been made upon the more local spread by Handley. As described by Borrman, in the spread of carcinoma of the stomach through the stomach-wall, there is in the breast a radiating growth of the carcinoma in the lymphatic plexus which extends outward in connection with the deep fascia. The lymphatic channels distended with



Fig. 662.—Carcinoma of the breast showing retraction of the nipple and limited invasion of the fat.

tumor-cells become obliterated and disappear as the tumor growth passes outward, so that it is only in a zone, like the spread of a ringworm, that one finds these lymphatics actually filled with the tumor-cells. New nodules spring up into the skin from various points in their course, but by that time the channels much farther out are filled. In rare cases the skin of the whole chest wall may be involved in a layer of cancer growth which ulcerates at many points (*cancer en cuirasse*). Handley's ideas as to the further spread into lymph-glands and distant organs are not so convincing.

It is known that in nearly every case metastatic nodules are formed in the axillary lymph-glands, and that somewhat later the subclavicular and cervical glands may be involved. Deep invasion through the pectoral muscles and extension along fasciæ at that plane are common, and one not infrequently traces extension through the intercostal muscles to the pleura and finally to the lung.

While extension thus occurs by way of direct growth through connec-

tive-tissue spaces and along fasciae, as well as by continuous growth in the lymphatics or the transportation of isolated groups of cells in the lymph-stream to the axillary glands, there is also the possibility that further dissemination may occur by way of the blood-stream, and the metastases in the liver, bones, ovaries, and other distant organs seem explicable only on this basis. Handley's statement that emboli of tumor-cells in the blood-vessels are destroyed by the formation of a thrombus may be true for the majority of tumor-cell emboli, but I think we have good evidence that it is not true for all, and that it is probably no such mechanical influence which destroys any of them. Out of great numbers



Fig. 663.—Carcinoma of the breast metastasizing into the pleura and thence through all the lymphatic channels into the lung.

of such emboli, it seems that almost all persist, but a few only take root and grow, producing the distant metastases.

Microscopically, these tumors are found to resemble rather closely in their general arrangement the softer forms of epithelioma, since they are composed of ramifying solid strands of epithelial cells which push their way into the crevices of the stroma. Their appearance is seen in Figs. 664, 665, 666. The striking feature in all is, of course, the unbridled growth of the cells, which is so energetic that no basement membrane can restrain them and they penetrate along the lines of least resistance everywhere.

An interesting point lies in their relation to the adenomata of the breast and to the so-called cystic mastitis of old people. It is not uncommon to find in sections of a breast tumor taken for diagnosis that the tissue has almost everywhere the appearance of a typical benign adenomatous growth. Indeed, it is surprising to learn how frequently those specimens which offer any difficulty in diagnosis are of this character. It is necessary then to determine whether in all places the epithelial strands and tubules maintain strictly their orderly form and their



Fig. 664.—Medullary cancer of the breast with necrosis in some of the epithelial strands.

sharp outline which is produced by the basement membrane. In true innocent adenomata this basement membrane is often exaggerated, so that it appears as a broad, pink-staining hyaline membrane, which, of course, leaves no doubt as to the benign nature of that particular area of the growth. With the beginning of a cancerous growth, which one may often detect in very early stages, the cells evidently grow so rapidly as to burst through this membrane and spread rapidly without it. Their contact with the connective tissue immediately becomes far more in-

timate, and they are found lying loose, strewn in continuous or broken strands through the spaces in the stroma (Fig. 667). This seems to be the crucial test of carcinoma growth, for while the cells do assume an appearance different from that of the normal, it is not a change definite enough to afford any chance for a decision as to the carcinomatous nature of the tumor.

In such cases it seems necessary to conclude that the carcinoma has developed from an adenoma, but there is no more difficulty in this as-



Fig. 665.—Carcinoma of the breast showing area of hyaline degeneration with advancing strands of epithelial cells.

sumption than in the more usual one that it develops from the normal epithelium of the gland.

Carcinoma growth seems especially common as a sequel of the senile hyperplasia with cyst formation, which is often referred to as *chronic cystic mastitis*. This condition comes on with the menopause or later, and leads to the formation of rather dense fibrous tissue throughout the gland, with hypertrophy of the acinous tissue into adenomatous structures, often with the formation of many cysts. It is not thought to be

due to any infectious or traumatic injury, and the scarring is really a normal process at the time of menopause, but the formation of cysts, adenomata, and papillomatous growths must be considered as abnormal.

The *scirrhus* tumors, the arrangement of which is shown in Fig. 668, grow and metastasize much more slowly than do the softer forms, so that such a tumor may exist for many years without producing a fatal extension. Nevertheless Bloodgood finds, by statistical study of the hos-



Fig. 666.—Carcinoma of breast. The epithelial cells are growing almost in single file into every crevice of the stroma.

pital cases, that these are the most tenacious, and finally lead to the most unfavorable results.

The *adenocarcinomata* derived from the ducts or from adenomatous nodules are, in some instances, as in the form described by Halsted, relatively benign. In one case such a tumor was extirpated from each breast of an old woman who has survived many years without lymph-node metastases or local recurrence.

In other cases, however, there may be found a very large tumor mass composed chiefly of cysts filled with glairy fluid, and lined with high columnar or cubical epithelium. Between these are dense adenomatous masses. From the walls of such cysts an invasion may take its origin.

The *colloid* tumors are uncommon, but Lange collected 75 cases, and from their study learned that metastases were rare, and that the tumors grow very slowly and are relatively benign (Fig. 669).

**Carcinomata of the ovary** may be primary or secondary. Although tumors distinctly secondary to mammary, gastric, or intestinal carcinomata have been found in this organ, their occurrence is rare and most of the ovarian cancers are primary. It is difficult to explain why they so frequently occur simultaneously in both ovaries. They are solid

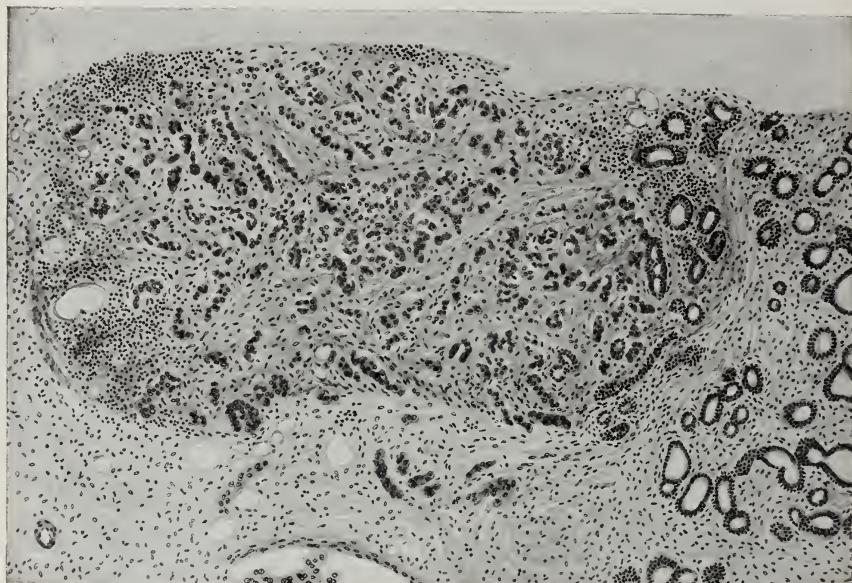


Fig. 667.—Development of a carcinomatous nodule in an adenofibroma of the breast.  
The invasive character of the carcinoma cells is apparent.

tumors, tumors combined with cystomata, or papillomatous growths, and almost every type of cancer observed elsewhere seems to be represented here. When the carcinoma is cystic or develops in connection with a small cyst, it may be surmised that the tumor began as a carcinoma. When, however, the malignant growth appears in the wall of a large cystadenoma of long standing, it must be supposed that its relation to the cystadenoma is analogous to that of the carcinoma of the breast to the adenoma within which it develops.

Metastases (Fig. 670) vary with the character of the tumor, and may be confined to intraperitoneal implantations in the papillary forms. In one which we studied both ovaries were replaced by cysts of about orange size, in the walls of which there were thick, yellow masses of

solid tumor. There were metastases in the liver, and especially interesting was a continuous chain of white nodules along the round ligament extending into the substance of the liver. It is possible that further study may reveal an unusual method of invasion of the liver by extension along the lymphatics of that cord. Handley discusses a similar occurrence in connection with mammary carcinomata.



Fig. 668.—Scirrhouous cancer of the breast. The epithelial cells are greatly reduced in number and scattered in an extremely dense hyaline stroma. The blood vessels show thick hyaline walls.

The carcinomata of the ovaries, like the cystadenomata, are evidently derived from invaginations of the surface epithelium, although many other hypotheses have been offered as to their source. There seems to be no good evidence that they arise from the Pflüger cords or from Graafian follicles.

Krukenberg, who worked under Marchand, described in 1896 a peculiar bilateral tumor of the ovary of slow growth and occurring in

old and young. This tumor, which he called fibrosarcoma ovarii mucocellulare, or fibrosarcoma carcinomatodes, is made up of spindle-cells with many large swollen cells each with a globule of colloid or gelatinous fluid. Marchand felt that they were primary in the ovary, but many such cases have been described since, and the great frequency with which they are associated with a cancer of the stomach or other part of the gastro-intestinal tract has led Major and others to regard them as defi-



Fig. 669.—Colloid carcinoma of the breast. The colloid appears to be developed in the stroma in which the epithelial cells are isolated.

nitely carcinomatous and secondary to the carcinoma of the stomach or of some other portion of the digestive tract.

**Carcinomata of the Thyroid.**—These tumors have been studied especially by v. Eiselsberg, Kocher, and Langhans, who find that they can distinguish several groups, among which a form of adenocarcinoma or proliferating struma is especially common. These occur as single nodules containing every transition between solid strands of cells and colloid-containing alveoli, closely resembling those of the normal gland. They

are not very malignant, but occasionally metastasize in distant organs or bones. The second group, called by Langhans *carcinomatous struma*, has the arrangement in irregular solid strands of epithelial cells seen in many carcinomata of the breast. These quickly burst through the capsule of the gland and metastasize abundantly. *Metastasizing colloid struma* forms the third group, with numerous secondary nodules, composed of colloid-holding vesicles in which no striking morphological signs of its malignancy are to be seen. The tumors of the fourth group, named

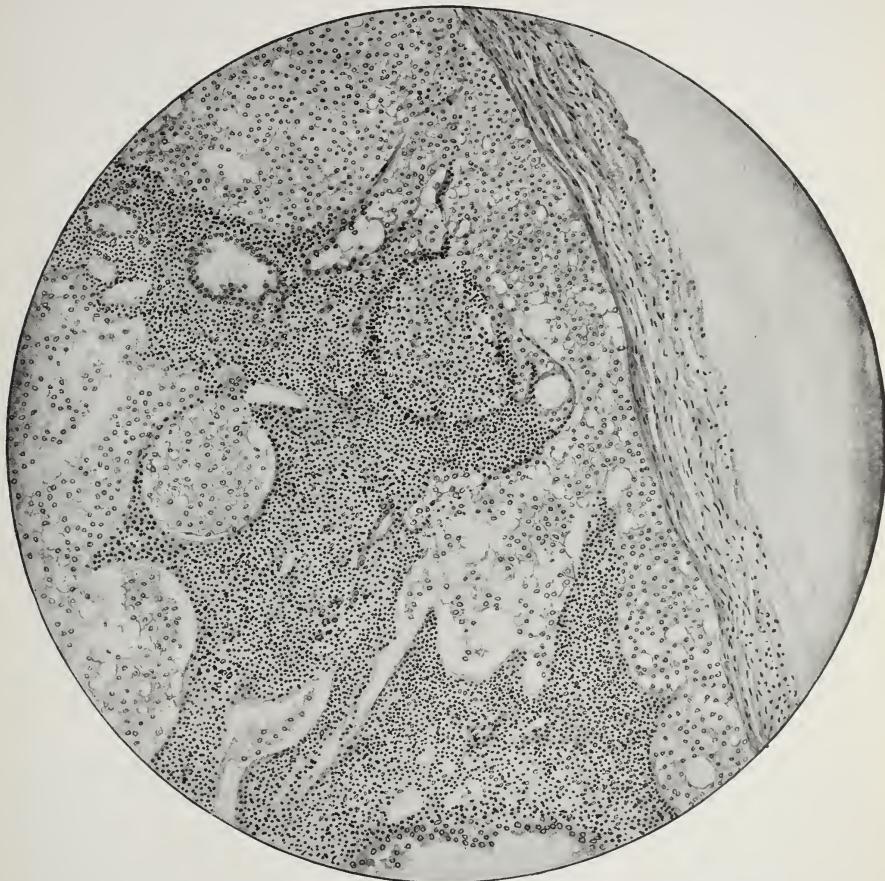


Fig. 670.—Metastasis from carcinoma of the ovary in an axillary lymph-gland. The lymph-sinuses are filled with epithelial cells.

*alveolar large-cell struma*, are also malignant, and give rise to numerous metastases. They are composed of large cuboidal or cylindrical cells, arranged in small alveoli or in tubular or strand-like structures. The cells in these tumors are occasionally very large, with deeply stained nuclei. The other groups comprise the papillomatous tumors of the thyroid, in which branching processes grow into cysts or cavities in the subthyroid, and squamous-cell epithelioma, which may occur in the sub-

stance of the gland and must be ascribed to a congenital displacement of cells.

**Primary Carcinoma of the Liver.**—Reference has already been made to the cylindrical-cell cancers of the liver which originate in the epithelium of the bile-ducts, and appear as solid white masses in the substance of the organ. There is another type quite different from this which is so characteristic and constant in form that, once seen, it can never be forgotten or mistaken for any other tumor. This is the primary cancer which originates from the liver-cells themselves, and occurs in multiple nodules closely set throughout the whole liver. The remainder of the liver is very often in a state of extreme cirrhosis (Fig. 672), but this is by no means always the case, and that illustrated in Fig. 671 showed no cirrhosis whatever. The liver is greatly enlarged, as a rule, by the pres-



Fig. 671.—Primary carcinoma of liver without cirrhosis. There is invasion of the large veins.

ence of dark green or grayish, rounded nodules which project everywhere. On section nearly the whole cut surface is occupied by these velvety green or grayish-red, rounded masses which stand up from the remaining liver substance. There is often deep jaundice, generally ascites, and sometimes a terminal haemorrhage from the rupture of some softened nodule which projects into the peritoneal cavity.

Metastases are often quite lacking, but of the nine cases that we have seen, six showed secondary growths involving especially the lymph-nodes and lungs, although the bones and peritoneal surfaces were also affected in two. The tumor tends especially to grow into the portal and hepatic veins, where it hangs in thready tassels closely packed together, but liable to dislodgment, so that we have in two cases found the small twigs of the pulmonary artery packed with emboli of such strands.

Microscopically it is found that these nodules are fairly sharply outlined against the surrounding liver tissue, although in some places the delimitation is due mainly to the different size and staining of the cells. They are composed of anastomosing strands of large cells almost identical with liver-cells, although more irregular and staining more deeply. These are separated like the liver-cells by endothelium-lined blood-channels, although often there are several rows of tumor-cells between two blood-spaces. Indeed, in many of the nodules it seems that strands of tumor-cells covered with endothelium are packed together in the lumen of a vein, all of which, taken together in cross-section, looks like a tumor nodule, and this seems to be the general character of the gross invasions of the portal and hepatic veins. In one case (Fig. 671) there are thousands of discrete spherical nodules of very small size as well as large masses, and these minute nodules show in their periphery cells like



Fig. 672.—Primary carcinoma of the liver with cirrhosis. There are multiple nodules and the portal vein with its branches is filled with the tumor.

the liver-cells, although larger; toward the centre these gradually change into tubular structures like bile-ducts filled with bile-pigment. The reconstruction of such nodules from serial sections should be interesting, and it is already clear that the tumor nodules produce bile.

The intimate relation of tumor-cells with liver-cells and the numerous places in which there are insensible transitions from one to the other make it seem unquestionable that the tumor is derived directly from the liver-cells. Whether it is of multicentric origin has long been discussed, and most writers think it is, although Winternitz had the idea that a primary nodule invading the portal vein produced multiple metastases in the liver. The extrahepatic metastases are of similar character, although in the cases we have seen they have been white or pale yellow and apparently had no bile-forming powers.

The remainder of the liver may be merely compressed, but it has long

been looked upon as quite characteristic that it should be extremely scarred. Indeed, in our earlier cases (Travis, Fabyan) we leaned to the idea that the origin of the tumor must be from those enlarged nodules of liver tissue which arise in the course of compensatory hyperplasia in cirrhosis of the liver. McIndoe and Counseller describe a case of extremely advanced cirrhosis in which at autopsy two small carcinomatous nodules were found in the right and left lobes with no evidence of a common embolic origin. They must have arisen independently.

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#### OVARIAN TUMORS

Several peculiar tumors occur in the ovary and exhibit, in the case of two at least, remarkable hormonal influences. Of these, the simplest seem to be the disgerminoma and the Brenner's tumor, while those affecting the sexual characteristics of the woman are the granulosa-cell tumor and the arrhenoblastoma.

**Disgerminoma.**—The disgerminoma of R. Meyer is thought to be derived from primitive germ-cells before their differentiation, which have lost their functional power as sex-cells and multiply into a tumor of large size which produces no disturbance except by its bulk. It is composed of large cells accompanied often by lymphoid cells and differs from a very similar tumor which may occur in the testis through the absence of the seminiferous tubules which in the male may be invaded by the tumor. It occurs generally in young women.

**Brenner's Tumor.**—The Brenner tumors occur in the ovary of rather older women and never in children. They are solid or form part of a cyst-wall and are composed of dense fibrous tissue in which are strands and masses of rather squamous-looking epithelium which, however, in places have a lumen containing a mucoid material and lined by a layer of more columnar cells. These, too, have no disturbing influence on the sexual characteristics.

