and have a tendency to disappear spontaneously at about the time of puberty or earlier. They consist of localized irregular thickening of the epidermis and slight infiltration of the stroma by lymphocytes and large mononuclear phagocytes. Since carcinomas are almost unknown in this age group, malignant disease does not often come into question in the differential diagnosis. Removal of the tumors is often followed by recurrence. Viruses are generally thought to be the causative agent. No contributing causes are recognized. In the adult, a similar papillary tumor occurs on the anterior one-third of the vocal cords or any other portion of the larynx. They do not show the same tendency to recur as observed in young children. Since they are most frequently seen in the same sites as carcinoma, biopsy and microscopic examination are essential for establishing the diagnosis in the early stages. See also discussion on page 708.

Mesothelioma of the Pleura (Pleural Endothelioma).—In rare instances, the pleura is found at necropsy to be extensively thickened and infiltrated with tumor cells completely covered by large plaques of firm gray tumor tissue. Before the turn of the century, many of these cases were classified as primary endothelioma of the pleura, while, at the same time, cases of bronchial carcinoma were rarely recorded. During the last four decades, cases of bronchial carcinoma have been recognized with progressively greater frequency and primary neoplastic disease of the pleura has become a rarity. Undoubtedly most of the instances of diffuse neoplastic involvement of the pleura were cases of unrecognized bronchial carcinoma with extensive secondary pleural involvement, but there appears to be a small residue of cases in which, even with meticulous examination of the bronchi, no intrapulmonary tumor can be discovered. These are thought by some to be primary neoplastic growths of pleural mesothelium. The visceral pleural is more extensively involved, but there may be extensions to the parietal pleura as well. If the parietal membranes are more seriously involved than the visceral, the mammary glands should be examined carefully for the site of a primary tumor.

The histologic picture is not uniform. Both large cell and small cell "mesotheliomas" have been described. Some resemble carcinomas and some sarcomas. All of the appearances which have been described as characteristic of mesotheliomas can be imitated by bronchial carcinomas. Much more evidence than is now available must be produced before the question of the existence of primary neoplasms of the pleural mesothelium can be decided.

MEDIASTINAL TUMORS

The commonest tumors of the mediastinum are the solid, malignant neoplasms which occur as lymphogenous metastases to the mediastinal groups of lymph nodes, either arising from primary cancers of bronchi, mammary glands, or intra-abdominal organs, or occurring as a part of the more general involvement of lymph nodes by malignant metaplasia of the hematopoietic system (e.g., lymphosarcomatosis, leukemia).

The anterior mediastinum is the site of most of the tumors of developmental origin. Lobules of thyroid tissue, misplaced during embryonic development, occasionally come to lie posterior to the sternum but do not give rise to symptoms unless great enlargement occurs as a result of hyperinvolution with nodulation and cyst formation or rapid swelling as the result of intracystic hemorrhage. The commonest disturbance is that of displacement and compression of the trachea. Hyperplasia and neoplasia of the thymus are discussed in Chapter 33, page 956. The dermoid and teratoid tumors which arise in this location are structurally similar to those more commonly found in the gonads. The theories of embryogenesis have been critically reviewed by Schlumberger[136] who accepts the view that "teratoma of the anterior mediastinum probably arises from tissue dislocations in the anlage of the thymus." There are all gradations between the so-called dermoid cysts, lined by epidermis with its appendages, often including hair, and the complex teratomas which are composed of derivatives of all three germ layers. A relatively large proportion of the latter give rise to malignant neoplasms but considering the entire group, about nine-tenths are benign. Most of these tumors have been discovered in children and young adults. They are equally uncommon in the two sexes.

In addition to these, but much less numerous, are developmental cysts springing from misplaced tracheal or bronchial buds (bronchial cysts), abnormal buds from the foregut (gastric cysts and gastroenteric cysts), and maldevelopment of mesodermal tissues (pericardial celomic cysts and cystic lymphangioma). The bronchial cysts usually lie near the tracheal bifurcation in the upper portion of the posterior mediastinum but may be found almost anywhere along the trachea or bronchi. The usual site of the gastroenteric cysts also is in the posterior mediastinum. In addition to six types of congenital cysts, Laipply[137] has included three types of acquired cysts of the mediastinum (parasitic cysts, cystic degeneration of solid neoplasms, and cystic degeneration of hematomas).

Other tumors which are peculiar to the posterior mediastinum are chiefly those derived from the sympathetic nerves and ganglia. Their characteristics are similar to those of the neurogenic tumors of the neck, posterior abdominal wall, and pelvis. The more malignant forms, the neuroblastomas, sympathogoniomas, and ganglioneuroblastomas, tend to occur in the younger age groups while the more mature, encapsulated, slowly growing neurofibromas, neurinomas, and ganglioneuromas (see page 1303) are more often seen in the older age groups. Both types are uncommon, particularly the malignant forms.

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Chapter 24

THE ORGANS OF SPECIAL SENSES

J. E. Ash

This chapter is intended to emphasize special features in the pathology of the eye, ear, nose, throat, and larynx. A basal cell carcinoma of the eyelid or a transitional cell carcinoma of the tonsil is not a special problem to the general pathologist, but there are few of the latter who know what the ophthalmologist means by keratic precipitates or who understand the significance of an epibulbar nevus. The selection of subjects is influenced by experience gained through the various registries at the Armed Forces Institute of Pathology.

EAR

Perichondritis is a not uncommon lesion, and important because of its serious clinical possibilities. A low-grade infection begins in the subcutaneous tissue, usually in the upper margin of the helix, or as a furuncle in the external auditory canal with a serous to purulent exudate causing elevation of the perichondrium. If the condition is not carefully treated, it may run a protracted course and lead to destruction of the cartilage of the entire concha to produce marked deformity. Characteristic are the cyst-like spaces beneath the perichondrium which may contain clear fluid. In the more virulent infections, pus may fill the cystic spaces and a purulent exudate invade the cartilage. The hyperplasia and ulceration of the overlying epidermis can be misinterpreted as carcinoma.[1] (Fig. 569.)

Cauliflower ear is simply a deformity of the external ear produced by keloid hyperplasia of connective tissue beneath the epithelium, the result of repeated trauma experienced by prize fighters and wrestlers. It has the persistence of keloid in other situations and the pathologic changes are the same.

Gouty tophus is an almost extinct lesion of the external ear. Deposits of sodium biurate in the soft tissue and cartilage produce focal foreign body reaction and chronic productive

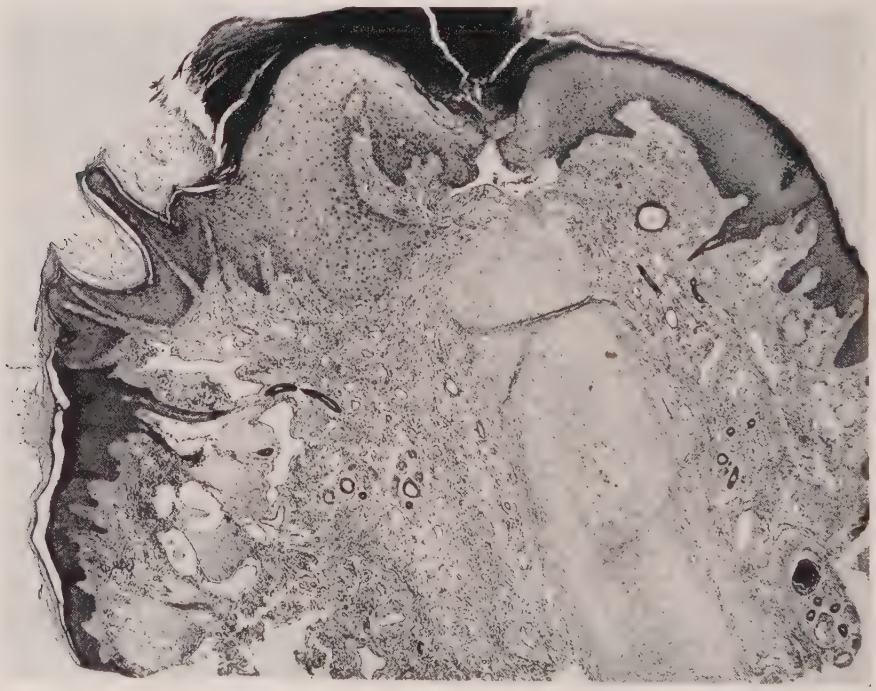

Fig. 569.—Perichondritis helices. Verrucal hyperplastic and ulcerated epidermis, chronic inflammatory reaction involving perichondrium.

All illustrations throughout this chapter are from the files of the Armed Forces Institute of Pathology.

fibrosis. There is atrophy of the overlying skin, but ulceration, if present, is the result of trauma.

The troublesome inflammatory conditions of the external auditory canal are of more interest to the clinician than to the pathologist, but the latter may be called on to help in their differentiation by smears and cultures.

Folliculitis of the hair follicles is the most painful. This is comparable pathologically to acne, but is usually more fulminant. It may be accompanied by a pyogenic eczema, or the latter may occur alone.

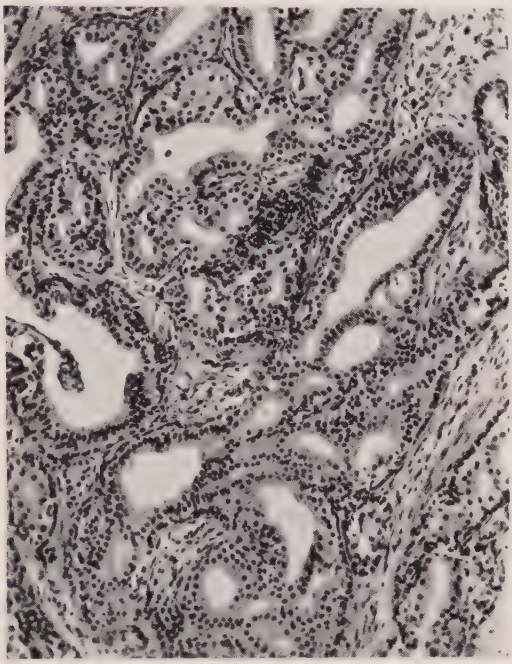

Fig. 570.—Adenoma, external auditory canal.

Otomycosis is a refractory eczematoid and lichenoid involvement of the skin of the canal. A variety of fungi have been incriminated, but the two commonest are *Aspergillus* and *Penicillium.* The identification of mycelia and spores among the outer layers of the epidermis in direct sodium hydroxide preparations is the specific feature in histologic examination. In the absence of pyogenic infection there is surprisingly little subcutaneous inflammatory reaction, but when complicated by pyogenic infections, the cartilage of the canal may be involved. The tympanic membrane is rarely so, however.

Seborrheic dermatitis is characterized clinically by eczematoid, scaly, slightly moist changes in the lining of the external canal and in the epidermis of the external ear. The scalp and other hairy parts of the body are commonly involved, an aid in its diagnosis. Unless actively treated by the dermatologist, seborrheic dermatitis may be protracted and may be complicated by secondary pyogenic infection. The histologic picture is not specific but is a subacute dermatitis, not distinguishable from eczema, with acanthosis, spongiosis, and possible vesicle formation. In contrast to the dermatomycoses there is perivascular inflammatory reaction which may extend below the capillary bed.

There are two tumors of the external canal worthy of note. **Osteoma,** which is not always truly neoplastic but more in the nature of exostosis, is possibly the result of an inflammatory process. This bony mass, found most commonly at the junction of the osseous and cartilaginous canal, may be of sufficient size to occlude the canal. Histologically the picture is that of well-differentiated periosteal bone. A rarer tumor is **adenoma** arising from ceruminous glands. The gland elements bear a close resemblance to those in the so-called Warthin's tumor (papillary cystadenoma lymphomatosum) of the neck, but there is not the associated papillomatous feature nor the lymphatic tissue element. This tumor can be considered benign (Fig. 570). It is commoner in dogs and cats.

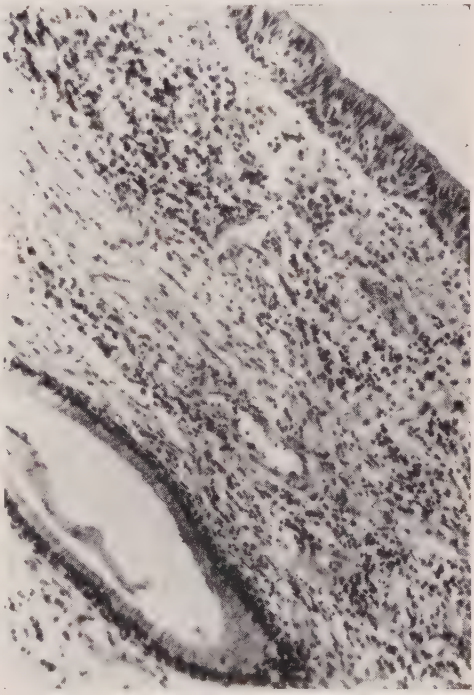

Fig. 571.—Aural polyp with pseudogland inclusion.

The tumor most frequently referred to the pathologist is the **aural polyp.** It arises in the middle ear as a complication of chronic suppurative otitis media and protrudes into the external canal through a perforated tympanic membrane.

The histologic picture varies considerably; the most usual one, however, is that of richly vascular granulation tissue with the stroma liberally filled with polymorphonuclear and mononuclear exudate, although at times the

fibrous stroma is of a more neoplastic character. The covering epithelium varies from the normal cuboidal or columnar cells of the tympanic cavity to the stratified epithelium of epidermal nature. Ulceration of the surface is common. At times, glandlike masses of the columnar epithelium are found in the deeper portions of the tumor. These inclusions may develop into retention cysts (Fig. 571). In instances in which the included epithelium is squamous there may be a keratoma, one of the clinical forms of cholesteatoma.

Cholesteatoma is a serious sequel of chronic otitis media and mastoiditis. The term is an unfortunate one but will be hard to eradicate because it is so fixed in clinical parlance. Cholesterol is present at times, but actually the lesions are simply squamous epithelium growing in a confined space and, if they must be considered neoplastic, would more appropriately be called keratomas or pearly tumors. The origin of the squamous epithelium is, in the large majority of instances, from the epidermidalization of the mucosa of the middle ear or mastoid,

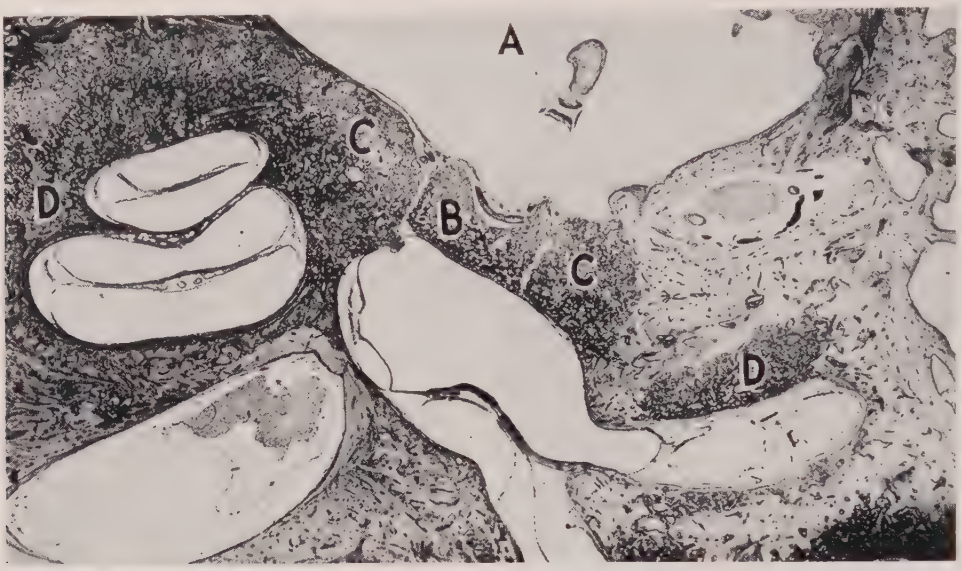

Fig. 572.—Otosclerosis, middle ear (*A*), including section of incus, and stapes, foot of which (*B*), is greatly thickened and ankylosed to rim of oval window (*C*). Portions of the bony labyrinth (*D*) and the rim of the oval window are also involved.

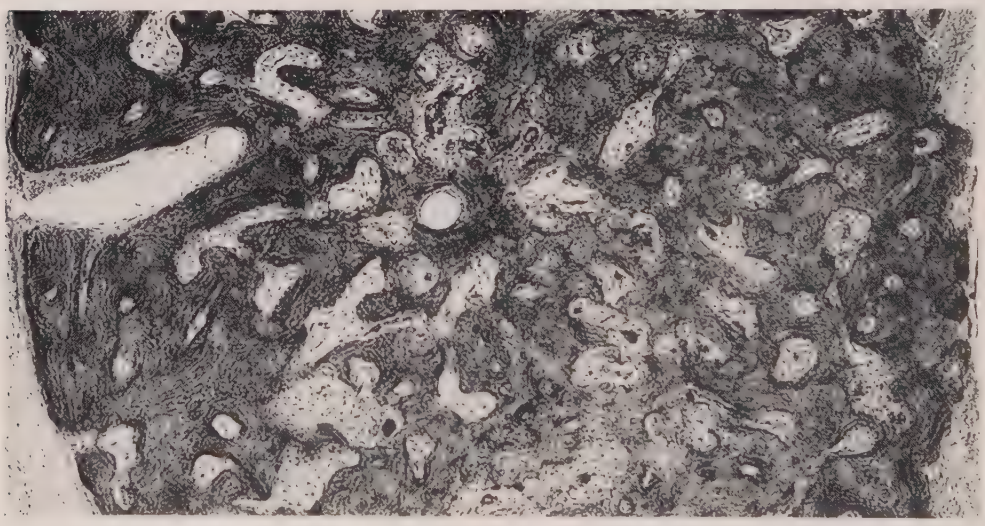

Fig. 573.—Otosclerosis, high power. (Courtesy Dr. S. Guild, Baltimore, Md.)

either by extension of the squamous epithelium of the external canal through a perforation in the tympanic membrane, or by metaplasia of the local epithelium to a squamous type. The occasional instance of cholesteatoma without previous chronic suppurative inflammation is possibly the result of epidermal inclusion during the development of the ear. The seriousness of cholesteatoma depends on its location. If it is an element in a polyp, or confined to the external canal it may be readily eliminated, but if it is in more inaccessible portions of the temporal bone, such as the attic or the mastoid, there may be pressure erosion of the bone into vital structures, e.g., the lateral sinus or cranial fossae. Extirpation, except by radical surgery, is difficult even when only the tympanic cavity is involved, because the epithelium may have extended into the Haversian canals of the bone and thus escape removal. Lesions in the mastoid have a distinctive appearance in the x-ray picture.

The pathologist usually receives fragments of tissue that consist of well-differentiated squamous epithelium with rete pegs and a robust malpighian layer—unless they have been distorted by too great pressure—that are overlaid by flakes of keratinous debris. Cholesterol crystals are more likely to be found in tumors in which the contents have more substance, indicating complication by hemorrhage or exudate. **Squamous cell carcinoma** in the middle ear or mastoid is a rare complication of epidermidalization.

Aerotitis media has attracted much attention in aviation medicine. The pathogenesis is not as yet entirely clear, but aerotitis media is generally accepted to be due to rapid and repeated changes in barometric pressure in the presence of anatomic or inflammatory obstruction of the eustachian tube. The difficulty arises from the persistence of low pressure in the middle ear acquired at high altitudes after descent to the high pressure at low levels. The condition is characterized clinically by pain, tinnitus, and partial deafness. The drum is usually reddened and retracted, and there may be hemorrhage into the middle ear. After recurrent episodes the chronic inflammatory reaction in the tympanic cavity may produce permanent middle-ear deafness. The commonest pathologic change is hyperplasia of the lymphatic tissue elements about the pharyngeal orifice of the eustachian tubes. Considerable strides have been made in the prevention of aerotitis by reducing this tissue with radium. In other instances, however, the obstruction is the result of chronic inflammatory reaction in the mucosa, including hyperplasia of the mucous glands that are normally present in considerable numbers around the tubal orifice.

Otosclerosis is a dystrophy of portions of the bony labyrinth, especially that about the oval window. It is a common finding in the routine examination of temporal bones even when it is not evident clinically. When the hearing is affected, ankylosis of the foot of the stapes to the rim of the oval window is usual. The pathogenesis is not clear although a hereditary predisposition is probable, or it may be on a phylogenetic basis, representing a reversion to a piscine type of labyrinth which contains no oval or round windows. The condition is more common in females than males and is said to be rare among Negroes.

The distinctive pathologic features are localized patches of hyperplasia of the bone lamellae with a consequent narrowing of the Haversian spaces and a greater number of osteoblasts and osteoclasts than in the surrounding normal bone. There is little or no inflammatory reaction. The common sites of hyperplasia are the rim of the oval window involving the foot of the stapes, the promontory, and around the apex of the cochlea (Fig. 572), which are all at the junction of the periosteal and enchondral portions of the bony capsule. The changes never extend beyond the capsule and are usually confined to the enchondral portion.[2]

NOSE

Rhinophyma *(Pfundnase)*, an end result of acne rosacea, is characterized by nodular enlargement of the skin of the nose, especially of the alae, due to hypertrophy and questionable hyperplasia of the sebaceous glands. There may be a history of chronic alcoholism and a primary vascular involvement of the portions of the face which flush most easily, the nose, the malleolar eminences, and the chin, followed by acne rosacea.

The essential histologic features are greatly dilated sebaceous ducts filled with epithelial debris, inspissated sebaceous material, and marked hypertrophy of the acini. Not infrequently the mite *Demodex folliculorum* may be recognized in sections because of the basophilic and eosinophilic staining of its various structures. There may be chronic inflammatory reaction and scarring of the surrounding dermis. The squamous metaplasia of the gland epithelium at times may lead to an erroneous diagnosis of carcinoma. The process is amenable to surgical removal.

Rhinitis and Sinusitis

There are several points concerning rhinitis and sinusitis which should be emphasized because of their practical value. First, the mucosa of the turbinates, particularly of the middle, is characterized by its cavernous blood spaces and is classified as erectile tissue. This normal feature may be mistakenly interpreted as pathologic hyperplasia of vascular elements. Second, the mucosa of the turbinates, particularly of the lower and middle, is richly supplied with mucous glands, a feature which at times is also misinterpreted as pathologic. Glands are relatively abundant in the antral mucosa about the orifice, but are scarce in the mucosa of the other sinuses.

There is considerable parallelism in the lesions of the nasal and sinus mucosae. Biopsy is most common in *allergic* inflammation which, in its chronic and active state, is characterized by marked eosinophilia in the mucosa as well as in smears of the surface exudate, hyaline thickening of the basement membrane of the mucosa, and some degree of polypoid thickening. The specificity of the microscopic picture, the edema, and the eosinophilia, varies with the activity of the process. The appearance can be further complicated by secondary infection. In non-

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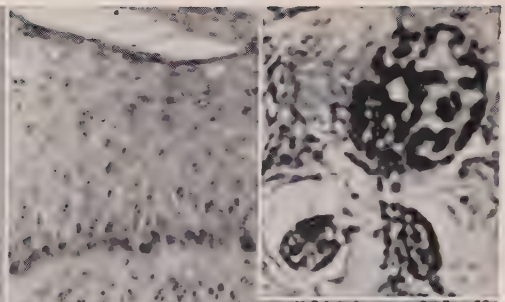

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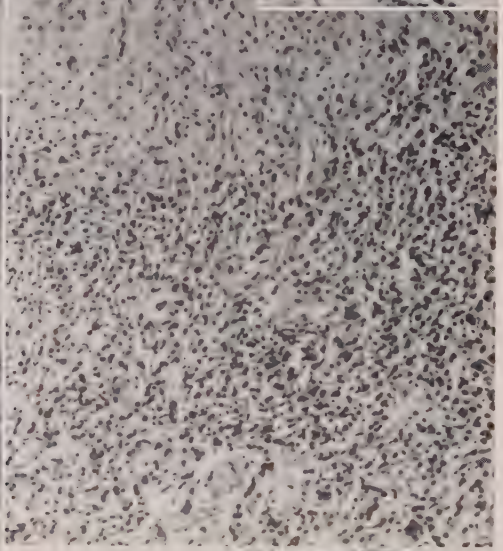

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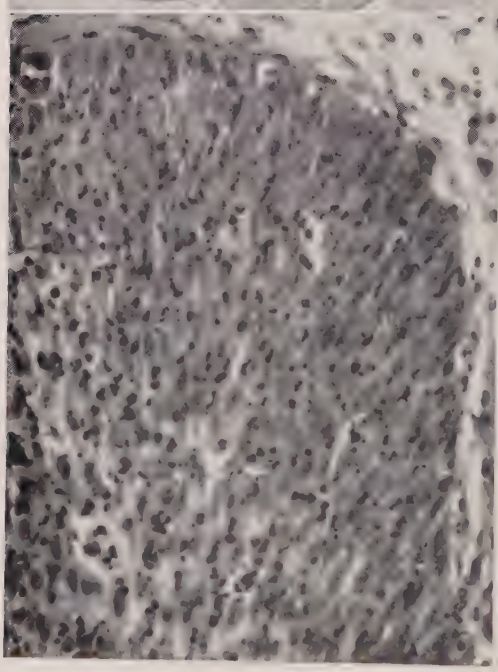

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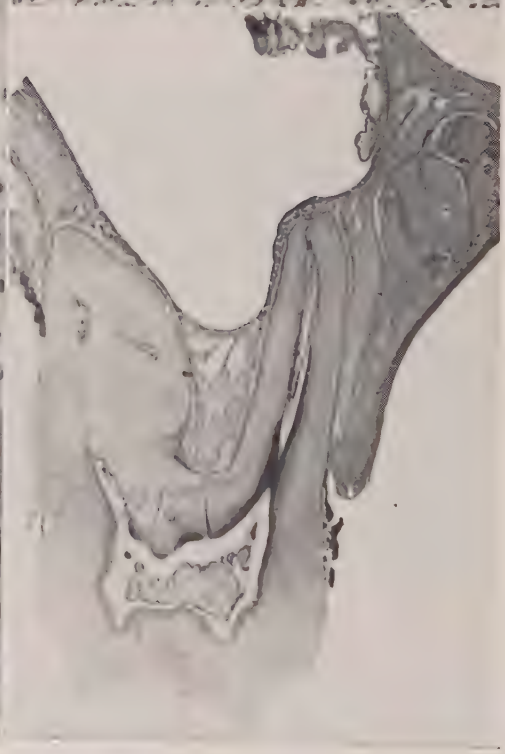

Figs. 574-579.—*For legends see opposite page.*

allergic types of inflammation there may be a small percentage of eosinophiles, and in long-standing conditions there may be diffuse fibrosis, secondary lymphatic nodule formation, metaplasia of epithelium, possible ulceration, and hemorrhage.[3] The striking feature in all forms, even in those of infectious etiology, is the relative sparseness of polymorphonuclear content in the exudate except at sites of active ulceration.

One of two specific types of rhinitis which require mention is **atrophic rhinitis**, or **ozena**, characterized clinically by widening of the nasal passages, marked crusting of the nasal mucosa, and a foul odor. The histologic appearance varies with the age of the condition. Early there is abundant mononuclear exudate, chiefly plasma cells and a few eosinophiles, and loss of cilia from the epithelium. Later, the exudate becomes more localized to the perivascular tissue, there is an increasing fibrosis of the stroma with atrophy of gland and vascular elements, and loss of surface epithelium. Characteristic is the marked muscular hyperplasia in the larger deep arteries.

The second specific lesion is **scleroma (rhinoscleroma)**, endemic in Mediterranean countries but occasionally met with in this country. It is so serious in its implications that it is necessary that its distinctive features be familiar to general pathologists. It is characterized clinically by nodular masses in the nose accompanied by more or less ulceration and a foul discharge. There is a persistent hyperplastic extension of the process that eventually fills the nostrils and the nasopharynx and may extend into the oral pharynx and trachea (Fig. 574). The tissue is characterized clinically by its cartilaginous consistency. The process is limited to the mucosa and to the skin. The deeper structures are not involved except at times by pressure atrophy.

The nonulcerated epithelium may undergo metaplasia to the squamous type and be acanthotic. There is great thickening of the subepithelial stroma by granulation tissue, by older fibrosis, and by areas of dense plasma cell and lymphocytic infiltration. Strands of dense collagenous scarring may extend irregularly through the tissue. Usually in the deeper layers, but at times superficially, are found the typical foamy mononuclear cells—the Mikulicz cells—in which *Klebsiella rhinoscleromatis* can be demonstrated (Figs. 575 and 576). This organism was formerly accepted as the etiological agent, but more recently it is suspected that scleroma may be a viral disease or one of symbiotic etiology.[4]

Rhinosporidiosis is a localized fungus infection which derives its name from its predilection for the mucous membrane of the nose, although it may involve any of the external mucous membranes. The lesions are pinkish red, friable, sessile or pedunculated polyps. The sporocysts are often visible grossly as white or yellow dots.

The disease is particularly prevalent in India, is apparently a water-borne infection, and rarely involves females. It is seen sporadically in this country. Though commonest in the nose, the conjunctiva, urethral mucosa and other areas may be involved. It remains a superficial infection.

In a vascular, edematous stroma, with many infiltrating cells, mainly lymphocytes and plasma cells, are the sporocysts in all stages of development, even the smallest of them with a doubly contoured, chitinous wall. The cyst grows as the nucleus undergoes repeated divisions until it reaches a diameter of from 200 to 300 microns and is packed with spores, only some of which mature. The sporangium, as it is called at this stage, ruptures at the pore, releasing the spores. There is a typical foreign body reaction to the collapsed sporangium[5] (see also page 350).