**Granulosa-cell Tumor.**—The granulosa-cell tumors, also described by Meyer, are thought to be derived from isolated masses of granulosa cells,

quite independent of the follicles, which are occasionally to be seen in the more central parts of the normal ovary. The tumors grow to a considerable size and show histologically a variety of forms, among which the

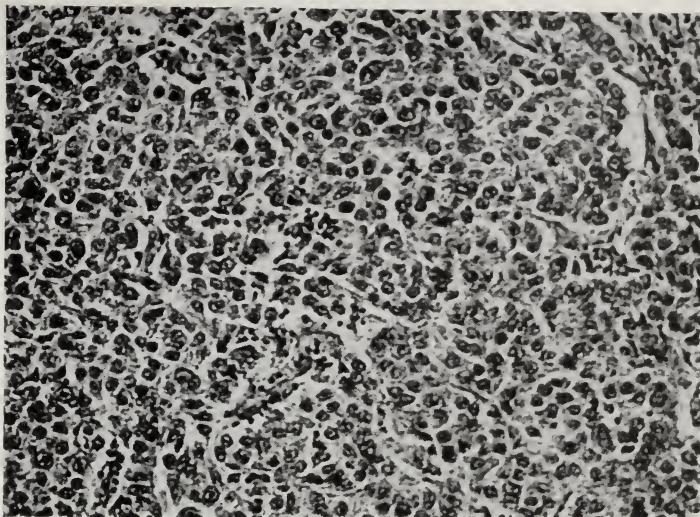


Fig. 673.—Disgerminoma.

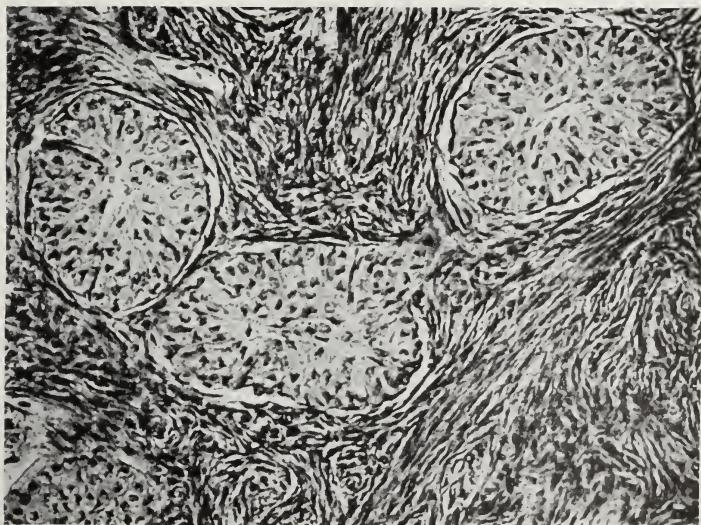


Fig. 674.—Brenner's tumor of ovary.

approach to a follicular or cystic type is rare, while most common is the solid sarcoma-like mass, often with areas of hyaline degeneration. They are generally well supplied with capillaries about which the cells are in some places radially arranged.

Most interesting is the effect produced by their presence. In young children of six or seven years all the evidences of sexual maturity appear with menstruation, growth of the breasts, even with colostrum production, and abundant growth of hair. In old women far past the climacterium there may be a sort of rejuvenation with return of the menses. It seems that the tumor produces folliculin or theelin and in the old women there is hyperplasia of the endometrium as in normal menstruation.

Benda and Kraus described one in which the granulosa cells were luteinized, with amenorrhœa. Removal of the tumor causes the disappearance of these symptoms—the child goes back to childhood and begins again in a normal development.

The fourth type is the *arrhenoblastoma* in which the tissue assumes sometimes a tubular arrangement, more often a strand-like grouping of

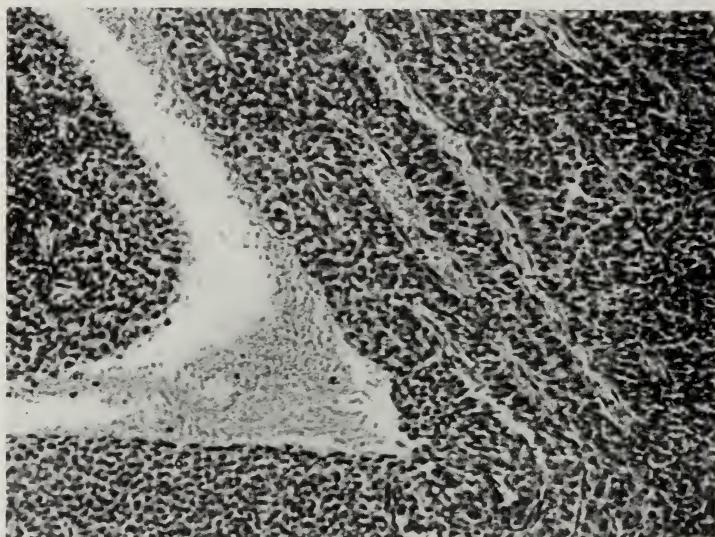


Fig. 675.—Granulosa-cell tumor.

the cells, generally with an admixture in places of some rather larger cells with abundant granular, slightly eosinophile cytoplasm which seem analogous with the Leydig cells of the testes. The diffuse strand-like arrangement is most powerful in producing the extraordinary masculinization of the woman. The hair falls out, the subcutaneous fat distribution of female type is lost, there is atrophy of the breasts and uterus with amenorrhœa. At the same time there appear distinctly masculine characters, such as growth of a beard, enlargement of the clitoris, and a deep-toned voice. But when the tumor is extirpated, the woman returns to normal and may even become pregnant again, but later, if there is a recurrence, the whole picture of masculine alteration recurs. Meyer points out the occurrence in the hilum of the ovary of undifferentiated tissue which later produces the rete ovarii, and medullary cords which

are homologues of the rete testis and tubuli recti of the male. The tubular forms of the arrhenoblastoma are thought by Kleine to arise from the rete which is the remnant of a duct of the ovary, the more solid forms

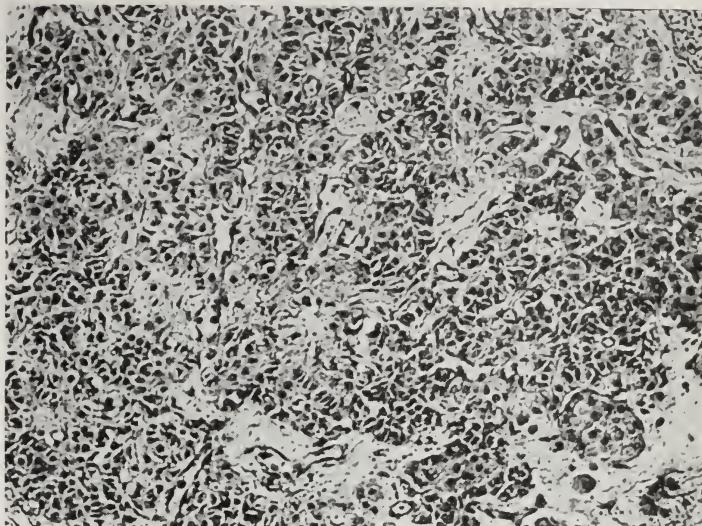


Fig. 676.—Arrhenoblastoma showing larger granular cells in groups.

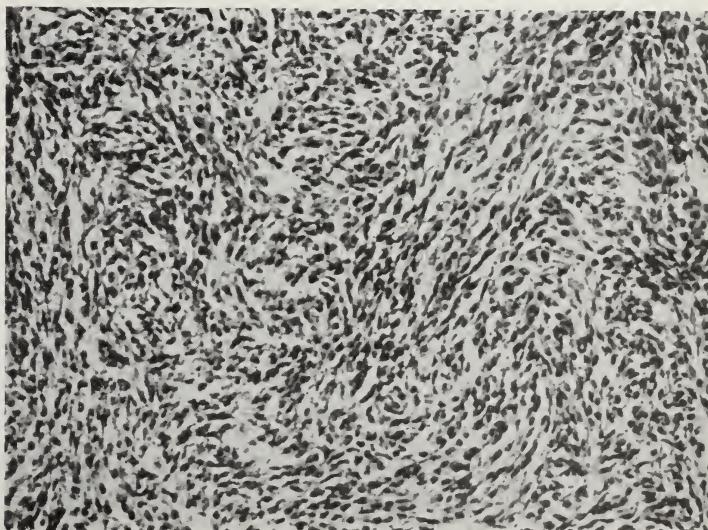


Fig. 677.—Arrhenoblastoma, diffuse spindle-cell type.

from the medullary cords. The associated interstitial cells are thought to be analogous with the Leydig cells. None of these have to do with spermatogenesis and there is no relation with hermaphroditism but it is

strongly suggested that while the granulosa cells and ova are closely related to sex hormones in the woman, the Leydig cells are essential in man although this is opposed by others.

Studies of the hormone production are as yet incomplete. The arrhenoblastoma contains no oestrin, and nothing suggesting an inhibiting substance affecting the ovary has been found in the blood. The condition of the hypophysis remains to be studied. It must be remembered that many instances are recorded in which tumors of the adrenal cortex produce the same general type of masculinization, reversed by their surgical removal. Something resembling androsterone must be sought for in all these cases.

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#### CHORIONIC EPITHELIOMATA

In the study of the formation of the placenta there has never been complete unanimity of opinion as to the origin of the syncytial layer which covers the chorionic villi. The other cells which cover these villi and which are arranged in a more sharply defined layer (Langhans' cell layer) are universally recognized as the foetal ectoderm, but for the syncytium at least three ideas have been expressed: (a) That it is derived from the maternal uterine epithelium; (b) that it is a modification of maternal endothelium, and (c) that it belongs, like the Langhans layer, to the foetal ectoderm. The weight of evidence seems to be in favor of the last view.

During pregnancy there is normally a curious invasive growth of the chorionic villi into the uterine wall, and it is by no means uncommon to find masses of syncytium-like giant-cells, with many nuclei lodged in the interstices of the muscle, quite deep down in the uterine wall. Indeed, such masses have been found to invade blood-vessels and to be carried as emboli into distant organs. Nevertheless, this invasive growth ends harmlessly, and the cells presently disappear from the tissue as though the body had some mechanism for destroying them when pregnancy is over.

Two curious abnormal conditions may arise during pregnancy which bring about a result quite different from the usual normal ending. One of these is the development of the hydatidiform mole, the other the growth and metastases of the chorionic epithelioma. In the case of the *hydatidiform mole* it is found that, when pregnancy approaches its termination, there may be expelled from the uterus, not a child with the cord and placenta, but a great mass of polypoid, gelatinous structures, which hang together like a huge bunch of grapes (Fig. 678). There may be no foetus at all, or the shrunken remnants of one, and the placenta is converted into the villous mole, which receives its name from its re-

semblance to the clusters of hydatids or cysts of the *tænia* larvæ which are sometimes seen. (Mole is used here in the old sense—mass.) Microscopically, these polypoid blebs are swollen chorionic villi enormously enlarged and covered with greatly proliferated epithelium. It is rare to see such a mass *in situ*, but in the uterus removed after the expulsion of the mole it is found that the villi grow into the uterine musculature and sometimes give rise to malignant, tumor-like extension and metastasis. Nevertheless, such invasive growth is by no means constant, and the woman may recover her health perfectly and even give birth to a second or third hydatidiform mole.

This has intimate relations, as will be seen, with the *chorionic epithelioma*. The pregnancy may be interrupted by the development of a



Fig. 678.—Hydatidiform mole.

haemorrhagic tumor in the uterine wall, or after pregnancy is over such a tumor may develop even several months later. Curettings have the appearance of placental tissue, except that the cells are more profuse in these growths and are much better preserved than those found in curetted remnants of retained placenta. Still, it is only through determining the relation of the tissue to the uterine muscle, together with the alarming clinical symptoms of haemorrhage, that a diagnosis can be made with any certainty. Frequently there is found a conspicuous haemorrhagic tumor in the vaginal wall which will make the diagnosis clear.

With such partial removal of the tumor as is possible by curettage complete recovery occurs in some cases, and all traces of tumor growth disappear. In other cases the patient coughs up blood and bleeds from the uterus, and at the autopsy there is found a tumor invading the uterine

wall and growing in metastatic nodules in the lungs, liver, brain, and elsewhere. The tumor in the uterine wall is a soft, ragged, intensely haemorrhagic mass, variegated in color by gray or whitish areas, and by brownish patches in which the blood has undergone decomposition, with the formation of pigment. The metastases in the lungs are often round nodules, of about the size of a cherry, scattered abundantly through the organ. They, too, are deep red from haemorrhage. There may be large, more ragged, and pigmented masses. In the brain the metastatic tumor may produce apoplectiform symptoms from haemorrhage and compression.

Microscopically, these tumors are found to be made up almost entirely of broad, irregular, and ragged anastomosing strands of the two types of chorionic epithelium, in which the Langhans cells can be readily



Fig. 679.—Chorio-epithelioma with metastases in the lungs.

distinguished by their smaller and more regular form, with pale or almost clear protoplasm, and fairly sharp cell outline, while the syncytial material spreads over them or forms solid areas of protoplasm which stains much more deeply, and in which numerous nuclei, often of great size, are embedded. The stroma and blood-vessels are inconspicuous or entirely lacking, since the tumor seems to grow into blood-channels, and everywhere the tissue is torn and disarranged by extensive haemorrhages (Fig. 680).

It was thought for a long time that these tumors were of sarcomatous or endothelial nature, and that they had preceded pregnancy and were stimulated by it to more rapid growth. It was thought by others that they were derived from the decidua, and they were, therefore, spoken of

as malignant deciduomata, but the work of Marchand cleared up the whole situation by showing clearly that none of these theories had any foundation, and that the tumor originates in the chorionic epithelium or foetal ectoderm of the placenta, and that both layers of this epithelium are involved.

The tumors are especially interesting from the fact that a somewhat analogous growth and invasion of the chorionic epithelium occurs normally, and that an exaggeration of the development of the villi, often ending in the formation of a malignant tumor, is found in the hydatidi-

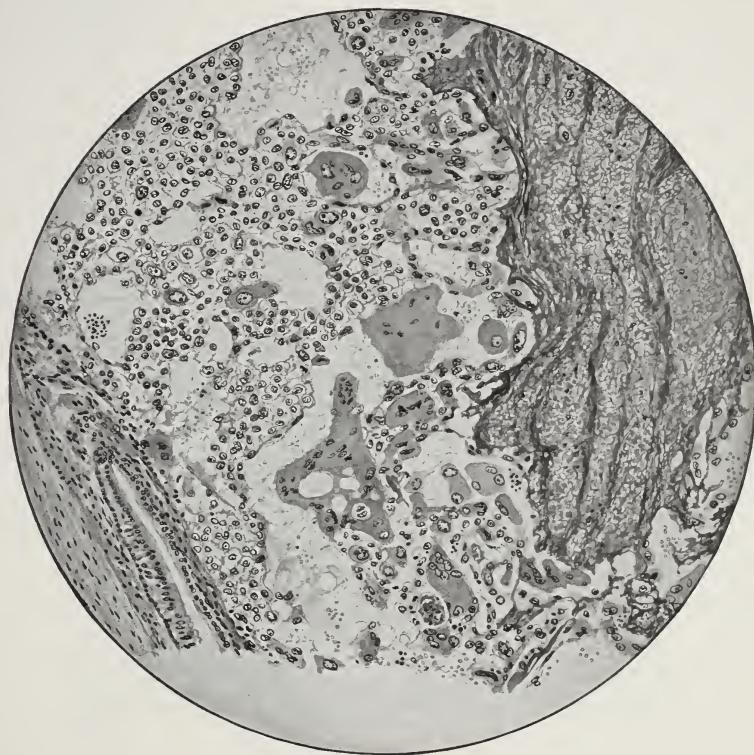


Fig. 680.—Chorionic epithelioma, metastatic nodule in the lung, showing Langhans' cells and syncytium.

form mole. The fact that definite chorionic epitheliomata seem to regress sometimes and disappear completely is also peculiar, and has led to speculation (Fleischmann) as to whether there is some substance formed in the maternal blood at the end of pregnancy, which, like the experimentally produced syncytolysin of Scholten and Veit, has the function of destroying the syncytial elements which remain buried in the uterine wall or lodged in distant organs. The failure of this substance might allow the unchecked development of the tissue into a destructive tumor, while its late formation might account for the disappearance of the tumor.

On the other hand, it is found that in a large proportion of cases the

development of a hydatidiform mole or a chorionic epithelioma is accompanied by a peculiar enlargement of the ovaries, sometimes to the size of a large grape-fruit. This is due to the formation of numerous cysts, most of which are, like the cysts derived from corpora lutea, lined with several layers of yellow lutein cells. The well-known theory of Fraenkel and Born, according to which the corpus luteum is an organ of internal secretion controlling and forwarding the embedding of the ovum and the development of the placenta, is brought into play by Runge, Pick, and others as a ready explanation of this association. If there is a great overgrowth and excessive activity of the corpus luteum tissue, it may produce excessive growth of the chorionic villi over which its secretion is supposed to preside. Dunger reverses the idea and suggests that the excessive growth of the chorion requires the development of additional corpus luteum tissue. L. Loeb finds that irritation and injury of the mucosa of the uterus in guinea-pigs after coitus will, under certain conditions, produce very large growths of tissue, which he calls placentomata. In his papers he emphasizes the alteration in environmental conditions of the mucosa, and recognizes in these and other papers the importance of the influence of the corpora lutea.

The matter requires further study, and it seems to offer an extremely interesting border-line condition the comprehension of which might throw much light upon tumor growth in general.

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## CHAPTER LXXI

### CONGENITAL MALFORMATIONS

*General character: Repetition of typical forms. Defective embryonic development in localized areas of the body. Medullary groove, face, genito-urinary apparatus, etc. Double monsters. Twins.*

AT this point it may be well to diverge for a brief interval from our discussion of tumors to review in outline the malformations of the body which have from the earliest ages profoundly impressed mankind, and have led to all sorts of myths and superstitions. Anyone will, even from such names as Cyclops, Siren, Janus, etc., realize that the ancients must have seen the actual types of malformation to have composed such dramatic figures. But they exaggerated and elaborated upon what they had really seen and gave their monsters wings and tails and horns, or even told of centaurs which have no place in our list of malformations.



Fig. 681.—Craniorachischisis.



Fig. 682.—Anencephaly.

Harvey was the first to realize that such malformations were due to abnormal development of the embryo. But even yet although many abnormalities resembling those which occur typically have been produced experimentally in accessible embryos, the mechanism by which they originate in utero is not quite clear. Only the slightest reference can be made here to the various forms which occur with such accurate reproduction of type that in any museum or atlas one may at once recognize the familiar forms. It seems, therefore, that for each type the mechanism of production must be a special one and interfere at the same stage with the normal course of development. The explanation in each case must depend upon an understanding of the normal course which has been perverted.

Those which are most frequently seen at autopsy are the malformations of the heart of which some outline was given in an earlier chapter.

The nervous system shows the results of interference with the proper closure of the original medullary groove which may result in anencephaly in which there is no brain. No cranium is formed but the skin with a fringe of hair passes over into a soft moist layer of thin sheets of tissue spread in wrinkles over the floor of the skull. The face is frog-like and the head sharply bent back by an angular deformity of the cervical spine. The same remaining open of the medullary groove may extend down the spine, "rachischisis," or when both brain and spinal cord are involved, craniorachischisis. This may involve only the lower part of the cord and at any point there may be a sacular bulging varying in its com-



Fig. 683.

Fig. 684.

Fig. 683.—Sympodia (Siren).

Fig. 684.—Diprosopus tetrostus with anencephaly.

position—myelocele or meningomyelocele or meningocele, as the case may be—commonly called a *spina bifida*.

The closure of the embryonic clefts in the formation of the face may be imperfect and leave a harelip or cleft palate, or if more extreme, the eyes may slip down into the middle of the face and the processes which should form the nose be moved up so that we have the cyclops with fused eyes in the midline and the rudimentary nose in the middle of the forehead (Fig. 686).

And so on with other organs and the extremities. It is important to remember in observing club-feet or extra fingers, or the various anomalies of the genito-urinary apparatus, that the normal development has been disturbed at some point in a way that is followed by a typical

abnormal continuation of the embryonic growth so that the malformations at least repeat certain familiar types.

More interesting at this point, in their relation to the formation of certain tumors, are the double monsters. These are variously explained but the most acceptable idea seems to be that after fertilization of the ovum and the first segmentation, the two segmentation spheres may be separated and each develop into a complete individual—these are the identical or single ovum twins. But the separation may be incomplete in varying degrees, leaving the two segmentation spheres connected in different ways and at different points. It is perhaps even possible that the partial separation might take place at the next division so that the portions would be unequal. With birth, after this associated development is finished, we may have such relatively complete individuals as the Siamese twins or they may be united at other points. The com-



Fig. 685.—Cephalothoracopagus janiceps. The face is a composite of right and left halves belonging to different bodies—on the other side a less perfect face similarly formed.

monest is the thoracopagus, where the liver usually extends across the bridge between the two, but they may be united by the sacral regions (pygopagus) or the pelvic regions laterally (ischiopagus), or even at the tops of their heads (craniopagus). Commonly the fusion is much more intimate and there may be four arms and four legs and two heads from what appears to be one body, or there are two heads on one body or two heads fused so that two faces look in different ways (Janiceps). When they are still more unequal one of the twins may be partly buried in the body of the other as in the cases where two legs project from the front of the chest, or even more strikingly when a deformed mass representing the twin projects from the mouth (epignathus). Finally, the less developed twin may be completely enclosed within the body of the other and then it is looked upon as a teratoma. This may happen at almost any point but is most common perhaps in the abdomen in relation with the

sacrum, although we have recently seen a good example in the pleural cavity, crowding the heart and lungs of the grown individual who bore it. This was a mass covered with skin with hair and sebaceous and sweat glands, the interior containing bone, pancreas, brain tissue and lung, awkwardly mingled.

It is important to realize that such masses of which more will be said, are twin brothers, that is of the same generation while other complex tumors which contain several tissues and which develop in the generative

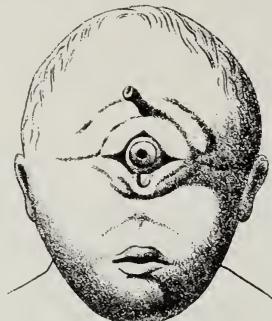


Fig. 686.—Cyclops. From Ahlfeld's *Atlas der Missbildungen*.

organs, sometimes with associated placental tissue (chorionic epithelium), are really in a sense offspring and belong to the next generation.

The student should look through the following works at least and form some idea of the manifold appearances of these extraordinary malformations.

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## CHAPTER LXXII

### TERATOMATA; COMPOSITE TUMORS

*Chorionic epithelium in tumors of the male, and in female apart from pregnancy. Teratomata, their composition. Theories of origin; inclusion of blastomere, parthenogenetic development of sex-cell. Experimental production of teratomata by auto-implantation of such a cell, character, and maturity of tissues of teratoma, malignant character. Teratomata of testis. Dermoid cysts. Mixed tumors of salivaries.*

In the last pages there has been given a description of the hydatidiform mole and of the chorionic epithelioma which may develop in connection with pregnancy, and it was pointed out that these are tumors of a more suggestively parasitic nature than the others which have been considered in previous chapters, since they are composed of the tissue of a different individual. This is not enough to shake our faith in the belief that the ordinary tumors are composed of the tissue of the same individual, but at least it causes us to reflect upon this question.

The existence of tumors morphologically identical with the chorionic epithelioma of women, but growing in the testicle of men, is especially calculated to rouse our interest in this question. These tumors belong to the composite type called teratomata, which contain tissue of many sorts, representing all of the three germinal layers, and give rise to metastases which are composed of Langhans' cells and syncytium. Chorionic epithelium occurs also in the tumors themselves, and may, indeed, be the only tissue found, in which case it is thought that the other types have been overgrown and obliterated by it. Scott and Longcope described a tumor of the testicle composed entirely of chorionic epithelium, and Frank had a similar case, but most of these tumors have contained a mixture of other tissues as well, which often resemble distorted organs in such a way as to suggest an abortive attempt at the formation of a foetus.

We have recently seen a beautiful example of this type of tumor in which metastases in the brain, lungs, omentum, and elsewhere had all the characteristics of a chorionic epithelioma. The original tumor in the testicle showed, however, cartilage, various gland-like epithelial structures, and other tissues of complex foetal inclusion. Of all the tissues concerned in the abortive growth of an included foetus, only those of the rudimentary chorion metastasized.

Kantrowitz has described a similar case in a male, occurring however in the mediastinum, the testes being quite free of any tumor growth. Chorio-epitheliomatous metastases were present in the lungs and the Aschheim-Zondek test for pregnancy was positive both in the urine and in extracts of the tumor tissue. Frank, in his discussion, points out the value of this test in diagnosis and prognosis, since it may become negative after the removal of the primary tumor and again become positive when metastases appear.

In the ovary, although tumors containing representatives of almost all the tissues of a foetus have been frequent, the literature contains hardly any descriptions of such tumors accompanied by chorionic epithelial growths. Risel accepts only the case of Pick in which an ovarian tumor in a nine-year-old girl was associated with a growth of chorionic epithelium. The others he ascribes to metastasis from an ordinary chorionic epithelioma following a recent pregnancy. The existence of such tumors seems to me most important because it has a bearing upon the whole question of the formation of teratomata.

In the case of the testicular tumor with chorionic epithelium Schlagenhaufer points out the value of the observation in settling the origin of the syncytial layer of the chorion. It must be derived from foetal ectoderm, since in this situation there is no uterine mucosa to give it origin. He regards the tumor as an imperfect foetus which has formed about itself foetal membranes which can invade and metastasize as in the ordinary chorionic epithelioma.

**Teratomata.**—While such foetus-like tumors with chorionic epithelium are rare, there are others in which rudimentary, organ-like masses of tissue are mingled together as though in an unsuccessful attempt to form a foetus, but without any development of chorionic elements. These are the solid *teratomata* or *embryomata* which are not very uncommon, and may occur in the ovary or testicle, or in almost any other situation in the body. They are especially frequently found at the poles of the body, springing from the roof of the mouth or from the sacrum, or, in somewhat different form, in the brain, in the orbit, in the mediastinum, or abdomen. Some of them project outwardly and are covered with skin, even presenting at times a vague resemblance to limbs or other parts of the body; others are completely inclosed within the body cavity, where they may be connected by a stalk with surrounding organs or enveloped in a capsule.

Dissection of such masses shows that they are not like ordinary tumors, inasmuch as they are not merely composed of one type of tissue, but contain representatives of all three germinal layers. There are structures of every degree of complexity, composed of skin and its appendages; malformed teeth are found sometimes in connection with bony structures, sometimes embedded in soft tissues. Misshapen eyes or masses of brain tissue, portions of intestinal mucosa or convoluted canals resembling the intestines alternate with cysts lined with epithelium difficult to recognize, and masses of cartilage or thyroid tissue (Fig. 688). There is no tissue which may not be represented, although liver and pancreas, testicle and ovarian tissue, and chorionic epithelium are usually absent. Ganglion-cells are abundant, as a rule, embedded in connective tissue which may assume almost any form. More detailed description of any one case would hardly repay us, because in the next a different set of tissues might be found. But it is evident that the whole mass represents in some sense a frustrated attempt at the formation of a human body in which the whole plan has failed through the lack of the necessary parts, and the distortion and disarrangement of those which were available. It is obvious that, for an explanation, we must go back to the beginnings of

embryonic development, in the hope that at some point a mechanism may be recognized by which it is possible for one individual or a rudiment of an individual to be enclosed within another.

The most diverse theories have been proposed to explain the potency of the rudiment from which these tumors spring. The fertilized ovum is totipotent; that is, it is capable of giving rise to all the tissues of the body. So, too, are the first segmentation spheres, as is proved by the development of twins from a single ovum. These twins are always of the same sex, and resemble each other very closely—they are more nearly related than other brothers and sisters.

In later stages of segmentation the blastomeres remain multipotent or capable of producing several tissues, but probably not a perfect individual. Still later the destiny of the cells becomes much more rigidly prescribed, and they are limited to the formation of certain tissues. When the germ layers are defined, elements from each of these layers have the power of producing ectoderm, entoderm, or mesodermal structures only, and are even more closely confined, according to their point of origin in the layer.

Nevertheless, it is obvious that there is a chance for the development of a mass of tissue of almost any degree of complexity from a blastomere, if we are willing to assume that it may become independent of the others at an early enough stage in the segmentation. This idea involves the further assumption that this independently growing blastomere may remain attached to the main embryo, or become partly or completely surrounded by it in its growth, so as to be finally included in its body.

This is the very generally accepted theory of Marchand and of Bonnet, although Marchand also suggests that a polar body might be fertilized simultaneously with the ovum and included among the segmenting cells to give rise later to the tumor. For this, however, there is no evidence.

It has been known for some time that in the development of the ovum the process of segmentation leads shortly to the special separation of many germinal or primitive sex-cells which wander from an isolated position in front of the primitive streak into the tissues and finally lodge in the genital organs and become ultimately ova and spermatogonia. Some of these become marooned or caught up in other tissues on the way and never reach the genital glands. If such cells at any stage in their wandering could be fertilized or stirred to development without fertilization, they would offer a satisfactory explanation for the growth of such complicated masses as the teratomata, and especially for those which arise in the testicle and more rarely in the ovary and are accompanied by chorionic villus formation. Such tumors are like a pregnancy and could not be explained as the outgrowth of a somatic blastomere very well, although the others found in the sacrum or in the roof of the mouth or elsewhere could well be so explained. Indeed, it seems to me that there are two very distinct classes of teratoma of which one class appears to spring from the stimulation to development of a primitive sex-cell, the other from the inclusion of a somatic blastomere. These two types, as is

plain, belong to different generations, the first is analogous to an offspring, the second to a twin brother.

The student, if he reads nothing else, should read the masterly paper of Bosaeus on the genesis of ovarian embryomata, in which this whole question is discussed, with historical review and a remarkable series of experiments on the growth of teratomatous tumors from parthenogenetic development of ova transplanted into the tissues. It was discovered by Jacques Loeb that many sorts of chemical and physical injuries of extremely slight intensity will cause unfertilized ova of lower animals and even of frogs to segment and develop. The completely mature frogs developed from parthenogenetic ova have always been a matter of wonder. The corresponding stimulation of a male sex-cell to development into a mature individual (ephebogenesis) has not, as far as I know, been carried out experimentally, but there seems no reason why it should not occur.

Fischel, Askanazy, and others have maintained that such parthenogenetic development of primitive sex-cells, either in the course of their wandering or after reaching the genital gland, might explain the growth of teratomata, and it seems to me that this would particularly well explain the teratomata of the genital glands with chorionic epitheliomatous growth.

It remained for Bosaeus, however, to remove from frog's ovaries the unfertilized ova, prick them with a needle so as to start the parthenogenetic development, and then reimplant them into the *same* frog. Such ova developed into complicated teratomata with all sorts of tissue. If planted in the tissues of another frog than the mother (homotransplantation) the growth is soon destroyed.

This, and perhaps especially the last point concerning dependence upon autotransplantation, seems to be very strong evidence in favor of the possibility of the formation of this type of teratoma from the parthenogenetic or ephebogenetic development of a primitive sex-cell. It is true that these experiments were carried out in frogs, but one can see no reason why they should not apply to man, even though it is always objected that there is no evidence of the existence of parthenogenesis in mammals.

I may quote the last paragraph of Bosaeus' paper:

"In that I caused parthenogenetic frog embryos to develop in the lymph sac, pleuroperitoneal cavity, or ovaries of their own mother's body under conditions which correspond with those surrounding the spontaneous development of teratomata, I have produced tumor masses which have essentially the same structure as the spontaneous adult teratomata or cystic embryomata. Unlike the usual experimental teratoids, these tumors are derived from the tissues of one individual, as is the case with spontaneous teratomata or embryomata, and throughout a period of observation of as much as 475 days they persisted and stirred up no noteworthy inflammatory reaction on the part of the tissue of the mother organism. It seems probable that these formations are essentially equivalent to the spontaneous adult teratomata and cystic embryomata, and the results of my investigations constitute strong evidence for the idea

that the cystic ovarian embryomata of vertebrates arise through parthenogenesis."

To return to the theory of the inclusion of an isolated somatic blastomere: it has been said that the complete separation of the first two segmentation spheres results in the so-called single ovum twins. The developing segments may, however, remain attached or fuse in the course of their development, as we see in the case of the well-known Siamese twins, and in hosts of other double monsters in which the two bodies are united by their sternal, sacral, or cranial regions. While these individuals seem to be more or less independent, there are important structures common to the two bodies, and other double monsters are not wanting in which the fusion becomes much more complete. When the isolated blastomere or group of blastomeres is derived from a somewhat later stage, so as to be incapable of producing a whole body, or when a totipotent blastomere in its development is outgrown by the other, there results a parasitic monster; that is, an incomplete individual attached to its brother or partly embedded in his body and deriving all its nutrition thence. Such an abortive individual may project in the form of incomplete arms or legs from the epigastric or pubic or other region of the host or "autosite." From this it is but a short step to the still more rudimentary organ masses, which are completely inclosed within the abdomen or thoracic cavity, and which, while maintaining a degree of independence, draw their blood-supply from the adjacent tissue of the host. The solid teratomata, with their cysts and aimless organ rudiments, are practically of this nature. Of course, if the isolated blastomere and the main group of segmentation spheres begin to develop at the same time, we should expect the tissues of host and teratoma to appear to be of the same age or maturity, while if the isolated blastomere should remain stagnant during the growth of the host, it might be expected to produce by later growth a teratoma composed of embryonic tissues. It is said that this distinction can be made. But it is pointed out that when teeth of the second dentition are found in a dermoid cyst and adult tissues of other sorts, even including mature external genitals with pubic hair in more complex teratomas, it is because the organs of internal secretion of the host individual promote this maturity in the included twin.

Embryomata or teratomata have never been found to include genital cells, which is thought by R. Meyer to show that they must be derived from somatic blastomeres, but Bosaeus has shown that none of the teratoid masses produced by implanting fertilized ova or parthenogenetically developing ova in the mother organism develops any sex-cells, so that this objection does not hold. Even the amorphous or acardiae monsters are found to have no genital glands.

It seems that for such teratomatous tumors as approach in form the parasitic or partially included twins, and are situated in such places as the sacrum or in the brain, the evidence is in favor of their origin from an isolated blastomere, and this is true too of those of less complexity down to the simplest cysts composed of only one or two types of tissue, while those occurring in the genital glands and accompanied by chorionic membranes are more probably derived from the development of primitive

sex-cells stirred to development by some chemical or physical disturbance comparable with those used in the experimental parthenogenetic development of frog's eggs.