Polyps arising from the nasal and sinus mucosae, while indistinguishable histologically, vary in clinical behavior depending on their origin. Those arising from the turbinates are not so apt to recur as those that arise from the sinuses. The maxillary and ethmoidal sinuses are the commonest sites of origin. Polyps rarely develop in the frontal or sphenoidal sinus. The choanal polyp is one having its origin in the nose or antrum and extending by a lengthened pedicle into the nasopharynx.

In the older writings the nasal polyp was classified as a soft fibroma. It is true that neoplastic proliferation of connective tissue is at times a feature, but ordinarily the polypoid character is the result of edema, chronic mononuclear and eosinophilic exudate, vascular dilatation, and, at times, cysts. These are of two types: true retention cysts developing in occluded mucous-gland elements, and false cysts without a cellular lining, the result of pooling of the serous fluid. Secondary lymphatic follicles are not an uncommon finding.

The classification of polyps according to histologic contents has little practical significance but nevertheless is presented as follows: adenomatous, the result of origin near the orifice of the antrum or

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Fig. 574.—Rhinoscleroma extending to palate and pharynx.

Fig. 575.—Rhinoscleroma, histologic characteristics, scarring and dense plasma cell infiltrate.

Fig. 576.—Rhinoscleroma, high power of Mikulicz cell containing K. *rhinoscleromatis*.

Fig. 577.—Epithelial papilloma, nose, showing characteristic ribbony contour.

Fig. 578.—Epithelial papilloma of nose. In this instance, epithelium of transitional type and shows dyskeratosis.

Fig. 579.—Section of maxilla to show the tenuous barrier between the roots of molar tooth and the sinus cavity.

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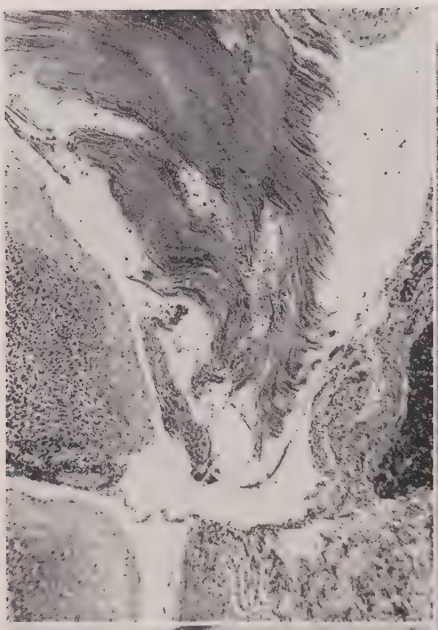

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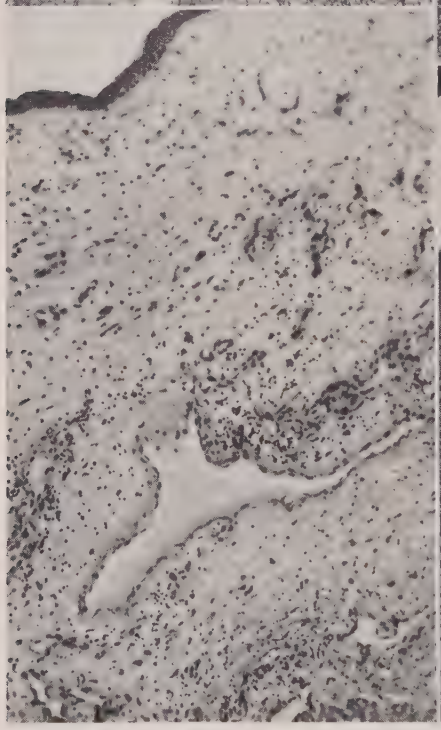

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Fig. 580.—Hyperkeratosis, tonsil, showing keratinous plug in crypt.
Fig. 581.—Pharyngeal bursa.
Fig. 582.—Juvenile pharyngeal fibroma.
Fig. 583.—"Amyloid tumor," vocal cord.

from the turbinates; cystic, from the presence of retention cysts or of pseudocysts; angioid, the result either of origin from the turbinates or development of secondary granulation tissue.

A specific type of polyp that is of considerable importance arises from the nasal mucosa, most frequently from the posterior portion of the middle turbinate, is more definitely neoplastic, and is characterized by its covering of transitional epithelium, which shows more or less mitosis and atypism. This polyp, which has been called **epithelial papilloma** by Ewing, is apt to recur locally, and occasionally undergoes malignant change (Figs. 577 and 578).

is not infrequently included in tissue from a nonhealing socket. Second, in frontal sinusitis, aside from the possibility of extension of the infection through the bone cortex, either subdurally or subperiosteally, diffuse osteomyelitis may result from dissemination of infection along the veins of the diploe. Since the process may not be evident grossly during operation, disregard of this possibility is a frequent cause of failure in surgical procedures on the frontal sinus.

Tumors of the Nose and Sinuses

Basal cell tumors are not uncommon at the mucocutaneous junction of the

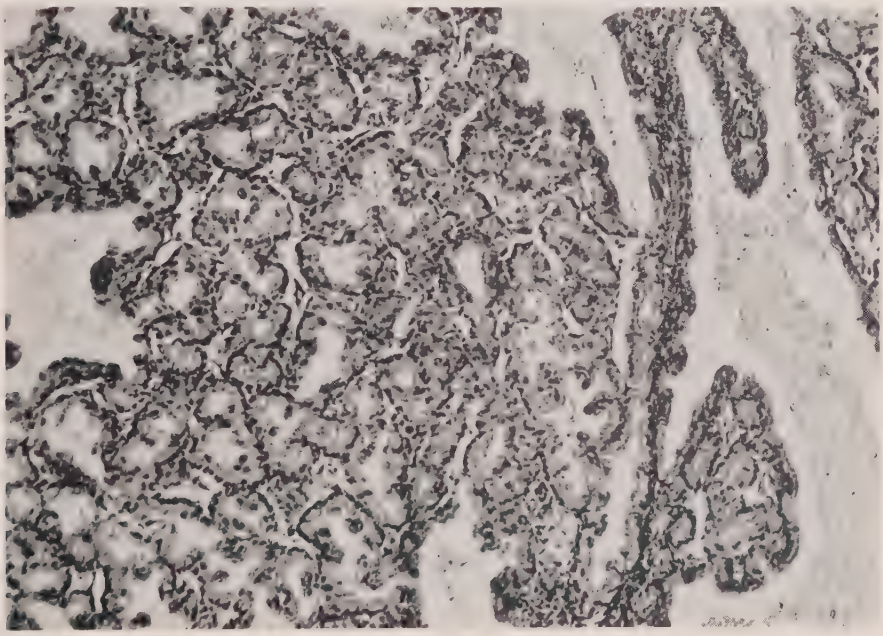

Fig. 584.—Adenomatous tumor of paranasal sinus. Massive and destructive locally, but did not metastasize.

Sinusitis.—Two practical points must be emphasized in the discussion of sinusitis: First, the intimate relationship existing between the roots of the molar teeth and the floor of the maxillary sinuses (Fig. 579) which makes possible an interchange of infections. During extraction of an upper molar the thin lamina of bone may be broken and the tooth pushed into the antrum. If a communication develops between the antrum and the tooth socket, prolapse of antral mucosa into the socket may occur. Antral mucosa

nares. The commonest tumor of the nasal septum is an angioma[6] indistinguishable histologically from granuloma pyogenicum. Giant cell tumors, ossifying fibromas, and osteogenic sarcomas arising in the maxilla usually involve the maxillary sinus very early and soon result in obliteration of the sinus. Less common are the mixed tumors in the palate of the salivary-gland type which may extend into the maxillary sinus or into the nose. It has been our experience that these tumors more frequently exhibit malignant tendencies than do mixed

tumors of the salivary glands. They may assume the character of adenocystic basal cell carcinoma or of more differentiated adenocarcinoma. They invade contiguous structures and occasionally metastasize to the cervical lymph nodes and lungs. The prognosis, therefore, must be much more guarded than for the usual mixed tumors of the salivary glands.

A frequent but benign tumor of the sinuses, most commonly in the frontal sinus, is the simple **osteoma.** A less definite pathologic entity is the **plasmocytoma** found in the nasopharynx more often than in the nose. In this location it is necessary to differentiate the true neoplasm from a purely inflammatory lesion. It is most common in adult males and may terminate in the multiple osseous myeloma. A skeletal survey, therefore, is indicated.[7]

serious clinically because they may grow "silently" until they have filled the nasal and/or sinus cavities. A diverting initial symptom may be lacrimation from involvement of the lacrimal sac in the thin bony medial wall of the maxillary sinus. They do not metastasize with the frequency of the nasopharyngeal carcinomas and they occur in an older age group.

Epithelial Tumors of the Nasopharynx.—Epithelial tumors of the nasopharynx, on the other hand, do not show the wide cellular variation but are predominantly transitional with a marked tendency to squamous differentiation. They occur in younger individuals and are characterized clinically by early metastasis to cervical lymph nodes while still insignificant and easily overlooked primary tumors. The tumor is particularly common in Mongolian races. It is the type that was called lymphoepithelioma by Regaud and Schmincke, and while in the local tumor this relationship of epithelium and lym-

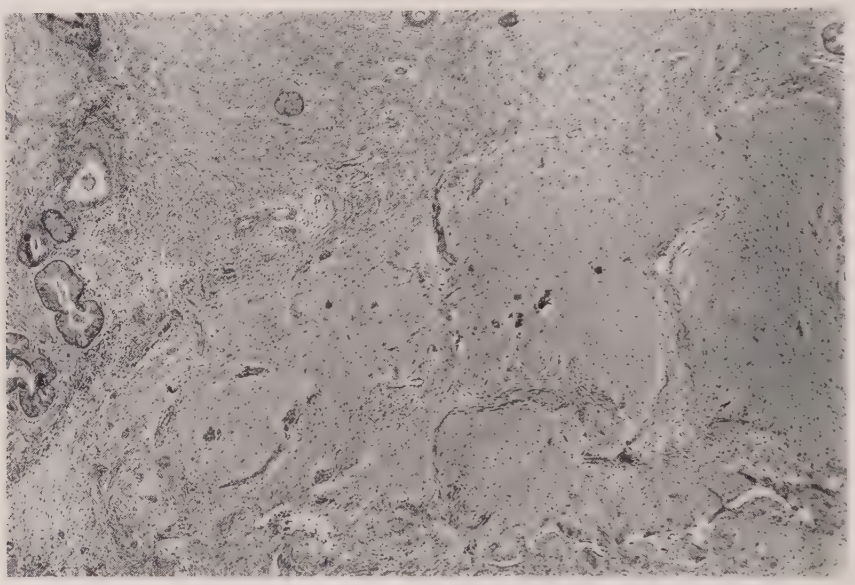

Fig. 585.—Neurogenous tumor of nose. Congenital "polyp" containing brain cortical elements and glia principally.

Epithelial Tumors of the Upper Respiratory Tract.—Epithelial tumors of the upper respiratory tract fall into two categories: those arising from Schneiderian mucosa of the nose and paranasal sinuses and those from the lymphoepithelial type mucosa of the nasopharynx. The tumors in the first group, whether arising from nose or sinuses, show a great variation in cell type, the majority of them being transitional or frankly squamous, but they may vary in different tumors or in different portions of the same tumor from the differentiated squamous to a basaloid type. Tumors of adenomatous epithelium are not common but do occur. They are less malignant than the others. In fact, they are usually more properly classed as adenomas, papillary or not, rather than adenocarcinomas. All of these tumors are

phatic tissue element may be maintained, it is not always evident. This term might well be discarded. The presenting clinical symptom may be the enlargement of the cervical nodes. Occurring as they do frequently in the fossa of Rosenmüller, the initial symptom may be difficulty with the ear. The nasopharyngeal carcinoma is particularly sensitive to irradiation.

To distinguish these two groups of tumors and to simplify the terminology that has accumulated it is suggested that nonadenomatous epithelial carcinomas arising from the nose and paranasal sinus be called schneiderian carcinomas, and those from the lymphoepithelium of the nasopharynx, nasopharyngeal carcinomas.

Reticulum cell sarcoma is not an uncommon tumor of the nasopharynx and its differentiation from an anaplastic carcinoma is difficult.

Craniopharyngioma and chordoma, rare but serious tumors in the nasopharynx, are discussed elsewhere.

An interesting but rare tumor of the nose and nasopharynx is of neural origin. It may be developmental, i.e., an extrusion of brain element through a dehiscence in the cranial bones, and contain nerve cells and gliomatous elements. These may present in the nasal cavity, or more externally at the base of the nose. Other tumors apparently arise from neural rests in the nose, especially at the site of the olfactory plaque, or in the nasopharynx. These have a wide variety of histologic pictures. They may be sympathogonic, neurofibromatous, gliomatous, or neurocellular, or an assortment of these elements. They tend to grow expansively and invade the bony cavities and to recur, but not to metastasize. This tumor has been called olfactory esthesioneuroblastoma.[8, 9]

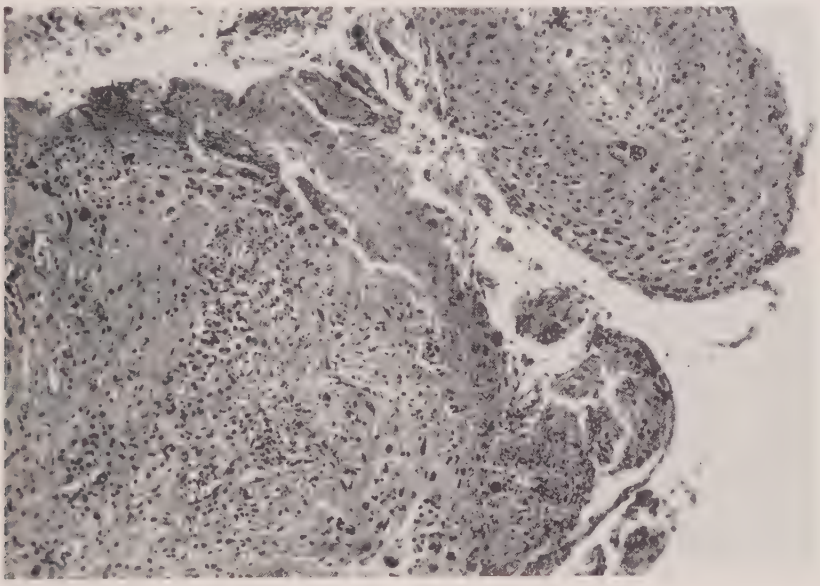

Fig. 586.—Regaud type carcinoma of nasopharynx showing a papillary architecture and the intimate relation of lymphatic tissue and epithelium.

TONSILS

Hyperkeratosis (mycosis leptothrica) is a term applied by the otolaryngologist to a clinical entity characterized by the presence of white flakes, usually on the tonsils, but occasionally on other portions of the pharynx and larynx in which there is lymphatic tissue. Clinically it resembles follicular tonsillitis but without the accompanying inflammatory reaction of the mucosa. There is no bleeding on removal of the white specks. It is a disease of young adults, is refractory to treatment but runs its course in several years.

Histologic examination shows that the white spots are produced by hyperplasia and hyperkeratosis of the squamous epithelium to form keratin plugs in the tonsillar crypts. There may be atrophy and fibrosis of the underlying lymphatic tissue. *Leptothrix* is practically always associated with the condition. Mycelia can be demonstrated in smears, and colonies are to be found in the tonsillar crypts. There is very little inflammatory reaction (Fig. 580).

Mycelia are fairly commonly found in the tonsillar crypts. Ordinarily these are saprophytes, but occasionally they prove to be pathogenic actinomyces which may become the nidus of an infection.

Cartilage and bone are frequently encountered in the hilum and capsule of the tonsil.[10] They are the remains of branchial arches which have undergone metaplasia. The bone occasionally is an extension of the styloid process.

Tornwaldt's Disease.—The adenoid tissue in the posterior wall of the nasopharynx surrounds a deep crypt lined by ciliated, pseudostratified columnar epithelium. This is called the pharyngeal bursa (Fig. 581). The orifice of this crypt may become occluded by hyperplasia of the lymphatic tissue, and distention of the bursa may follow, as a result of exudate from an infection or of mucoid secretion and cellular debris, including cholesterol. Tornwaldt's disease, or pharyngeal bursitis, is usually seen in young persons because the bursa is practically obliterated after puberty.

Nasopharyngeal fibroma is a tumor of juvenile males which most often springs from the base of the sphenoid, but which may develop on the lateral wall of the nasopharynx; it may have a multicentric origin, or may arise from the posterior portion of the nose and extend into the pharynx.[11] The tumor may grow rapidly but it does not metastasize. It is not only expansive but invasive and is dangerous because it can invade the orifices in the base of the skull, or, by pressure, erode into the cranial cavity. A clinical

characteristic of this tumor is that it tends to regress spontaneously in early adult life.

The basic element of the tumor is vascular tissue with a varyingly cellular fibrous tissue stroma. This accounts for the frequency of hemorrhage and for the decided operative risk. If the growth persists into later life, this vascular element becomes less conspicuous and the fibrous tissue less cellular with a larger collagen content (Fig. 582).

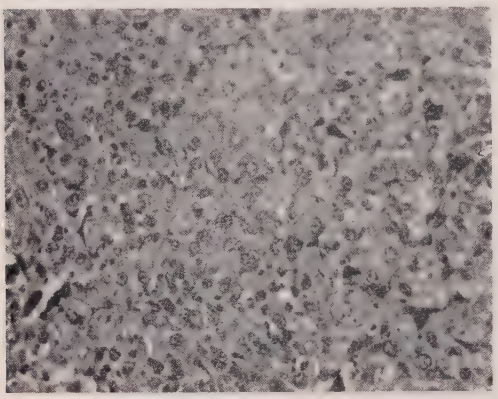

Fig. 587.—Schmincke type nasopharyngeal carcinoma, undifferentiated.

LARYNX

Cysts of the epiglottis are comparatively rare and are of two types: (1) the simple retention cyst developing in a mucous gland; (2) the cyst resulting from the inclusion of lymphoepithelium of the entoderm, histogenetically therefore, a branchial cyst.

Papilloma of the larynx, a simple tumor histologically, is serious clinically because of its location and its persistent tendency to recur. It is most common in childhood, though rarely malignant at that time, and it may regress in later years. In these respects it must be differentiated from adult papilloma of the larynx that frequently results in squamous cell carcinoma. *Leukoplakia* of the vocal cords is troublesome to both clinician and pathologist. There is little that can be done for it by the former until the pathologist after examining repeated little biopsies recognizes malignant changes. Then the clinician must decide between a laryngeal fissure or the radical laryngectomy. It may remain dormant for years, however. The laryngologist refers to the innocent hyperplasia or acanthosis of the mucosa as *pachydermia.* As a result of chronic irritation, the respiratory epithelium undergoes squamous metaplasia, including dyskeratosis to the point of being as disconcerting as the changes in the epithelium of the cervix uteri (Fig. 589).

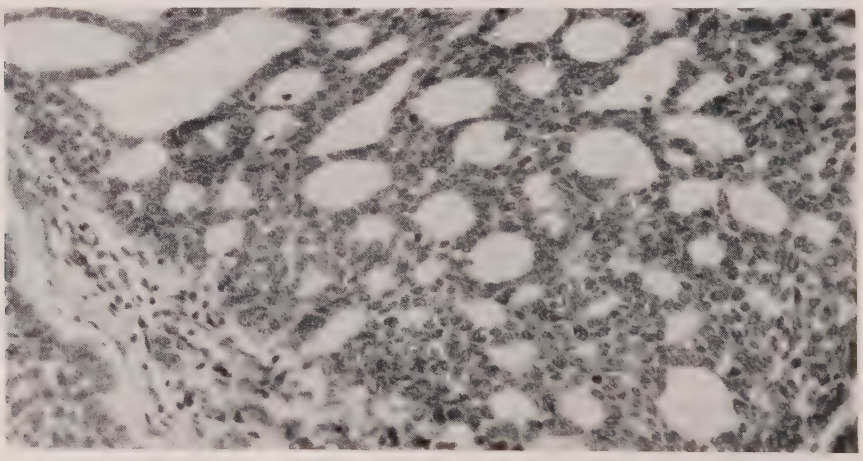

Fig. 588.—Adenocystic basaloid type nasopharyngeal carcinoma, similar to that seen in bronchial adenomas and in mixed tumors of salivary glands.

The commonest pharyngeal tumor seen by the pathologist, with the exception of polyps, is the simple **papilloma.** It most often arises about the fossa of the tonsils, but it may spring from any portion of the oral or oral-pharyngeal mucosa.

The papilloma is usually small with a delicate stalk, and its histologic appearance includes branching stroma with hyperplastic, but well-differentiated, squamous-epithelial covering. Occasionally the process is diffuse, involving faucial, hypopharyngeal, and laryngeal mucosae. We have no record of one being malignant.

Laryngeal nodule (singer's node) is a thickening of the mucosa of the true cord, most commonly near the anterior commissure, and in the subglottic tissue. These nodes are amenable to simple surgical removal, although they do recur. They usually are found in white men over 30 years of age, especially in those who have misused their voices. A study of a large number of specimens in the Registry has established four stages in their development.[12] The first is a fibrous thickening of the stroma in the so-called Reinke's layer, a normally narrow zone between the elastica of the true cord and

the overlying squamous epithelium of the edges of the true cords. The second is polypoid in character due to edema and dilatation of the vessels, and occurs in the course of months or years. The third, or varix, stage is produced by extreme dilatation of the very thin-walled vessels. The fourth is the hyaline stage, or the so-called amyloid tumor (Fig. 583). In none of our cases, however, did the hyalin take the specific stain for amyloid. The hyalin develops in the stroma, in the walls of the dilated vessels, and in the lumina of the vessels. The overlying squamous epithelium may become atrophic; less frequently, hyperplastic with acanthosis, and occasionally leukoplakic with dyskeratosis. The hyperplasia may occasionally be of the pseudo-epitheliomatous type and be misinterpreted as squamous cell carcinoma, but we have only one instance of actual malignancy in over one hundred cases.

Fig. 589.—Laryngeal ventricle to show squamous metaplasia of glandular elements from chronic irritation. *A*, False cord; *B*, true cord; *C*, laryngeal ventricle.

Chondroma of the larynx is included here because the diagnosis, in the majority of cases coming to the Registry so diagnosed, has been due to misinterpretation of the elastic cartilage, sometimes conspicuous in the true cord, as being neoplastic. Actual chondromas, however, do occur in the larynx and their neoplastic nature is obvious when they are compared with the normal elastic cartilage. Chondromas arise most frequently from the thyroid and arytenoid cartilages.

Fibroma of the larynx is occasionally seen. It may be histologically malignant but it does not as a rule metastasize. We have seen several instances of **myoblastoma** in the glottal region and adjacent fossae.

Carcinoma of the larynx is discussed on page 694.

EYE

The eye is so complicated a structure and so specialized physiologically that its pathology is a highly specialized field. Considerable ground can be covered in a few words by giving a glossary of certain terms commonly used by ophthalmologists.

Buphthalmos, a term used loosely to signify any great enlargement of the eyeball, is more properly restricted to enlargement secondary to inflammatory processes that lead to anterior staphyloma. Enlargement due to congenital absence of the canal of Schlemm is called **hydrophthalmos.**

Coloboma is absence of a portion of one or more of the coats of the eye. Congenital colobomas most commonly involve the iris and ciliary body, the choroid, or optic disc, and are the result of failure of closure of the optic vesicle. The term is also applied to the loss of structure from trauma or operation.

Corpora arenacea (corpora amylacea) are hyaline and calcified bodies found in the leptomeninges of the optic nerve. They are of the same structure as the brain sand in the meninges of older people.

Cytoid bodies are cell-like masses, usually round or polygonal, with or without a nucleoid element, found in clusters, usually in the nerve-fiber layer of the retina, particularly in albuminuric retinopathy and in choked disc. Their genesis is not clear, but they are probably necrotic remains of ganglion cells, macrophages, or, as thought by some, varicose nerve fibers. They, as well as serous exudates in the outer plexiform layer, are recognizable through the ophthalmoscope as "cotton wool" patches (Fig. 590, *A*).

Dalen-Fuchs nodule is a focal collection of mononuclear cells on Bruch's membrane differing from drüsen in the absence of hyaline, but like drüsen most commonly seen in retinal detachment incident to inflammatory processes, par-

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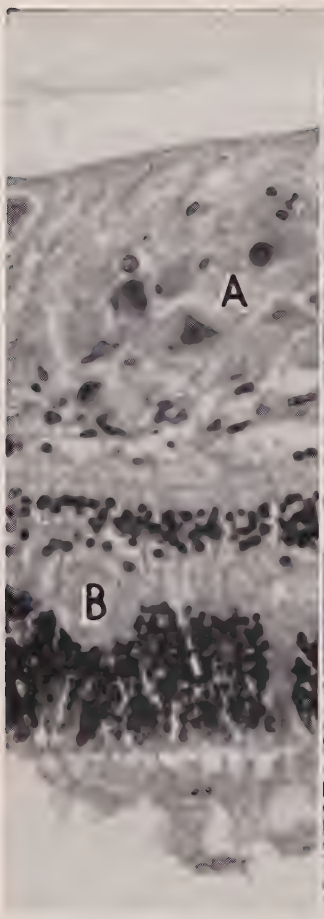

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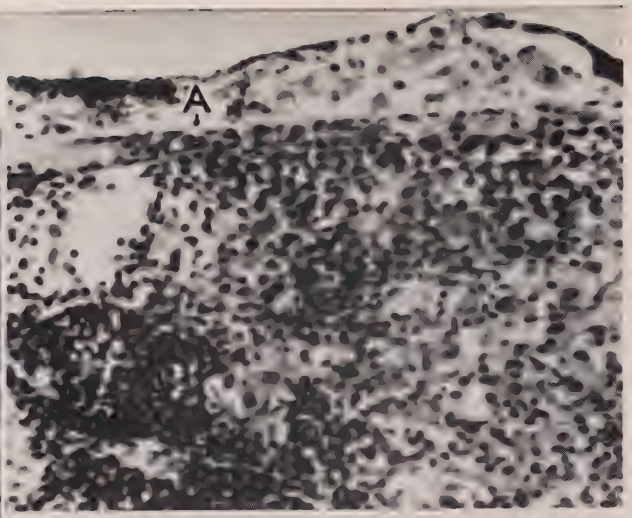

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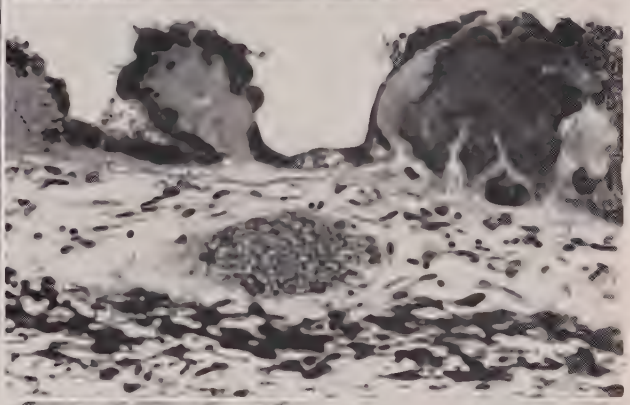

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Figs. 590-593.—*For legends see opposite page.*

ticularly sympathetic ophthalmia. The cells are most likely macrophages, rather than pigment epithelium of the retina as they originally were thought to be (Fig. 591).

Drüsen are hyaline excrescences on Bruch's membrane (lamina vitrea) developing as a sequel of injury or chronic inflammation.[13] They are hyaline, usually laminated, and covered by the pigment epithelium of the retina. It is believed by some that the masses increase in size through the proliferation and the excretory activity of the pigment epithelium. They frequently become calcified and sometimes ossified. While there usually is an accompanying retinal detachment, this is not invariable. Drüsen are particularly prominent in phthisis bulbi (Fig. 592).

Ectropion uveae is an extension of the pigment-epithelial layer of the posterior surface of the iris around the pupillary margin onto the anterior surface. It is the result of chronic iritis in which scar tissue contraction everts the pupillary margin, and it is also seen in glaucoma and in congenital and senile conditions. Ectropion uveae gives a fish-hook appearance to the pigment epithelial layer in sections (Fig. 593, *A*). *Entropion uveae* results from contracture that pulls the pupillary edge of the iris inward.

Henle wart is a hyaline excrescence on Descemet's membrane. It is one of the changes in senile eyes.

Iris bombée is a complete adhesion between the pupillary margin of the iris and the anterior surface of the lens (posterior synechia), cutting off the drainage through the pupil and causing fluid to accumulate behind the iris, thus making it bulge forward (Fig. 594). There usually is accompanying anterior peripheral synechia obliterating the filtration angle. Iris bombée may be a sequel of chronic iridocyclitis from any cause.

Keratic precipitates (K.P.'s) are accumulations on the posterior surface of the cornea, usually of mononuclear cells, including not only macrophages but also cells proliferating from the endothelium covering Descemet's membrane, the posterior limiting membrane of the cornea. K.P.'s are seen in chronic inflammatory conditions, tuberculous chorioretinitis, for example. They are visible through the ophthalmoscope and the slit lamp. The ophthalmologist speaks of the condition in which K.P.'s occur as keratitis punctata (Fig. 595).

Lipoid histiocytes are simply lipoid-containing macrophages which have accumulated in areas of retinal serous exudate or hemorrhage, usually in the outer plexiform layer of the retina, particularly in the macular region. They are recognizable through the ophthalmoscope as stellate bodies (Fig. 596, *A*).

Pannus degenerativus is an extension of granulation tissue from the limbus over the cornea, separating the corneal epithelium from Bowman's membrane. There is at times a duplication of the membrane. The granulation tissue undergoes the same changes here as it does elsewhere—reduction in cellularity and vascularity, scarring, and, eventually, even calcification. This process usually is associated with chronic glaucoma (Fig. 597).

Plasmacytoid cell is an intermediate form between the plasma cell and the Russell-Fuchs body. It is differentiated from a tissue eosinophile by its larger size, its pyknotic nucleus, and the greater prominence of its acidophilic intracellular material (Fig. 598).