The solid teratomata may grow to a great size, especially when they are enclosed in the abdominal cavity and attached to the retroperitoneal tissue or sacrum, but they are, as a rule, in themselves quite benign masses with no capacity for unlimited growth. Nevertheless they produce extraordinary mechanical disturbances at times. I remember one case especially well in which a great mass appeared in the abdomen of a man and grew slowly. It was found impossible to extirpate it, and after some months he died with signs of the presence of a tumor in the lung. At the autopsy there was found a huge mass, inextricably entangled in the intestines, and springing from the retroperitoneal region. It contained convoluted, intestine-like channels and several large cysts, in the walls of one of which a carcinoma had developed. All the rest of the mass showed only an organ-like arrangement of tissue, and the metastases in the man's lungs were from this carcinoma. While it is true that the teratoma itself is benign, it is not at all uncommon to find the development of a distinct carcinoma at some point in its epithelium, exactly as we find it in the body in general.

There are a few vague references in the literature to the metastasis of combinations of tissue (Neuhauser, Pfannenstiel), but these seem extremely uncertain, and it would be very difficult to form any idea of a mechanism by which several types of tissue could appear in a metastasis unless, indeed, an embolus containing several types of tissue were to be carried to a distant organ, for the potentialities of the original cell have already been expressed in its differentiation into various tissues which are spread out in the original tumor. But what really has been observed is the metastasis of one type of cell to remote organs, and Neuhauser found numerous nodules of glial tissue in the omentum and peritoneum in such a case.

**Teratomata of the Testicle.**—All the tumors of the testicles are regarded with suspicion as to their teratomatous origin and should be searched most carefully in serial sections for evidence of the presence of several types of tissue. Many of them present the appearance of a homogeneous sarcoma-like growth composed of large rounded cells (Figs. 594, 687), but even these have often been shown to contain masses of cartilage and epithelial-lined cysts. Tumors have, of course, been found which can be traced to an origin in the interstitial cells of Leydig or in the cells of the seminiferous tubules, but these are relatively infrequent. The most evident teratomata are those composed, as described above, of intermingled abortive structures representing ectoderm, mesoderm, and endoderm—masses of cartilage, cysts lined with various types of epithelium, neuroglial masses with ganglia, etc. (Fig. 688). These may be sharply outlined or they may extend into the veins of the spermatic cord, and secondary growths have been observed elsewhere, as in the abdomen. In all cases the impression is strong that the testicular tumors may behave as malignant growths. A peculiar form is that which we had an opportunity to study (Fig. 689) in which the original tumor was

a rapidly growing mass, apparently of one complex form of tissue without any admixture of cartilage, epithelium, or other types, and with extraordinary invasion of the veins, up into the heart, by clustered grape-like masses covered with a layer of cells which looked like endothelium and protected the blood from clotting. Several other cases have been seen exactly like this, and Schlagenhauer thought they were like hydatidiform moles and thus derived from chorionic ectoderm, but this has been shown not to be true (Risel). These branching growths are really covered with endothelium and have only a superficial resemblance to the villi of the hydatidiform mole.



Fig. 687.—Teratomatous tumor of the testicle composed largely of tissue like that of a round-cell sarcoma.

**Dermoid Cysts.**—A simpler form of teratoma is that which is known as a *dermoid cyst*. These may occur almost anywhere, but are perhaps most common in the ovary, where there may be several. They are, as the name implies, composed essentially of derivatives of the ectodermal layer, but there is no line between them and the more complex teratomata; indeed, all dermoids on closer examination prove to have a more complicated structure than is apparent at first sight. A dermoid cyst is round or irregularly multilocular, and on incision is found to have a tough, hard wall and to be filled with a soft, greasy mass of granular, buttery consistency, in which there are often tangles of hair (Fig. 690). Sometimes the hair may be extremely long and abundant. It does not

spring evenly from the whole wall, but has its roots in a thickened patch which is constantly present in the wall of such cysts (Wilms). The thick area projects into the lumen of the cyst, and is sometimes



Fig. 688.—Teratoma of testicle with cartilage: *a*, Nerves, striated muscle, and cavities (*b*) lined with various kinds of epithelium.

very irregular and rough. It is covered with thick epidermis, and bears the roots of the hairs and an exaggerated array of sebaceous glands (Fig. 691, 692). It is from these sebaceous glands that the buttery

contents of the cyst are secreted. They may open in the hair-sheaths, but most commonly open directly into the cyst. There are sebaceous glands around the whole wall of the cyst, quite away from the hair-bearing patch. Opposite this patch the distal ends of the hairs may

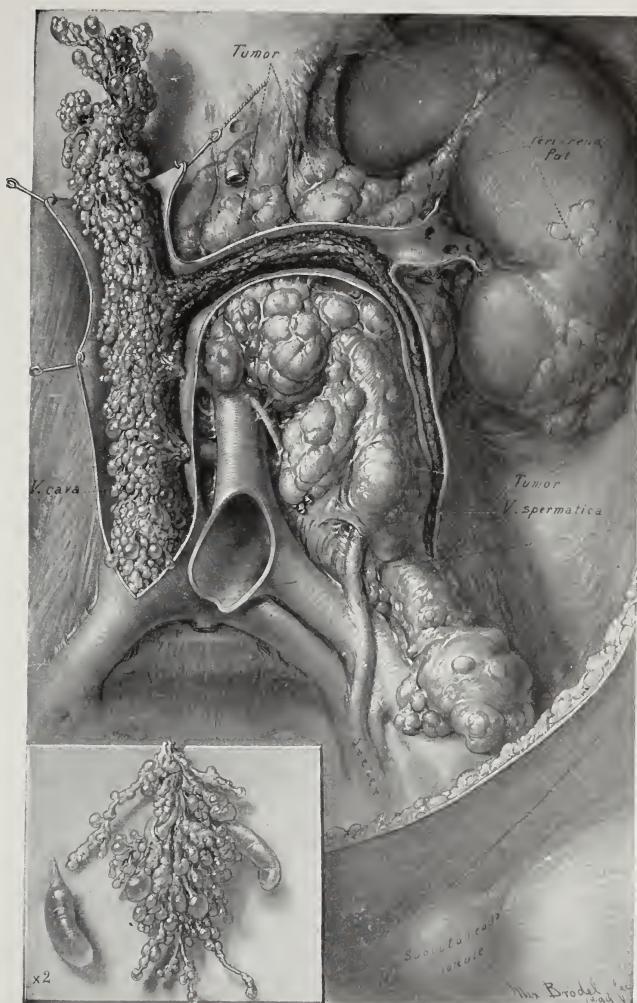


Fig. 689.—Teratomatous tumor of testicle invading vena cava through spermatic and renal veins. Hydatidiform, grape-like structures hang free in the circulating blood.

become buried in the wall and encapsulated by granulation tissue, so that they seem to have taken root there. In the mass of tissue which projects into the cavity there may be smooth muscle, like the arrectores pilorum, and fat and dense connective tissue. That these dermoid cysts verge on the more solid teratomata is seen from the fact that some of



Fig. 690.—Dermoid cyst of ovary, showing sebaceous material and hair.

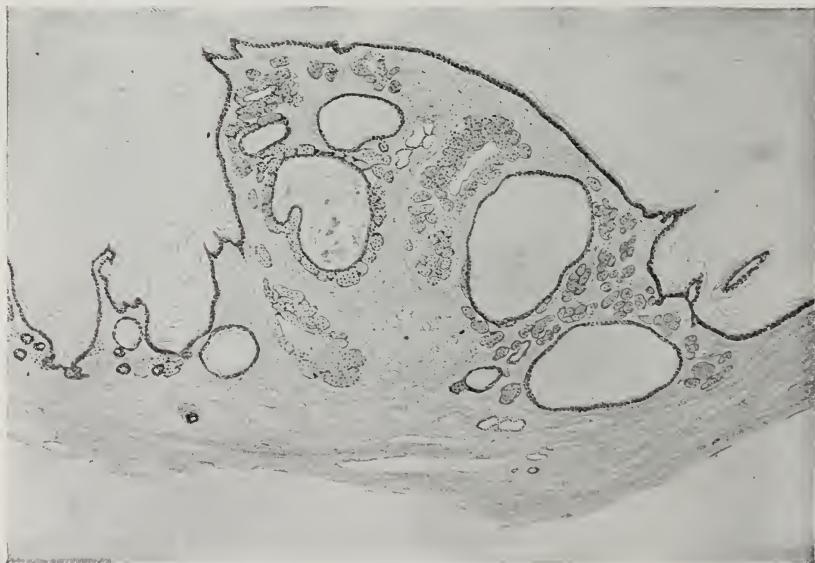


Fig. 691.—Wall of dermoid cyst, showing solid projection covered with epidermis. There are many small cysts, hair follicles, and sebaceous glands near the surface.

them have teeth in their walls often set in connection with a bony mass which lies deeper in the wall (Fig. 693). If there are pigmented rudiments of an eye or elements of the central nervous system, the approach to the complexity of the more solid teratomata is even closer. Wilms points out the fact that most of the structures seen in dermoid cysts are such as might be developed from the head, that part of the embryo which develops most rapidly. Various degenerative changes occur in such cysts, the walls become calcified, their epithelium disappears and is replaced by granulation tissue, the sebaceous contents shrink and be-



Fig. 692.—Wall of teratomatous cyst of the ovary. There is an epidermal lining with sebaceous glands. In the deeper portions there is a mass of cartilage and structures resembling salivary glands.

come solidified, and in some cases carcinomatous tissue develops in the wall.

Still simpler cysts occur in which the origin from a misplaced blastomere is not so evident. These are the wens or epidermoid cysts, which are found in the scalp, and are lined with stratified epithelium which grows in quantity and is desquamated into the interior to form a soft, flaky substance. They may perhaps be explained as displacements of ectoderm at a much later stage. So, too, with the atheromatous cysts or *branchial cysts*, which are developed from an imperfectly obliterated

and isolated part of a branchial cleft. Either cylindrical or squamous epithelium may form their lining, and they sometimes grow in a ramifying way far up behind the ear and down into the neck. In one which we studied the epithelial lining was very thick, and had desquamated enough of its cells to produce a soft, yellowish material like the caseous centre of a tubercle. They are hard to extirpate and tend to recur.

**Cholesteatomata.**—Another teratoid growth which may occur in the brain in connection with the meninges, or about the hypophysis, is a thin



Fig. 693.—Teratomatous cystoma of the ovary, containing teeth and a tongue-like structure covered with hair.

epidermal sac, which, from its abundant content of cholesterine crystals mixed with epidermal scales, is called a cholesteatoma. Such growths, which are lined with skin-like epidermis and distended with desquamated epidermal cells, may occur in the orbit, or at times in the middle ear, where they do harm by occupying space.

**Mixed Tumors.**—This leads us to the composite or *mixed tumors*, which represent the teratomata derived from the isolation of cells already in an advanced state of differentiation, whose capabilities are,

therefore, limited and pretty strictly determined. There is much dispute as to their nature and origin, but this explanation seems to me most acceptable and credible. Such tumors are found in immediate connection with the salivary glands, in the kidneys in children, in the breast, and elsewhere, but it must not be supposed that they resemble each other in these different situations. All they have in common is the principle upon which they are formed.



Fig. 694.—Mixed tumor of the parotid gland, showing cartilage and narrow strands of epithelial cells.

**Mixed Tumors of the Salivary Glands.**—In their gross appearance these tumors resemble one another very closely—they are rounded or nodular, elastic masses, which grow, as a rule, not in the gland, but in close proximity to it, being generally attached to its capsule. They spring in this way from the parotid or submaxillary, and may reach a very great size. On extirpation they may recur, but even then they run a benign course. On section such a tumor presents extensive, rather

translucent areas, with occasional patches of denser opaque tissue and rare points of calcification. Microscopically, the most varied appearances are seen (Fig. 694). The stroma is hyaline or like the matrix of cartilage; there may be true cartilage, mingled with dense fibrous tissue. Everywhere there are masses of cells arranged in tubules or cysts, or in long tapering strands which anastomose and finally fade into the crevices of the stroma. In some cases, but not in all, there are patches of this cellular tissue which are distinctly and unmistakably composed of stratified epithelium with concentric epithelial pearls. These were recognized by Landsteiner, who declared the tumors to be of epithelial origin. Volkmann had studied many cases, and had decided that the narrow strands of cells were derived from endothelium, and indeed these parotid tumors make up a great part of the material for his monograph on endotheliomata. Krompecher thinks of them as basal-cell tumors. Marchand, Wilms, and others regard them now as composite tumors in which epithelium plays the most prominent part, and trace them to an origin analogous to that of the teratomata, except in that the embryonic rudiment is separated at a later stage.

**Composite Tumors of the Kidney.**—In infants and children there occur tumors of the kidney which grow to an enormous size, and metastasize into distant organs. They may appear as congenital growths in new-born infants, and are composed of a mixture of tissues in which cartilage, fat, smooth muscle, and myxomatous connective tissue, together with complex arrangements of epithelium, take part. Unlike the hypernephromata, they cause no haematuria, and are recognized by their growth to a great mass in the abdomen. Wilms, Busse, Hedren, and others discuss their origin at length. While Busse thinks they may be derived from the kidney, or at least from its embryonal rudiment, Wilms places their origin farther back, in the middle plate, after its separation from the myotome. This tissue might well furnish all the elements which are found in such tumors. Striated muscle does not occur, and hence the myotome is not involved, but stratified epithelium does occur, and offers difficulties to Wilms' view. Nevertheless the intimate relation of the anterior end of the Wolffian duct to the ectoderm—possibly a remaining trace of its old arrangement as a nephridial tube opening on the skin—may account for this epithelium.

The morphology of these tumors is so variable that no single description will apply. The student is referred to the paper of Hedren, in which the literature is reviewed and in which there are many illustrations. In general, the epithelial cells are small and are arranged in irregular, gland-like tubules, interspersed with solid cords.

**Congenital Cystic Kidney.**—There is no good place in which to mention this condition, since our knowledge of its nature is so unsatisfactory, and for that reason a brief space may be devoted to it here.

This is a peculiar affection of the kidneys which leads, during embryonic development, to the formation of cysts throughout both kidneys, and frequently to the formation of cysts in the liver as well. Most of the substance of the kidneys is occupied by these cysts, and there is extremely little functional tissue left between them. Yet such people may grow to adult life without knowing that there is any-

thing amiss with their kidneys. In later life they may die of renal insufficiency after the injury of the scarcely sufficient tissue. In infancy the kidneys form huge masses of gelatinous cystic tissue, so large in one case which I studied that they had to be removed before birth was possible. This child was otherwise extensively malformed.

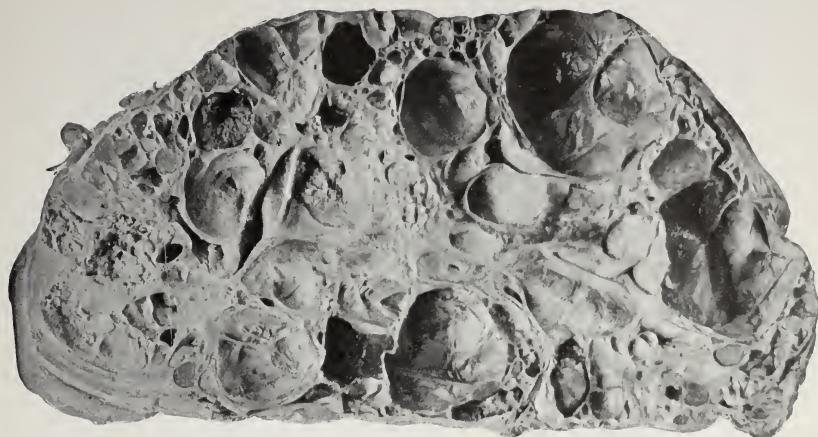


Fig. 695.—Congenital cystic kidney. Remnants of a pelvis are seen in the centre at the lower part of the figure.

Reconstruction (Meader) shows that the cysts may be in immediate relationship with the glomeruli, or may be developed in the first part of the convoluted tubule and connected by a narrow canal with the glomeruli.

Ribbert puts forth a theory that the cysts are caused by interference with the union of the glomerular part of the tubule with the other rudiment, which grows



Fig. 696.—Congenital cystic kidney.

up from the ureter to join it. Hence the glomerular portion dilates into a cyst. The end of the ureteral portion may also become cystic. Others regard the whole process as an adenomatous growth, which it is said might account for the similar growth of cysts in the liver. It seems to me more plausible to base the change on anomalies of embryonic development.

In the adult the cystic kidneys may form two huge tumors occupying the whole abdominal cavity on each side (Fig. 695). At autopsy they are found to be no longer gelatinous, but made up of cysts about the size of a cherry or larger, filled with clear, or dark brown, or turbid fluid. Between these cysts, which are lined with low cubical epithelium, there are scattered normal tubules and glomeruli.



Fig. 697.—Congenital cystic liver from same case.

In infants one may occasionally see another type of cystic dilatation of the tubule which occupies the pyramid and leads to the fusiform widening of the conducting tubules.

**Chordomata.**—Mention may be made here of a rather rare tumor which usually springs from the body of the sphenoid bone, and projects into the cranial cavity, compressing the brain and the cranial nerves. Similar tumors may arise from the sacrum and other parts of the vertebral column. They are shown to be malignant by their invasive mode of growth, which allows them to destroy the bone extensively and to penetrate into veins. Nevertheless, no metastases in other organs have been found. The tumor is lobulated, the lobules being composed of groups and strands of large and small cells in a homogeneous ground-substance which takes a bluish stain with haematoxylin. They are rich in glycogen. The work of various authors, and particularly that of Marchand's pupil, Nebelthau, has shown that these growths are derived from remnants of the chorda dorsalis.

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## CHAPTER LXXIII

### CLASSIFICATION OF TUMORS

THE only satisfactory classification of tumors would be on the basis of their aetiology. Since we know nothing of this, they are classed very much as animals or plants would be, on the basis of their most striking characters. The most fundamental available characteristics are: (1) The type of tissue which they resemble, and from which we suppose them to be derived; (2) the degree in which they diverge from the type, and the extent to which they have acquired the power of invasion and colonization, and (3) the form which the tumor assumes, that is, its architecture as a papillary, cystic, glandular, or solid growth.

In other words, we have tumors derived from one or more of the three germ layers, or more specifically from a tissue originating from one of these layers. They may be benign or malignant, and may grow in one or other of the many arrangements adopted by normal tissues, or in combinations or perversions of these forms. Rather than assume too accurate a knowledge of the ultimate derivation of the tumors, I have preferred to arrange them according to the general character of their tissues, both anatomical and biological, and their form.

Other classifications as given in the various text-books and treatises on the subject should be consulted. The following list is mainly for convenience in summarizing the various forms as they have been considered here. It is an arrangement, not a classification.

1. Benign tumors of connective-tissue character:
  - Fibroma.
  - Lipoma.
  - Chondroma.
  - Osteoma.
2. Tumors composed of tissue of muscular character:
  - Leiomyoma.
  - Rhabdomyoma.
3. Tumors composed of tissue of nervous character:
  - Neuroblastoma.
  - Ganglioneuroma, neurinoma.
  - Paraganglioma.
  - Gliomatous tumors.
4. Tumors composed of blood- and lymph-channels—angioma:
  - Hæmangioma.
  - Lymphangioma.
5. Malignant tumors of connective-tissue character—sarcomata:
  - Spindle-cell sarcoma.
  - Mixed-cell sarcoma.
  - Round-cell sarcoma.

- Alveolar sarcoma.
- Giant-cell sarcoma.
- Osteosarcoma.
- Myxoma.
- 6. Pigmented tumors:
  - Nævus.
  - Melanotic sarcoma or melanoma.
- 7. Tumor composed of tissue resembling adrenal cortex:
  - Hypernephroma.
- 8. Tumors thought to originate from endothelium—"endotheliomata":
  - Lymphangioendothelioma.
  - Cylindroma.
  - Pleural and peritoneal tumors.
  - Meningeal tumors.
  - Hæmangioendothelioma.
- 9. Benign epithelial tumors:
  - Papilloma.
  - Adenoma.
  - Adamantinoma.
  - Cystadenoma.
- 10. Malignant epithelial tumors—carcinomata:
  - Flat-celled epithelioma.
  - Basal-cell cancer.
  - Cylindrical-cell cancer or adenocarcinoma.
  - Gland-cell cancer.
- 11. Chorionic epithelioma.
- 12. Mixed tumors and teratomata.

## CHAPTER LXXIV

### GENERAL DISCUSSION OF TUMORS

*General character of tumors: origin from tissue of host. Independence of laws governing growth of normal tissue. Mode of growth: idea of return to embryonic state; dependence upon host for nutrition. Implantation, invasion, metastasis, recurrences. Predisposing and actual causes of tumor growth. Experimental production in normal animals. Recent work on tar derivatives. Parasites as inciting cause. Viruses in production of tumor growth. Influence of internal secretions, senility; heredity.*

**General Character of Tumors.**—Up to this point we have considered the characters of tumors as though they were plants in a garden, observing their general structure and their mode of growth in individual cases. It is necessary now to make an attempt to learn whether there are common features in these respects, and whether we can discover the causes of their appearance and growth and of the peculiar relations to the host. Otherwise it must remain extremely difficult to give a definition of what a tumor really is.

It is clear from what has been said of all these tumors that they are composed of the tissue of the host. This was recognized by Johannes Müller, and in spite of Virchow's rather generous idea that carcinomata, as well as other tumors, might be formed in a connective-tissue matrix, Waldeyer insisted that the specific relation was closer and that cancers which are composed of epithelium could arise only from epithelium. After that the intimate relationship of each tumor to one form or other of normal tissue was looked for and usually found, although we are still puzzled to trace this relationship in many cases.

But if it is possible to feel that a given tumor is of epithelial or connective-tissue origin, or even that it belongs to the stratified or cylindrical epithelium, it is nevertheless equally certain that it does not resemble that tissue precisely.

The laws which govern the growth of normal human tissue and organs are very rigid. The form of the normal cells is so constant, and their relations to one another in the architecture of the organ so fixed, that we become familiar with their appearance, and instantly recognize any divergence from the accepted form. We know well too what changes occur in the morphology of normal cells as the result of variations in their functional activity, and, above all, we know the plan upon which they grow. Their reactions in all these respects, to a great variety of recognizable injuries and pathological disturbances, are very familiar, and we realize that under those circumstances the cells and tissues still obey the laws which govern their growth under normal conditions, and strive to restore as quickly as possible the forms and relations which have been established by ages of evolution.

In tumors we find the cells abnormal in form, in their relations to one another, and in their relation to surrounding tissues. They are abnormal in every functional activity, and in many cases in their increased vigor of growth. Great stress is usually laid upon this increased energy of growth, although in many tumors it is at a very low ebb, and in the most rapidly invading forms is not to be compared with that of the growing embryo.

The really essential difference between tumors and normal tissue is not the increased energy of growth, but the emancipation of the tissue from obedience to the laws which govern the growth of normal tissues. That this is closely related to the abnormality in the form of the cells is probable. It is as a direct expression of this complete lawlessness that the tissue produced by these cells has no regular architectural arrangement, that it never forms organs that could be of any possible use, and that it pays no regard to the rights of other organs, but bursts its way recklessly through their boundaries and their tissues, destroying their cells as it goes. Its behavior is like a complete disregard of international law, which has been established for the welfare of the whole world.

In the development of the body some people may hold that the equilibrium which is maintained between various tissues depends entirely upon the power of each to grow, but it is evident enough that a balance is maintained by a higher law than this, and that such an organ as the liver does not maintain a precise number of cells because it has not the power to form more, but because the law of the general welfare demands that many, and no more. If some are destroyed, or if the general situation is changed, the liver will form more cells to restore precisely the balance. Hence even though it can be defined only vaguely, we are aware that there is a delicate but effective power which controls, possibly by way of the nervous system, the relations of tissues to one another. They are disciplined, and grow when they are required, but not of their own initiative.

It is far otherwise with tumors. No tumor of glandular character has a duct, nor have its glands any such arrangement that they could effectively discharge a secretion. It is true that tumors of the organs of internal secretion may sometimes form a useful secretion, but one has the impression that this is a rare occurrence and inadvertent on their part. No tumors are known to be under the control of the nervous system. They seem to have no nerves except those accidentally enclosed in their growth and possibly vasomotor nerves in their blood-vessels. It is true that Young was able to demonstrate the nerve-fibres in a number of tumors by staining with methylene-blue, but he could not show that they really belonged to the tumor tissue, and, as far as I can learn, no one has been more successful. Tumors are not even subject to the normal conditions of nutrition, and withstand in the most surprising way starvation which causes the rest of the body to waste. A lipoma in a starving animal remains a plump tumor, distended with fat when all the other fat has disappeared. It is true that Moreschi found that, by starving mice inoculated with a tumor, he could inhibit its growth, but Rous found that if the tumor were well established, it continued to grow.

In human beings the contrast between the appearance of huge cancerous growths in full progress, and extreme emaciation of the rest of the body, is often very striking.

Thus the isolation and independence of the tumor form the essential difference between its nature and that of the normal tissues. In virtue of this it behaves in such a way as to be, in nearly every instance, harmful to its host, either through occupying space and requiring nutrition, or by actually invading and destroying useful tissues. Since tumors are composed of human tissues, however, we cannot accept this inimical attitude as a natural thing as we would in the case of an animal parasite, and every effort has been directed toward learning why and how such independence has been attained.

Notwithstanding this general statement that a tumor is a growth of abnormal tissue which is largely independent of the laws governing and controlling the growth of normal tissues, it is often very difficult to decide what is, and what is not, to be called a tumor. Histological study often leaves us uncertain, and some growths are so sluggish that even a survey of their whole biological relations is hardly sufficient to inform us as to whether they have arisen as a response to some injury, or are really independent and transgressing the regulations which govern the normal tissues. Indeed, we not infrequently discover that something which has long been regarded as a tumor is really the slow product of a chronic infection, and Virchow's great book, *Die krankhaften Geschwülste*, is, perhaps intentionally, full of such examples. Tumors are simulated, on the one hand, by the relations of the body to infection and injury, which often produce considerable masses of new and peculiar tissue; on the other hand, by malformations and displacements of tissue, with which, as has already been shown, their relations are especially intimate. Whether we can draw a boundary line to separate sharply the group of tumors from these is doubtful. It is relatively easy in the case of such typical malignant tumors as the carcinomata, but not easy when we consider such processes as Hodgkin's disease, leukaemia, leukosarcoma, and lymphosarcoma. In the case of *x*-ray burns, tar cancer, xeroderma, etc., it is not even easy to say when the normal reaction ceases and tumor growth begins; nor at the other extreme is it easy to determine when a mixed tumor becomes a teratoma, or where the term teratoma should be given up and reference be made to an imperfect or abnormal foetus, or even to a twin brother.

It seems, however, that if we were able, in each instance, to decide accurately as to whether the normal laws of growth had been broken or not, we could outline sharply the whole group of tumors. The independence of tumors involves the progressive and unlimited character of their growth. They never reach any goal and are never complete, nor do their cells ever reach any stage comparable to maturity and functional perfection. The reaction to infection and mechanical or chemical irritation keeps pace with the injury; it exists only so long as the injury persists, and then, in complete obedience to the laws of growth and the regulation of the internal relations of the tissues, returns as quickly as possible to the normal. Misplaced embryonic tissues, no matter how

complicated, proceed to the ordinary maturity of the tissue, and then remain as stationary as normal tissues. They are still abnormal and harmful to the host because they are out of place, but not because they are actively transgressing the law of the interrelation of organs. Of course, many teratomata show themselves ultimately to be malignant tumors, but these are instances in which a tumor has developed in the tissues of a teratoma and grown to invade the tissues of the host. Such a tumor grows usually from only one of the types of tissue which make up the teratoma, and is precisely comparable to a tumor which develops anywhere else in the host. So too after long irritation or infection the reacting tissue may reveal itself as a carcinoma, but it is a tumor which has freshly developed in pathological tissue, just as it might anywhere else. Far more often the reacting tissue does not give rise to a tumor growth.

In this state of knowledge it seems best to hold to the one striking feature of tumor growth as contrasted with that of other tissue growth—its independence of the mechanical laws which govern the hereditary form of the body.

Of course, we must some day discover the cause of this alteration in the behavior of the tumor-cells, and it is conceivable that it may prove to be some parasite which accompanies or lives in the cells, perverting their course of life from that which is normal, and keeping them forever growing and dividing to produce new cells. It is difficult to imagine, however, what kind of parasite that could be. One may implant a carcinoma of a mouse into a normal mouse and from that, after it has grown, transplant a fragment to another mouse, and repeat this for hundreds of generations until the mouse from which the tumor was originally taken, and all its contemporaries and their offspring, have been dead for years of old age, and still the tumor-cells are alive and thriving with exactly the same anatomical and histological characters that they possessed at first. It is a kind of artificial immortality that seems to require only nutrition, and none of the reinvigoration which other living things usually gain from a sexual union with their kind. Nevertheless, it is not yet proved that unicellular organisms die after long periods of multiplication by fission without sexual conjugation, and Woodruff seems to hold that they may go on indefinitely in this way. Plants, such as banana trees, have in the same way been cultivated for hundreds of years from cuttings without any recourse to fertilization and seed planting.

We may pause here to review the general character of tumor growths before discussing the theories which have been proposed as to their causation.

#### GENERAL CHARACTERS OF TUMOR GROWTH

Tumors are composed of the tissues of the host, as has long been agreed, in spite of such efforts as those of Kelling, who attempted to prove that they are made up of the tissues of cows, pigs, or chickens which had been used for food. By the enormous amount of work which has been done in the last ten years in transplanting tumors from one animal to

another it has been shown that their tissues are exquisitely specific and will grow continuously only in another animal of the same species. Thus a carcinoma of a white mouse will grow in another white mouse, but fails to reach any considerable size in a gray, or wild mouse, or in a rat, and finally undergoes retrogression. This explains easily the complete failure of those experiments in which it has been attempted to transplant human tumors to dogs, rabbits, and other animals. Even in monkeys such transplants have failed.

**Resemblance to Normal Cells.**—We have observed in previous chapters the extent of the resemblance of tumors to normal tissues both in appearance and in histological characters, and have realized that there are extreme variations, so that, while the cells of some tumors are almost precisely like the normal cells, even in their arrangement (thyroid tumors, etc.), others depart very widely from this form and become quite unrecognizable. We have learned that many tumors are composed of cells which seem to belong unquestionably to the same stage of development as those of the surrounding tissues, while others are made up of tumor-cells which have the morphology and arrangement, and possibly also the biological characters of the cells of some tissue in the early stages of its development. Examples of the latter condition are found in the neuroblastomata, in which cells belonging to an early stage in the development of the sympathetic nervous system persist in that stage, and multiply excessively to form a tumor, and in rhabdomyomata, which contain cells resembling embryonic muscle-cells. Nevertheless, I have never used the expression "return to an embryonic state" in speaking of such tumors as sarcomata, which are commonly spoken of as composed of "undifferentiated" or "unripe" connective tissue, because I do not believe that there is evidence to show that there is anything embryonic about that tissue. It is true that the cells are unlike the normal cells, but they do not especially resemble the connective-tissue cells of the embryo, and are often extremely unlike them. It seems far more plausible that they are cells so modified that their sole function is to reproduce themselves rapidly, for which reason they never assume the form of the normal cells, nor lie dormant in abundant intercellular substance. It is conceivable that they are cells which have, like the neuroblasts, never passed the embryonic stage of development, but this is a difficult explanation which is neither required nor supported by any facts. It does not seem at all probable that any cell of a mature animal can ever return to the embryonic condition. Even those cells of the blood-forming organs which continually produce new blood-cells, and the cells of the epidermis, which form new epithelial cells, are in no true sense embryonic cells. They have retained the function of becoming differentiated into one type of cell, but are even then far advanced from the condition of embryonic cells. The idea that cells may in tumor formation return to the embryonic state is based no doubt upon the desire to explain their new energy of growth, but this new character of their growth is not at all like that of embryonic cells. In the embryo, the cells pass through a definite development to become mature. If they grow rapidly, it is only in this respect that the cells of a tumor resemble them, because tumor-

cells pass through no such regular development but merely continue to grow and divide. They do not approach the character of the embryonic cells, but assume a totally new character, in which they only roughly resemble the cells of the embryo in form and in the rate at which they grow. It is difficult enough to believe that embryonic cells can be isolated and remain latent for years embedded in the normal growing tissues, but for more difficult to believe that normal cells, once matured, can return to the embryonic state. For the former possibly we have proofs; for the latter we have no evidence whatever, so far as I can see.

Although we speak so easily of deriving tumor-cells from tissue of one type or another, we really depend largely upon their morphological resemblance for our proof of the relation. It is possible that we are often wrong in this, but, on the whole, the chance of error seems relatively slight.

**Dependence upon Host for Nutrition.**—Tumors, whatever the independence of their cells, are dependent upon their host for their nutrition. If the host dies, the tumor dies too. If a blood-vessel is plugged in a tumor, the area which should be supplied with blood becomes an infarct, just as it would in the kidney. Bashford has compared the mouse, in which a huge tumor larger than itself is growing, to a sort of nutritive machine engaged in feeding the tumor. Its heart hypertrophies to keep up the pumping of blood through the enormous mass of new tissue. Its liver and sometimes its kidneys enlarge. Price Jones found no great modification in the differential count of the bone-marrow of these animals, but states that there was great enlargement of the spleen. Studies of the vascular supply of tumors by methods of injection show that great numbers of blood-vessels run to the rapidly growing tumor—numbers far in excess of those which supply normal tissues. These are new formed at the demand of the growing tumor, and carry with them the supporting stroma of connective tissue. Bashford and his co-workers make much of the importance of the stroma, which they think is especially adapted to each type of tumor. It is their belief that it is only in animals which respond by the production of an adequate stroma and blood-supply that an implanted tumor can succeed in growing. Others lay much less stress upon the importance of the stroma.

When a tumor is implanted in a susceptible animal, its stroma and part of its specific cells undergo necrosis, but the surviving tumor-cells grow and are quickly invaded by a new stroma formed from the host, with new blood-vessels. It seems clear that the tumor-cells act as a dominant tissue, controlling and stirring up the development of the vascular stroma, practically as epithelial cells do in the development of an organ in the embryo. Subservient as this stroma is, it does not always remain so. Ehrlich and others have found that, after a time, when a carcinoma has been implanted, the stroma itself may assume the characters of tumor tissue, and grow vigorously as a sarcoma, oppressing and finally destroying the epithelial cells. Such a tumor, when transplanted, may continue its growth as a sarcoma, extorting now the new formation of another vascular stroma from its host. Ewing, how-

ever, feels that in such cases one is still dealing with epithelial tumor-cells, although much modified in form.

Still, little has been observed as to the ingrowth of nerves into such a tumor, although this would seem to be a matter of the utmost importance. Young, Ichikawa, and Oertel have, indeed, demonstrated nerve-fibrils in tumors, but their precise relations and significance are still to be studied. Little is written of the formation of lymphatic channels, although we know by injection experiments (Evans) that lymphatics are present in abundance in human tumors of many sorts.

**Atypical Character of Tumor Cells—Adaptation.**—All the tumor cells are atypical in the ways mentioned. They are characterized not only by their powers of growth, but especially by their tendency to continue indefinitely to divide and produce new cells, regardless of any need or of any plan for the arrangement of these new cells or even of the existence of any space in which they can be lodged, and these new cells proceed in the same aimless way to produce others. That they are specifically related to animals of their own species is shown by their ability to grow indefinitely in contact with the tissues of that species only. But the adaptation can be intensified by repeated transplantation into animals of the same species, for at first it is necessary to transplant a great number of pieces from a spontaneous tumor into as many mice in order to obtain one successful implantation. After that, however, with repeated transplantations the tumor acquires the power to grow in practically every mouse. This does not necessarily mean that it grows more rapidly, or more destructively, or to a larger size. It is merely a matter of adaptation to its surroundings, and whether we regard the cell as independently originating the growth, or as impelled by some parasite, the explanation of the adaptation must be the same.