Retinal exudates are focal accumulations of serous, albuminous, or fibrinous exudate in the retina. They are seen most commonly in the outer plexiform layer in albuminuric retinopathy. These, too, may be identified through the ophthalmoscope as "cotton wool" patches (Figs. 599 and 590, *B*).

Russell-Fuchs bodies are the hyaline particles seen in plasma-cell exudates wherever these occur, although the ophthalmologist lays more than the usual stress on them. While usually round or lobate, they may be square or oblong.

Staphyloma, anterior (corneal) is an ectatic scar of the cornea and iris. It follows corneal perforation, either inflammatory or traumatic, with prolapse of the iris, in this way differing from the various scleral staphylomas which are simply focal ectasias. It may involve the entire cornea or be limited to the site of trauma or ulceration.

Synechiae are defined by their location: (a) An adhesion between the root of the iris and the posterior surface of the pectinate ligament and cornea is a peripheral anterior synechia. This kind is a common sequel of iridocyclitis, usually leading to obliteration of the filtration angle and to secondary glaucoma (Figs. 593, *B* and 594, *B*). It is practically always present in chronic inflammatory glaucoma. (b) Adhesions between the posterior surface of the pupillary margin of the iris and the anterior capsule of the lens is posterior synechia, a sequel of iritis, leading to deformity of the pupil. After the adhesion has been broken, histologic evidence of its existence is the presence of pigment epithelium of the iris attached to the anterior capsule of the lens (Fig. 593, *C*).

EYELIDS

Chalazion is a chronic lesion of the eyelid due to obstruction of the duct of a meibomian gland, usually complicated by secondary infection. The meibomian glands are embedded in the tarsal plate. Occlusion of the duct, which opens on the lid margin, produces pressure causing early atrophy of the acinar epithelium and

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Fig. 590.—Retina. Cytoid bodies in the nerve-fiber layer (*A*); serous exudate in the outer plexiform layer (*B*).

Fig. 591.—Dalen-Fuchs nodule on Bruch's membrane (*A*). Choroid densely infiltrated with mononuclear exudate.

Fig. 592.—Drüsen, partially calcified and covered by retinal-pigment epithelium.

Fig. 593.—Ectropion uveae (*A*); anterior synechia (*B*) obliterating filtration angle; posterior synechia (*C*); exudate in anterior and posterior chambers.

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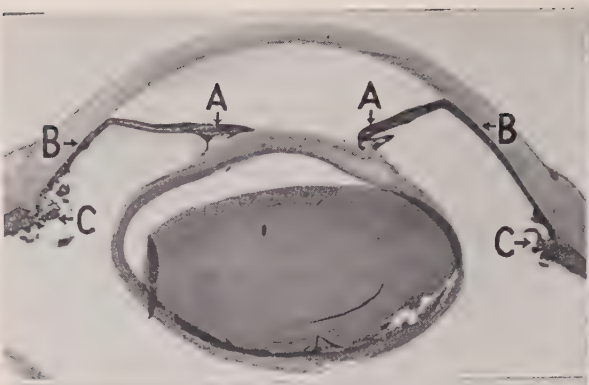

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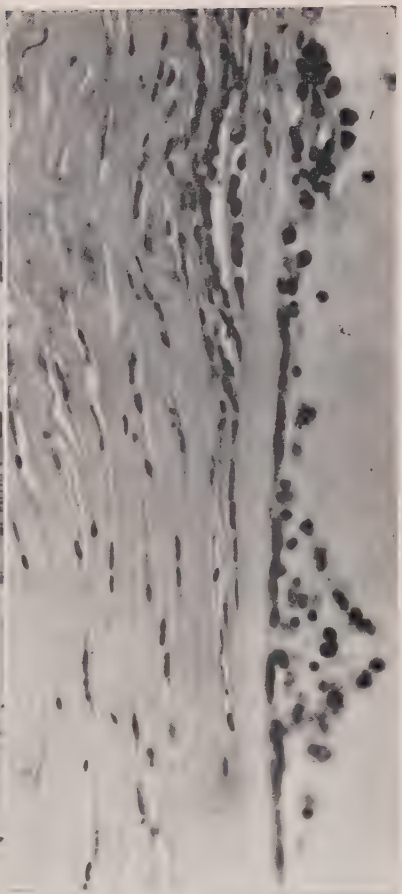

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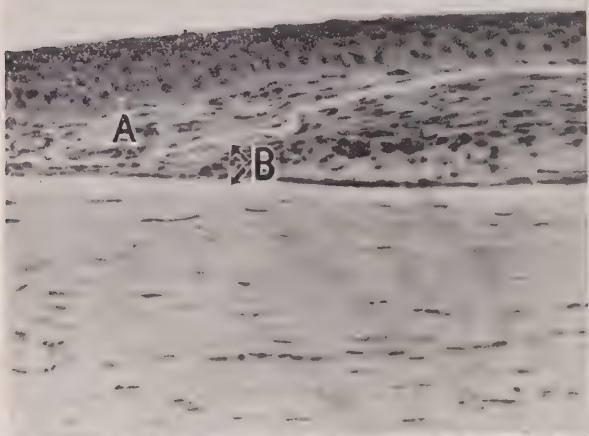

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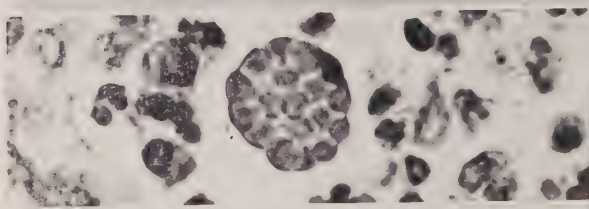

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Figs. 594-599.—*For legends see opposite page.*

liberation of dried sebaceous material into the tissues. The granulomatous inflammation which results, closely simulates infectious granuloma and is frequently diagnosed as such. There are typical tubercles, and the Langhans type giant cells may contain fat globules or cholesterol crystals (Fig. 600).

Conjunctivitis

A histologic characteristic of the conjunctiva that becomes an important feature in conjunctivitis is the lymphatic tissue normally present, particularly in the palpebral portion near the upper fornix. It is more abundant in children, but there may be remnants in older people. These follicles become conspicuous in any chronic inflammatory reaction of the conjunctiva and add to the difficulty in differentiation. Sometimes this lymphatic tissue element is very prominent, particularly on the bulbar conjunctiva, and may be clinically recognizable as a tumor—*lymphoma*. Sometimes misinterpreted as malignant, it rarely is unless it is a local manifestation of a general lymphatic tumor or of a leukemia (Fig. 601).

Three types of chronic conjunctivitis are most significant not only because their differential diagnosis is important but also because their pathologic pictures are so similar.

Vernal catarrh (vernal conjunctivitis) is a chronic inflammatory reaction of the conjunctiva due to exposure to allergens and is characterized clinically by seasonal exacerbations. The palpebral conjunctiva becomes milky and there may be some involvement of the bulbar conjunctiva, especially at the corneal margins. Histologically, it is characterized by a low, broad, papillary formation of the conjunctival surface, a metaplasia of the conjunctival epithelium in the crypts to a columnar type, and a high percentage of eosinophiles in the stromal exudate, the number varying with the intensity of the process. Lymphocytes, plasma cells, and secondary lymphatic follicles also are present in the stroma. Adhesions of the orifices of crypts lead to isolation of the columnar epithelium to form pseudoglands (Fig. 602).

Follicular conjunctivitis, usually seen in children, is characterized by the development of small nodules on the palpebral conjunctiva, particularly in the folds, with a relative absence of inflammatory symptoms. It is important because of its clinical and pathologic similarity to the early stages of trachoma. Beneath the conjunctival epithelium are large secondary lymphatic follicles with a varying amount of chronic inflammatory reaction in the intervening stroma, but without the internodular scarring of trachoma. Neither is there the epithelial metaplasia with pseudogland formation characteristic of both trachoma and vernal catarrh (Fig. 603).

Trachoma, the most important single cause of blindness throughout the world, is the chronic inflammatory disease of the palpebral conjunctiva resulting in the formation of granules and much scarring. It begins in the upper fornix and extends finally to the bulbar conjunctiva and to the cornea. The scarring causes inversion of the lid margins—entropion—which results in further irritation of the cornea.[14, 15]

The pathologic changes vary with the stage of the disease. Early there is secondary lymphatic follicle formation, as in follicular conjunctivitis, metaplasia of the epithelium and formation of pseudoglands as in vernal catarrh, and at times the development of gross cysts. A papillary change of the surface like that seen in vernal catarrh may develop. The stroma is diffusely infiltrated with lymphocytes, plasma cells, and a few large mononuclear cells; eosinophiles are practically absent. The inflammatory reaction extends more deeply into the lid structures than in vernal catarrh, and may involve the various glands of the lids. The germinal centers of the lymphatic follicles are prone to undergo necrosis. As the process advances, the granulation tissue which develops between the follicles subsequently becomes scar tissue, compresses the follicles and may cause them to rupture. When the cornea is involved there is less follicle formation, but there is a diffuse pannus covered by epithelium that has undergone metaplasia to a squamous type. There is no pathognomonic feature in the histology of trachoma, although scarring is the most suggestive finding. The diagnosis can be made only by the correlation of the clinical and pathologic data (Figs. 604, 605, and 606) (see also page 334).

Inclusion bodies in the conjunctiva are worthy of a few words. Prowazek[16] in 1907 demonstrated basophilic inclusions in the cytoplasm of epithelial cells in cases of trachoma. For a long time afterward inclusion bodies were considered pathognomonic of that disease, but more recently they have been demonstrated in other forms of conjunctivitis including vernal catarrh. Furthermore, they have been found to be very rare in advanced stages of trachoma. Two types of inclusion bodies are now recognized: Basophilic as found in trachoma, inclusion blennorrhea of the newborn, follicular conjunctivitis of swimming, vernal catarrh, and follicular conjunctivitis. In these conditions they are always *cytoplasmic inclusions.* The clear haloes seen about the masses at times lead to their mistaken designation as *Chlamy-*

Fig. 594.—Iris bombée. Posterior marginal synechia (*A*); anterior synechia (*B*); lens shows morgagnian cataract; ciliary processes atrophic (*C*).

Fig. 595.—Keratic precipitates on posterior surface of cornea (Descemet's membrane).

Fig. 596.—Lipoid histiocytes (*A*); albuminous exudate (*B*) in outer plexiform layer of retina.

Fig. 597.—Pannus degenerativus (*A*) between corneal epithelium and Bowman's membrane (*B*) which shows duplication.

Fig. 598.—Plasma-cytoid cell.

Fig. 599.—Large serous exudates in outer plexiform layer of retina.

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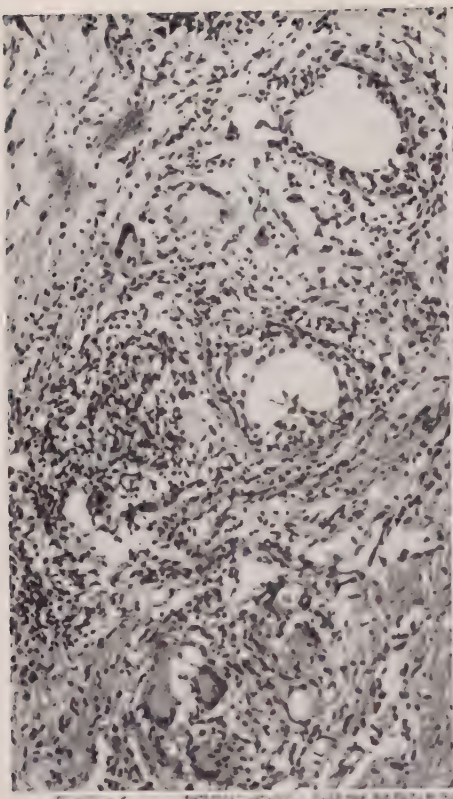

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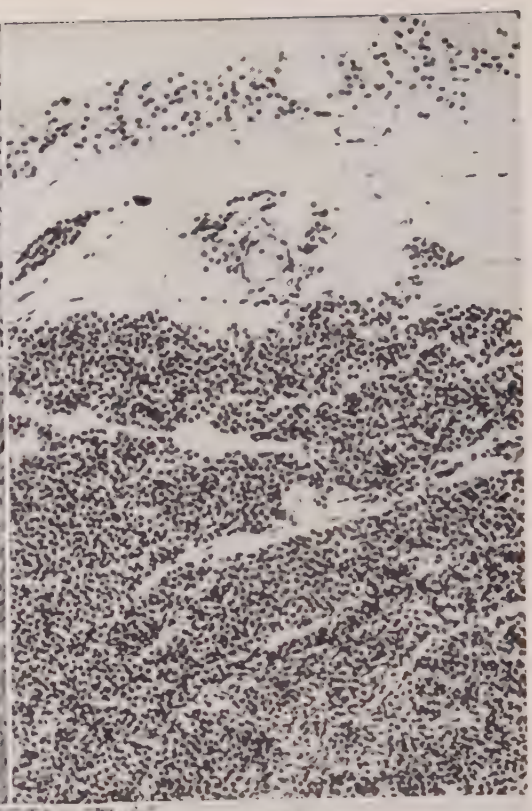

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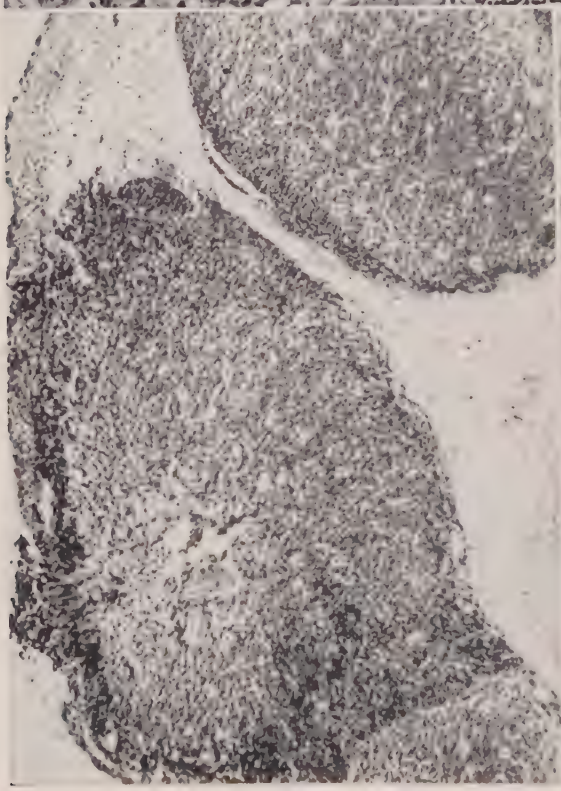

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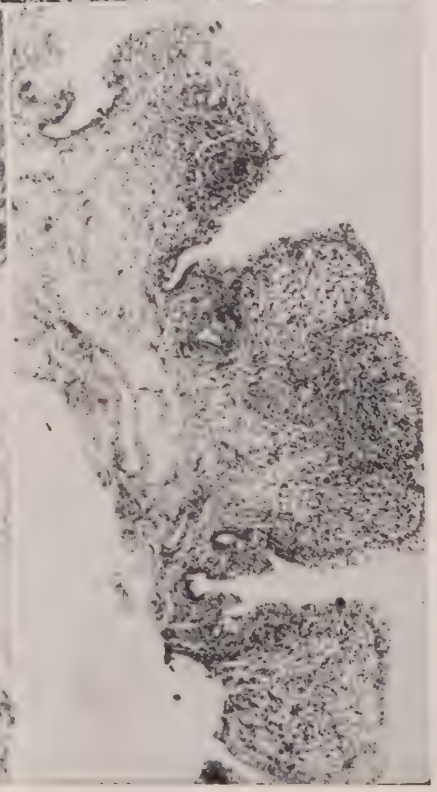

Figs. 600-603.—*For legends see opposite page.*

dozoa.[16] The second type of inclusion body is acidophilic and it is usually intranuclear, especially in the epithelium of the cornea. Acidophilic forms are seen in the viral exanthems such as herpes, vaccinia, and smallpox.

Rhinosporidiosis occasionally affects the conjunctiva, where it manifests itself, as in the nose, as a red pedunculated polyp.[17] In sections the organisms, *Rhinosporidia seeberi,* are prominent, lying in the edematous, infiltrated stroma (see page 703).

Parinaud's conjunctivitis, a clinical syndrome rather than a pathologic entity, is characterized by granulomatous involvement of the palpebral conjunctiva, usually unilateral, and associated preauricular swelling.[18] The use of the term, Parinaud's syndrome, is confusing because it has already been applied to a supranuclear paralysis of associated movements of the eyeballs. Since Parinaud's original description in 1889 it has been found that the clinical picture can result from a variety of specific infections: tuberculosis, syphilis, tularemia, leptothricosis, and lymphogranuloma venereum. Pathologically, therefore, the picture is that of an infectious granuloma with specific characteristics due to a particular etiology. Lymphadenitis of the preauricular nodes is a possible complication of other ocular infections.

Intraocular Inflammations

A classification of intraocular inflammations arranged on an anatomical basis follows:

Iritis—Inflammation of the iris.

Iridocyclitis—Inflammation of iris and ciliary body.

Choroiditis—Inflammation limited to the choroid coat.

Uveitis—Involvement of the entire uveal tract, that is, iris, ciliary body, and choroid.

Retinitis—Inflammation limited to the retina, frequently used incorrectly for the retinopathies—arteriosclerotic, diabetic, etc.

Chorioretinitis—Involvement of the choroid and retina, usually chronic and a feature of systemic disease (syphilis, tuberculosis, etc.).

Endophthalmitis—Involvement of the inner structures including vitreous; usually subacute, the result of a metastatic infection such as meningococcic meningitis.

Scleritis—Involvement of the sclera. Brawny scleritis[19] is a granuloma of unknown etiology. Other coats of the eye are usually affected, particularly the stroma of the limbus, from which the inflammation can spread to ciliary body and other inner structures. Old age and syphilis have been considered etiological factors, but evidence is accumulating to indicate that it is a focal necrosis of scleral stroma manifesting a general "collagen" disease, especially rheumatoid arthritis.

Panophthalmitis—Inflammation of all coats and structures of the eye and seen particularly in pyogenic infections secondary to trauma.

Episcleritis—Involvement of the superficial layers of the sclera only.

Except when they are the result of trauma and metastatic acute infections like meningitis and gonorrhea, inflammations of the uveal tract and of the retina are chronic, and are of interest to the pathologist chiefly because of secondary changes. The most important sequel is anterior synechia which may lead to glaucoma as a result of obliteration of the filtration angle. Posterior synechia may cause deformity and fixation of the pupil, and scars may obliterate portions of the retina. The exudate is predominantly of plasma cells with a smaller percentage of lymphocytes. Russell-Fuchs bodies and plasmacytoid cells are present in varying numbers.

Iritis of nonspecific type may be a fulminant focal lesion that will regress without permanent damage, except possible local scarring. A second type is less fulminant but recurs persistently as smaller nodular foci scattered through the iris. After repeated recurrences there may be complete posterior synechia, cataract, and glaucoma. The same sort of involvement, focal or diffuse, is found in the ciliary body and choroid. More or less scarring and destruction of the choroid and retina and scattering of retinal pigment occur. Inflammation of the ciliary body alone is characterized clinically by intense pain, tenderness, and turbid vitreous.

The etiology of the subacute and chronic inflammations of the uveal tract is not clear. Syphilis and tuberculosis are often suspected even when the respective organisms cannot be demonstrated. It is probable that they are more in the nature of ids than local infections. Focal bacterial infections in other parts of the body seem to be the basis in some cases, and in this connection the frequently seen association with arthritis may be significant.

Specific granulomatous inflammations of the uveal tract, such as tuberculosis and Boeck's sarcoid, are not uncommon, and of great importance is sympathetic ophthalmia. The histologic detail of infectious granulomas of the uveal tract does not differ materially from that of the infections in other parts of the body, and identification of the causative organism is usually necessary for positive diagnosis. Certain characteristics of distribution as indicated below are of some help in the differentiation. All infectious granulomas are most common in the anterior hemisphere of the eye, particularly in the ciliary body and the iris.

Fig. 600.—Chalazion. Tubercle-like granulomas; giant cells containing lipoid material; dilated meibomian glands.

Fig. 601.—Lymphoma, conjunctiva.

Fig. 602.—Vernal conjunctivitis.

Fig. 603.—Follicular conjunctivitis.

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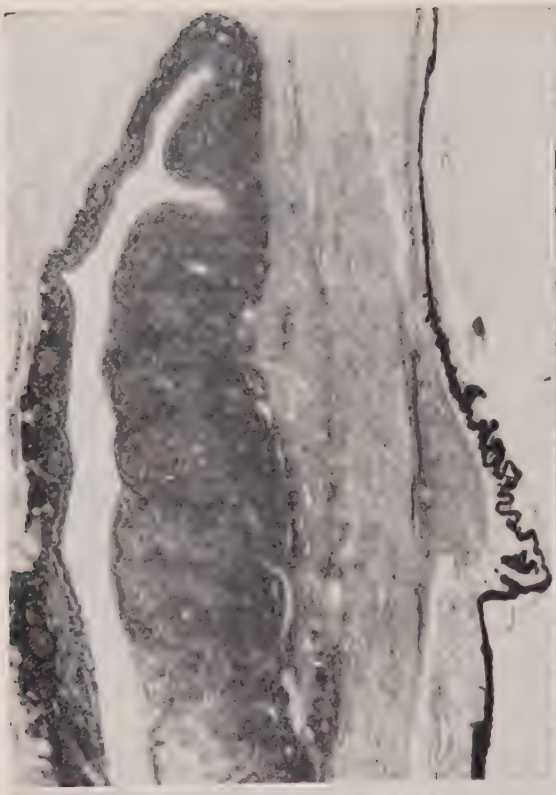

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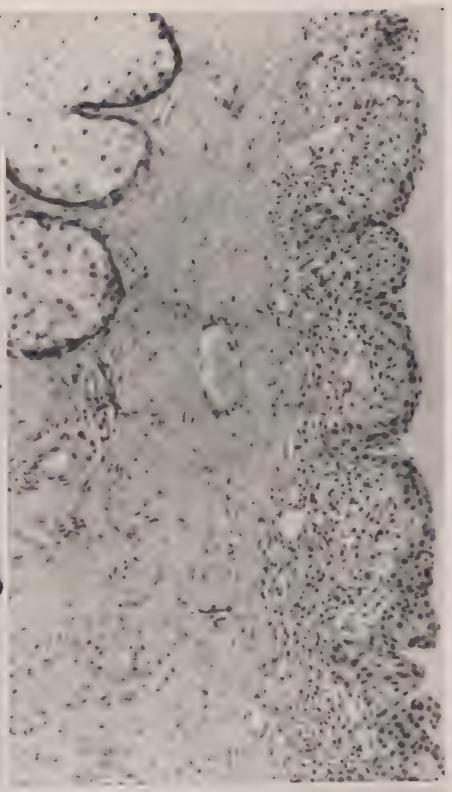

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Fig. 604.—Trachoma. Upper fornix; bulbar conjunctiva greatly thickened by secondary lymphatic follicles.

Fig. 605.—Trachoma. Early necrosis of germinal centers.

Fig. 606.—Trachoma, chronic, palpebral conjunctiva.

Tuberculosis of the eye may occur in the late stages of generalized miliary tuberculosis or in the presence of a quiescent focus, usually in the lung or the lymph nodes of the chest. While massive caseous lesions do occur, usually in conjunction with active pulmonary tuberculosis, the commonest ones are the small epithelioid collections, scattered throughout the uveal tract. The massive lesion is usually situated in the anterior portion (Fig. 607) but is occasionally confined to the posterior hemisphere. As a rule the disseminated form is limited to the uveal tract but by extension may involve the retina, and it is usually associated with the blood vessels. A specific clinical entity is **phlyctenular keratitis and conjunctivitis,** usually seen in children with tuberculosis. The histologic structure of these lesions, however, is not specific. They are focal collections of mononuclear cells, including histiocytes, beneath the epithelium of the conjunctiva or cornea. As they enlarge they may break through the epithelium and form superficial ulcers. This is another example of an id. *Mycobacterium tuberculosis* cannot be demonstrated in them.

Boeck's sarcoid is a process which often involves the eyelids but sometimes occurs in the uveal tract and retina. The most common intraocular location of the tubercles is in the anterior portion of the uveal tract (see page 670). Wilder[20] has recently demonstrated another cause for intraocular granulomatous lesions. After most painstaking examination of the eosinophilic granulomas in 46 eyes, she found larvae of nematodes in 24. They have been identified tentatively as hookworm. Still more recently she has demonstrated toxoplasma in a number of granulomas previously passed over as of unknown etiology.

Sympathetic ophthalmia (sympathogenic uveitis) is a granulomatous inflammation developing in a small percentage of perforating wounds of the anterior half of the eyeball. It is particularly serious because it involves the normal eye as well as the injured, or exciting, eye. The pathologic changes in both eyes are the same. Although the pathogenesis has been the subject of much study, it is still not clear. Friedenwald[21] has produced experimental evidence that suggests that the cause may be sensitivity to uveal pigment. Extension to the normal eye can be avoided by enucleation of the exciting eye in the first few weeks following injury, because it usually takes several weeks for the sympathetic lesion to develop.

The histologic picture is one of diffuse inflammatory reaction in the whole uveal tract. The exudate is predominantly small mononuclear cells, with tubercle-like focal collections of epithelioid cells (Fig. 608) and occasional giant cells of the Langhans type. Necrosis in the tubercles may make them individually indistinguishable from tuberculous or other infectious granulomas, but limitation to the uveal tract is a very important differentiating point. Necrosis is rarely as advanced as that seen in tuberculosis, and the necrotic portions sometimes show a characteristic linear streaking (Fig. 609). A tendency for the tubercles to be restricted to the posterior portion of the iris forming dense posterior synechia is distinctive, since in tuberculosis they are apt to involve the anterior surface and subsequently the cornea (Fig. 607). The exudate may extend along the perforating vessels and to that extent involve the sclera, but the retina is seldom affected as it is in tuberculosis. Dalen-Fuchs nodules (Fig. 591) may develop on Bruch's membrane. The presence of pigment in the epithelioid cells and giant cells is characteristic (Fig. 608) but not necessarily diagnostic, because other inflammatory reactions cause diffusion of the choroidal and retinal pigments that may be phagocytosed. The condition is sluggish, characterized clinically by exacerbations. Eventually there may be secondary glaucoma or even phthisis bulbi. Extension of inflammatory tissue over the pupillary portion of the lens capsule produces that valuable clinical sign of sympathetic ophthalmia, felting of the cornea.

Sequelae of Injury

The eye is peculiar in that an injury or inflammation of any one part so frequently leads to involvement of all the internal structures. Infections gain entrance to the eye either through penetrating wounds or through the blood. If the inflammation is most intense in the anterior portion of the eye, the blockage of the filtration angle is a frequent complication, with the development of secondary glaucoma. If the infection is concentrated in the posterior segment, the result may be a soft eye with shrinkage and deterioration of the inner coats.

Phthisis Bulbi.—With the loss of intraocular fluid the retina becomes detached, serous or albuminous exudate accumulates under it, and eventually the detachment is complete and the nerve head is pulled into the vitreous. There is deterioration of the retinal elements, gliosis, and obliteration of the blood vessels. Hyaline excrescences form on Bruch's membrane (drüsen); there is obliteration of the choroidal vessels, scarring of the choroid, and subsequent calcification. Frequently in phthisis bulbi, ossification of the entire choroid and ciliary body occurs and may involve the cyclitic membrane which practically always develops over the posterior surface of the lens. The eye continues to decrease in size, the cornea and sclera become thickened and the cornea also epidermidalized. While the usual history in phthisical eyes is that of an old injury, the process may develop

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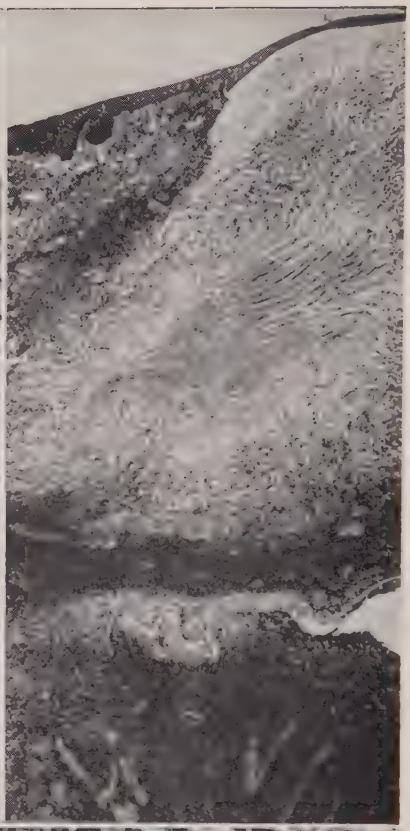

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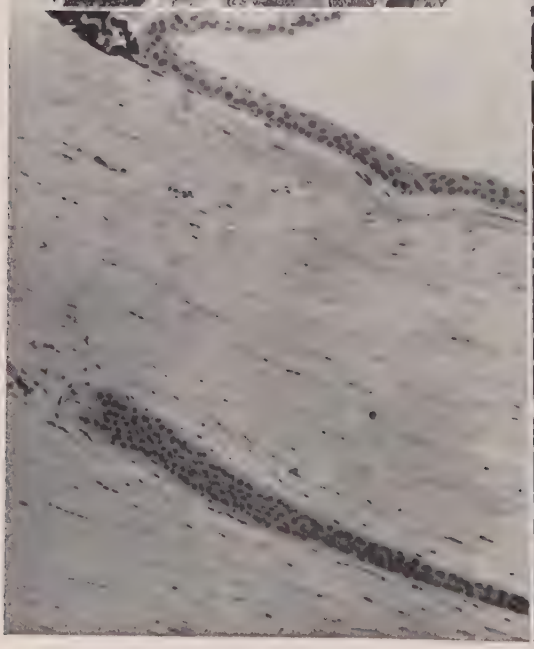

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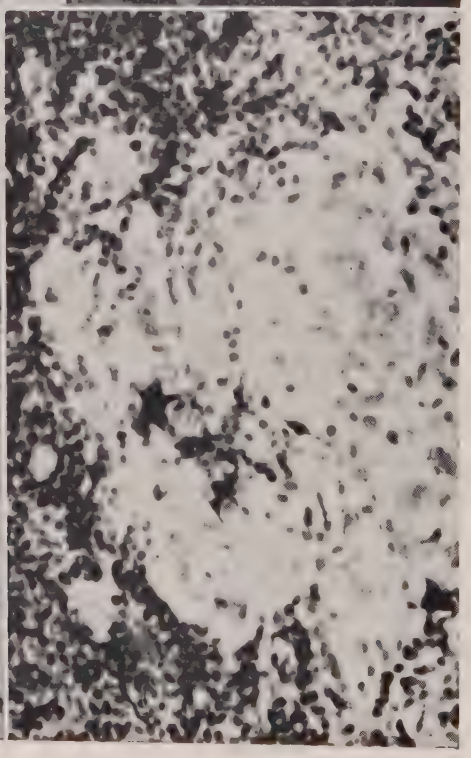

Figs. 607-611.—*For legends see opposite page.*

in a matter of weeks following injury or inflammation (Fig. 610).