#### FORM OF GROWTH, EXTENSION; IMPLANTATION; METASTASIS

The form of the growth is, as we have learned, extremely variable, and there are all gradations between tumors which surround themselves with a smooth capsule and grow expansively, and those which scatter their isolated cells like spray in every direction, or send out long threads of cells which insinuate themselves between the cells and fibres of the tissues, and even into the walls of blood-vessels and lymphatics. The former mode of growth usually appears in a benign tumor, the latter in a malignant tumor. These two forms are doubtless in large part the expression of differences in the rate and continuity of multiplication of the cells. The encapsulated benign form is far less exposed to the action of the cells and fluids of the organism than the spreading malignant form. Through this very fact the latter seems to become adapted to existence anywhere in the body, and is thereby aided in spreading and even in establishing colonies in distant organs.

As to the spread or extension, we have already described several forms.

**Implantations.**—In the older literature there were many descriptions of instances in which a carcinoma was thought to be transmitted

by contact to another person. Some of these were cases in which, through intimate contact, as in the transfer of a genital carcinoma from husband to wife or the reverse, there was a semblance of probability, but in others, in which, for example, a nurse contracted a carcinoma of the breast from tending a patient with a similar carcinoma, there was unquestionably only a coincidence. Recent reports of such occurrences are rare. There are, however, instances of implantation of a tumor upon contiguous epithelial surfaces in the same individual, as, for example, the formation of a carcinoma of the vagina opposite the ulcerated surface of a carcinoma of the cervix uteri. These, too, seem questionable, and it is perhaps more probable that such tumors are really due to transportation by way of the lymph-channels, although theoretically there is no reason why some abrasion of the opposite mucous surface should not allow the implantation of cancer-cells.

Much more familiar is the implantation of the cells of a tumor in the raw edges of a wound made for the extirpation of the growth, with the development of nodules in the resulting scar. Even this is a rather uncommon occurrence, however. Within the body, the implantation of free fragments of tumor or tumor-cells is frequently seen in the peritoneal cavity and other serous cavities. It is especially common with papillomatous cystadenomata of the ovary and with colloid carcinomata, but it occurs also with various other tumors. Whether the nodules so often found on the surface of the lungs as growths secondary to a carcinoma, or sarcoma situated elsewhere are produced by implantation from the pleural cavity or by extension from the substance of the lungs is rather difficult to tell. They occur as large, button-like nodules, or as smaller masses like beads, or even as tiny, flattened, confluent, or discrete thickenings of the pleura, and in every case they are continuous with growths of tumor-cells in the underlying lymph-channels. Sometimes these extend in the interlobular spaces or in the walls of blood-vessels or bronchi quite through the lung to the hilum, where the lymph-glands are generally involved. Thus it is possible that the tumor may have grown from the hilum or any part of the lung through the lymphatics to the surface, spreading out and developing there, and, indeed, in the absence of a tumor mass invading the pleural cavity this seems the more probable course. In other cases in which a tumor of the stomach or gall-bladder has distributed metastases on the under side of the diaphragm, the course of its extension to the pleural cavity and the surface of the lungs can be readily traced through the diaphragmatic lymphatics.

**Extension.**—The actual extension of an invasive tumor occurs, as we have seen, through the growth of strands of tumor-cells into the interstices of the surrounding tissue. These cells may become really isolated, but, as a rule, the strands or threads of cells maintain their continuity for a long time. With the widening of the strands the peripheral parts of the tumor become more condensed and the intervening normal tissue is destroyed. Frequently the advancing margin is much more compact, and the normal tissue is largely pushed aside and compressed, so that the tumor grows by the invasion of coarse projecting masses. In many

instances these, as well as the finer strands, are guided by meeting with a dense fascia or other resistant tissue, and spread along its surface.

Far more commonly, however, the cells break through the walls of *lymphatic channels* and spread themselves like an injection mass along their lumina so as to fill them completely. This is particularly characteristic of the carcinomata, and has been studied carefully for such cancers as are of common occurrence (breast, uterus, etc.). Handley finds that the extension in carcinoma of the breast is through the plexus of lymphatic channels which accompany the fasciæ, and that these may become obliterated after the tumor has moved along their course. Thus in a wide halo around the tumor there are lymph-channels full of tumor-cells ready to grow into nodules or to wander farther, although the obliterated channels by which they reached that point are no longer visible. That this network of lymphatics in the deeper part of the skin and in the fasciæ may act in this way is shown by the numerous small tumor nodules which often appear in these regions, quite far from the original tumor. Handley, therefore, suggests that an extremely wide area of skin should be removed in order to extirpate the tumor completely.

**Metastasis.**—Even more familiar and common is the transportation of loose clumps of tumor-cells, or even single cells, by the stream of lymphatic fluid along the course of the channel until they are caught and held in the complex sinuses of a lymph-gland. Since the distribution of the lymphatics is well known, one may foretell easily which gland is likely to receive the first emboli of this nature. There the tumor-cells develop into a new tumor which gradually invades and replaces the tissue of the lymph-gland. Other emboli of the cells may pass to more distant lymph-glands, or the process may be repeated with the metastatic nodule as the source for new emboli. If such floating cells reach the thoracic duct, they may lodge in its walls and there grow, but they are far more likely to be swept on into the blood-stream, whence they are caught up in the capillaries of the lungs.

While such metastasis by way of the lymphatic channels is very common for carcinomata, it is somewhat less common for sarcomata and some other malignant tumors. These tend to grow in such a way as to penetrate the walls of the veins and discharge themselves directly into the blood-stream. Carcinomata do this also and it is by no means uncommon to find metastatic nodules which could be explained in no other way than by a transportation of the carcinoma cells by way of the blood. The invasion of sarcomata is frequently a very gross process, so that great masses of the tumor hang in the vein, or fill it completely. This is especially true of the hypernephromata, and we have already described a case in which the whole vena cava was filled with a tumor mass. The carcinomata primary in the liver exhibit the same tendency.

The transportation of liberated cells proceeds, of course, with the stream of blood, and we should expect to find them lodged, first of all, in the lungs. That this is commonly the case is shown by the development of numerous tumor nodules in the lung tissue, but it is quite common to find metastases only in the liver, or in some other organ in the systemic

circulation. Of course, if the primary tumor is situated in the intestinal tract, it is easy to comprehend that the tumor-cells carried by the portal blood should lodge and grow in the liver, but in other cases we must assume that the floating cells have passed through the wide capillaries of the lung to reach the other organs, unless there are also large metastases in the lungs themselves from which a secondary embolism might occur.

**Distribution of Metastases.**—Numerous curious distributions of metastases occur, as when a neuroblastoma beginning in the adrenal gives rise to multiple secondary growths which are confined to the liver, or when a carcinoma of the prostate establishes practically all its secondary growths in the marrow of the bones. Virchow made the statement that in those organs in which tumors are commonly primary, metastases rarely occur, while primary growths are rare in those situations which seem to form the best soil for secondary nodules. Thus the stomach and uterus are common sources of primary tumors, but rarely the seat of metastases, while the reverse is true of the liver. Although this cannot be said to be universally true, it introduces the suggestion that certain tissues form an especially suitable ground upon which the tumor-cells may take root and thrive, and, further, that this is not the same for all types of tumors. Indeed, there are many tissues, such as the pancreas, thyroid, heart-wall, muscle, etc., which seem especially unsuited to support the growth of the tumor-cells, although these tissues must receive many emboli. There is no difficulty in accepting the idea that the tumor-cells may slip through the capillaries of the lungs, for in many cases they are not much larger than the blood-cells and ought to pass readily. It should be realized, however, that many emboli must pass into the organs and even into those most favorable to their growth, without ever developing into tumor-nodules. Instead, as M. B. Schmidt has shown, they are surrounded by minute thrombi and later destroyed.

The secondary growth may far outstrip in size the primary tumor: As a rule, it reproduces the histological structure of the primary nodule with considerable fidelity, so that one may often form an idea of the position of that tumor by examining the secondary growth. Nevertheless, as Hansemann points out, the metastasis tends to diverge further from the normal architecture than did the primary growth. A tertiary nodule, derived by metastasis from the secondary one, might show an even greater departure from the normal. Hansemann describes this as an increase in *anaplasia*, by which he means a peculiar divergence from the normal morphology and functional nature which is characteristic of tumor-cells and which is often associated with irregularities in the process of mitosis.

**Nature of Metastasis.**—The phenomena of metastatic growth show that the formation of a tumor in a distant organ depends upon the transposition of the cells of the original tumor to a new site, and the secondary nodule is seen to develop from these cells, and to reproduce the type of tissue which makes up the original growth. This is a totally different process from the metastasis which occurs in infections, in which we can recognize the causative agent, since there the infective agent alone is transported, and any nodule of new tissue which it may produce in the

new situation is seen to be derived entirely from the tissue of the organ in which it lodges together with wandering cells and leucocytes. It is the result of the reaction of those tissues to injury, and proceeds according to the well-known laws which govern the behavior of normal tissues when they act in unison to combat an injury. In the tumor-nodule one tissue opposes another—the local tissue antagonizes the immigrant tissue. If we assume that a parasite is the cause of the growth of tumor-cells, we have no evidence that it can exist without them, for we never find secondary tumors derived from the tissues of the organs in which they form. Since such hypothetical parasites must be so closely dependent upon the cells originally affected as to be an inseparable constituent of them, and absolutely incapable of associating themselves with any other cells, it is quite as easy to assume that the cells themselves take the initiative in the abnormal process.

**Recurrences.**—Tumors removed at operation may recur in the same place, or in the neighborhood, and from this it must be assumed that, in the field of operation, particles or cells have been left in the tissues which may grow again after the wound has progressed toward healing. This may be because the excision was not extensive enough to include in the extirpation all the prolongations of the tumor, or because, in the course of the manipulations, loose cells were strewn in the exposed wound surface. Regional recurrences which appear in the skin or deeper tissues at a little distance from the site of the original tumor are explained as growths from those lymphatics filled with tumor-cells which have been shown to radiate from the original growth.

#### CONTRIBUTORY CAUSES OF TUMOR GROWTH

It may be said in advance that little is definitely known as yet of the causes and nature of tumor growth although the work of the past few years in connection with viruses, specific chemical compounds, hormones, etc., has opened great fields for exploration whose horizons are yet very indistinct. The older ideas with regard to the predisposing or causative effect of mechanical injury or trauma of the tissues, and even of protracted irritation, are giving place to more definite conceptions of the part played by chemical substances whose structural formula has been determined and which have even been synthesized. The close relation of such structural formulæ to those recently determined for the oestrogenic hormones has roused great interest and will be mentioned later. The nature of the materials produced by those worm parasites which have been found associated with tumor growth has not been revealed although the part played by viruses is becoming clearer.

The predisposing effect of trauma which is so naturally thought of by each patient in whom a tumor appears, who at length remembers some blow that bruised that place long ago, is treated in detail by Ewing. He concludes that there is no evidence that any single trauma of normal tissues can lead to the production of a malignant tumor and that only those tumor-like masses can be referred to trauma in which the structure represents an exaggeration or variation of the normal healing process and its sequelæ. Even in the many cases in which chronic or repeated me-

Chemical irritation has long been thought to be productive of cancer, a survey in the still dim light of recent investigations suggests the explanation by the action of one or other of the specific agents which are now being recognized. Precisely how they act is still to be learned but it is at least evident that the most potent carcinogenic substances are not irritant while great numbers of irritating chemicals have no power to produce cancer. This non-irritating character is of course not always true of the cancer-stimulating influences but at least it seems that the irritation with consequent chronic inflammation and scar formation is not the essential factor.

Continuous exposure to *x*-rays which was of frequent occurrence in the early days when their effect was not realized, resulted in many cases in the production of severe burns on the hands of the operators. These failed to heal readily and, after a long course, tumors of epithelial origin appeared which ultimately metastasized and led to the death of the radiologist. Exactly how the rays act upon the cells to stir this change in their whole character it seems impossible to say. There is much discussion, too, of the possible causation of cancer by the rays of the sun and various artificial forms of light but of this the information is slight.

While the majority of tumors seem to arise without any obvious hint as to their cause, there are some, such as the chimney-sweep's cancers, cancer of the bladder in aniline workers, etc., which suggest the action of some chemical from outside the body, and on this basis much experimental work has been done.

B. Fisher found that the injection into the skin of Scharlach R or Sudan III, dissolved in oil, would, if the solution were injected with force, result in the production of an extraordinary tumor-like growth of epithelium. Others have confirmed this, and Helmholtz was able to produce in this way a tumor composed of cartilage. With the absorption of the stain and the oil these growths gradually recede and disappear. They never form metastases.

Certain aniline bases had a similar but much less marked effect, and a 4 per cent. solution of ether in water was found by others to accelerate greatly and intensify the growth of tissues. Askanazy found that implanted embryonic tissue, if first treated with ether water, would grow into a large teratoma, more bulky than those which grew without this treatment. Loeb and others have pointed out that these are all lipoid solvents, and that their effect is in some way related to the existence of a lipoid capsule about each cell.

Yamagiwa and Ichikawa have found it possible to produce abundant nodular growths of epithelium on the skin of rabbits by rubbing in crude tar for a long time. These growths have all the appearances of epitheliomata and, indeed, metastasize into the regional lymph-glands. Nevertheless in many if not in most cases they tend to undergo retrogression, and are healed by scar formation and new-growth of epithelium over the ulcer left by their necrosis and disintegration. This has been repeated by many workers and very extensive and widely distributed tumors produced. Dr. Maisin tells me that the application of tar has a general effect in reducing resistance to the growth of tumors and, in

such animals as have received this treatment for a time, but have not developed tumors, the inoculation of transplantable tumors is more successful than in untreated controls, and metastasis occurs in a way not seen in normal animals inoculated with the same tumor.

Woglom has reviewed the literature upon this subject up to 1926, when little had been added to the results of Yamagiwa and Ichikawa, but since that time great advances have been made especially by Kenneway who with his co-workers Cook, Burrows, Hieger, Mayneord, and others, has isolated many hydrocarbons from tars or synthesized them so that their interrelations are known from their structural formulae. Some of these are inactive while others such as 1:2:5:6-dibenzanthracene are particularly powerful in producing, on injection of minimal quantities dissolved in lard into the tissues of mice and rats, spindle-cell sarcomas which metastasize and can be transplanted into other mice and rats for many generations. These are pure hydrocarbons all of which contain the phenanthrene ring. They examined 71 such compounds with negative results as far as the production of tumors was concerned unless they contained the 1:2-benzanthracene ring—for example, they find the 5:6-cyclo-penteno-1:2-benzanthracene and 6 isopropyl-1:2-benzanthracene carcinogenic.

There is a relation with sterols, bile acids, sex hormones and Vitamin D and even with morphine and codeine and digitalis which is brought out in the formulæ given in the papers of Dodds, Lundgren and others. Morton, Clapp and Branch have reported since this two other hydrocarbons quite unrelated to those of Cook which produce cancer in mice—these are triphenylbenzene and tetraphenylmethane. Martland has shown that thorium is capable of producing tumors and Roussey, Oberling and Guérin also report that thorotrust which is colloidal thorium dioxide, used as an opaque material for *x*-ray studies, will produce cancer in rats.

The relationship of carcinogenesis to the oestrogenic hormones has been ably reviewed by L. Loeb. He shows that because of their structural relation with the sterols which occur naturally in the body, these carcinogenic agents might arise from them. The follicular hormone and the luteal hormone have chemical constitutions closely related to that of the sterols and it is suggested that their activity in inducing active cell proliferation could depend upon the presence of those arrangements of their constituent elements which are comparable with those of the cancer-producing substances. This is supported by finding that two active carcinogenic compounds, 1:2-benzpyrene and 5:6-cyclopenteno-1:2-benzanthracene, are oestrogenic although other phenanthrene derivatives including 1:2:5:6-dibenzanthracene have no oestrogenic action. Ovarian hormones when injected have even been found capable of stirring the formation of mammary cancer in mice but this, when it does occur, is closer to a natural influence than the effect of the tar products which produce cancer in whatever tissue they are applied to.

Butenandt reviews the constitutional structure of the sex hormones and finds that theelin, progestin and androsterone are close to cholesterol and contain a phenanthrene nucleus. It is most interesting to find

that these hormones, which in the case of the theelin and progestin at least, are so obviously concerned in the stirring of the growth of new cells in the various processes which accompany pregnancy, should show this analogy in chemical structure with the tar derivatives which can cause the formation of tumors in animals when applied to the tissues either by rubbing them in or by injection. The difference is, of course, in the progressive character of the tumor growths which make us ask what at the termination of pregnancy so completely checks any further progress in the changes initiated by the sex hormones.

No answer seems available at the moment, if we really think of their action as parallel with that of the tar derivatives.

The tumors produced in animals by such things as 1:2:5:6-dibenzanthracene grow apace, metastasize and can be transplanted as already stated to mouse after mouse but so far no quite satisfactory evidence of their transmissibility by a cell-free filtrate has been reached although a few authors have thought it possible (McIntosh and others). It would be difficult to explain the success of such a transmission in the absence of a living virus and even as it is we are confronted with the necessity of imagining some explanation for the extraordinary independence of these cells conferred by the tar derivative which allows them to take root with such vigor in another animal of the same species and grow at the expense of its tissues and again and again in a long series until it is impossible to conceive of the persistence of enough of the hydrocarbon to maintain its influence on the propagation of these cells. This question is discussed at length by Lewis in speaking of "malignant cells" as contrasted with normal cells, with especial emphasis on chromosomal changes. To this we must return later. It would seem most desirable, now that such purified and effective agents are available for stirring the production of such cells, to apply one of them in great dilution to cultures of normal cells *in vitro* so that this change in the character of the cells could be traced under the microscope.