Epithelial Implants.—Conjunctival epithelium may be forced into the eye by penetrating foreign bodies or during operative procedures. The anterior chamber is a particularly fertile field for continued growth of this epithelium, which may completely line the anterior chamber or form localized cysts difficult to eradicate and usually necessitating enucleation. Frequently the epithelium is limited to the corneal or scleral scar (Fig. 611).

Fig. 612.—Eosinophilic abscess at site of nematode larva in vitreous, destroying retina and choroid. (Courtesy Mrs. Helenor Campbell Wilder and the American Academy of Ophthalmology and Otolaryngology.)

Siderosis Bulbi.—Metallic foreign bodies remaining in the globe cause serious general damage, particularly to the retina, in which the result is eventual atrophy. Ionization and oxidation lead to dissemination of the metal by the intraocular fluids, particularly if the foreign bodies are ferrous or copper. The distribution from an iron-containing particle is readily demonstrated by the Prussian-blue reaction. The pigment is most abundant in the epithelial cells of the ciliary body and in the inner layers of the retina, but it also may be found on the posterior surface of the cornea, in the iris, and beneath the capsule of the lens.

Glaucoma

Increased intraocular pressure due to any cause results in a series of characteristic changes in the eye structures known as glaucoma. Three types of glaucoma are recognized primary, secondary, and hemorrhagic. Any of these may terminate in absolute glaucoma in which the following changes are seen: cupping of the optic disc, anterior displacement of the iris and lens, atrophy of the iris, ciliary body, and retina, edema of the cornea, and obliteration of the filtration angle by anterior synechiae.

The cornea in chronic glaucoma is very susceptible to infection. This may lead to ulcer and rather typically to development of pannus de-

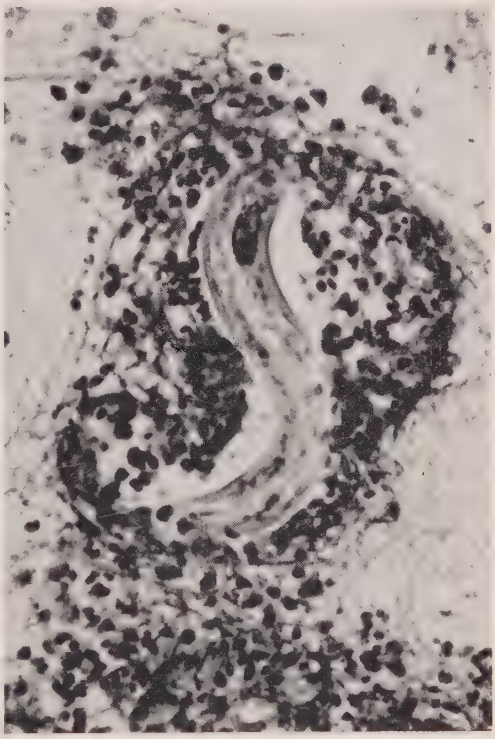

Fig. 613.—Nematode larva surrounded by eosinophiles. (Courtesy Mrs. Helenor Campbell Wilder and the American Academy of Ophthalmology and Otolaryngology.)

Fig. 607.—Tuberculosis. Note the extension of tubercles through the anterior surface of iris and ciliary body.

Fig. 608.—Sympathetic ophthalmia. Epithelioid cells and giant cells contain uveal pigment.

Fig. 609.—Sympathetic ophthalmia. Note streaky character of the necrosis.

Fig. 610.—Phthisis bulbi. Anterior staphyloma (*A*); lens swollen by morgagnian cataract; complete, conical detachment of retina with serous exudate beneath it; base of cone is a cyclitic membrane; choroid also detached and extensively ossified.

Fig. 611.—Epithelial implant between lamellae of cornea and epithelization of anterior chamber, following operation.

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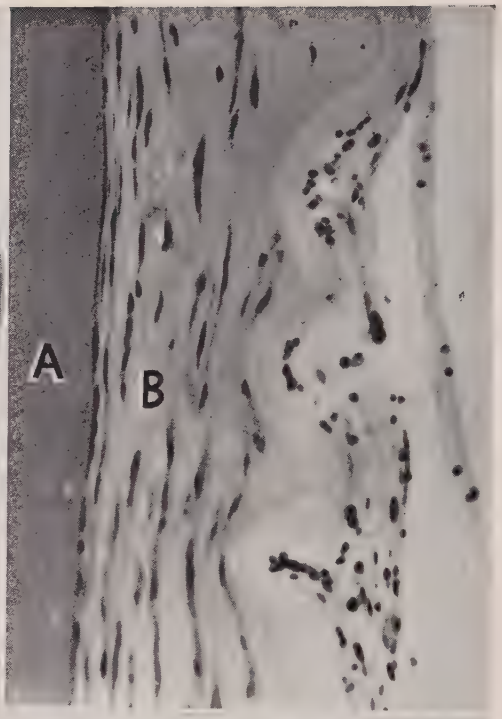

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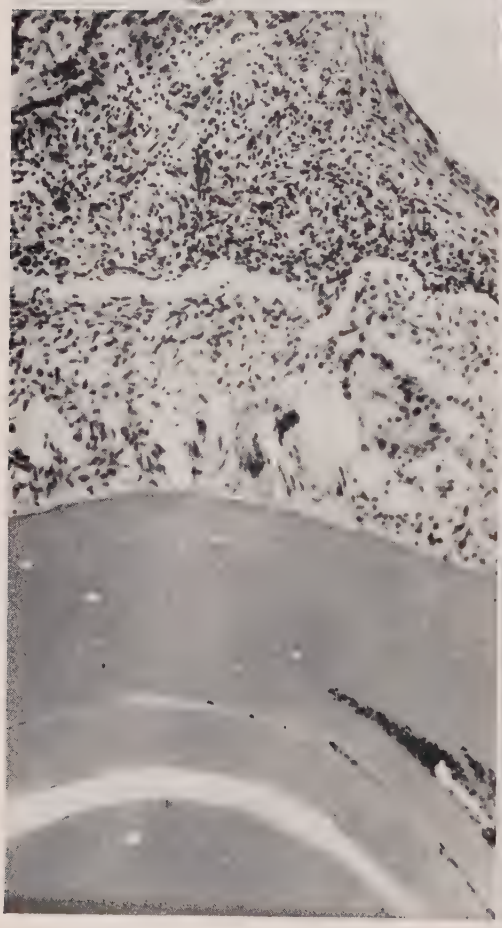

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Figs. 614-617.—*For legends see opposite page.*

generativus. With the increase in size of the globe there is atrophy of the coats including the sclera, and secondary atrophy of the optic nerve, sometimes iris bombée, and commonly ectropion uveae (Fig. 614).

The criterion of a true cupping of the disc is the outward bowing of the lamina cribrosa. The true cup may be obliterated by swelling of the nerve head or by the presence of organized exudate. On the other hand, false cupping, in which the lamina cribrosa is in its normal position, may result from atrophy of the optic nerve, especially from cavernous atrophy not associated with glaucoma.

The mechanism which produces *secondary glaucoma* is obvious. The ciliary bodies continue to secrete fluid but drainage is cut off by obliteration of the filtration angle, and particularly by blocking of the spaces of Fontana. The mechanism of *primary glaucoma* is not as clear because morphologically the filtration angle appears intact in the early stages. It has been suggested that primary glaucoma tends to occur in unusually small eyes because growth of the lens interferes with drainage between the vitreous and the posterior chamber. Others believe that it is due to sclerosis of the fibers of the pectinate ligament preventing drainage into Schlemm's canal. It may possibly be due to a vasomotor crisis which increases the permeability of the capillaries and ciliary processes.[22]

Primary glaucoma manifests itself as one of three clinical types; acute, subacute, and chronic. In acute glaucoma there is sudden onset, very high intraocular tension, and great pain. Subacute glaucoma results from repeated acute attacks, which permanently raise the intraocular tension. In the chronic form, the increase in tension is not so great, nor is it accompanied by the pain and congestion characteristic of the other forms. A morphologic feature of acute primary glaucoma is the edema of the ciliary processes, which may be of such an extent as to be recognizable clinically by producing anterior dislocation of the lens or necrosis of the pupillary margin of the iris. In long-standing cases anterior synechiae usually develop even in the absence of an inflammatory process.

Hemorrhagic glaucoma is usually the result of obstruction of the central vein. Hemorrhages occur through the retina; they may escape into the subretinal space to cause retinal detachment, into the vitreous to cause retinitis proliferans, or into the anterior chamber to become organized over the anterior surface of the iris. The usual evidences of increased intraocular pressure are present. Hemorrhagic glaucoma usually occurs in old persons, and almost always is accompanied by evidence of arteriosclerosis. Occlusion of the central vessels is frequently diagnosed clinically when it is not evident microscopically.

Cataract

The lens is a unique structure composed entirely of epithelium without stroma or vascular elements. It receives its nourishment by absorption from the aqueous humor. It is enclosed in a tough hyaline capsule beneath which, anteriorly and including the lateral poles, is the growing layer of epithelium. The inner cells mature to the specialized lens fibers. One important difference between the lens and surface epithelium, therefore, is that while in the latter the final keratinized material is on the surface and is exfoliated, in the lens the oldest portion is packed in the center to form a nucleus which becomes larger and denser and more homogeneous with the years. With this simple structure, morphologic changes are limited and simple no matter what the condition may be. These changes are essentially (1) abnormal growth of the lens epithelium, (2) coagulation of the protein of the lens fibers with disintegration of the fibers, and (3) rupture of the capsule, whereupon the picture is modified by infection and exudate from without.

Fig. 618.—Retrolental fibroplasia. A thick cyclitic membrane (*A*) that includes detached retina has developed in back of the cataractous lens (*B*). (Courtesy Miss Eleanor V. Paul and the American Academy of Ophthalmology and Otolaryngology.)

Fig. 614.—Glaucoma, secondary. Peripheral anterior synechia; sclera thin; deep cup in optic disc; ciliary body and processes atrophic.

Fig. 615.—Cataract, morgagnian.

Fig. 616.—Cataract, anterior capsular. Lens substance (*A*), hyperplastic lens epithelium (*B*), beneath wrinkled capsule, overlaid by inflammatory exudate.

Fig. 617.—Phaco-anaphylaxis. Granulomatous inflammation beneath lens capsule; inflammatory reaction in adjacent ciliary process; exudate between lamellae of lens.

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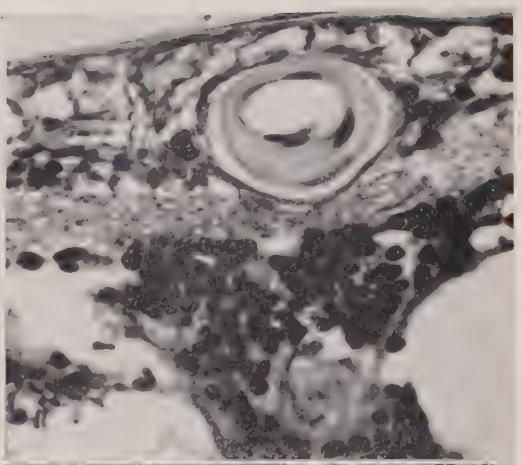

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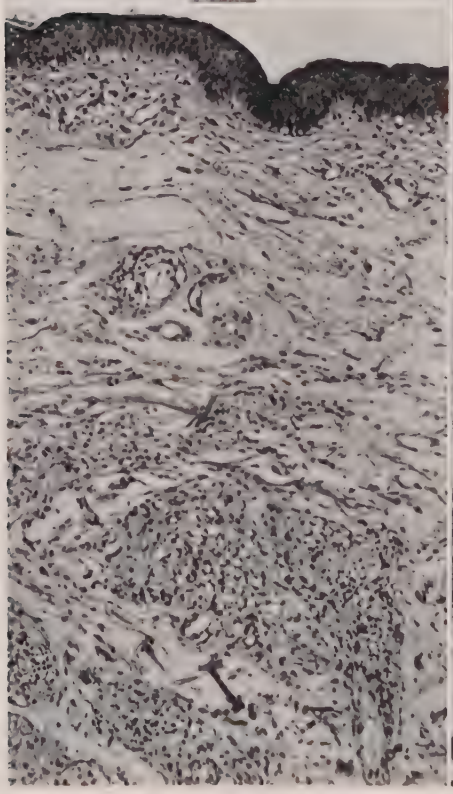

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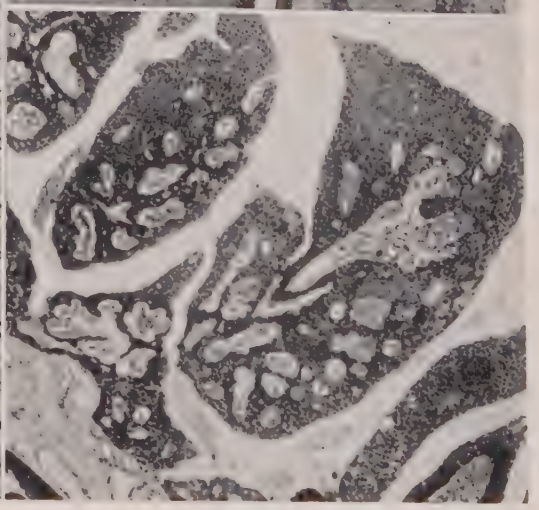


Figs. 619-623.—*For legends see opposite page.*

Certain toxins such as naphthalin and ergot seem to act specifically on the epithelium. Certain definite causes of cataract of which the mechanism is not entirely clear include diabetes, radiant energy, and electric shock. This is true also of the commonest cause of cataract, age, although alteration of permeability of the capsule, interfering with the normal metabolism of the lens, is probably largely responsible. The changes incident to age are manifest in three ways. One, slowly extending sclerosis involving the central fibers, which begins in the thirties and might be considered a normal physiologic process. It does not alter the transparency of the lens so much as it does its refractive properties. The only morphologic change is absence of normal fibrillation since the dead fibrils are fused into a solid hyaline mass which stains poorly. Two, rapid death of the more peripheral fibers that shrink and break up into varying sized masses called Morgagnian globules (Fig. 615). Fluid accumulates in the spaces created by shrinkage of fibrils and causes some swelling of the lens. When this process is advanced, the nucleus is left to float in the collection of albuminous fluid and disintegrated peripheral fibrils, and this stage is called the **hypermature cataract.** While the Morgagnian type of change is seen in **senile cataract,** it is also a feature of cataracts from any other cause. Fluid may be diffused out through the capsule causing it to wrinkle. Three, proliferation of lens epithelium. Injury may cause the epithelium to proliferate not only to form a membrane beneath the capsule anteriorly, **anterior capsular cataract** (Fig. 616), but also possibly to extend, still beneath the capsule, over the posterior surface of the lens. This continuation of the epithelium around the posterior pole is seen particularly in cataract occurring as a complication of other intraocular diseases, such as iridocyclitis. Subcapsular cataracts may also result from contusion in which the capsule is not necessarily ruptured, or from direct injury with rupture of the capsule. When the capsule ruptures the disintegrated lens substance may escape, an abscess may develop in the lens from invasion not only by polymorphonuclear cells but also by macrophages. The lens substance may undergo lipoid change or calcification.

Lens substance is toxic, and certain individuals are allergic to it. When it escapes from the capsule, therefore, there may be a granulomatous inflammation in response to the foreign material, and a diffuse inflammation of the inner coats of the eye—endophthalmitis, which may be evidence of an anaphylaxis. This complication is called *phaco-anaphylaxis* (Fig. 617).

Congenital cataract is a different lesion, usually associated with other congenital abnormalities of the eye. Two types are recognized: The more frequent consists of opacities in the deeper layers of the cortex, is bilateral, and may be found in more than one member of the family. The other form is caused by persistence of parts of the vascular net which surrounds the lens in the embryo, most commonly those over the anterior or posterior pole of the lens. There may be accompanying changes in the deeper cortical lens fibers, a persistent hyaloid artery, or a pupillary membrane.

Retrolental Fibroplasia.—There has recently been considerable controversy among ophthalmologists about fibrous growths on the posterior surface of the lens with more or less detachment of the retina occurring in infants and young children. Terry has named this retrolental fibroplasia, and considered that it developed from persistent embryonal structures of the hyaloid artery and tunica vasculosa lentis, influenced by nutritional insufficiency, and that it occurred in premature infants. It is evident, however, that this serious end result occurs other than under these circumstances of prematurity and persistent embryonal structures. Heath,[23] in a recent comprehensive survey of the controversy, contends that it may also be the result of secondary angiofibrous reaction to retinal disease, including hemorrhages, or to the incidental reparative reaction to ocular injury at any age. The term, therefore, has lost its original significance as a congenital lesion of premature infants, and is now applied to the end results of any process that will produce organization and repair on the posterior surface of the lens and retinal detachment. The histologic picture varies, therefore, with the etiology and with the stage of the process.

Choked Disc (Papilledema)

Choked disc is edema of the head of the optic nerve usually extending into the surrounding retina (Fig. 619). Although it is often seen in conditions which cause increased intracranial pressure, its mechanism is still the subject of controversy (see page 1338). The characteristic change is simply an accumulation of fluid between the nerve fibers internal to the lamina cribrosa. There may or may not be broadening of the subarachnoid spaces about the nerve outside the lamina cribrosa. The swelling may extend laterally, pushing the retina into small folds, and the edema may extend into the nerve-fiber layer of the surrounding retina. The position of the lamina cribrosa is not altered. When the condition is of long standing or has progressed with unusual rapidity, there may be hemorrhages and serous accumulations in the nerve head and adjacent retina. The hemorrhages may be sufficiently extensive to break into the vitreous. There may be atrophy of the nerve fibers eventually, with infiltration of lipoid histiocytes and with gliosis,

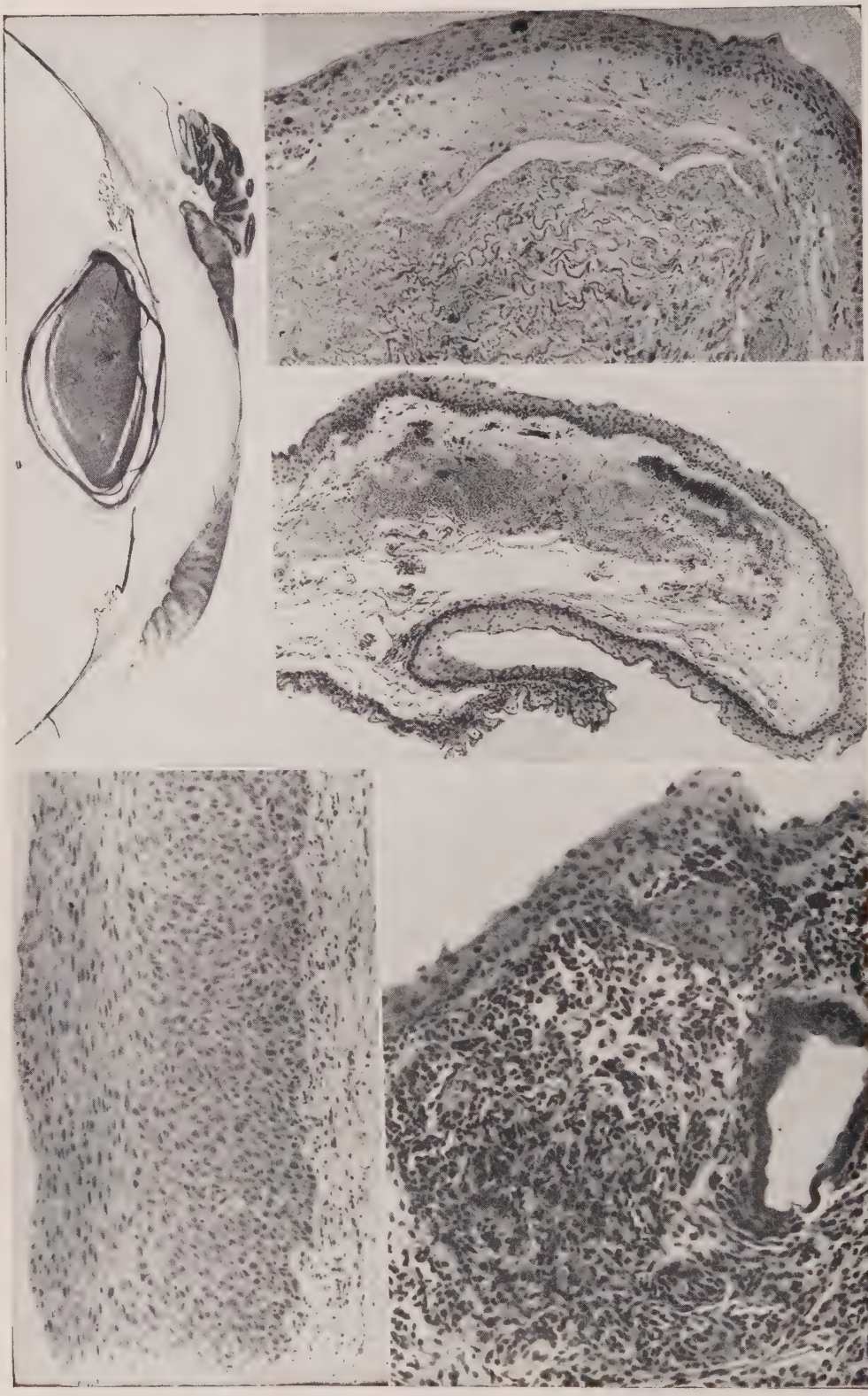
Fig. 619.—Choked disc. Edema of the disc and contiguous retina is limited posteriorly by the lamina cribrosa.

Fig. 620.—Retinopathia, arteriolosclerotic. Hyaline thickening of retinal arteriole—copper-wire vessel.

Fig. 621.—Retinopathia, diabetic. Albuminous exudates (hyaline) in outer plexiform layers. Serous exudate between rod and cone layer and pigment epithelium.

Fig. 622.—Xanthelasma. Xanthoma cells particularly numerous about the blood vessels.

Fig. 623.—Papilloma of conjunctiva at the caruncle. Note the basal character of the cells.



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Figs. 624-628.—*For legends see opposite page.*

also serous exudates in the retina as far as the macula, sometimes with colloidal deposits. The picture then becomes confused with that of arteriolosclerotic changes. When the changes in the optic nerve are far advanced, the condition is called cavernous atrophy.

Retinopathies: Albuminuric, Arteriolosclerotic, and Diabetic

It is claimed by some ophthalmologists that when nephritis is absent, hypertension produces little or no change in the retina. It also is claimed that diabetic retinitis is a separate entity. The basis for the changes seen in each instance, however, is largely if not entirely vascular damage. There are only a limited number of results manifested in the retina by these changes, and any or all of them may be present in each of the three clinical types of retinopathy. There are certain peculiarities, however, especially in diabetic retinitis, that make morphologic differentiation possible in some instances.[24]

The blood vessels of the retina are peculiar in that they contain little or no muscle. Under conditions that produce sclerosis, therefore, the walls become thickened by lipoid and hyaline material rather than by muscular hyperplasia. Ordinarily the hyaline is homogeneous, but sometimes lipoid histiocytes are present. There frequently is an accompanying increase in the lining endothelium. Sclerosis may go to the point of complete occlusion, whereupon the vessels are designated by the ophthalmologist as silver-wire vessels; those retaining narrow lumens are called copper-wire vessels (Fig. 620). The vascular changes are best seen in the nerve-fiber layer of the retina. The vessels of the choroid, the central vessels, and the arterioles in the episcleral tissue will show varying degrees of sclerosis with muscular hyperplasia, duplication of elastica, and intimal changes. Sometimes the central artery becomes thrombosed and subsequently canalized. The outer layers of the retina, receiving nutrition from the choroidal vessels, are relatively little affected by occlusion of the central vessels. In the retinal vessels there is not a uniformly diffuse process, and this accounts for the beaded appearance of the vessels through the ophthalmoscope. The thickened, more resistant arteries compress the veins which they cross, and this can also be recognized ophthalmoscopically.

The interference with the blood supply produces deterioration of the retinal elements, particularly of the ganglion cells, but actual infarction in the ordinary sense is not observed. There are, however, collections of fluid, usually albuminous but at times containing fibrin, most commonly in the outer plexiform layer, called serous exudates by the ophthalmologist (Fig. 599). Macrophages wander into these exudates and become laden with lipoid material (Fig. 596). In the nerve-fiber layer cytoid bodies appear (Fig. 590). These details have been described in the glossary. The cells of both nuclear layers may show microcystic edema. Retinal arteriolosclerosis is of considerable importance as one of the earliest manifestations of an impending hypertensive state.

Diabetic retinopathy is one that may develop in diabetes on the basis of arteriolar changes producing the same features as in albuminuric retinopathy, including intraretinal hemorrhages. The exudates are more frequently hyaline (Fig. 621) than in the other forms of retinitis but a more specific diagnostic feature is the microcystic change in the pigment epithelium on the posterior surface of the iris. A frequent, although not specific change, is noninflammatory vascularization of the anterior iris surface and of the pupillary zone (rubeosis iridis). Secondary glaucoma usually develops in eyes with diabetic retinopathy.

Retinal hemorrhage is seen in a variety of conditions. If it occurs in the outer plexiform layer, it is globular or ovoid, being limited by the perpendicular fibers of that layer. If it occurs in the nerve-fiber layer, it will extend parallel to the surface. If the hemorrhage is large, there may be sufficient destruction of retinal tissue to lead either to scarring with gliosis or foreign body reaction from cholesterol deposits. When these occur in the deeper layers, the gliosis and foreign body tubercles may be extensive. This condition has been called **Coats' disease.** If the hemorrhage is more superficial and breaks into the vitreous, there is organization, and it is known as retinitis proliferans. Subretinal and choroidal hemorrhages may be absorbed and leave little or no obvious residuum.

Tumors

Tumors of the Eyelid

One of the commonest lesions of the eyelid is **xanthelasma,** strictly speaking not a neoplasm. It is manifested clinically as yellow streaks and patches, usually on the upper lid of elderly persons. An indication of altered lipoid metabolism, it is often associated with atheroma of the larger blood vessels or appears as a part of the diabetic diathesis. The lesion is simply an accumulation of lipoid-laden histiocytes, in the early stages confined to perivascular tissue, but later diffusing into the stroma to form more definite tumefaction (Fig. 622).

An allied condition is **arcus senilis,** which is a deposition of the lipoidal material, usually phagocytosed, into the cornea. Eventually a white ring forms, leaving a clear zone of cornea to the limbus.

The eyelid is the commonest site for **molluscum contagiosum,** the lesions of which are frequently multiple (see page 331).

Fig. 624.—Pterygium showing elastosis.
Fig. 625.—Pinguecula.
Fig. 626.—Papilloma of conjunctiva. Epidermidalization of corneal epithelium.
Fig. 627.—Bowen-type dyskeratosis of conjunctival epithelium.
Fig. 628.—Nevus, benign, conjunctiva. Note the gland.

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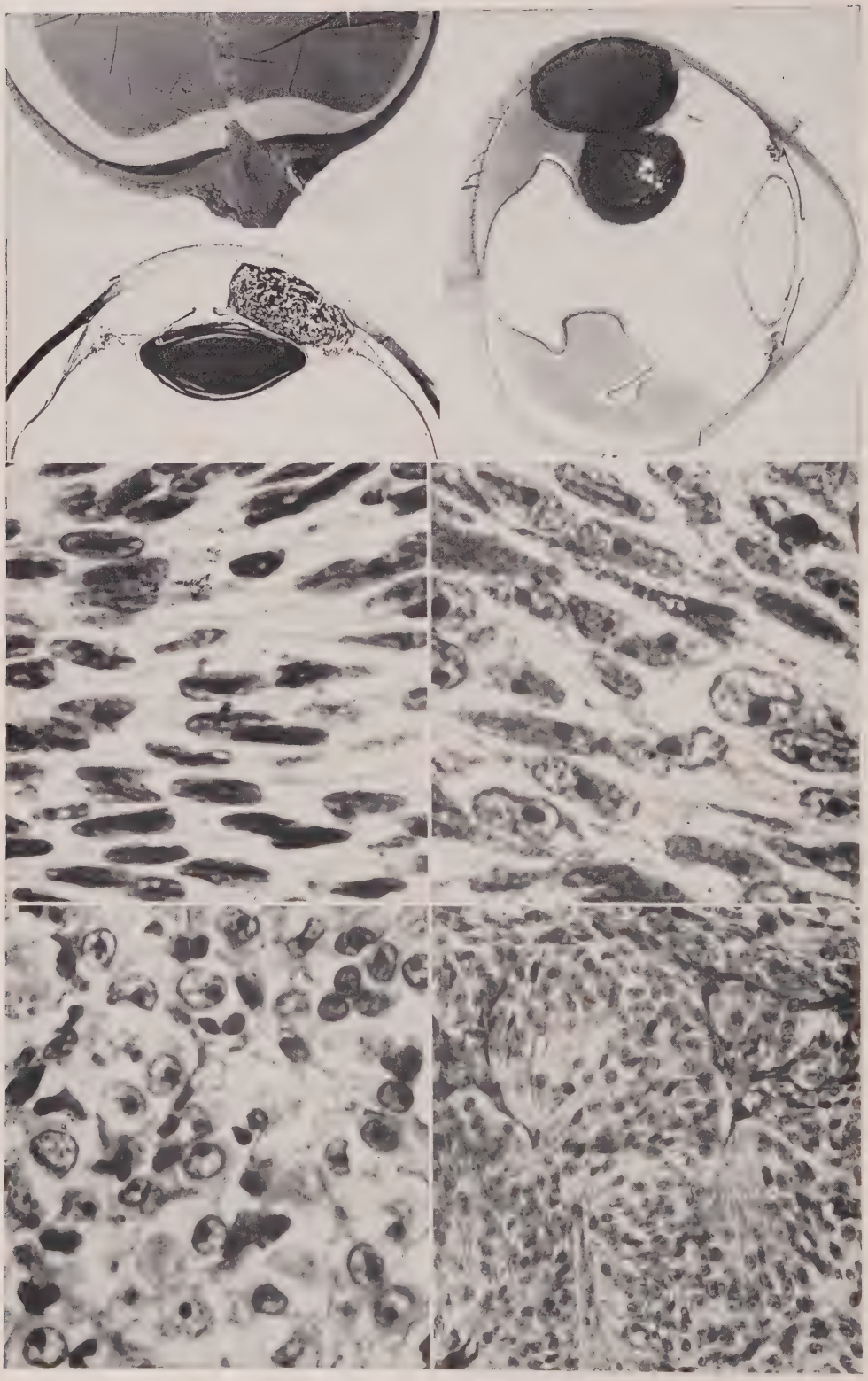

Figs. 629-635.—*For legends see opposite page.*

Dermoid cyst is not uncommon in the upper eyelid, particularly near the outer angle in or below the eyebrow.

Papilloma of the conjunctiva at the caruncle is a common tumor and is of some importance because it may be misinterpreted by the pathologist as a basal cell carcinoma. The epithelium covering the delicate stalks is very likely to retain an undifferentiated basal character (Fig. 623).

Carcinoma of the eyelids is usually of basal type and is most often found at the inner canthus. A fairly common lesion is a verrucal type of **senile keratosis** appearing clinically as a warty projection usually along the lid margin. The epithelium shows a dyskeratosis that may precede squamous cell carcinoma.

Orbital Tumors

The pathologist sees the **mixed tumor** of the lachrymal gland more often than any other orbital tumor. It has the same pathologic features and clinical characteristics as the mixed tumor of the salivary glands, showing the same variation in components and the same tendency to recur if the entire capsule is not excised. It is, however, less aggressive and metastasizes much less frequently than the comparable salivary gland neoplasm.

A fairly common orbital tumor is the **meningioma.** This may be primary, arising in the meninges of the optic nerve, or secondary, by erosion into the orbit from an intracranial tumor. It is usually of the "endothelial" type and has the characteristic whorls, but it may appear in any of the outer meningioma types, vascular or sarcomatous.

Neurogenic fibroma with characteristic palisading of nuclei is occasionally seen; more often simple **lipoma.** A more specific tumor is the **glioma of the optic nerve,** producing a circumscribed swelling of the intraorbital portion of the nerve. Histologically, the polymorphic cell picture, with glioblasts of various sizes and shapes, medulloblasts, and occasional astrocytes, leads to confusion as to exact classification. The clinician recognizes a pseudotumor, an inflammatory mass, the histology of which varies with the etiology, but which usually is that of an infectious granuloma.

Hemangiomas of the orbit sometimes occur and are likely to be of the cavernous type. They may cause pressure erosion of the orbital bones.

The possibility of **metastatic tumors,** especially of sympathicoblastoma (Hutchinson type) must be borne in mind.

Epibulbar Tumors

The lesion of the bulbar conjunctiva most often seen by the pathologist is the **pterygium.** It is a triangular tumefaction of the bulbar conjunctiva that coincides with the palpebral slit and is therefore elongated laterally. Its advancing head is in the cornea where it destroys Bowman's membrane and the corneal lamellae.

The stroma consists of loose hyalinized connective tissue containing an excess of elastic fibrils. In addition there may be telangiectasis, edema, inflammatory reaction, and calcification. The epithelium practically always shows metaplasia to the epidermal type, and it may be acanthotic, very rarely with a leukoplakic type of dyskeratosis. **Pinguecula** is a yellowish mass in the conjunctiva near the limbus which has the same histology as the pterygium, especially the elastosis, and is usually conceded to be the same process (Figs. 624 and 625).

Dermoid is a relatively common lesion of the conjunctiva. It consists of an area of congenital epidermidalization, including any or all of the skin appendages. It is usually on the bulbar conjunctiva near the limbus. It is benign but may be irritating because of hairs. Since it rarely occurs in the cystic form on the conjunctiva, "dermoid" rather than "dermoid cyst" is the appropriate term. As stated before, dermoid cysts are relatively common in the region of the lacrymal gland and in the outer portion of the eyebrow.

The important tumors of the bulbar conjunctiva, usually located at the limbus, may be divided into an *epithelioma series* and a *melanoma series.* The conjunctival epithelium exposed through the palpebral fissure frequently becomes epidermidalized, whereupon this changed epithelium may react in a number of ways. It commonly develops into a simple papilloma (Fig. 626), which may reach great size and protrude through the palpebral fissure. Dyskeratosis, usually of the leukoplakic type, may appear, preceding the stage of frank malignancy. Occasionally in the nonpapillomatous lesion the dyskeratosis is the same as that seen in Bowen's disease (Fig. 627) of the skin, but malignancy is not so common a sequel in this type. The epidermidalization may involve the corneal epithelium well in advance of the papillary process.

This series is of clinical importance in that even in the presence of malignancy, unless there is sufficient involvement of the cornea to make complete excision impracticable, conservative treatment by local removal is justified. This is borne out by experience[25] with a large group of cases in which it was seen that local recurrence will precede metastasis. Irradiation is inadvisable.

Fig. 629.—Melanoma, choroid, flat diffuse type.

Fig. 630.—Melanoma, choroid, collar-button type, extension through break in Bruch's membrane; extensive retinal detachment; serous exudate beneath the retina.

Fig. 631.—Melanoma, malignant, ciliary body and iris.

Fig. 632.—Melanoma, malignant, Callender spindle cell A.

Fig. 633.—Melanoma, malignant, spindle cell B.

Fig. 634.—Melanoma, malignant, epithelioid cell type.

Fig. 635.—Melanoma, malignant, fascicular cell type.

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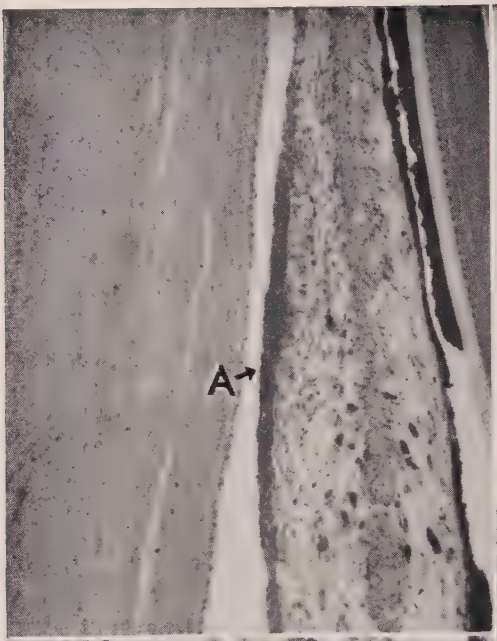

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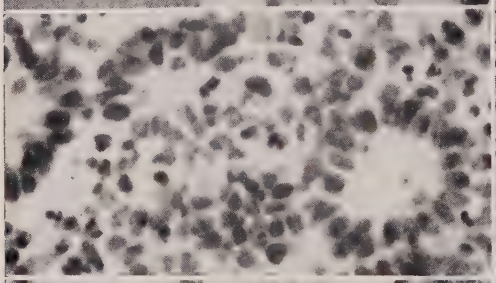

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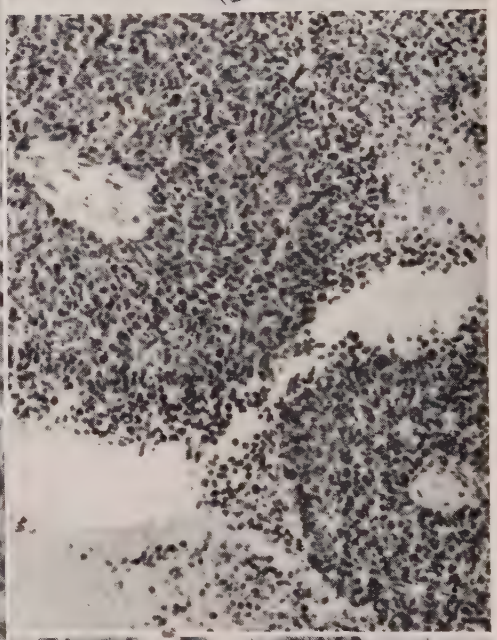

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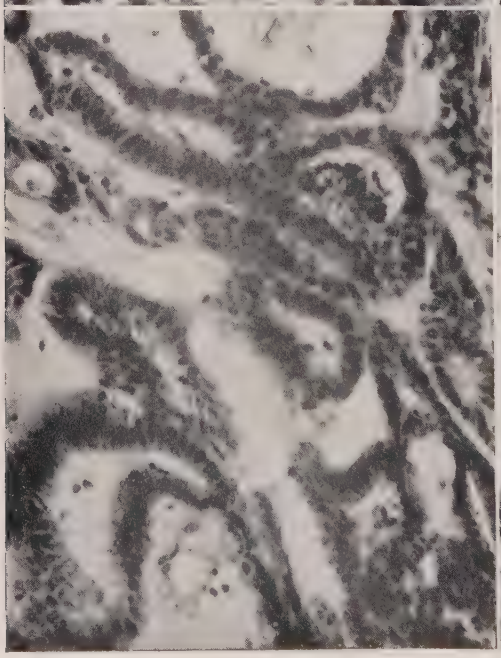

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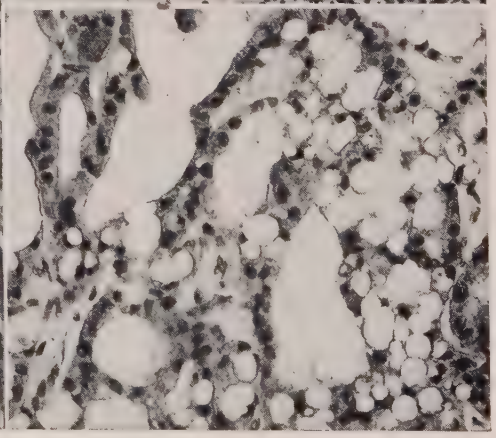

Figs. 636-641.—*For legends see opposite page.*

The **melanomas** are of two types, the **nevus** and the **malignant melanoma.** The nevus is a replica of the skin lesion; it may be purely dermal and benign or more commonly of the dermal-epidermal type and potentially malignant (see page 1165). The inclusion of glandlike epithelial structures and of some hair follicles, particularly of the lanugo type, serves to confuse the picture of the conjunctival nevus, often resulting in its being mistakenly diagnosed as malignant (Fig. 628). The tumor is amenable to simple complete excision.[25]

The malignant melanoma is identical histologically and clinically with the intraocular melanoma, having the same variation in cell type, the same invasiveness, and the same tendency to metastasize by the blood stream. Judging from the Registry experience, however, those of the spindle-cell type, which have not invaded so extensively that they cannot be completely removed, are amenable to excision. Those that extend posteriorly give a less favorable prognosis than those that extend to the cornea.

Intraocular Tumors

The most important intraocular tumor is the **melanoma of the uveal tract.** This is a tumor predominantly of advanced years, at least clinically, but recent experience with a large number of eyes removed following trauma from the military age group indicates that it may be present in the subclinical form at an early age. It is a tumor of melanoblasts which have their origin in the neuroepithelium of the neural crest. It shows all the cell variation of malignant melanoma of the skin. It occurs most commonly in the posterior segment of the choroid (Figs. 629 and 630) but may have its origin in the ciliary body or iris (Fig. 631). In the choroid, melanomas grow as disclike masses until they break through Bruch's membrane and then mushroom out beneath the retina. In the ciliary body they are more diffuse, extending into the choroid, the root of the iris, and at times along the ciliary vessels and nerves through the sclera. Those arising in the choroid seldom extend into the orbital tissue. Those arising in the iris are readily visible at an early stage and if they have not extended to the root of the iris are amenable to local excision, thus avoiding enucleation which is necessary if the tumor is in any other location. The chief primary clinical manifestation of choroidal melanoma is retinal detachment. The experienced ophthalmologist has come to suspect melanoma when he discovers an area of retinal detachment, particularly if it is in the posterior hemisphere.

Melanomas are about evenly distributed between the sexes, but there is a wide disparity in the incidence in the white and Negro races. In an analysis of 1,500 of the cases in the Registry of Ophthalmic Pathology it was found that only seven were in Negroes (see also page 1167).

Extrabulbar extension of melanomas is not common although extension may occur along the ciliary nerves and vessels and occasionally into the optic nerve. Recurrence, therefore, in the orbital tissue after enucleation is rare. Postoperative irradiation is contraindicated, since the tumor is not radiosensitive. Melanomas may extend along the lines of operative or traumatic wounds in the cornea or sclera, and if neglected may break through the sclera to form massive intraorbital tumors.

The clinician must differentiate between tumor, foci of pigmentation of the disc, and the blue-ointment patches in the retinal field.

There is a wide variation in the death rate in relation to cell type (Table VII). There is an over-all mortality rate of about 50 per cent based on follow-ups of five years and longer. A discouraging feature of the tumor, however, is the impracticability of declaring a patient cured even after five years. Death from general metastasis has occurred as long as nineteen years after enucleation. Metastasis is by the blood stream so that general seeding throughout the body, including the skin, often occurs, although the liver is usually most heavily involved. Callender's[26] classification of melanoma by cell type and arrangement is of more than academic interest. He recognizes five forms:

Spindle cell A—cells uniform in size and shape, relatively small amount of cytoplasm, a condensed nucleus with absence of nucleolus but

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Fig. 636.—Nevus, anterior surface of iris (*A*), Posterior synechia; pigment attached to lens capsule.

Fig. 637.—Retinoblastoma. Complete detachment of retina; posterior half replaced by tumor that has invaded the optic nerve; peripheral anterior synechia; morgagnian cataract.

Fig. 638.—Retinoblastoma. Concentration of tumor cells about blood vessels, and intervening necrosis.

Fig. 639.—Retinoblastoma. True rosette of Flexner.

Fig. 640.—Diktyoma, ciliary body.

Fig. 641.—Pigmented epithelioma, ciliary processes.

frequently with a longitudinal fold through the center of the chromatin (Fig. 632).

Spindle cell B—larger spindle cells with more cytoplasm, nucleus more vesicular and with a definite, usually centrally placed nucleolus (Fig. 633).

Epithelioid cell—both large and small polyhedral cells with a liberal amount of cytoplasm and with vesicular nuclei (Fig. 634). Ordinarily there is not the great pleomorphism seen in the epithelioid type of cutaneous melanoma.

Mixed cell—a combination of the above forms, usually spindle B and epithelioid.

Fascicular—of the spindle B type arranged in palisaded groups, carried to such extremes at times as to simulate adenocarcinoma (Fig. 635).

It has been our experience that about 10 per cent of the tumors are so necrotic that satisfactory cell typing is not possible.

TABLE VII

INTRAOCULAR MELANOMA. OUTCOME ACCORDING TO CELL TYPE

	LIVING	DEAD	TOTAL	PER CENT DEAD
Spindle A	33	2	35	6
Spindle B	88	29	117	25
Fascicular	8	5	13	38
Necrotic	23	22	45	49
Mixed	105	171	276	62
Epithelioid	4	10	14	71
Total	261	239	500	48

Distribution of cell type and the outcome are indicated in Table VII, prepared from 500 cases that have been followed for five years or more.[27]

Wilder[27] and Callender[26] have studied the argyrophil-fiber content of the melanomas and have found that the mortality rate is in indirect ratio to the degree of fibrillation; 10 per cent in those heavily fibered and 80 per cent in those with few or no fibers. Pigment content of melanomas varies considerably, being less in the epithelioid-cell tumors.

The tumors in the eyes of younger persons have been in the suprachoroidea and we assume that it is the usual site of origin. Benign melanomas of the intradermal nevus type do occur in the uveal tract and especially in the iris (Fig. 636) but they are not as common as in the skin.

Retinoblastoma (glioma, or neurocytoma retinae) is a tumor of early childhood arising from the neuroepithelium of the retina. It is sufficiently differentiated to justify a specific name rather than the general ones, glioma and neurocytoma.

Bilateral involvement is not rare in cases of retinoblastoma; in a Registry series of 232 cases, 48 were bilateral. The tumor becomes apparent in children during the first two years of life, and because of the peculiar cat's-eye reflections it gives the eye, is often first noticed by the parents. Approximately 75 per cent of the Registry cases have been in children under 3, and only three patients have been over 12 years of age. There is no significant difference in sex incidence. Occasionally several children in the same family are involved.

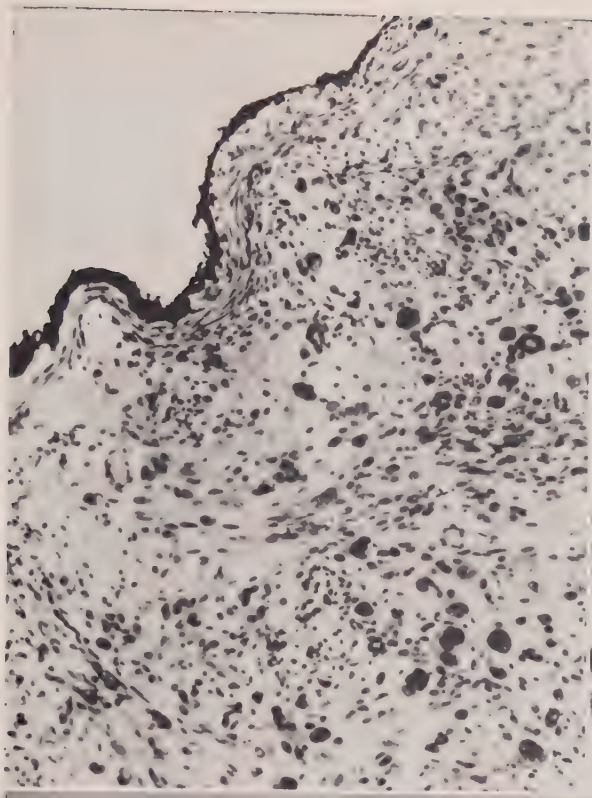
The tumor arises most commonly in the posterior hemisphere, so that extension into the optic nerve may be early (Fig. 637). Metastases occur, but they are neither as frequent nor as widely distributed as in melanoma, and they are usually located in the regional lymph nodes, the cranial bones, and the lungs.

Because of the frequency of extraocular extension along the optic nerve, recurrence in the orbit after enucleation is much more common than in melanoma. Retinoblastoma is more radiosensitive than melanoma. The mortality rate is about 50 per cent, and death usually follows within a year after enucleation. In the Registry series death has not occurred in any case in which the patient survived enucleation by as much as four years. The death rate is much higher, of course, in cases in which there is extrabulbar extension at the time of enucleation. Bilateral involvement, according to the records in the Registry, does not seem to increase the death rate. Histologically the tumor shows some of the characteristics of neurocytomas in other locations, particularly rosette formation, perivascular clustering, and the tendency to necrosis (Fig. 638). Occasionally, necrosis obliterates the tumor. The differentiation may go on to the extent of imitating rods and cones, and the rosettes usually have an inner limiting membrane suggesting the external limiting membrane of the retina. The tumor grows rapidly from the inner surface of the retina, invades the vitreous, and scatters implants on the surface of the retina. If it breaks through the outer portion of the retina, there is soon complete detachment. It does not as a rule break through the sclera, but frequently it extends into the optic nerve, and the commonest cause of death is direct extension into the cranial cavity.

A true rosette, as described by Flexner, is made up of a palisaded group of columnar cells with an inner limiting membrane through which fibrils converge toward the center (Fig. 639). Another type of rosette is formed by the palisading of cells about a blood vessel. Both types may be present in the same tumor.

Closely allied to, and probably of the same histogenesis as retinoblastomas are the rare tumors in the ciliary body which arise from the pigment epithelium, either of the ciliary body or of the posterior surface of the iris. One type is **medulloepithelioma (diktyoma)** in which the epithelium is generally well differentiated to columnar pigmented type, and the cells are arranged in glandlike structures or in columns and are associated with less differentiated or primitive retinoblasts showing ill-defined rosettes (Fig. 640). The tumor is malignant and requires radical treatment. The second, **pigmented epithelioma** (Fig. 641), a still rarer tumor, is characterized by cystic spaces formed by cuboidal pigment epithelium and without the differentiated element of the diktyoma. These tumors grow slowly and, so far as is known, do not metastasize. Clinically they could not be differentiated from melanoma arising in the ciliary body or in the root of the iris.

642.



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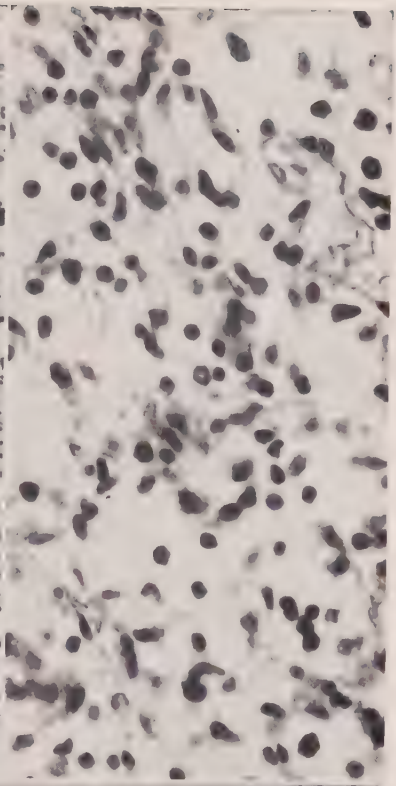

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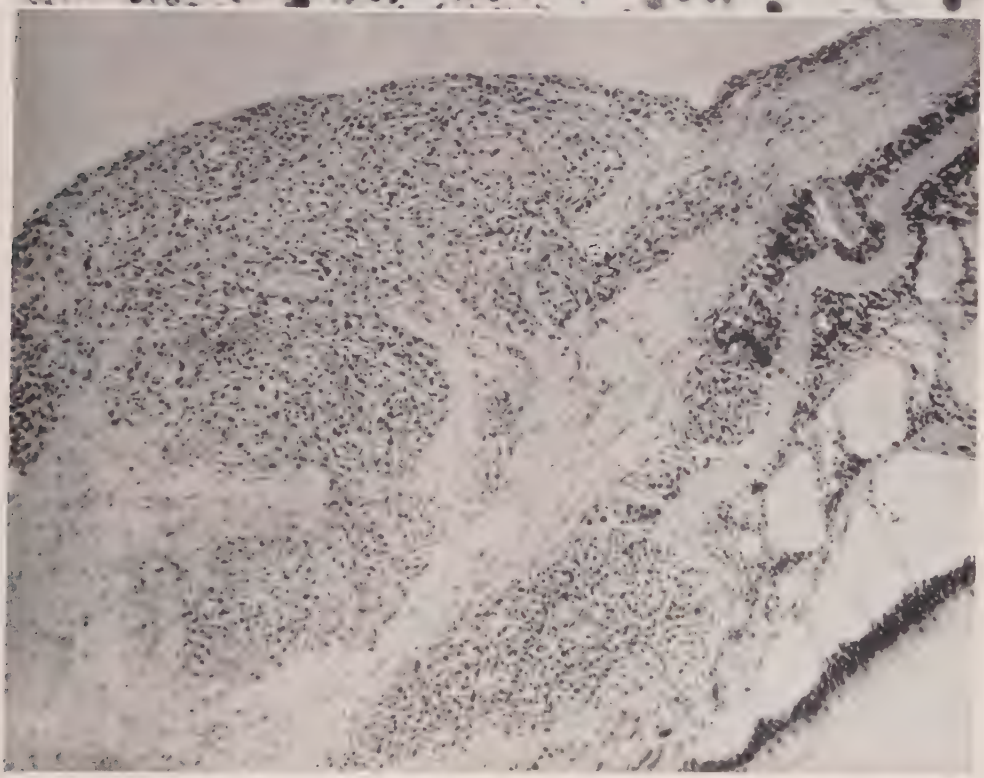

Fig. 642.—Leiomyoma, iris.

Fig. 643.—Von Hippel's disease. Angiomatous and gliomatous tumor at the disc; large cysts in the outer layers of retina.

Fig. 644.—Von Hippel's disease. High power to show vascular and glial elements.

Tumors of the Iris.—Aside from the benign nevus and melanoma already described, a tumor of the iris of considerable and practical import, although rare, is **leiomyoma** (Fig. 642). In the older literature it is called **leukosarcoma** because it is grossly nonpigmented. It arises near the pupillary margin of the iris, grows slowly, and is made up of spindle cells which have the morphologic and tinctorial characteristics of smooth muscle, and of epithelioid cells. There may be a deceiving pleomorphism, however. The tumor, including the cells of epithelial character, arises from the sphincter muscle of the iris. The epithelioid cells are easily explained since the iris musculature is derived from the embryonic anterior layer of neuroepithelium of the iris. The tumor is benign clinically and, if not too large, is amenable to simple excision. There are several examples in the Registry material of unnecessary enucleation resulting from a histologic diagnosis of sarcoma.

Hemangioma.—Intraocular hemangiomas are not common, but those of the retina are of considerable importance because of their possible association with lesions elsewhere.

Hemangiomas of the choroid are remarkably uniform in location and histologic appearance: they are usually in the posterior hemisphere and crescentic; histologically, they are made up of thin-walled, roomy vessels, and there is little or no stroma or cellular reaction. They are sometimes associated with a vascular nevus of the face.

Hemangioma of the retina (Figs. 643 and 644) was established as a clinical entity by von Hippel[28, 29] and is known to the ophthalmologist as von Hippel's disease. It is a lesion usually of the nerve fiber layer of the retina but the exact nature of the tumor is still in question, particularly as to whether it is primarily a vascular tumor or a focal inflammatory lesion that has led to gliosis and vascularization. The majority of pathologists consider it an angioblastoma, the gliosis being secondary. Early enucleation is sometimes performed because the tumor is interpreted clinically as malignant. It is a benign lesion and is practically always associated with retinal detachment, cystic deterioration of the retina, and, in the course of years, glaucoma. Its clinical importance is due to the fact that in about 20 per cent there are associated cystic lesions in the cerebellum, spinal cord, and pancreas, and hypernephroid tumors of the kidney, epididymis, and bones, any one or a combination of these. This association was first described by Lindau[30] and the syndrome is known by his name.

Hemangioma of the iris is serious clinically because hemorrhage into the anterior chamber is likely to occur, with subsequent organization and the development of glaucoma.

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Note: The American Academy of Ophthalmology and Otolaryngology has sponsored new editions of the *Atlases of Ophthalmic and Otolaryngic Pathology* prepared at the Armed Forces Institute of Pathology where they are available. These cover the special fields comprehensively. The first is published by W. B. Saunders Co., Philadelphia, and the second by the American Registry of Pathology (A. F. I. P.)

Chapter 25

THE LIPS, MOUTH, TEETH, AND NECK

William H. Bauer

LIPS

Development.—The upper lip develops from the tissue that covers the medial nasal process and the two lateral maxillary processes. The normal formation of the upper lip depends upon the eventual complete union of these processes. The lower lip originates from the tissue that covers the mandibular arch. The two lateral sulci are gradually closed upon the disappearance of the central groove of the mandibular arch in the early embryonic life.

Developmental Malformations

Cleft lip (harelip) occurs most frequently in the upper lip. The cleft either splits only the lip, involves the alveolar process, or extends into the hard and soft palate. In the latter case the cleft cuts along the union of the premaxilla and maxilla, unilaterally or bilaterally, or through the premaxilla alone. The rare cleft of the lower lip runs along the median line.

Cleft lip is a hereditary malformation and results from a failure of the mesodermal tissue to penetrate and replace the epithelial junction between the processes of the maxilla.[1] The persisting epithelial sheet breaks, thus leaving a cleft.

When the maxilla is involved, a harelip may be associated with abnormalities of position, shape, or number of the incisors. The lateral incisors are most commonly involved; they may be missing, remain unerupted, or two or even three lateral incisors may be present along or behind the cleft.

Clefts through the lip that extend to the eye are called oblique facial clefts. These result from cuts by amniotic bands rather than failure of the medial or lateral nasal and maxillary processes to unite.

Macrostomia, or large mouth, is due to the failure of the upper and lower lips to unite and form the cheeks.

Fordyce's disease is a tissue malformation in which displaced sebaceous glands form single or confluent small yellowish elevations on the mucosa of the lips. The openings of their ducts appear in the centers of small papules which are covered by parakeratotic epithelium. These changes sometimes extend into the mucosa of the cheek and may even involve the gingiva.