Of course, for years the effort has been made in every country to discover an aetiological agent at work in producing cancer and every conceivable sort of parasite has been described, both such as resemble known organisms and such as have no resemblance to any recognized living thing. But none of these has stood before the ordinary tests which are applied to the recognition of the causal relation of bacteria in infectious diseases. Borrel has tried to show the intimate relationship between certain acarines, including the *Demodex folliculorum*, and epithelial tumor growth, and has insisted that, even though they may have no power in themselves to cause the growth of the tumor, they may transfer the unknown virus from one animal to another. The number of spontaneous tumors in mice kept in cages infected with these mites is very striking. Somewhat similar is the observation of Fibiger, who found that a type of flat-cell epithelioma of the stomach and oesophagus occurs in rats in which a peculiar nematode worm, a species of *spiroptera* which passes its larval stage in the cockroach, is found embedded among the cells of the tumor. Such tumors could be produced in normal rats by feeding with cockroaches containing the larvæ.

Metastases are found in distant organs in which no nematodes or their eggs are discoverable. Fibiger thinks that the tumor is produced by the irritating action of some poison formed by the nematode, and states that this is the first instance of the experimental production of a metastasizing tumor.

Bullock, Rohdenburg, and Curtis, working with F. C. Wood, have reported the production of a sarcoma of the liver in rats about the cysts formed by the larvae of the *Tænia crassicollis* of the cat which grow in the rat as *Cysticercus fasciolaris*. The tumors begin about these cysts in a large proportion of the infected rats and are capable of extensive growth, invasion and metastasis, and easy transplantation to other rats.

Analogous to this are the numerous observations of the development of carcinomata in the bladder wall in Bilharzia infection, in the liver in infection with other trematodes (*Opisthorchis*, *Schistosomum japonicum*, etc.), and in the neighborhood of cysticerci from tæniæ in various situations. No adequate explanation of this change in the tissues about a worm larvae has been offered although it is, of course, conceivable that some stimulating chemical substance, a hormone-like substance or even a virus, is brought by the worm to its lodging place in the tissues.

Recently a new era in the study of tumors has been opened by the work of Peyton Rous and his associates who discovered a peculiar tumor of a hen which could be transplanted to other hens of the same breed. The tumor in the course of repeated transplantation acquired an astounding power of growth and adaptation, and could be successfully inoculated by the mere introduction into tissues of a needle which had been plunged into the growth. It was then possible to transplant it to fowl of other breeds. The tumor has the form of a sarcoma with long, spindle-shaped and branched cells, and produces huge tumor masses in the connective tissues of the fowl. Most significant, however, is the fact that this tumor can be successfully transmitted by the inoculation of dried and powdered material, or even by the injection into the tissues of the normal animal of a clear cell-free fluid, obtained by filtering a suspension of the ground-up tumor through a Berkefeld filter. Efforts have been made to show that cells of the host pass through but this is disproven.

Such filtrates in producing the tumor growth in another bird differ from the effects of the hydrocarbons described above in that they act at once to produce a tumor and not after a long interval with repeated injections and further in that with the growth of the tumor the virus is multiplied so that after a great many transplantations a filtrate is just as effective as in the first case. Tar derivatives and worm parasites are thought to act only indirectly when they are first brought into contact with the tissues although it must be admitted that if in the future any of those tumors are shown to be transmissible by a filtrate which is cell-free, this question will have to be reconsidered.

The Rous sarcoma has proven capable of adaptation to other birds after long acclimation, much as normal tissues can be transplanted to

the bodies of other individuals if gradually accustomed to their fluids in tissue culture.

Practically everyone tends to accept the virus nature of this transmissible agent although great efforts have been made to oppose this conception. Antibodies are developed in the blood of inoculated animals but these are apparently incapable of affecting tumor cells when once established.

The tumors produced act in all respect like the recognized true tumors and give rise to true metastases by the transmission of tumor-cells to other organs where they grow, and not merely by circulation of the virus. One wonders why the primary effect of a virus should be so localized. Here again it would be interesting to watch the effect of filtered virus upon cells of a normal animal cultivated in vitro.

Since Rous' first discovery of such a tumor, many others have been found such as Shope's rabbit fibroma, Fujinami's sarcoma of ducks and of fowls, Shope's papilloma of rabbits, filtrable warts of various animals, the myxoma of rabbits, etc. Rous and Beard have recently transferred the Shope infectious papilloma of cottontail rabbits to domestic rabbits with development of malignant metastasizing epitheliomata. The rabbit fibroma can be transmitted by a Berkefeld filtrate. Indeed, one is reminded of the work of Furth, Ellerman and Bang, and of Oberling and Guérin upon leukæmia which can in a similar way be transmitted by cell-free filtrates at least in birds.

The student will find a most interesting discussion of the relation of viruses to the aetiology of tumors in the lectures of C. H. Andrewes (*Lancet*, 1934, II, 63, 117).

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**Effects of Internal Secretions in Relation to Tissue and Tumor Growth.**—There are many examples of the extraordinary growths of tissues which appear to be associated with activity of the organs of internal secretion, and most of these have been mentioned elsewhere. The growth of the breasts during pregnancy, of the antlers of the deer during the season of rut, of various transitory tissue masses in frogs

and salamanders and fishes during the analogous period, are instances in point. The theory of Fraenkel and Born, which is to the effect that the secretion of the corpus luteum is necessary to the proper progress of pregnancy, may throw some light on the development of malignant growths from the chorionic epithelium, since masses of persistent corpus luteum tissue are found in the enlarged ovaries in many of those cases. L. Loeb has even suggested that the internal secretion of the ovary or some of its derivatives has an influence upon the growth of mammary cancer, for mice castrated at an early age were found to develop cancer in far fewer cases than those not castrated.

**Disposition; Senility; Heredity.**—We have some vague information with regard to these predisposing causes of tumor growth, but it is unsatisfactory. That there may be a constitutional tendency to the development of a tumor may easily be said, but it is, after all, a matter about which in the case of human beings only a general impression can be gained because generations succeed one another so slowly and we are so ill informed about the occurrence of cancer in the ancestors of most people. Hereditary transmission of tumor growth or, rather, of susceptibility to tumor growth should be accessible to more exact investigation. Bashford, in analyzing English statistics, concludes that there is no trustworthy evidence whatever to show the existence of any such hereditary taint, and states that in his thousands of experimental animals there has been nothing to show that it occurs. Even when carcinoma-bearing animals were intentionally inbred, so as to increase the chance of inheritance, no larger number of spontaneous tumors was found than occurred in normal mice. Murray shows, however, in a later paper from Bashford's laboratory that the incidence of spontaneous cancer is much higher in mice whose immediate ancestors developed cancer than in those in whose pedigree only remote ancestors were cancerous. Tyzzer found that the susceptibility of a parent mouse to inoculation with a certain tumor may be transmitted to its offspring even though the other parent be insusceptible, and Maud Slye, from a large experience with mice, states that spontaneous tumors occur in the offspring of those which have had tumors, in accordance with Mendel's law. In her more recent experiments she has been able to mate animals, on the basis of her knowledge of this Mendelian heredity, in such a way as to bring about the appearance of tumors in the offspring, and even to plan for the development of a known type of tumor in a particular organ or location.

Wells, in a most interesting paper, discusses the whole question of our knowledge of the effect of heredity in the development of tumors, and concludes that resistance to the appearance of a tumor is a dominant character, while susceptibility is a recessive character in the Mendelian sense. He shows clearly that our knowledge of the exact cause of death, especially with regard to internally situated tumors, is extremely inaccurate and incomplete in the case of grandparents and other more remote relations, and that it must be so in a population where autopsies are so infrequent and the lapse of time with slowly succeeding generations so great. It will require a very long time to arrive at sufficiently

· accurate observations in the case of man. Even in mice the time required is long, and it is especially necessary that all the mice should be kept until their natural death and carefully studied at autopsy. This has been done by Maud Slye with more than 40,000 mice, and it becomes quite clear that the susceptibility to tumor growth is inherited precisely according to Mendel's laws, as shown by the appearance of tumors in the offspring of parents both of which had cancer, and the lack of tumors in the first generation when only one parent had cancer, although these offspring transmit, if mated with a cancerous mouse, the susceptibility to the next generation, in which cancer will then appear. The family charts showing the incidence of cancer must be studied in Wells' paper, where there are also diagrammatic charts of Mendelian inheritance, or in the papers of Maud Slye.

With this knowledge it has been possible to breed strains in which, since the mice are kept alive into old age, almost every individual will develop the particular type of tumor to which it has inherited the susceptibility. It is not a process which through death from the tumor obliterates itself, because the tumor does not appear until after sexual maturity and the production of offspring is over. Wells further emphasizes the extraordinary variety of tumors affecting all organs of the body that occur in the mice of this great collection, although, as in the experience of others, mammary cancers are most common. It is remarkable that a carcinoma of the liver, so rarely observed as a spontaneous tumor in mice, has been so cultivated by the inbreeding of those mice in which it occurred as to cause the death of nearly every one of the offspring for generations.

There seems every reason, from these observations, to believe that the same principles must exist in human beings, and that in them, too, resistance is the dominant, susceptibility the recessive character, and that the difficulty in recognizing concentrated strains of susceptibility is owing to the fact that inbreeding, in itself not productive of susceptibility, is avoided and uncommon, and that outbreeding tends strongly to annul the chance of such inheritance.

Morgan and his students have done something similar in flies, in which both malignant lethal and benign tumors develop. Their work has been especially concerned with the recognition of the particular chromosome with which this hereditary growth is associated. These studies appear to offer a whole new conception of the nature of tumor growths, but it is scarcely yet possible to interpret them with certainty.

The incidence as affected by age is more clearly recorded. It is a matter of general experience that carcinomata tend to appear in persons who have reached or passed middle age and are rare in young people. On the contrary, many sarcomata and those mixed tumors which sometimes occur congenitally are more frequent in young people. It is possible that some of the contributory causes which favor tumor growth are really necessary in the case of cancerous tumors, for it is known that, while cancers originate in old persons and old animals which have long been exposed to those influences, young mice are far more susceptible than old ones to the artificial implantation of these tumors.

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## CHAPTER LXXV

### GENERAL DISCUSSION OF TUMORS (Continued)

*Resistance and immunity. Theories as to the aetiology of tumors: Parasitic origin; effect of irritants; disturbance of equilibrium of tissues; displacement of embryonic cells. Changes in structure and mitosis in cells; abnormal metabolic activities of cells. Fundamental changes in cells releasing them from laws of normal growth.*

#### RESISTANCE AND IMMUNITY

ONLY the briefest outline of this subject can be given here, although an enormous amount of labor has been devoted to it in recent years.

Undoubtedly, many persons are highly resistant or incapable of harboring certain forms of tumor growth, although they may be susceptible enough to the growth and extension of another form. We have no way of determining this accurately, but we do know that when a tumor is already established in the body and is discharging into the circulation many emboli of its cells, most of these may be destroyed by the activities of the tissue fluids. Much light has been shed upon the question by the experimental study of tumors in animals. In mice, for example, malignant tumors which are transplanted from spontaneously developed nodules to normal mice fail to take at first, except in a very small percentage of the experiments. Later, with increasing adaptation to the conditions met with in the body of the mouse, the tumors, after repeated transplantation, acquire the power of growing in nearly every inoculated mouse. Nevertheless, there are some mice which show themselves refractory to the best adapted tumors. This is a natural immunity. If a mouse recovers spontaneously by destroying the tumor growth already begun in its tissues, or even if the tumor is completely extirpated after growing for a time there, it becomes immune and cannot be again inoculated successfully with that tumor. It is even immune with respect to other tumors, and Ehrlich has named this condition panning immunity. In this respect immunity from experimental tumors differs from the more specific immunity against infections. Even the inoculation of tissue or blood from another normal animal of the same species will confer an immunity from tumor inoculation. In all cases the immunity is dependent upon the inoculation of living cells, whether they be tumor-cells or those of the normal tissue. Ehrlich has offered an explanation of immunity which rests on the idea that a tumor requires for its growth a certain specific substance. He found that, by inoculation of a rapidly growing tumor, he could render impossible the growth of a second tumor, and, thinking that the first tumor had used up all this specific food substance, called this condition *athrepsia*. There have been many attacks on the validity of this theory, and it is not yet decided whether it will hold, since many investigators have found it possible to implant a second tumor in an animal already bearing one.

The well-known zigzag transplantation from mouse to rat and back formed the strongest element of Ehrlich's proof. A mouse tumor implanted in a rat grows for a few days, but then regresses and dies, unless it be retransplanted into a mouse, where it once more thrives. Ehrlich thinks that the tumor must have lacked a particular food-stuff in the rat, necessary for its growth.

These principles have not been applied to any great extent to the study of human tumors, and little is known of the conditions of immunity in the human body.

**Histological Character of the Immunity Reactions.**—Several writers, among whom da Fano may be mentioned, have studied the histological reaction to the invasion of tumors and have found that lymphocytes and plasma-cells are especially concerned in this reaction. Murphy and his associates have found, that the susceptibility to tumor implantation is enormously increased by the destruction of the lymphocytes by exposure to the *x*-ray or by the administration of benzol. They look upon the accumulation of lymphocytes about a tumor, for this reason, as a protective or combative reaction. These views are supported by others of their experiments which show that an embryo in which no lymphocytes have yet appeared is extremely susceptible to tumor inoculation, while the implantation of a fragment of lymphoid tissue from an adult into the body of the embryo confers upon it a resistance practically equal to that of the adult. It is surprising, if this proves to be true, that the metastases from malignant tumors are usually primarily in lymph-nodes where they grow, surrounded by lymphoid cells.

Shirai (Japan Med. World, 1921, i, 14) has shown that, if the inoculation be made into the substance of the brain, a tumor can be transplanted from one animal to another of quite different species and will grow to a large size. Mouse tumors thrive in the brain of a rat or of a pigeon. Murphy and Sturm have confirmed this, except that they have not succeeded in so implanting a spontaneous tumor, and they show further that the transplantation of a tumor already long adapted to experimental inoculation will thrive in the brain of the heterologous animal only if it be completely buried in brain tissue. If the graft extend into the ventricle or is in contact with the meninges it is soon destroyed. They also show that the growth of the foreign tissue in the brain may be completely inhibited by the simultaneous inoculation of a small bit of autologous but not by a bit of homologous spleen tissue. Mice highly immune to subcutaneous transplants of mouse cancer show no resistance to such tumors when the inoculation is made into the brain.

The explanation of this is not easy, but it would appear that, as in the case of the embryo, which is so susceptible to the implantation of any tumor, the interior of the brain tissue is a place protected from the advent of lymphocytes which seem so important in the protection of the animal against tumor growth.

**THEORIES AS TO THE AETIOLOGY OF TUMORS**

We have already discussed several of the tendencies of the last few years toward explaining the growth of tumors by the influence of filterable viruses, specific hydrocarbons, or by the materials secreted by endocrine glands which are often so closely related in chemical structure to these specific hydrocarbons. But it is as well since these studies are practically at their very inception, to consider at least the ideas which have been put forward in former years as to the cause of tumor growths.

**Theory of the Parasitic Origin of Tumors.**—Even if we accept the existence of a living organism as the cause of tumor growth it will be necessary to think of it as indissolubly associated with its particular type of cell and unless, when a cell-free filtrate containing this virus is inoculated, the virus is immediately caught up locally by the appropriate cells it seems that it might be circulated and stimulate those cells in many parts of the body. But instead it seems to affect the cells with which it comes into direct contact and is so included in them as to multiply with them, producing quite remarkable changes in the whole behavior of those cells. In this intimate relation with the cells its inconspicuous presence is overshadowed by the new qualities in the tumor-cells and so far it has rarely been demonstrated. There must be a different parasite for each of the many sorts of tumors, and every one of these parasites must have these characters of intimate affinity for the special cells which it chooses to stimulate. It must merge its ability to produce antibodies in the affected animal in that of the cells, since that immunity seems to be of cytotoxic character and not very specific. Lambert has shown that tumor-cells will grow *in vitro* in the plasma of an animal insusceptible to the growth of that tumor, but are injured or destroyed by the plasma of an animal immunized against it. Since a cytotoxic immunity can be produced against the implantation of the tumor by the introduction of normal tissues of an animal of the same species, the parasite must be killed, too, and must, therefore, have acquired the specific character of the cells.

**Theories of Tumor Growth Based on the Effect of Irritants.**—Numerous instances of tumor growth following upon irritation or injury with inflammatory reaction have been mentioned, and there has long been a desultory argument tending toward the emphasis of their importance as causes of tumor growth. Bashford lays stress upon the direct connection which is so often observed, and although it fails in most cases, it is very striking when it does occur. Most of these tumors appear after the irritation has existed a long time and has produced extensive inflammatory infiltration and reparatory changes in the underlying connective tissues, as well as in the epithelium itself. No one has succeeded in producing them experimentally, except perhaps by the use of *x*-rays or tar, or the introduction of certain gross parasites, and the question arises as to whether a predisposition through senile changes or otherwise may not be necessary for their initiation.

The idea of the influence of irritants recalls to our attention the

whole question of the action of stimuli upon the growth of tissue, which has been so long discussed. Many investigators accept the existence of direct stimuli to growth, and bring forward numerous instances in the history of tuberculosis, syphilis, and a host of other infectious diseases and banal injuries. Others hold that the tendency to grow is roused only indirectly through functional needs, and Weigert has claimed that new-growth is essentially a reparatory process, attempting to make up for tissue which has been destroyed, thereby restoring the disturbed equilibrium of the tissues. In ordinary circumstances it is usually possible to explain the new-growth of tissue as the effect of reparatory processes, even though in some cases of excessive growth it often appears that it is the response to repeated injuries which may affect the repairing tissue itself. Nevertheless, this explanation is complicated, and it is much easier to assume that injuries or irritants may directly stimulate the tissues to grow. In any case the new tissue remains subject to the general laws which govern the architecture of the body, and tends to return to the normal relations when the irritation ceases.