Inflammation

Cheilitis Glandularis.—Inflammatory changes of the mucous ducts of the lips, usually the lower lip, cause dilation and multiplication of these glands. Small firm nodules are formed beneath the lip mucosa. The orifices of the glands are enlarged and visible grossly.

Cheilosis (Perlèche).—Cheilosis begins frequently at the angles of the mouth and spreads toward the center of the lips. It usually occurs in children, at times in epidemic form. The condition starts as a moderate hyperkeratosis of the epithelium, imparting a mother-of-pearl tinge to the surface. Wrinkles and transverse fissures develop later. There is very little tendency to bleed.

Finnerud[2] distinguishes three types of cheilosis, (1) an infectious variety of streptococcal, staphylococcal or monilial origin, (2) a mechanical type occurring in elderly persons, often due to faulty fitting dentures, and (3) a type resulting from vitamin deficiency. The last is encountered most frequently. It is maintained that riboflavin deficiency is the cause of this type of cheilosis, yet Cayer, Ruffin, and Perlzweig[3] showed that lack of nicotinic acid plays an even more important role.

Herpes Simplex.—Herpes simplex is a viral infection in which discrete single vesicular lesions develop along the mucocutaneous border of the lips. The blisters may become confluent and rupture. Extension may occur into the oral mucosa. Herpetic eruptions are apparently associated with a lowered resistance of the tissues due to various factors, since the virus of herpes simplex may be found in the saliva of healthy persons. Infants and children are particularly susceptible to the disease and in them the central nervous system may be involved. The virus is filtered with great difficulty. Intranuclear inclusions are observed in the cells of the herpetic lesions. Smith, Lemotte, and Reamer[4] and Whiteman, Wall, and Warren[5] demonstrated typical herpetic inclusions in the brain of cases of meningoencephalitis.

Furuncles and carbuncles of the lips deserve particular attention because of the danger of a thrombosis of the cavernous sinus.

Syphilis.—Congenital syphilis may be associated with mucous patches on the lips. These lesions leave permanent scars that radiate from the lips into the cheek (rhagades).

A chancre of the lips can be differentiated from a carcinoma by the presence of the *Treponema pallidum* in dark-field preparations, by the rapid development with early involvement of the regional lymph nodes, and by the perfect healing which occurs after several weeks.

Tumors

Benign connective tissue tumors such as fibroma, lipoma, and lipofibroma of the lips are

not common. Sarcomas of the lips are rarely observed and the few cases recorded so far have been of the round cell form. Epithelial tumors of the lips are more frequently found.

Papilloma.—This slightly elevated cauliflower-like growth may be connected with the mucosa of the lips by a broad or narrow base. The surface exposed to traumatization is usually keratinized. A papilloma combined with a flat simple keratosis must be considered as a precancerous lesion on the lips of elderly people. The occurrence of adenoma of the lips is rare.

Hemangioma.—Hemangiomas of the lips, particularly the lower, are more often observed than lymphangiomas. They may be of a capillary or cavernous type. Because of their location, they are exposed to traumatization and frequently bleed.

Retention Cysts.—Retention cysts of the submucosal labial glands are found more frequently in the lower lip than in the upper. They are small, bluish, rounded elevations, freely movable on the underlying tissue. The cyst wall is composed of an epithelial layer, the thickness of which varies according to the pressure of the mucous contents and the intensity of the inflammatory changes in the surrounding fibrous tissue. Hemorrhage into the cyst and inflammatory exudate from the surrounding tissue may increase its size.

So-called "Mixed Tumor."—"Mixed tumors" of the lips, showing the cytological feature of the pleomorphic adenoma of the salivary glands have been described.[6] They occur mainly in the upper lip. The "mixed tumors" are well encapsulated and show no tendency to break through the capsule and infiltrate the surrounding tissue. They originate from the labial glands.

Carcinoma.—Carcinoma of the lip occurs more frequently in males and on the lower lip. The tumors are either elevated and papillomatous, or flat and ulcerating. The two types differ in degree of malignancy. The projecting cauliflowerlike carcinoma soon becomes deeply ulcerated, advances rather quickly, and may extend into the cheek. The regional lymph nodes become involved rather early. The flat carcinoma of the lip grows very slowly and lymph node invasion occurs late, if ever.

Carcinoma of the lip is of the squamous type, but a basal cell carcinoma originating in the skin may spread into the lips. Any chronic irritation such as continuous exposure to rough weather and excessive sunshine (sailors and farmers of ruddy or fair complexions) may be a factor in the development of a carcinoma of the lip. Probably too much emphasis has been placed upon smoking as an etiological factor.

ORAL MUCOSA

The freely movable mucosa of the cheek, the floor of the mouth, and the soft palate differ in morphologic structure from the immobile mucosa (gingiva) around the teeth and on the hard palate. The latter is occasionally hornified and is firmly attached to the periosteum of the underlying bone by dense collagenous fibers. The movable mucosa is supported by loose fibrous tissue with glands. Diffuse inflammation of the oral mucosa is called stomatitis, whereas involvement of the gingiva is termed gingivitis. They often occur together.

The oral mucosa is exposed to mechanical and thermal injuries during mastication. These injuries, together with the multitude of microorganisms normally present in the mouth, often account for inflammatory changes observed in the mucosa. Early manifestations of blood dyscrasias, vitamin deficiencies (mainly vitamins B and C), endocrine disturbances, various dermatoses, infectious diseases, changes of sex hormones, and metal poisonings (lead, mercury, bismuth, copper, phosphorus) may develop in the oral mucosa. Allergic reactions to various drugs may also occur here. Atrophic changes of the oral, tongue and upper alimentary tract mucosa together with an iron deficiency anemia and dysphagia are observed in Plummer-Vinson syndrome.

Inflammatory and Hyperplastic Lesions

Catarrhal stomatitis or gingivitis is usually associated with acute infectious diseases or gastrointestinal disturbances. There is a hyperemia of the uppermost layer of the mucosa, associated with an increased secretion by the mucous glands which are surrounded by inflamed tissue. The epithelium of the mucosa shows proliferation and marked round cell infiltration. Edema and perivascular infiltration are present in the submucosa. Sometimes desquamated epithelial cells together with the exudate form a pseudomembrane upon the surface.

Ulceromembranous stomatitis or gingivitis, often called trench mouth, Vincent's infection or fusospirochetal gingivostomatitis, is most common in young individuals and occasionally occurs in endemic form. It may occur also in edentulous mouths. The disease usually starts with general malaise, at times even before the manifestations on the mucosa become obvious. Sharply outlined ulcers in the interdental papillae extend along the marginal gingiva, and are associated with hemorrhages, swelling of the regional lymph nodes, and fever. Marked sialorrhea and an offensive odor are important symptoms. The ulcerative membranous lesions may spread over all parts of the oral mucosa, including the mucosa of the tongue, the pharynx, and the tonsils.

A smear taken from the ulcers shows an accumulation of oral spirochetes and fusiform bacilli. These microorganisms are normal inhabitants of the oral cavity. It is very likely that a lowered resistance of the oral mucosa as a result of defective nutrition or exhaustion paves the way for the action of these organisms. The condition ordinarily cannot be trans-

mitted to a healthy individual by exudate from active lesions. However, repeated and protracted inoculation may be effective.

Herpetic stomatitis is a definite clinical and pathologic entity characterized by grouped vesicles and disclike, grayish, sensitive areas on the oral mucosa, encircled by an inflamed border.[7] These lesions may be small or large due to coalescence. Children, less frequently adults, who are weakened by defective nutrition and infectious diseases are most commonly affected. The appearance of the ulcers may be associated with slight fever and malaise. Histologically, there is superficial necrosis of the mucosal epithelium with a fibrinous exudate and small cell infiltration of the submucosa.

The ulcers are infectious and highly contagious. Exudate from these lesions produces an herpetic keratoconjunctivitis with typical acidophilic intranuclear inclusions in the corneal epithelium of rabbits and is often followed by encephalitis.[8, 9] Scott, Steigman, and Convey[8] report the development of herpes neutralizing antibodies in the blood of convalescent children. Black[9] denies any importance of the fusospirochetal organisms in this disease which he calls "acute infectious gingivostomatitis."

Habitual aphthosis is manifested by recurring small, oval, painful ulcers on the oral mucosa. They may appear at definite intervals, particularly in women during or after menstruation. These lesions begin as minute vesicles in the stratum granulosum of the mucosal epithelium. The compressed epithelium soon breaks down and exposes the submucosa which microscopically displays a small cell infiltration. The cause of these recurrent aphthae is unknown. Allergy is thought to play an exciting role.

Gangrenous stomatitis or noma occurs in children debilitated by infectious diseases, usually measles or typhoid fever, but may be seen in adults without evident deficiency. There seems to be a predilection for males. The necrosis starts either at the mucocutaneous border of one of the angles of the mouth or in the mucosa of the cheek in the region of the third molar. The gangrenous process proceeds rapidly, destroying lips and cheek and may involve the jaws. As many as 70 to 80 per cent of the cases terminate in death. Degenerative and necrotic lesions are found in spleen and liver. Low local tissue resistance together with virulent Plaut-Vincent's organisms are supposed to be causative factors.[11]

Hypertrophic gingivitis is a proliferative inflammation of the marginal gingiva, mainly the interdental papillae. Lack of proper mouth hygiene, malocclusion, or certain systemic diseases (diabetes) appear to render the gingiva more susceptible to inflammation. Microscopically, there is loose granulation tissue with lymphocytes, plasma cells, and a proliferation of the epithelium. In later stages, a scarlike fibrous tissue develops. Hypertrophic gingivitis is common in pregnant women,[12] since the gingiva appears to be more susceptible to inflammation, due to the altered chemical and physiological mechanisms of the body. About 2 per cent of pregnant women develop an excessive growth of an interdental papilla, usually in an area of irritation. This hypertrophy, the so-called "**pregnancy tumor,**" presents a variety of features. Most of these "tumors" have the microscopic characteristics of a capillary angioma with a fibrous stroma. Others consist of simple granulation tissue or a granulation tissue with many giant cells and resemble a giant cell tumor. The covering epithelium may show ulceration.

Moniliasis (thrush) of the oral cavity is caused by the yeastlike *Monilia albicans*. This fungus penetrates into the oral epithelium of infants, debilitated adults, and the aged. The mucosa of the lips, cheeks, tongue, palate, pharynx, and larynx may become involved. Small, milk-white, elevated, granular spots appear on the mucosa. These sometimes coalesce to form a kind of pseudomembrane. This membrane consists of the monilial organisms and thickened, sometimes necrotic, epithelium. The membrane is firmly attached to the mucosa, and when it is rubbed off, bleeding spots of the moderately inflamed submucosa become apparent. In a few instances, the mycelia have penetrated into the submucosa and even have invaded and obstructed vessels.

In infants, lack of proper mouth hygiene or cleanliness of the attendant, may be a causative factor in thrush. In adults, however, only a mucosa of weakened resistance due to catarrhal inflammation or systemic disorder becomes involved. Riboflavin deficiency is supposed to favor the development of thrush. (See also page 350.)

Koplik's spots appear in measles in the mucosa of the cheek opposite to the molars a few days before the typical skin rash. These pinhead-sized elevations are of a whitish color and are surrounded by a red zone. Their microscopic features somewhat resemble those of the skin eruptions in measles. The center of the macular lesions of the mucosa shows early necrosis of the superficial layer of the thickened epithelium. This necrosis, together with a spotty fibrin accumulation and proliferation of the epithelium, is the result of a productive and exudative inflammation in the submucosa.

Foot and mouth disease is a contagious disease transmitted by the milk of infected cattle or by direct contact to man. The causative agent is a filtrable virus. The lesions in the oral mucosa are blisters with exudate which becomes purulent. The vesicles rupture and give way to small ulcers which heal quickly. The manifestations in the oral cavity are often associated with identical lesions on the palms and soles.

Fibromatosis gingivae is a fibroma-like diffuse enlargement of the entire gingiva. Unlike the inflammatory hypertrophic gingivitis there is absence of gross or microscopic signs of inflammation. There is a tendency to recurrence after surgical excision but not after the removal of the teeth. Microscopically, the tissue presents the features of a keloid with dense collagenous fibers, a few narrow blood vessels, and many lymph spaces. Occasionally, the epithelium shows proliferation and hyperkeratosis. Certain individuals seem to be predisposed to this disease. A familial hereditary tendency has been suggested.

Epulis is a topographical term applied to various growths of the gingiva. The

clinical and microscopic features of these tumorlike lesions vary. They are found in children, young adults, and also during pregnancy. They may be pedunculated or sessile, small or large, soft or firm, and of reddish-blue or pink color. Although the epulis occasionally assumes a size such as to interfere with mastication, and

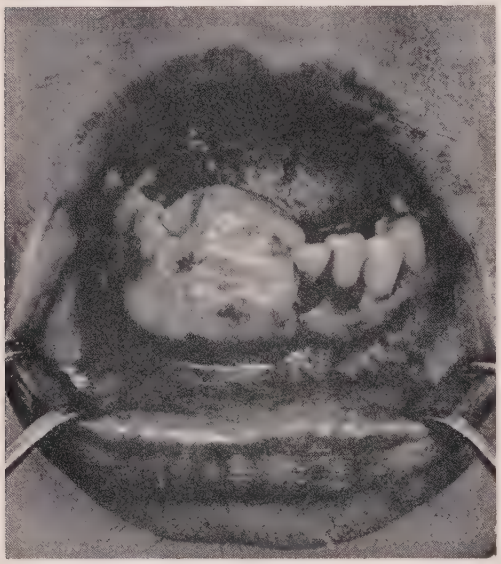

Fig. 645.—"Epulis" covering mandibular incisors.

tends to recur after surgical removal, it is not a true neoplasm. It is either a simple hypertrophic inflammatory growth due to a local mechanical irritation, or an exuberant reaction of the gingiva to an inflammatory resorptive and regenerative process which started in the alveolar process. Transition of one type into the other can be found. Microscopically, the hypertrophic inflammatory lesion ("epulis") is composed of granulation tissue with abundant capillaries, leukocytes, lymphocytes, plasma cells, hemorrhages, and hemosiderin. It is covered by proliferated epithelium. In time the cellularity and vascularity decreases gradually so that eventually a predominantly fibrous tissue develops which is responsible for the fibroma-like gross feature of the "epulis fibromatosa." The microscopic picture of an early classic epulis, the formation of which was stimulated by an inflammatory resorptive process in the marrow of the alveolar bone, is dominated by abundant multinucleated giant cells found in a vascular and cellular connective tissue associated with hemorrhages and hemosiderin in macrophages. This type is called "giant-cell epulis." The "giant-cell epulis" may undergo a slow transformation into a fibrous lesion with few giant cells and newly formed bone trabeculae.

"Congenital epulis" of newborn infants, predominantly females, located near the midline of the jaws, notably the maxilla, and protruding into the mouth is a clinical and pathological entity. Custer and Fust[13] found epithelial inclusions similar to the enamel organ in accumulations of large elongated cells with a distinct membrane and acidophilic granular cytoplasm. They consider this growth to be an embryonal hamartoma of the very early tooth anlage. Bauer and Bauer[13a] conceive of the "congenital epulis" as a "granular cell fibroblastoma." They did not observe islands of epithelial cells in their case and maintain that parts of the dental lamina, normally present in the gingiva of a newborn infant, may be accidentally included into the centrifugally expanding granular cell fibroblastoma.

Dilantin gingivitis develops in about 50 per cent of patients who receive Dilantin Sodium. It is an hypertrophy of the gingiva propria in which, independent of sex and age, the grade of the overgrowth seems to depend upon the dose of Dilantin and the duration of the administration. Poor oral hygiene is an aggravating factor. The hypertrophy starts in the interdental papillae and finally involves the marginal gingiva, which may become so massive as to extend to the occlusal surface of the tooth. Microscopically, the gingival epithelium shows keratosis, parakeratosis, and fingerlike proliferations into the lamina propria, the collagenous fibers of which are hypertrophic. A moderate small cell infiltration is found around the capillaries in the subepithelial layer. The cause of Dilantin gingivitis is not well understood.

Leukoplakia is a hyperplasia of the oral epithelium not uncommon in people above 50 years of age. The favorite sites of leukoplakia are the buccal mucosa especially in the molar region, the corners of the mouth and the lower lip. The mucosa of the palate and the gingiva are involved less often.

The early sharply outlined lesion has a red granular appearance. Later it turns into a white or mother-of-pearl-like, slightly elevated and rough area. These patches show a tendency to extend and coalesce. Advanced lesions with fissures and ulcers in a warty horny mass must be suspected to be malignant. Leukoplakia is regarded as a precancerous lesion.

Microscopically there is a remarkable hyperkeratosis and acanthosis of the

thickened epithelium and extension into the moderately inflamed subepithelial tissue (Fig. 647). The intensity of these findings depends upon the severity of the lesion.

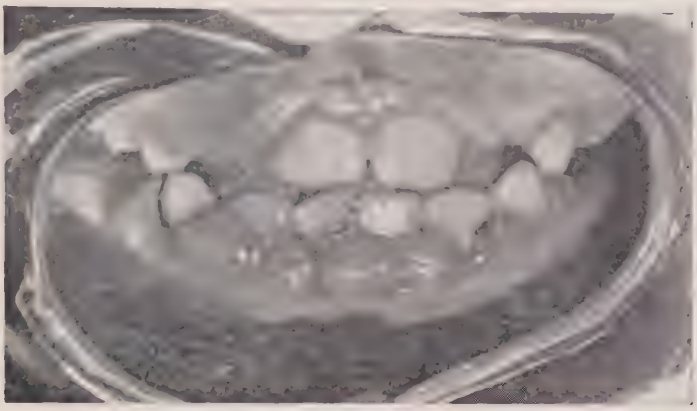

Fig. 646.—Dilantin hypertrophy of the gingiva.

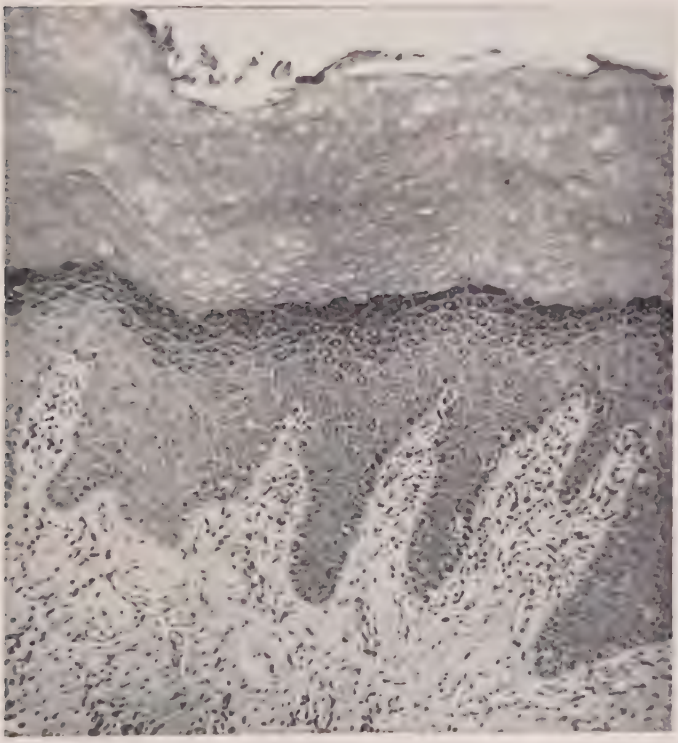

Fig. 647.—Leukoplakia of tongue. Extreme hyperkeratosis. Very moderate subepithelial inflammation.

Local irritants of chemical (tobacco) and mechanical nature (faulty fitting dentures) and general factors such as vitamin A deficiency, syphilis, and even hormonal disturbances have been suggested as causes of leukoplakia.

Leukemic hyperplasia of the gingiva may often be the first alarming sign of a myelogenous, monocytic, or lymphatic leukemia. The leukemic infiltrate in the interdental papillae and subsequently in the marginal gingiva brings about a remarkable swelling of a bluish-purple color. The gingiva bleeds easily and ulceration of the surface with necrosis is common.

Agranulocytic lesions of the gingiva and oral mucosa, the result of a primary malignant neutropenia or secondary neutropenia, show the characteristics of gangrenous tissue. The gangrenous process usually starts in the interdental papillae because of the numerous microorganisms in the gingival crevices. These easily invade the adjacent gingiva, which is inadequately defended because of lack of leukocytes.[14]

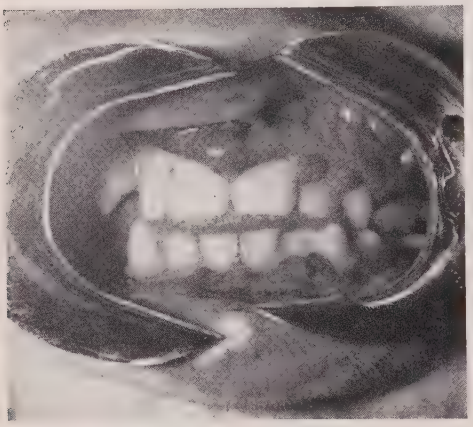

Fig. 648.—Infiltration of the gingiva in myelogenous leukemia.

Tumors of the Oral Mucosa

Lipomas are found less often than **fibromas** and **papillomas** in the cheek, palate, and mouth floor. **Sarcomas** involving the cheeks and palate are rare. **Adenomas** of the mucous glands of the oral mucosa are not uncommon.

Carcinoma deriving from the oral mucosa is of the more or less differentiated squamous type and starts usually on the gingiva, floor of the mouth, cheeks, and lips, either as an ulcer with a frayed, indurated margin or as a bulky mass. If the gingiva is the site of origin, the carcinoma invades the jaw but metastasizes into the lymph nodes only in the late stage. The carcinoma of the gingiva and cheek mucosa often develops on the basis of a leukoplakia. Any form of irradiation therapy either alone or preceded by excision is being successfully used. *Adenocarcinoma* may develop from the glands of the palate, lips, cheek, and floor of the mouth.

"**Mixed tumors**" of salivary gland type are not infrequently seen in the palate and cheeks. They may be well encapsulated, somewhat lobulated, and covered by freely movable mucosa. They originate from the small salivary glands. They consist of glandular formations, solid strands, and isolated islands of epithelium traversed by a fibrous, myxomatous, and pseudocartilagenous stroma (see page 751).

Ranula (froglike swelling) is a retention cyst of the sublingual or submaxillary gland with a yellowish mucinous content. It appears unilaterally as a translucent bluish swelling beneath the tongue. The wall is lined by cuboidal or flat epithelial cells or consists of a very thin layer of fibrous tissue without any epithelium, depending upon the pressure of the cyst contents.

TEETH

Teeth and Their Supporting Structures

The twenty deciduous teeth and thirty-two permanent teeth consist of enamel, of ectodermal origin, and dentin, cementum, and pulp which are mesodermal tissues. The tooth supporting structures comprise the gingiva, periodontal membrane, and alveolar process. These supporting tissues are connected with one another by blood vessels, lymphatics, and nerves. The pulp communicates with the periodontal membrane and, by this intermediary, with the marrow of the jaw.

The enamel is formed by ameloblasts. These are highly differentiated epithelial cells and constitute the innermost layer of the enamel organ. The enamel organ is derived from the oral ectoderm, and is composed of the following layers: outer enamel epithelium, stellate reticulum, stratum intermedium, and the ameloblasts. The stellate reticulum, which protects the young enamel during formation and calcification, disappears gradually as the enamel formation proceeds, so that the outer enamel epithelium unites with the inner layers. This united epithelium covers the enamel until the crown emerges into the oral cavity.

The dentin is a product of the mesodermal dental papilla which differentiates into the pulp. Cementum, periodontal membrane, and alveolar bone proper are derived from the connective tissue of the tooth sac which encases the tooth bud.

Anomalies and Disturbances of Development

Hereditary Enamel Hypoplasia.—Hereditary hypoplasia is a familial disease which follows the Mendelian pattern, is not sex limited, and is characterized by varying degrees of defective enamel of all deciduous and permanent teeth. The few cases studied so far have shown many impacted teeth with resorption of their crowns. A primary defect of the enamel-forming organ seems to be the cause.[15]

Dentinogenesis Imperfecta.—The congenital and also late osteogenesis imperfecta is occasionally associated with an involvement of the dentin of the deciduous and permanent teeth. The teeth appear amber-colored and translucent due to the very irregularly structured and calci-

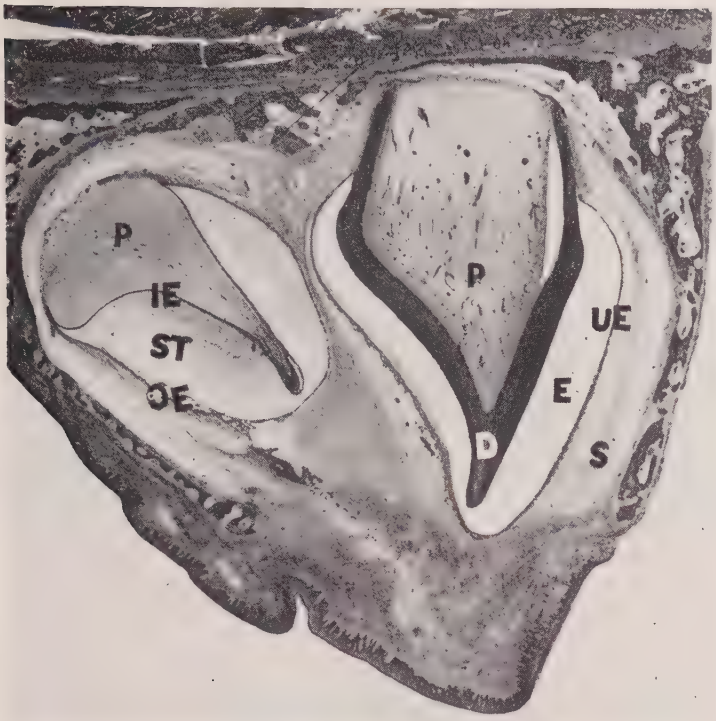

Fig. 649.—Normal development of the buds of a deciduous and permanent maxillary central incisor of a 4-month-old infant. The deciduous tooth bud, right; the permanent tooth bud, left. *P*, Pulp (dental papilla); *D*, dentin; *E*, enamel dissolved by decalcification; *UE*, united enamel epithelium; *IE*, inner epithelium; *ST*, stellate reticulum; *OE*, outer enamel epithelium; *S*, tooth sac.

Fig. 650.—Human rickets. Part of a tooth bud of an 11-month-old child. Enamel epithelium partly detached from enamel by transudate. Note sharp border between normal homogeneously calcified dentin and broad dentinoid with coarse granular calcification. Empty space between dentin and enamel artefact.

fied amorphous dentin which may obliterate the pulp cavity. Enamel and cementum are unaltered.

Hypoplasia of Enamel.—Symmetrical defects of enamel and dentin are associated with the disturbances of phosphorus and calcium metabolism observed in *rickets* and *tetany*. In both diseases ameloblasts become detached from the enamel of tooth buds by the accumulation of a transudate. The cells are destroyed by pressure atrophy and show vacuolar degenerative changes.[17] (Fig. 650.) This results in defects in the enamel matrix. When these teeth erupt, grooves and pits appear in the enamel, mostly in the incisal third. The dentin shows an extremely broad dentinoid zone along an irregularly calcified dentin with many interglobular areas. Deformities of the jaws due to tension of the muscles of mastication upon the soft bones and a delayed dentition may also be associated with rickets.

Congenital Syphilis.—In congenital syphilis there occurs a developmental dental deformity known as Hutchinson teeth. This consists of a barrel-shaped deformity of the maxillary incisors with a semilunar excavation of the incisal edge, malformations of other teeth, and mulberry-like hypoplasia of the first molars. These defects are a product of the syphilitic inflammatory destruction of parts of the ameloblast layer of the tooth buds. The tooth sac tissue is packed with *Treponema pallidum* and transformed into a syphilitic granulation tissue. The pulp tissue of the tooth buds contains masses of spirochetes which penetrate into the predentin and the dentinal tubules.

The climax of the inflammatory reaction of the tooth tissues to the invasion of the spirochetes is reached toward the end of intrauterine and in early postnatal life.[18]

Dentigerous and follicular cysts are local developmental disturbances of the tooth buds. They are observed mostly in the region of the third mandibular molar. A dentigerous cyst results from the liquefactive degeneration of the stellate reticulum of the enamel organ. Consequently the more or less developed crown of the unerupted tooth reaches into the cystic cavity, the epithelial lining of which is attached to the cemento-enamel junction. The less developed root is outside the cyst. The epithelial lining may give rise to an ameloblastoma. A follicular cyst develops when the liquefaction of the stellate reticulum occurs prior to the formation of dentin and enamel.

Dental Caries

The early carious process on the enamel surface starts with the formation of an amorphous mucinous bacterial plaque on the surface of the enamel. Enzymes of various acidogenic and aciduric microorganisms dissolve the dental and enamel cuticle, thus exposing the enamel proper. The acid decalcifies the enamel. Bacteria penetrate into the enamel along its organic parts, the lamellae and the "pseudolamellae."[20] The carious process reaching the dentinoenamel junction spreads laterally, undermines the enamel, and invades the dentin along the walls of the dentinal tubules. The lesser resistance of the dentin is due to the large amount of organic substance in its matrix and the dentinal tubules (Tome's fibers). Proteolytic and acid producing microorganisms quickly destroy the dentin and reach the pulp. Slowly progressive caries is counteracted by the pulp with a defensive action. The pulp produces secondary dentin, and the dentinal tubules in the path of the approaching caries become blocked by calcification (transparent or sclerotic dentin). This calcification is preceded by fatty degeneration of the Tome's fibers.

Pulpitis

The acute infectious inflammatory changes of the pulp following caries are identical with those of any other soft tissue, yet the result is modified by the following facts: the pulp is encased by an unyielding dentinal wall; there is a very narrow apical foramen in teeth of adults through which blood vessels enter the pulp; and the walls of the vessels of the pulp are thin. Therefore, any inflammatory exudate will destroy the pulp tissue unless it can be satisfactorily discharged through the carious defect in the crown. In such a case, a chronic pulpitis with the structural details of granulation tissue may ensue.

Periapical Periodontitis

If the microorganisms of a pulpitis or their toxins penetrate through the apical foramen of the tooth, an acute inflammatory lesion develops in the apical part of the periodontal membrane and may involve the neighboring bone marrow, producing a localized osteomyelitis. Pus may penetrate along the path of least resistance through the alveolar process to form a subperiosteal abscess. The periosteum may rupture and allow the pus to spread into the soft tissue (cellulitis). Pus may break through the mucosa or skin, thus forming a fistula. Abscesses of the maxillary incisors may penetrate into the nasal septum or nose floor, or those of the posterior maxillary teeth into the maxillary sinus (Fig. 651). Infected maxillary teeth may also lead to palatal abscesses. Abscesses of the posterior mandibular teeth extend often into the inferior alveolar canal or may perforate the cortical mandibular plate and cause a cellulitis of the mouth floor. Most of the acute periapical processes are exacerbations of chronic periapical lesions which in the form of granulation tissue extend diffusely into the surrounding bone or appear surrounded by a firm connective tissue membrane. The latter type has the misleading name, "granuloma." This granulation tissue very often contains strands of proliferated epithelial cells derived from epithelial rests (Malassez). These are remains of a part of the enamel organ and are present in the periodontal membrane. The inflammatory epithelial proliferation may encircle abscesses or undergo central necrosis and liquefaction, forming the so-called **"radicular cysts."**

The various periapical processes are not infrequently foci of infection. Cases of subacute bacterial endocarditis,[21] acute glomerulonephritis, pyelitis, and acute iritis have been found to be related to foci of dental infection.

Fig. 651.

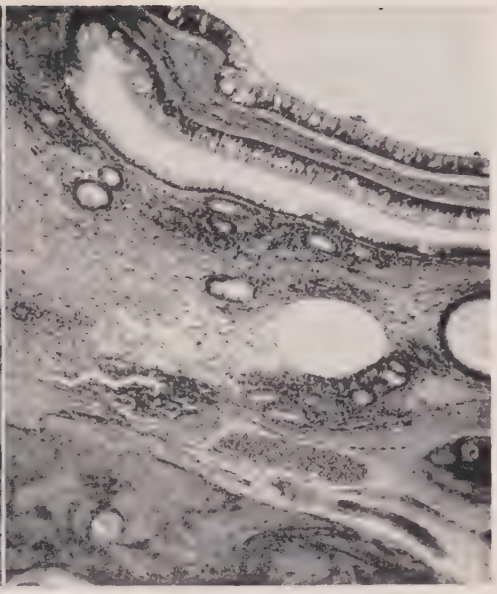

Fig. 652.

Fig. 651.—Buccolingual section through the root of a maxillary premolar with the surrounding structures. Large periapical abscess caused maxillary sinusitis.

Fig. 652.—Higher magnification of maxillary sinus mucosa of Fig. 651 showing chronic inflammation.

Fig. 653.—"Pyorrhea alveolaris profunda." Mesiodistal section through the mandibular incisors. Chronic inflammation of the gingiva followed by proliferation of the epithelium of the gingival attachment along the cementum, excessive osteoclastic resorption of the interdental bone, deep pocket formation between gingiva and surface of the roots.

Marginal and Profound Periodontitis (Pyorrhea Alveolaris)

Pyorrhea alveolaris is a widespread disease of the supporting tissue of the teeth which is observed mainly in people above 30 years of age, although it may also occur in children. In an overwhelming majority of cases it starts as a marginal gingivitis with pronounced small cell infiltration of the subepithelial tissue. The inflammation destroys the bundles of collagenous fibers (Sharpey's fibers) of the periodontal membrane and stimulates proliferation of the epithelium of the gingival attachment along the cementum of the root. The gingival crevice deepens. Simultaneously subepithelial inflammation extends into the marrow of the alveolar bone. Osteoclastic resorption of the alveolar bone destroys the insertion of the Sharpey's fibers and thickens the periodontal membrane, thereby loosening the tooth. (Fig. 653.) Masticatory stresses upon the loose tooth traumatize the deeper parts of the periodontal membrane and facilitate the advance of the inflammation. Periodontitis profunda is the result. The epithelium growing along the cementum eventually exfoliates the tooth.

Irritative factors causing a gingivitis supported by a disturbed alignment of the teeth and a constitutional or acquired susceptibility are supposed to be the common causes of this disease.

Systemic diseases of nutritional or endocrine origin may result in osteoporosis of the tooth-supporting bony structures and lower their resistance to inflammatory processes. By stressing the relative commonness of hyperparathyroidism, Strock,[22] Keating and Cook[23] called attention to the disturbance of the architecture of the jaws and the disappearance of the lamina dura due to demineralization in cases with classic or only mild involvement of the skeleton.

JAWS

Congenital Anomalies of the Jaws

Macrognathia is an anomaly characterized by an unusually large mandible or maxilla, or both. Heredity is supposed to be responsible for some of the reported cases. **Micrognathia** is a condition of extremely short jaws. One or both jaws may be involved. This hereditary anomaly is often associated with cleft palate and other deformities of the face and ear. **Agnathia** designates the congenital partial or complete absence of the jaw. **Cleft palate** is often associated with a cleft lip and may be unilateral or bilateral. In a bilateral cleft of lip and palate, the intermaxillary part, with or without teeth, may either protrude or be missing.

Inflammatory and Metabolic Lesions of the Jaws

Many of the systemic diseases that affect the long bones may have associated lesions in the jaws. Nutritional deficiencies, reticuloendothelioses, inflammatory diseases by known and unknown agents, blood dyscrasias, and endocrine disturbances produce changes in the jaws which are identical with those of the long bones.

Osteomyelitis of the jaws in adults occurs more often in the mandible than in the maxilla. It may result from extraction of an infected

TABLE VIII

CYSTS OF THE JAWS*

TYPE	ETIOLOGY AND PATHOGENESIS	MICROSCOPIC
Radicular cyst	Periapical granuloma resulting from gangrenous pulp	Cavity with fluid or semifluid necrotic material and lined with proliferated squamous epithelium
Follicular cyst	Liquefaction of the stellate reticulum of very early tooth anlage	Cavity containing fluid and lined with thin flattened epithelium
Dentigerous cyst	Fluid accumulation between reduced enamel epithelium and crown surface of unerupted tooth or tooth anomaly	Crown or larger part of tooth or tooth anomaly suspended by the stratified squamous epithelial lining within the cyst
Inclusion cyst	Epithelial inclusions in the anterior palatine fossa and between the maxillary and globular processes.	Cavity filled with fluid and lined with thin epithelial layer
Hemorrhagic cyst	Intramedullary hemorrhage	Irregularly shaped cavity filled with blood or serous transudate and surrounded by a vascular connective tissue membrane with hemosiderin, macrophages, and giant cells
Neoplasm	Ameloblastoma, various malignant tumors	
Primary hyperparathyroidism	Adenoma, or rarely carcinoma, of parathyroid	Hemorrhage or fluid in cavity lined with thin connective tissue membrane

*Clinical and roentgenographic data must be considered.

tooth, a periapical lesion, or a fracture of the jaw. Osteomyelitis of the mandible extends along the inferior alveolar canal. In infants, where the maxilla is the more common site, the infection may be blood-borne, or develop from a local lesion in the mouth. Osteomyelitis of the jaws of infants is usually complicated by the involvement and sequestration of the tooth buds. It may involve the temporomandibular joint and cause an ankylosis.

Tumors of Odontogenetic Origin

Odontoma.—Odontomas occur predominantly in the mandible of young people, originating from the tissues of the tooth bud. They may consist of an irregular mass of enamel, dentin, and cementum, or of a number of underdeveloped teeth connected with one another by a hard substance. This benign hard odontoma is a malformation rather than a true neoplasm.

more often in the mandible than the maxilla of younger people and connected with the periapical cementum of the tooth. Fused "cementicles" and cement exostoses and displaced fragments of cementum connected with the root-surface by callus do not belong in this category. The name "cementoma" is being applied to a growth the parenchyma of which is supposed to be cementum deposited by "cementoblasts" of a tissue which is no longer periodontal membrane but young undifferentiated connective tissue of the bone marrow and does not possess cementogenic potency but does have osteogenic capacity. The trabeculae formed in this tissue consist of irregularly calcified fibrous bone with broad osteoid zones, and there may occasionally be a few spherical bodies of dystrophic granular calcification. The name "cementoma" is misleading, since this lesion belongs in the group of localized fibrous dysplasia of bone. It should be named *"periapical ossifying fibrosis."* It lacks any tendency to display the characteristics of a tumor, yet may heal spontaneously.

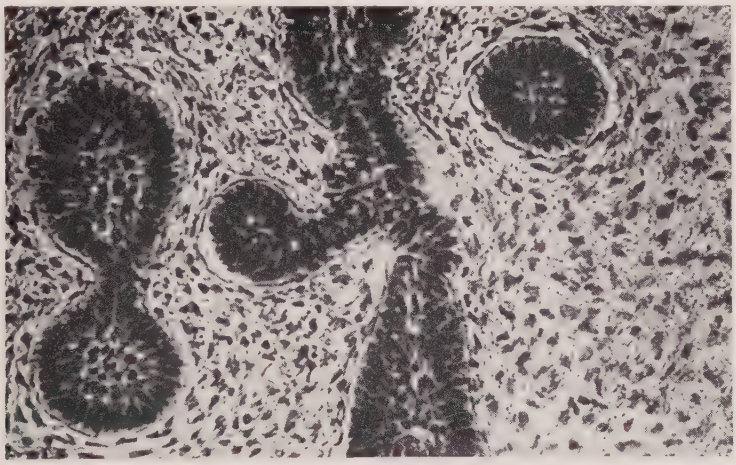

Fig. 654.—Soft odontoma of mandible. Strands of enamel epithelium in a dense accumulation of cells of the dental papilla. Note absence of hard tissue.

The so-called soft odontoma is a true infiltrative tumor which consists predominantly of proliferating undifferentiated connective tissue of the early dental papilla, and may contain some islands or strands of enamel epithelium (Fig. 654). The connective tissue assumes a fibroma-like appearance but does not produce hard substances.

Dentinoma.—A dentinoma is a rare tumor which consists of small accumulations of imperfect dentin scattered through a connective tissue stroma. Sometimes a combination of dentin and bone (osteodentin) is observed in the tissue.[25]

So-called "Cementoma."—This is an ill-defined, slowly extending, benign lesion found

Ameloblastoma (Adamantinoma).—An ameloblastoma is a tumor of slow growth which arises from the undifferentiated epithelium of the enamel organ or the lining epithelium of a dentigerous or radicular cyst. It occurs almost exclusively in the mandible, usually in the molar, less often in the premolar, and rarely in the frontal area. Most cases develop in the second and third decades of life. The neoplasm expands the jaw from within, so that the buccal, and sometimes also the lingual, plate becomes of parchment-paper thinness. A differentiation of these tumors into solid and cystic types is arbitrary, since the cystic

form develops by central necrosis and liquefaction of the solid type.[26]

The microscopic features of ameloblastomas vary greatly. Columns and aggregations of epithelial cells occur in various stages of differentiation. There may be solid nests and cords of cuboidal cells, or they may be arranged in a glandular pattern. Cylindrical cells resembling ameloblasts, occasionally accompanied by flat cells, surround a stellate reticulum, resembling the enamel organ. Sometimes squamous features with keratinization may be met with.

Fig. 655.

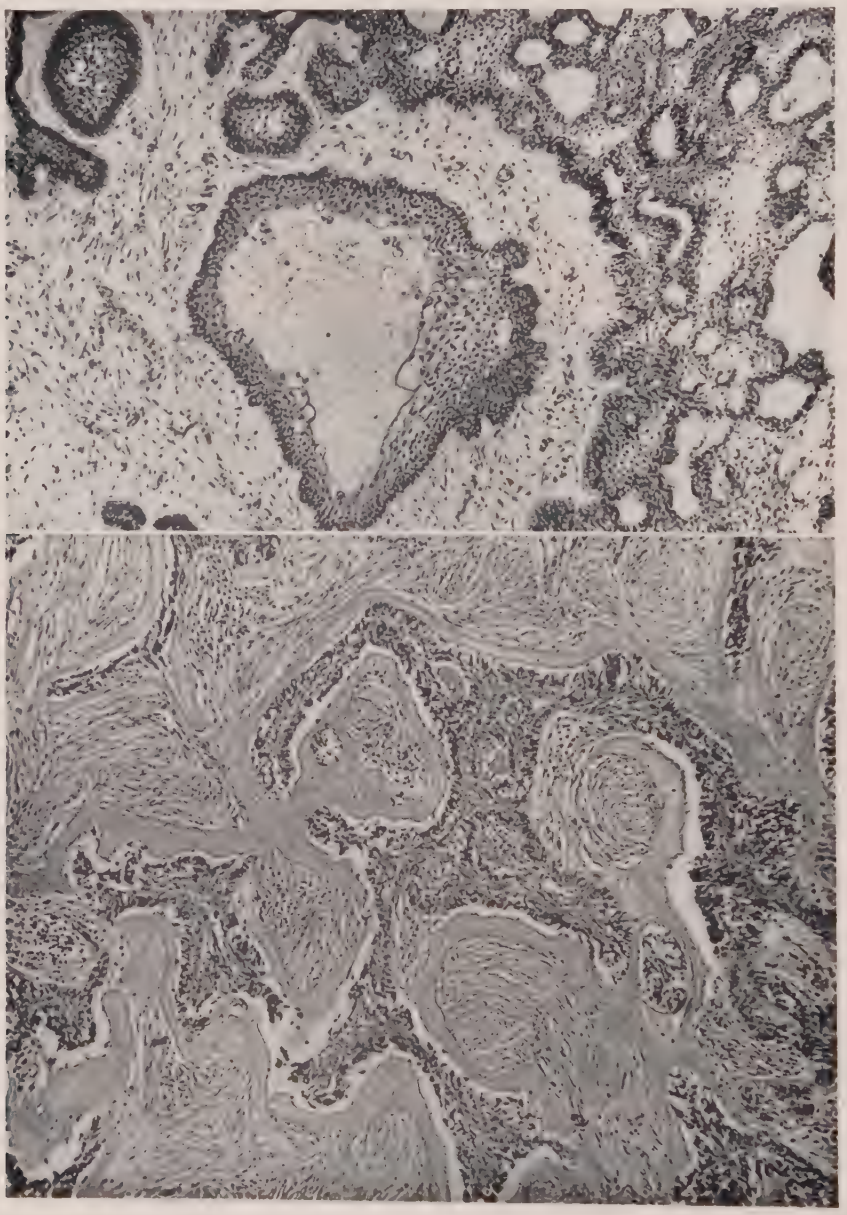

Fig. 656.

Fig. 655.—Ameloblastoma of mandible showing solid strands of enamel organ with formation of cysts. Fibrous stroma.

Fig. 656.—Atypical solid ameloblastoma of mandible. Cords of irregularly shaped epithelial cells surrounded by hyaline zone of very dense fibrous stroma.

Occasionally, the ameloblastoma resembles a basal cell carcinoma. The stellate reticulum may degenerate, giving rise to cysts. The high cylindrical cells are not fully developed ameloblasts, probably because of the absence of odontoblasts and consequently of dentin, which would stimulate their differentiation to true ameloblasts.[27] No enamel formation has ever been observed in these tumors. The outer surface of the cylindrical cells is sometimes coated with a zone of hyaline stroma.

Fig. 657.—Giant cell tumor ("central epulis") of the chin traversed by trabeculated bony walls. Brown tumor with hemorrhages and giant cells. Lingual cortical plate completely destroyed.

The stroma is composed of a loose connective tissue that may become very fibrous. Ameloblastomas tend to recur after surgical removal and may turn into adenoacanthoma, squamous cell carcinoma or, rarely, adenocarcinoma. Tumors of similar structure have been found in the hypophyseal duct,[28] the tibia,[29] and the femur.[30]

Tumors of Nonodontogenetic Origin

All primary and metastatic tumors of other bones are occasionally found in the jaws, most of them involving the mandible. Of the bones of the skull, the mandible is the most frequent site of giant cell tumors due to its exposure to mechanical trauma. (Fig. 657.)

Retinal Anlage Tumor.—Two of the three cases described in the literature involved the maxillae of infants.[31, 31a] Melanin containing epithelial-like cells of variable shape, neurocytes, and spindle cells are the cellular elements of this neoplasm which develops from misplaced optic remnants. The spindle cells are perhaps still undifferentiated smooth muscle fibers. The few instances of so-called "melanoameloblastoma" are probably tumors of retinal anlage.

Ossifying Fibroma.—This localized or diffuse, more or less sharply demarcated tumor or tumor-like lesion, mostly observed in the mandible and less often in the maxilla and cranial bones, has been described under various names, such as fibro-osteoma, hyperostosis, osteitis fibrosa

localisata, etc. It is likely that many cases classified as "leontiasis ossea" are diffuse ossifying fibromas. The ossifying fibroma chiefly develops in younger people and grows slowly. Microscopically, the early lesion consists of more or less immature irregularly calcified bone trabeculae and small round or oval psammoma-like bodies, within a proliferated young connective tissue (Fig. 658). In advanced stages lamellated bone spicules appear in a less cellular, highly collagenous connective tissue stroma. Sarcomatous changes have been observed in few cases.[32]

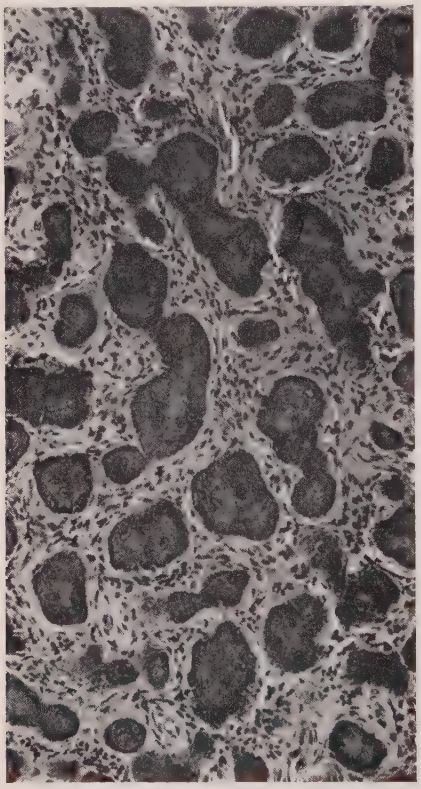

Fig. 658.—Ossifying fibroma of the mandible of immature type. Irregularly shaped bodies of coarsely but intensely calcified fibrous bone in a very cellular, vascular, and collagenous stroma.

Osteoarthritis Deformans of the Temporomandibular Joint

Disturbed balance of the jaws resulting from loss of the posterior teeth or all the teeth, or from an external injury, may damage the articular cartilage of the temporomandibular joint. The subchondral bone marrow reacts with a vascularization of the injured areas of cartilage. The connective tissue accompanying these capillaries deposits bone, thus producing the characteristic exostoses of osteoarthritis deformans of the condyle, the articular tubercle, and the mandibular fossa. The joint disc degenerates, undergoes occasionally dystrophic calcification, and may be destroyed.[33]

TONGUE

Anomalies

Cleft Tongue.—Cleft tongue is a rare anomaly and is due to the failure of union of the lateral tubercula of the mandibular arch.

Macroglossia.—Congenital macroglossia is seen in cretinism. An acquired enlargement occurs in myxedema and acromegaly. In the latter conditions the papillae and the keratinized layer of the epithelium thicken and the tongue surface appears folded. Anomalies of the tongue are caused not infrequently by developmental disturbances of the thyroid gland.

Lingual Thyroid.—This anomaly appears, mostly in females, as a nodular body close to the base of the tongue. It represents either an aberrant portion of the thyroid or the whole gland. It is due to the failure of the gland to grow caudally from the foramen cecum in the early embryonic life. (See page 994.)

Thyroglossal Duct Cyst.—If the thyroglossal duct does not disappear, a cyst may develop in the upper part at the base of the tongue. The cyst wall is lined with a ciliated epithelium which may become flattened by the pressure of the contents. The cyst may burst, and either a medial cervical fistula or an upper opening, or both together, may result.

Hyperplasia of the Lingual Epithelium

Leukoplakia.—Leukoplakia of the apical and lateral parts of the dorsum of the tongue is a frequent finding and occasionally may be associated with a syphilitic glossitis. The leukoplakic patches on the tongue become warty and leathery earlier than those which appear in the mucosa of the oral cavity. Leukoplakia of the tongue is a precancerous lesion. (Fig. 659.)

Black Hairy Tongue.—Dark, hyperplastic and hyperkeratotic filiform papillae resembling "hair" are the result of chronic irritation and pigment-producing microorganisms on the surface of the tongue.[34] Antibiotics (penicillin and aureomycin lozenges) may cause black hairy tongue.

Geographic Tongue.—Geographic tongue is characterized by irregular, denuded areas appearing principally on the lateral surface of the tongue. They are surrounded by slightly elevated, grayish, discolored margins which constantly are undergoing changes in position and shape. Microscopically, there is subepithelial inflammation with desquamation of the epithelium in the center of the lesions and hyperplasia at the border.

Atrophy of Lingual Epithelium

Hunter's or Moeller's glossitis is sometimes seen in pernicious anemia. It consists of atrophy of the papillae beginning at the margins and apex of the tongue, which may eventually involve the whole surface. Burning is the common complaint of the patients. There is micro-

scopically a round cell infiltration of the tunica propria. Eventual destruction of the papillae gives the tongue its beefy, red appearance. Glossodynia may be associated with steatorrhea following ileocolostomy.

Riboflavin deficiency produces a granular swelling and, ultimately, atrophy of the fungiform papillae. This is associated with a burning sensation.[35] **Nicotinic acid deficiency (pellagra)** results in atrophy of the papillae, followed by extremely painful marginal ulcers "bald tongue"). **Atrophy of the papillae** is also found in idiopathic hypochromic anemia and is common in hyperthyroidism and congestive heart failure.

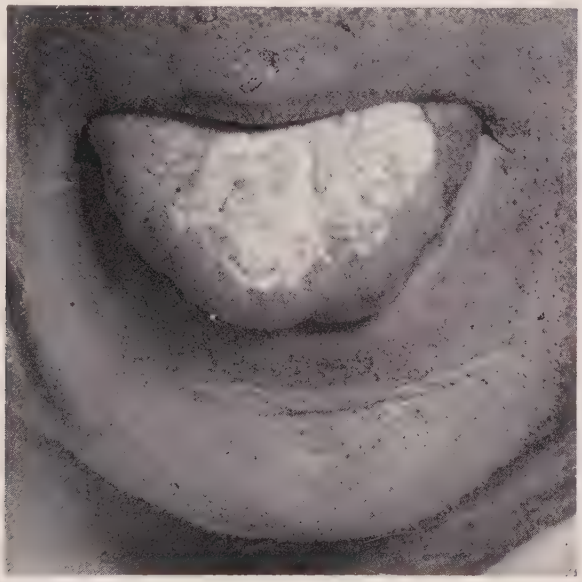

Fig. 659.—Leathery and warty leukoplakia of tongue associated with carcinoma of low-grade malignancy.

Inflammation of the Tongue

Scarlet Fever.—The so-called strawberry tongue is a characteristic feature in scarlet fever. After the second day of the disease the heavy coat that covers the tongue disappears at the margins and the tip, exposing an intensely red surface. This change gradually involves the whole tongue. Microscopically, there is an exudative inflammation of the subepithelial tissue with occasional necrosis of the covering epithelium.

Tuberculosis.—In approximately 1 per cent of cases of open pulmonary tuberculosis, tuberculous ulcers develop at the base and lateral margins (seldom the apex) of the tongue. They are due to autoinfection from the sputum and usually appear in areas previously traumatized by broken teeth. The tuberculous ulcer of the tongue penetrates deeply into the tissue, undermining the thick infiltrated margins. The base of the ulcer shows a greenish-gray discoloration.

Syphilis.—Chancre of the apex of the tongue is found in 1 to 7 per cent of cases of acquired extragenital syphilis. The characteristic syphilitic interstitial glossitis causes a smooth atrophy of the papillae and may lead to leukoplakia.

Tumors of the Tongue

Hemangiomas and the much rarer **lymphangiomas**[36] of the tongue may lead to a macroglossia. In a few instances many small cystic lymphangiomas have been found in the tongue. **Fibromas, neurilemomas,** and **lipomas** occur in the tongue. **Chondromas** and **"mixed tumors"** of the tongue are recorded, and an osteochondroma has been observed by the author on the apex of the tongue.

Granular cell myoblastoma (granular neuroma) of the tongue is a benign, more or less circumscribed, nodular, usually small tumor. It is slowly growing and fairly well encapsulated. Microscopically, the epithelium covering the growth may be atrophic or hyperkeratotic or proliferate into the depth. If its deepest projections are in direct contact and interwoven with the underlying tumor cells they may display features of low-grade malignancy. The variously shaped and sized tumor cells which may or may not show a cell membrane form a syncytium. They contain acidophilic granules and centrally placed nuclei which may be large

(7 to 10 micra in diameter), vesicular with one nucleolus, or small and hyperchromatic (Fig. 660).

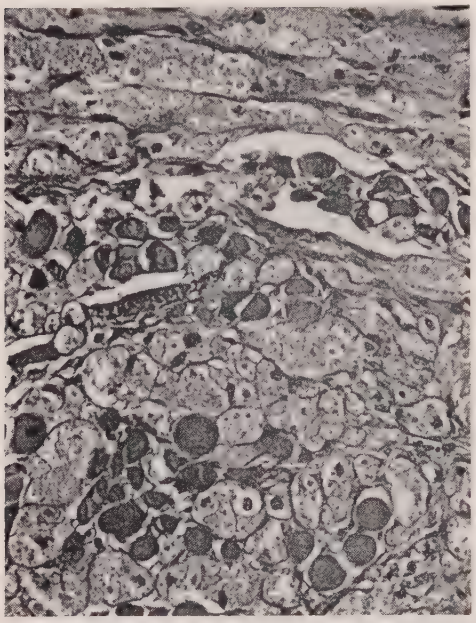

Fig. 660.—Granular cell myoblastoma of tongue. Groups of large polyhedral and elongated cells with granular cytoplasm and rounded nuclei.

The original conception of the muscular origin of this lesion (Abrikosoff,[37] Gray and Gruenfeld,[38] and others) has been abandoned in favor of the fibroblastic and neural pathogenesis though M. Murray[43] cultured granular-cell myoblastomas and found that their cultures show a resemblance to cultures of various skeletal muscles. Wegelin[39] regarded these cells as mesenchymal cells with stored lipoproteins. Pearce,[40] who employed a great variety of histochemical methods, concluded the lesion is a lipoid containing granular-cell fibroblastoma. Fust and Custer[41] studied 52 cases and considered the lingual and extralingual tumors to be neuromas. Ratzenhofer[42] supported the neurogenous theory and regarded the neuroplasma of the vegetative nervous system and the afferent and efferent nerve fibers as the origin.

Leiomyoma of the tongue may be derived from the smooth muscle of the blood vessels at the base of the tongue or from the hypertrophic circumvallate papillae on the outer surfaces of the tongue.[44]

Rhabdomyosarcoma of the tongue of congenital origin has been described in the literature in a few instances. They have been observed either within the striated muscle or in connection with it. They develop in the fifth and the sixth decades.[45] Among 19 cases of rhabdomyosarcoma of the head and neck, Stout found 10 instances of the involvement of the tongue. These tumors frequently metastasize to the lungs. Microscopically they are composed of bundles of large, elongated cells of variable shape with hyperchromatic nuclei and a more or less acidophilic cytoplasm which may show cross-striations (Fig. 661). Giant cells may be present.

Carcinoma of the Tongue.—Of all the oral tissues, the tongue is most frequently involved by carcinoma. Males are affected more than females. The lesion develops frequently at the edge of the dorsum of the tongue in an area of advanced leukoplakia, which may be of syphilitic origin. This stage of leukoplakia is characterized by induration and a leathery, papillomatous surface. The carcinoma commences in the deep fissures and forms an ulcer with everted, firm edges and has an infected base. In other cases a carcinomatous nodule forms beneath an apparently unaltered mucosa and breaks through the surface of the tongue.

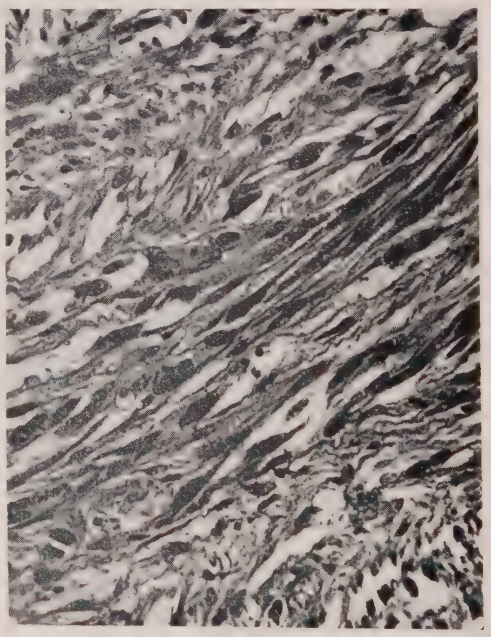

Fig. 661.—Rhabdomyosarcoma of tongue.

Microscopically, carcinoma of the tongue is a squamous cell epithelioma. Tumors of the anterior part of the tongue show excessive keratinization, while those of the posterior part tend to be less differentiated and of the transitional cell type. Occasional adenocarcinomas and lymphoepitheliomas of the tongue have been described.

Carcinoma of the tongue tends to spread to the regional lymph nodes. The invasion of the carcinoma or its metastases may erode large arteries, thereby causing a fatal hemorrhage. Infected material from a carcinoma may lead to an inhalation pneumonia.