In the case of a tumor, a new element is introduced by the failure of the tissue to evince this general tendency to return to the normal relations after the irritation has ceased. The finality of its departure from the laws of growth is as though a train suddenly ran off the track, and through the neighboring streets and houses. Even though we accept the idea that irritation may directly stimulate tissue to grow, our explanation of the history of a tumor must really begin with its continuous independent and unlimited growth, which might be initiated, but not maintained in distant situations, by such irritants as are usually discussed.

**Theories of Tumor Growth Depending upon Disturbance of the Equilibrium of Tissues.**—So firmly established is the evidence of mutual support and restraint among the tissues, that many writers have sought, in a disturbance of this equilibrium, the explanation of the unlimited growth of tumors. Thiersch thought that, with senility, the energy of growth of the connective tissue failed, so that the epithelium could invade it and grow at will, while Waldeyer offered the reverse explanation, stating that the failure of the epithelium to maintain its ranks enabled the connective tissue to surround and isolate some of it, which then grew in its new situation. The inadequacy of these explanations is evident, and Hansemann pointed out at once the fact that tumors occur in the young and are especially malignant. Ribbert has pursued these ideas, explaining the ingrowth of epithelium as dependent upon primary changes in the underlying connective tissue, which becomes relaxed and infiltrated with leucocytes, so that it is exposed to the invasion of the epithelium, which it surrounds and isolates, thereby allowing unlimited growth through the disarrangement of equilibrium. The inflammatory infiltration of lymphocytes, upon which Ribbert lays stress, appears now to be the protective reaction which Murphy has shown to be so important in preventing the extension of tumors. Ribbert, therefore, thinks of tumor growth as resulting from a displacement of cells, even in adults, produced by abnormalities in surrounding tissues,

and does not regard these cells as biologically different from normal cells, but turned to tumor growth by the unusual conditions in which they are placed.

**Theories of Tumor Growth Depending Upon Displacement of Embryonic Cells—Cohnheim's Theory.**—Another theory, associated especially with the name of Cohnheim, assumes that since certain tumors which occur congenitally are traceable to congenital maldevelopment, it is possible, or even probable, that a disarrangement of cells in the course of embryonic growth may lie at the root of tumor growth in general. Cohnheim's idea was that at some stage of embryonic life cells or blastomeres might become isolated while still possessed of great energy of growth and potentialities which would have carried them on to the development of some specific tissue of the body had they remained in their normal connection with the rest of the cells of the embryo. These cells are conceived of as lying dormant among the growing tissues, and showing no tendency to unfold their own powers of growth during years. Then, when the other tissues have become organs of an adult man, and commonly late in the life of this man, the hidden group of cells, still endowed with embryonic vigor, begins to grow. Cohnheim did not think that these cells would begin their growth without some stimulus, but that, once started, they would exhibit a capacity for growth comparable only to that of the embryo.

Numerous criticisms have been made, of course. It is difficult to believe that such misplaced cells or groups of cells could remain latent for many years and still maintain their youthful vigor. Further, it is known that when such displacements of tissue obviously occur the cells tend to proceed through their allotted course of maturation and development to produce finished tissue, rather than to continue as embryonic cells, although there are some teratomata in which the peculiar form of cells has been interpreted, rightly or wrongly, as embryonic. Since tumors may occur anywhere, and are frequently initiated by irritation, it is necessary to assume an extremely wide distribution of displaced cells if a group of them is to be ready wherever the irritation may act. While Cohnheim's theory may explain perfectly the teratomata and other growths which are obviously related to foetal inclusions, it does not explain the malignant type of growth, since it does not explain why the cells of a tumor behave differently from those of an embryo, in that they continue to grow in the same atypical form and never proceed to anything resembling the end-product of tissue growth.

Somewhat analogous to these theories which invoke the aid of the embryonic energy of growth are those more faintly expressed ideas which depend upon the possibility of a new fertilization. J. Loeb has shown that the eggs of some animals may be stirred to parthenogenetic development by the action of chemical substances. The disturbance of the lipoid sheath by some solvent, allowing the oxidative processes to go on, appears to be the mechanism concerned, and this explanation has been transferred to those experiments in which the introduction of scharlach oil, ether water, etc., have stirred up a new-growth of cells. There have, indeed, been efforts to show that an actual conjugation of

adjacent cells may take place after a preliminary heterotypic division, with reduction of chromosomes to half their normal number (Farmer, Moore, and Walker). Such conjugation ought to confer a new impulse to growth, exactly as in the fertilization of the ovum. Rotter has elaborated on this idea in that he recalls the possibility that primitive sex-cells, in their wandering into the tissues of the embryo, may accidentally lodge anywhere outside the ultimate sex-glands. Such cells, through a stimulus to parthenogenetic development, might be thought of as an origin for tumor growth. The idea is a most tempting one and the work of Bosaeus, described above, seems to support it strongly, at least as far as concerns the formation of teratomata.

**Theories of Tumor Growth Depending upon Changes in the Cells.—**

Hauser was among the first to insist that tumor growth could be explained only on the assumption of a profound change in the character of the cells of which it is composed. He speaks of new cell races, and recognizes especially their independence and their arrogance in overcoming other tissues and cells. Marchand, Beneke, and Ziegler hold somewhat similar views. Hansemann has elaborated the idea by attempting to define the character of this change in the cells, which he describes as *anaplasia*, an alteration in the cell not always easily recognizable by its form, but consisting in changed histological characters which allow it to proliferate rather than to functionate. This, in its more intense degrees, is accompanied by changes in form and arrangement of the cells, and is associated with atypical or asymmetrical mitoses. Anaplasia is not the cause of tumor growth, but the term is descriptive of the changes which occur in the cells. Borst, recalling the infinite complexity of the process of distribution of parental characters to all the cells of the developing body, regards the change in the cells which leads to tumor growth as due to some irregularity in the formation of their "idioplasm," which one-sided development does not necessarily incapacitate them for an ordinary function in the ranks of other cells, but leaves them capable of independent and atypical growth. Schwalbe adheres to this idea, which he expresses differently, inasmuch as he speaks of congenital pathological abnormality of the cells, or cell malformation.

Lewis feels that malignant tumor cells are readily recognizable as distinct from normal cells in live tissue cultures. Differences are evident in their cytoplasm, their nuclear division and in their metabolic activities as well as in their movements. He finds irregularities in the separation of chromosomes upon division which not only lead to the formation of more than two cells, but to cells with unequal numbers of chromosomes and even to the isolation of a few chromosomes in vesicles in the cytoplasm. The question has arisen as to whether such cells with few or many daughter chromosomes continue to live and divide, but apparently they do, as Lewis has shown. He favors the idea that cytoplasmic or general changes cause the peculiar behavior of tumor cells, and not especially the abnormalities of chromosome division.

It seems that these cells have lost respect for the laws which govern the relation of the cells of the normal tissues, and behave like outlaws.

Boycott suggests that they obey laws of their own, and indeed the recognized character of tumor growth may support this idea. Certainly they acquire a new nature which is different in its whole aim from that of normal cells and as permanent for them as the distinctive characters of animals and plants.

**Theories of Tumor Growth Depending Upon Metabolic Activities of the Cells.**—Warburg has recently brought forward the idea that the cells of a cancer differ from normal cells in that they have a very much greater power of glycolysis, with liberation of lactic acid, which process, as in the consumption of sugar by muscle, is associated with great production of energy which he thinks of as energy of growth. The respiratory oxidation is not greater than normal. The only normal tissue found to behave in this way is the retina, which has a great glycolytic power, while the tissue of an embryo has very little. It is not quite clear why it should be assumed tacitly that the energy from the decomposition of sugar should be applied to the forcing of cell division and growth, especially since we see no such result in the retina. It might perhaps be thought of as the effect of the rapid growth rather than its cause. Waterman writes in much the same sense, finding that the tissue of the pancreas is active in glycolysis. He thinks the acid produced is important in the act of cell division just as fatty acids are powerful excitants to parthenogenesis. Now that the whole theory of the metabolism of muscular contraction is changed, it seems that attention may perhaps be directed to the creatine-phosphate combination rather than to the lactic acid.

Falk and his collaborators compare the lipase action of tumors with that of normal tissues. Each tissue and tumor seems to produce characteristic but different curves the significance of which is not yet clear.

It was said in the beginning that we do not know the cause of tumor growth, and it seems quite unprofitable to attempt new theories except on the basis of adequate new facts. Those at our disposal have been so well pondered over that the newer theories prove to be merely the invention of new terms to express the old vague ideas.

Nevertheless, I must express my own impressions of what has been learned and written of tumor growth without advocating any new theory. We have a fairly clear conception of the laws of normal growth from the beginning to the end of life. Those laws apply equally well to the growth of the embryo and to the growth of the adult. Tumor growth does not obey these laws, but transgresses them in every direction. It seems idle, therefore, to attempt its explanation by assuming that embryonic cells persist and grow in the adult body. That may explain teratomata very well, since they are essentially finite growths that obey the normal laws as well as they can with their incomplete tissues and in their cramped situations. But it does not explain the growth of tumors.

On the other hand, we are quite familiar with the effects of every sort of injurious influence in disturbing temporarily the normal growth of tissue, and can formulate general laws for these effects which are found to be always respected. But tumors do not respect them at all.

For that reason I have written of tumor growth separately from all the rest of pathology as a thing apart, not to be dealt with according to the laws of reaction of normal tissues. Although we discuss every sort of injury as a possible cause of their growth, we cannot conceive of a mechanism by which injury could produce this result in normal cells, nor of a parasite that could do it.

We are left with the impression that there is somehow produced a sudden, profound, and permanent change in the character of the cells themselves, and that other tissues which are invaded or form the stroma are affected by their activity; but although we realize this irrevocable change, we cannot assign a reason for it, nor even tell precisely in what structural alteration it may be recognized.

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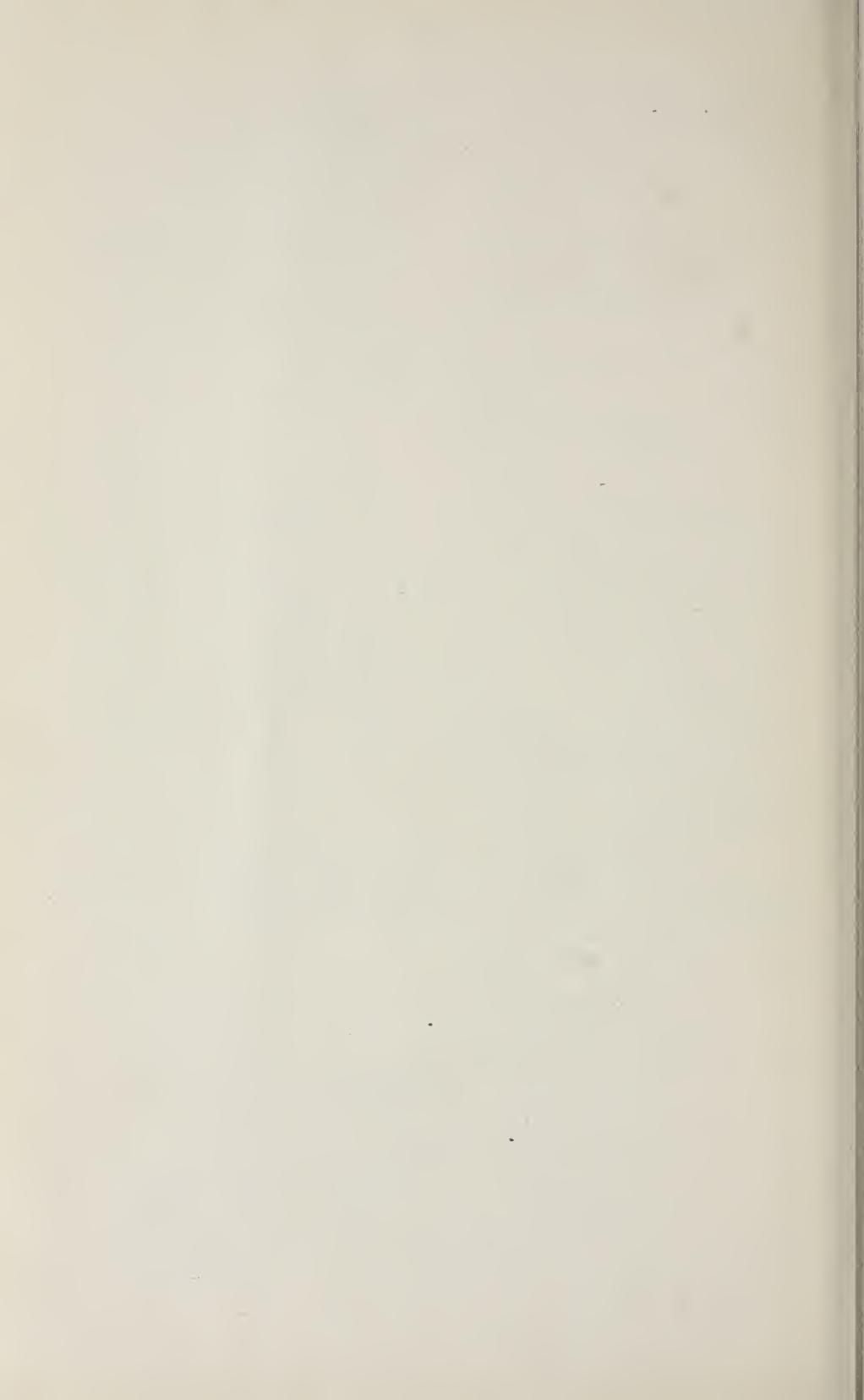
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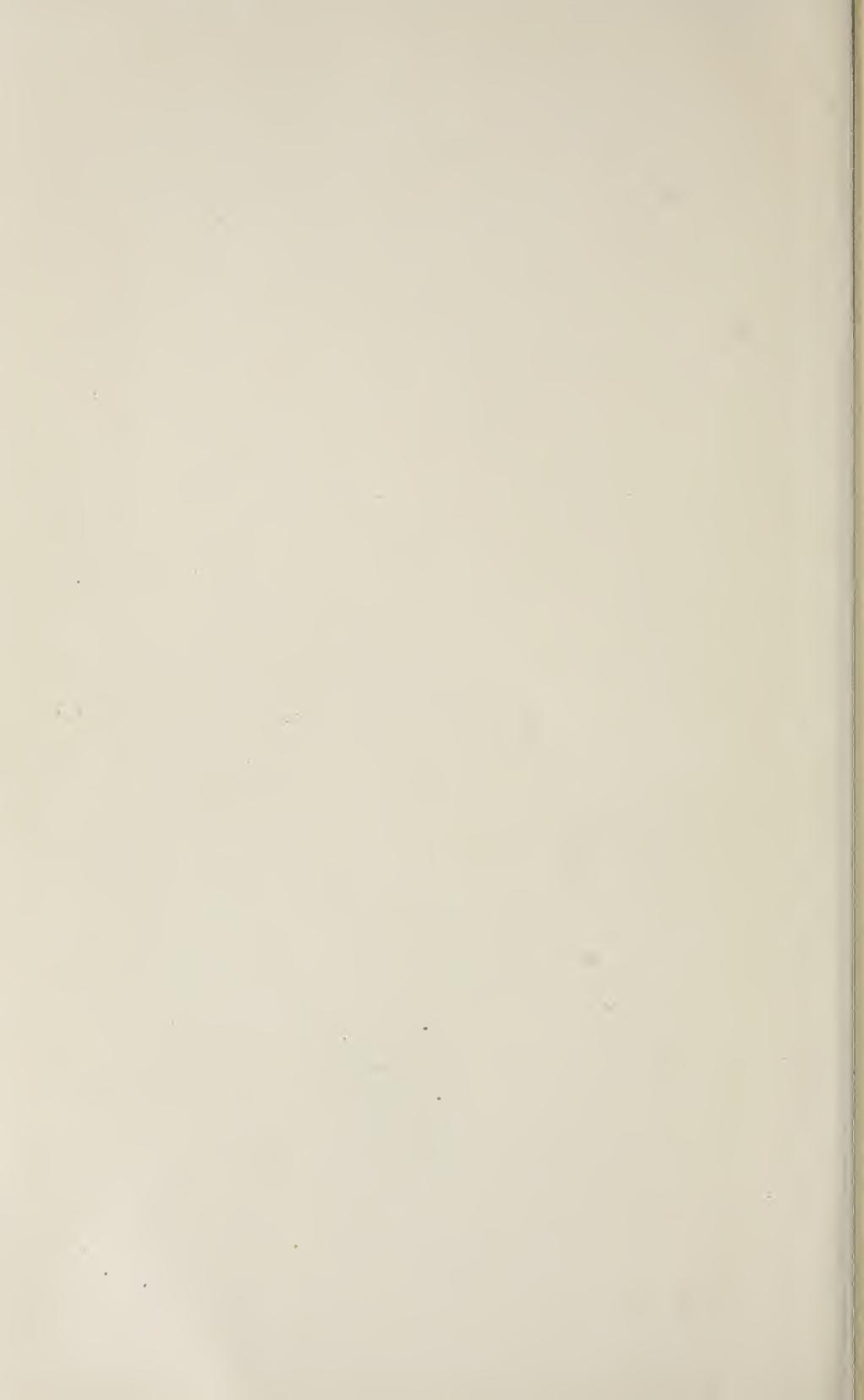
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