Mucoepidermoid Tumor.—A malignant variety of the rare mucoepidermoid tumor of the salivary glands has been observed in the tongue. It originates from the ducts of the mucous glands of the base and border of the tongue. (For details see section on salivary glands, page 754.)

SALIVARY GLANDS

The salivary glands of man, arranged in pairs, consist of the parotid, submaxillary, sublingual, and many small glands of the oral cavity. Parts of the larger glands may be displaced into the neighboring tissue, mainly the adjacent lymph nodes.

Microscopically, all salivary glands of the adult are of the tubuloalveolar structure and grouped in lobules. The lobules of the large glands form lobes. Lobules and lobes are supported by strands of loose connective tissue which contains many blood vessels. The alveoli are composed of either serous or mucous cells or of both types of cells. The so-called myoepithelial cells are located between the secretory cells and the basement membrane as well as between the cells themselves. The intercalated ducts or isthmuses are "zones of proliferation" and have a simple low cuboidal epithelium, while the larger striated tubules are lined with columnar epithelial cells. The secretory ducts have acidophilic pseudostratified cylindric cells and myoepithelial cells. The glandular elements are innervated by parasympathetic fibers.[46] There are often islands of lymphoid tissue in the large salivary glands, mainly the parotid gland, and there are often inclusions of salivary gland-elements in the preauricular lymph nodes.

The salivary glands are of epithelial origin and develop from a nodular invagination of the primitive oral epithelium into the adjacent mesodermal tissue. The parotid gland is the first to develop, appearing shortly after the fourth week of embryonal life. The epithelial cords proliferate and branch in a treelike fashion, thus forming the distally located alveoli. As a central lumen appears in the distal accumulations of the epithelial cells, they differentiate gradually into the characteristic cells of the salivary glands. The cords which remain connected with the oral epithelium give rise to the various ducts.

The most appropriate classification of salivary glands as serous, mucous, and mixed is based on the function of their cells. Saliva is the composite secretory and excretory substance discharged by the salivary glands. An adult secretes about 1,500 c.c. of saliva per day, but this is extremely variable. It is influenced by diet, age, emotion, drugs, and any irritation in the oral cavity.

Sialorrhea, or increased salivary secretion, may be associated with an acute stomatitis, with any kind of irritation of the special senses, and with the so-called "teething" of infants. **Xerostomia,** or decreased salivary secretion, may be the result of atrophy of the glands, of dehydration, of interference with the normal innervation, or of blockage of the salivary ducts by calculi. In rare instances salivary glands may be absent.

Salivary stones (calculi) are found in the ducts or the glandular tissue or in both. The submaxillary gland is more frequently involved than the parotid. The obstruction is initiated by a central collection of desquamated epithelial cells and colonies of organisms (often actinomyces) around which calcium salts are deposited. In a few instances, foreign bodies may form the core. The blockage of the flow of saliva causes congestion and possibly promotes inflammation of the gland if infectious material gains entrance.

Inflammation of Salivary Glands

Epidemic parotitis (mumps) is a highly contagious acute nonsuppurative infection of the parotid glands of children or adults. The submaxillary gland may occasionally be involved. The infection starts with a painful swelling of the gland on one side and is followed by involvement of the other. Mumps is caused by a filtrable virus with a generalized distribution in the body, but a special localization in major salivary glands.[48] The testes become involved in about 18 per cent of cases. The central nervous system, pancreas, and thyroid may be affected. The spleen is enlarged.[47] The virus can be isolated from the saliva of man in the very early stage of the disease and from the parotid gland of experimentally infected monkeys. Weller and Craig[49] isolated the virus from the parotid, pancreas, and ovary at autopsy of a 9-year-old girl with mumps. Microscopically, the parotid gland shows degenerative changes of the ductal epithelium with periductal interstitial infiltration with lymphocytes and mononuclears. Few polymorphonuclear cells are seen in the distended ducts. The acini may undergo a pressure atrophy.

Suppurative parotitis is observed as a postoperative complication, mainly after abdominal operations, and also during infectious disease such as pneumonia, typhoid fever, etc. It is now well established that, regardless of the primary cause, staphylococcic infection advances along the duct into the gland.[52] Dryness of the oral mucosa resulting from the loss of blood during the surgical procedure or from exhaustive infectious disease favors the ascending infection through the duct. A blood-borne infection of the parotid gland cannot be excluded, but the experimental study of Berndt, Buck, and von Buxton[53] showed that acute suppurative parotitis is produced with much greater facility by injection of microorganisms into the duct than into the nutrient artery of the parotid gland.

Abscesses, formed first around the ducts and later in the parenchyma, lead to a destruction of the epithelium.

Uveoparotitis (Heerfordt's syndrome) is a rare disease of young individuals. It is characterized by fever, bilateral iridocyclitis, bilateral

parotitis, and facial paralysis. There may be some relation between this disease and sarcoidosis[54] (see page 670). The disease is chronic but usually terminates with recovery.

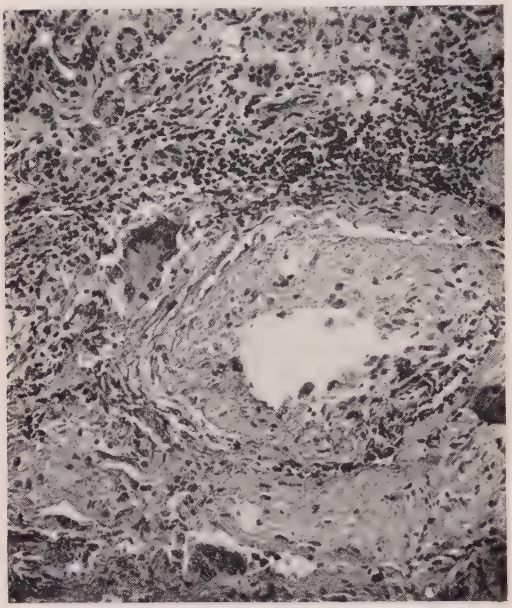

Fig. 662.—Uveoparotitis. Cells of epithelioid type with giant cells and admixture of lymphocytes.

Sjögren's disease involves elderly females and is manifested by an enlargement and decreased secretion of all salivary glands, the lacrimal glands, occasionally a lymphadenopathy, and subcutaneous nodules. The microscopic findings of perivascular round cell infiltration, atrophic changes with fibrosis in the above-mentioned glands, and a more or less necrotizing and proliferative arteritis place this disease perhaps in some relationship with rheumatoid arthritis.

Mikulicz's Disease.—Mikulicz's syndrome, resulting from leukemia, malignant lymphoma, sarcoidosis, tuberculosis and other systemic diseases, and Mikulicz's disease[55, 56] shows bilateral enlargement of all salivary and the lacrimal glands. Mikulicz's disease is of unknown etiology. Morgan and Castleman[57a] showed in their microscopic study of the excised enlarged parotid glands of 18 cases clinically diagnosed as Mikulicz's disease that lymphoid tissue replaced the acinous parenchyma while the ducts became obliterated by proliferation of epithelial and myoepithelial cells ("epimyoepithelial islands"). Since Morgan and Castleman[57a] found that their and Sjögren's cases displayed not only the same clinical features (enlargement of salivary and lacrimal glands associated with other conditions such as keratoconjunctivitis and rheumatoid arthritis) and observed "epimyoepithelial islands" also in *Sjögren's* original slides, they concluded that Mikulicz's disease is merely one variant of *Sjögren's syndrome.*

Inclusion bodies have been described in the epithelium of the ducts of the submaxillary gland and less often of the parotid (Fig. 663). Farber and Wolbach[58] found intranuclear and cytoplasmic inclusions associated with a lymphocytic infiltration in 12 per cent of infants and very young children. There was no other evidence, clinical or pathologic, of disease of the glands. It is very likely, however, that these inclusions are of viral origin. (See also page 335.) Generalized salivary gland virus infection (inclusion disease, cytomegalia infantum) is mainly observed during the first two years of life, seldom in adults.

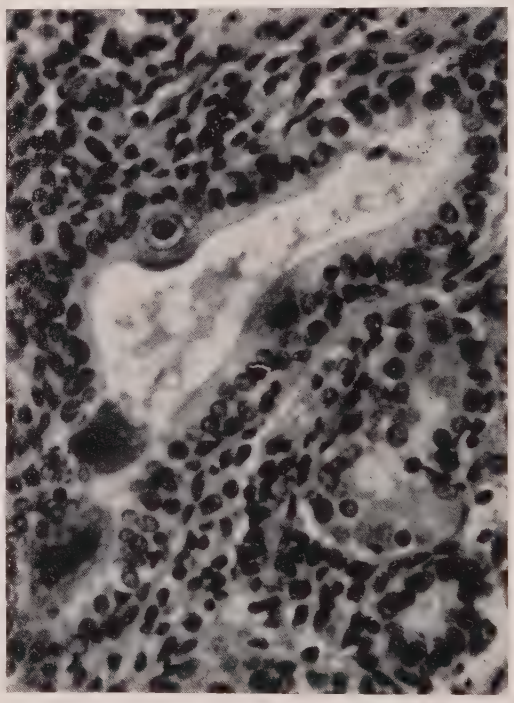

Fig. 663.—Inclusion bodies protruding into the lumen of an intercalated duct of the parotid gland of an infant who died of enteritis.

Tumors of Salivary Glands

Neurofibromas and hemangiomas are uncommon in the parotid gland. The occurrence of sarcomas is doubtful as it is more likely that the few reported sarcomas were anaplastic carcinomas (Willis).

The primary epithelial neoplasms of the salivary glands are adenomas. The cellular and structural differences result from the wide range of differentiation of the intercalated ductal epithelium which represents the main proliferation center for the parenchymal elements of the adenomas. These cells are capable of transformation into mucous, oxyphilic

granular (onkocytic), squamous, "water clear," and sebaceous cells.

"Mixed Tumors."—The great majority of salivary gland tumors is represented by the so-called "mixed tumors." This misleading term, so firmly engraved in the minds of pathologists and clinicians, should be replaced by the appropriate name "pleomorphic adenoma" as suggested by Willis. This tumor occurs most frequently in the parotid, less often in the submaxillary, and rarely in the sublingual gland and the small glands of the oral cavity. It is slow-growing, of a firm or elastic consistency, and usually nodular. It is inherently benign, yet may recur after surgical removal and even become malignant.[60] It is most common between 20 and 40 years of age. The overlying skin is freely movable but the tumor is firmly attached to and may spread into the gland.

The "mixed tumor" is fairly well encapsulated and its cut surface shows solid, usually soft, but occasionally hard areas, intermingled with cystic spaces that contain a thready material. Extensions of the capsule into the tumor bring about the lobulated architecture.

The parenchyma is composed of columns, tubules, nests, and glandular formations of epithelial cells. In most instances, proliferating myoepithelial cells also participate in the development of the tumor. The Masson stain helps to differentiate myoepithelial cells from secretory epithelial cells. The epithelial cells are of variable size, rounded or oval and polyhedral, and show a slightly granular cytoplasm which may be basophilic or eosinophilic. Flattened epithelial cells arranged in glands or ducts often surround a homogeneous, eosinophilic or basophilic secreted material, which may contain cell-debris and sloughed off keratinized particles. Occasionally, nests of squamous epithelium showing keratinization are noted.

In many places transition between solid epithelial structures and a loose stellate epithelial tissue can be seen. The cytoplasm of these starlike epithelial cells may undergo degeneration. (Fig. 664.) The nuclei of the degenerated cells, surrounded by vacuoles and scattered through a hyalinized stroma, impart a cartilage-like appearance to the tissue. The proliferation of the basket cells may surpass the activity of the secretory epithelial cells, yet both types of cells combine to form glandular or ductlike structures and sheets. In a few instances the epithelial cells predominate, producing an adenoma-like tumor.

The fibrous stroma, composed of extensions of the capsule into the tumor, may show areas of hyaline or myxomatous degeneration, which may be altered in appearance by the material secreted by the parenchyma. The connective tissue may sometimes produce true cartilage and even bone. The histogenesis of mixed tumors of the salivary glands has been much discussed. The mesodermal theory is not satisfactory and has been almost generally abandoned. The concept that the embryonal branchial anlage gives rise to the tumor can explain the mixed tumors of the salivary glands but not those in locations distant from the branchial clefts such as finger, lip, breast, testis, and others. The view that mixed tumors develop from misplaced embryonal tissue has recently been advanced by various authors. The author considers that the epithelial and myoepithelial cells are derived from the cells of the salivary ducts and acini. The pseudocartilage consists of degenerated secretory epithelial cells in a matrix of hyalinized stroma fused with epithelial secretions. The proliferating epithelium may occasionally have an inducing influence upon the stroma to produce true cartilage and even bone.

Myoepithelial cells participate and may even predominate in the formation of the pleomorphic adenoma and can be demonstrated with the erythrosin-safranin stain (Masson). The neoplasms composed of an excessive number of myoepithelial cells and lacking metaplastic changes of the stroma are myoepitheliomas[63] or adenomyoepitheliomas.[64]

Oxyphilic Granular Cell Adenoma (Onkocytoma).—This term proposed by Meza-Chávez[65] to replace the odd name onkocytoma indicates very well the morphology of this neoplasm of the parotid, rarely the submaxillary gland of older persons. It is composed of solid, tubular, and glandular formations of large irregularly shaped oxyphilic granular cells ("onkocyte" of Hamperl[66]) with usually round vesicular nuclei with one or two nucleoli (Fig. 665). Some of these cells are compressed, have a homogenous intensely eosinophilic cytoplasm, and contain a small, irregular, hyperchromatic nucleus. These cells should be regarded as degenerated oxyphilic granular cells. This explanation is supported

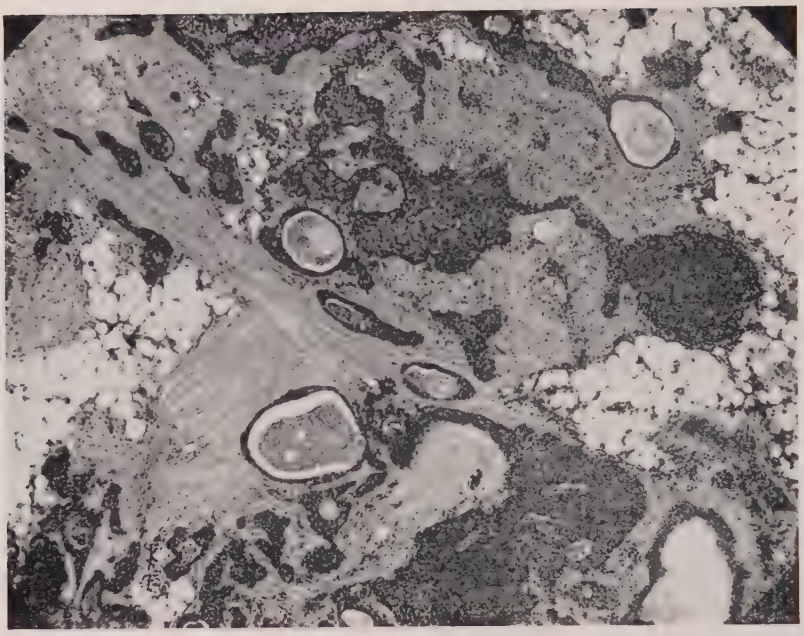

Fig. 664.—"Mixed tumor" of parotid glands. Ductlike structures with secretion, solid clusters and cords of polyhedral epithelial cells passing into a loose partly hyaline-cartilagenous tissue. Fibrillar stroma.

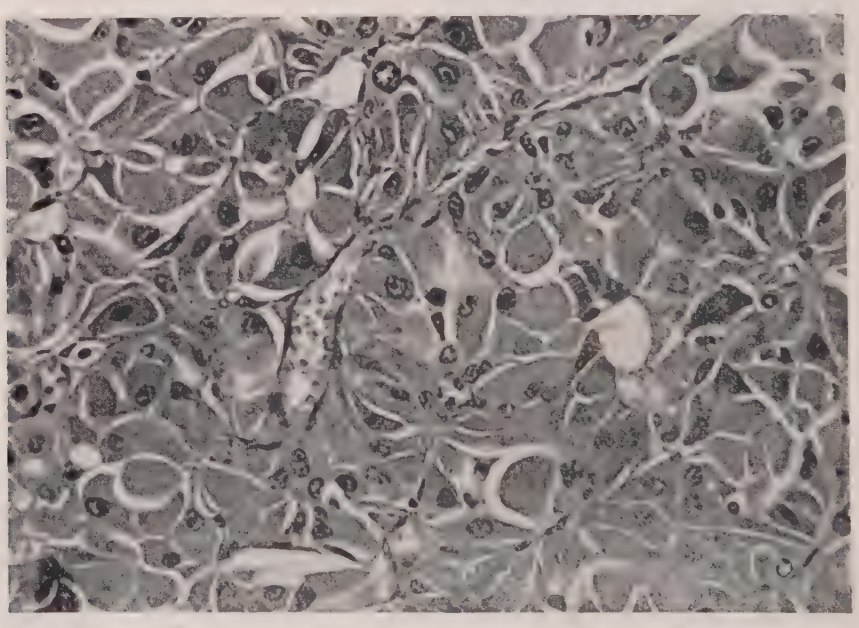

Fig. 665.—Oxyphilic granular cell adenoma (onkocytoma) of parotid. Sheets and glandular formations of tall columnar cells with eosinophile granular cytoplasm.

by the finding of debris of these cells in duct-like structures. In none of the five cases of oxyphilic granular cell adenoma studied by the author were large accumulations of lymphocytes detected. The oxyphilic granular cells originate from the multipotential lining cells of the intercalated ducts by a metaplasia of their cytoplasm. This process of unknown nature renders the cells capable of proliferation and tumor formation. Oxyphilic granular cells were found by Hamperl[66a] in many organs and by Hamperl and Stout[67] in the bronchi of adults and in bronchial adenomas.

Though the oxyphilic granular cell adenoma is considered to be a benign growth, the author has examined the sections of a malignant variant which led to metastases in the lung, liver, and brain.

desquamated epithelial cells. The papillary projections are covered by a layer of high columnar, slightly acidophilic, epithelial cells. A few globlet cells may be seen. The nuclei of the columnar cells stain deeply. These cells may be supported by two or three layers of cuboidal cells. The interstitial lymphoid tissue frequently contains large germinal centers and may undergo collagenous or fibrous changes. On the basis of the cytologic details, it seems evident that both the epithelial and lymphoid components participate in the formation of the tumor. The epithelial proliferation precedes the ingrowth of the lymphoid interstitial tissue. This explains the occasional finding of papillae covered by stratified columnar epithelium but without any lymphoid tissue. The origin of the cystadenoma lymphomatosum

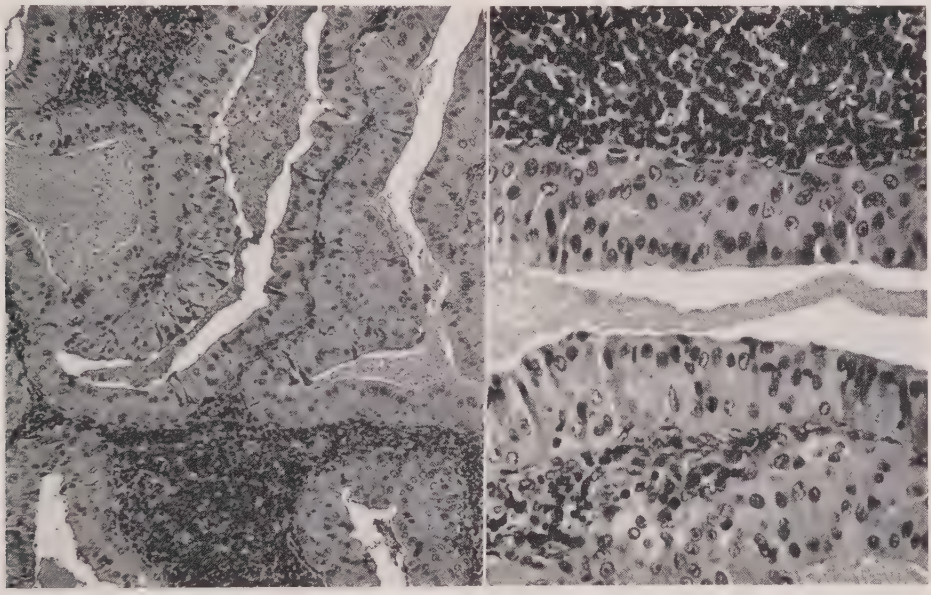

Fig. 666. Fig. 667.

Fig. 666.—Papillary cystadenoma lymphomatosum of parotid. Papillae extending into cavity contain lymphoid core coated with columnar epithelium.

Fig. 667.—Papillary cystadenoma lymphomatosum. High magnification of area of Fig. 666, showing layer of columnar epithelium and lymphoid tissue.

Papillary Cystadenoma Lymphomatosum (Warthin's Tumor[68]).—Papillary cystadenoma lymphomatosum is a slowly growing, usually benign tumor found next to the angle of the mandible involving the lower pole of the parotid. It occurs predominantly in males and at advanced ages, but has been observed also in children. It is well encapsulated, freely movable, and has a smooth or lobulated surface. The cut surface shows many cavities with a mucinous content. Microscopically, the tumor is composed of an epithelial parenchyma and a lymphoid interstitial tissue (Figs. 666, 667). Slender fingerlike papillae, sometimes with branches and club-shaped ends, project into cystic cavities which contain an eosinophile granular substance with few leukocytes and

has been much discussed.[69, 70] Origins of the tumor which have been considered include parotid gland tissue misplaced into lymph nodes, and the epithelium of the main excretory duct of the parotid. Warthin[68] held that the tumor arises from a dystopia of the mucosa of the auditory tube caused by a developmental disturbance of the anlage of this tube. The finding of fairly large lymphocytic accumulations in normal parotids and submaxillary glands of young people and adults makes it more likely that the salivary gland is the origin of this neoplasm and not the heterotopic salivary gland tissue occasionally found in adjacent lymph nodes.

Lymphomatoid Adenoma.—This term suggested by Bauer and Bauer[70a] distinguishes this

tumor of the parotid gland from the papillary cystadenoma lymphomatosum. Few neoplasms, very likely of this type, were reported as "adenolymphoma," "solid adenolymphoma," "lymphocytic tumor," "adenoma of preparotid lymph glands," and "lymphoepithelial lesion."[70b] Microscopically, some lobules of the observed six tumors were occupied by massive lymphoid tissue with germinal centers which replaced the parenchyma. The latter showed tubules and acini lined with several layers of epithelial cells. Occasionally, solid aggregations of epithelial cells were observed. The recurrence of two of our cases following parotidectomy and the definite increase of the adenomatous features in the lymphoid stroma in these cases compared with the sections of the original tumors indicated the neoplastic nature of these growths. The hyperplasia of the lymphoid tissue assumed a "lymphoma-like" feature and stimulated the adenomatous changes of acini and ducts. We were not able to determine whether these tumors originated from the lymphoid foci of some lobules of the gland or from adjacent lymph nodes.

by the absence of lymphoid interstitial tissue and by the slight affinity of the cuboidal or columnar epithelial cells of the papillary projections for basic stains (Figs. 668 and 669). Occasionally there are accumulations of large, polyhedral, clear, sharply bordered cells with small hyperchromatic nuclei. These clear cells contain neither mucin nor lipoid. They resemble the large clear cells of hypernephroma and are grouped in solid nests, rarely in acini (Fig. 670). In many areas the nuclei of these cells may disappear and the cell boundaries break down, leaving behind a honeycomb-like structure. The interstitial tissue consists of very delicate bands of highly vascular connective tissue with thin strands of collagen. Collections of red blood cells and hemosiderin are found throughout these areas as a result of torsion of the papillary projections. Nests of cholesterol crystals may be observed. The genesis of these large "empty" cells, the so-called "cellules claires," is obscure. The author observed two symmetrical benign parotid tumors of long standing which consisted entirely of these clear cells, arranged in papillae, and has noticed the same type of cell

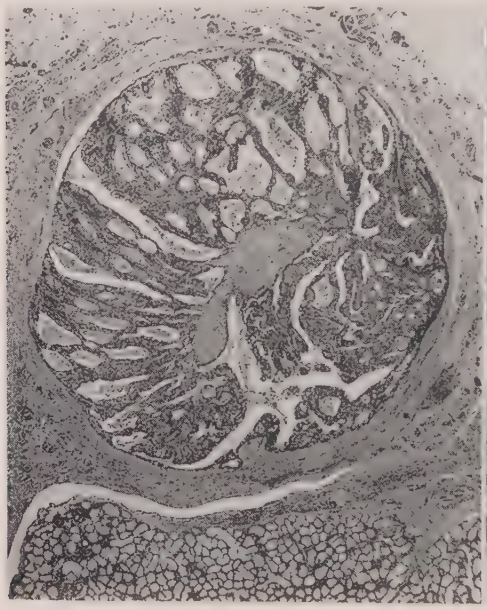

Fig. 668.

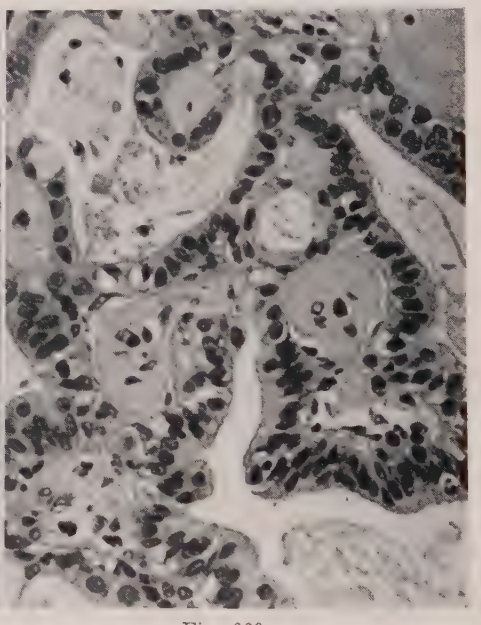

Fig. 669.

Fig. 668.—Well-defined papillary cystadenoma of mucous glands of soft palate surrounded by fibrous wall.

Fig. 669.—Higher magnification of Fig. 668. Papillae lined with stratified columnar epithelium project into cavities which contain a hyalinized material.

Papillary Cystadenoma.—Papillary cystadenoma is a rare, slowly growing salivary gland tumor. It occurs most frequently in the parotid and less often in the submaxillary gland or the glands of the oral mucosa. It may occur at any age and even be congenital. It is potentially malignant. The tumor is composed of soft and friable irregularly shaped nodules but is fairly well encapsulated. The cut surface is grayish-brown or reddish from the admixture of blood.

Microscopically, this tumor is differentiated from the papillary cystadenoma lymphomatosum

in other tumors of salivary glands. The occurence of smooth transitions from epithelial cells to large clear cells and the finding of these cells in the proliferating epithelium of the secretory ducts in tumors of salivary glands has led the author to the conclusion that "clear cells" are a product of cytoplasmic metamorphosis. Skorpil[71] considers its origin to be from cells of the excretory ducts.

Mucoepidermoid Tumor.—Mucoepidermoid tumors of the salivary glands were recently described by Stewart, Foote, and Becker.[72] The

authors claim that a little more than 5 per cent of all salivary gland tumors are of this type. The growth is solid or cystic, encapsulated or nonencapsulated, and originates from cells of the larger and intermediate ducts. The "mucus-forming epithelioma" of the salivary glands as described by Skorpil[73] bears a definite resemblance to this tumor. It is characterized by an abnormal differentiation into mucous cells and by epidermoid metaplasia. (Fig 671.) Keratin pearl formation may occur. According to Stewart, Foote, and Becker[72] benign and malignant types occur. The benign variant is composed of proliferating mucous cells, basket cells, and columnar cells. The mucous cells and basket cells are of importance, but the columnar cells do not play a prominent role. Occasional excessive production of mucus may rupture the glandular and ductlike formations. Inflammation and even necrosis may be encountered. Stewart, Foote, and Becker[72] included in their study a case in which large "empty" cells were noted, cells similar to those observed by the author in papillary cystadenomas. Occasionally, there may be transitional forms of these two types of tumors.

The *undifferentiated epidermoid carcinoma* of the salivary glands, chiefly of the parotid, is rapidly growing and highly malignant.

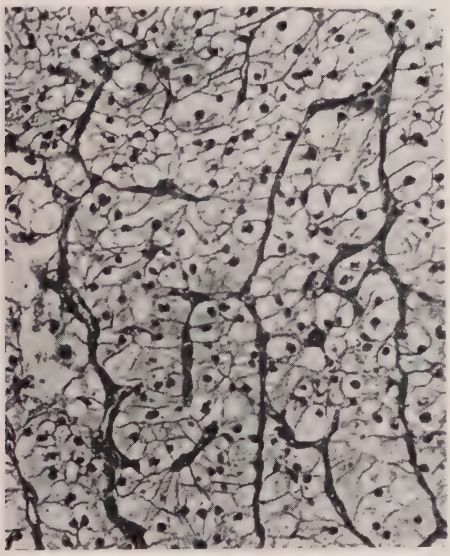

Fig. 670.—Papillary cystadenoma of the parotid composed of clusters of large clear cells. Highly vascular threads of interstitial tissue.

Adenocarcinoma.—Among the primary malignant tumors of the salivary glands, the adenocarcinoma deserves particular attention because of its great variety of patterns, infiltrating growth, frequent recurrence after removal, and tendency to metastasize. Dockerty and Mayo[74] separated this neoplasm of the submaxillary salivary glands from the mixed tumors, with which it has been confused. Because of its resemblance to the so-called cylindroma, they named it "adenocarcinoma of cylindroma type." Quattlebaum, Dockerty, and Mayo[75] observed this neoplasm unilaterally in 10 per cent of 210 cases of parotid tumors. The age of patients ranged between 32 and 65 years.

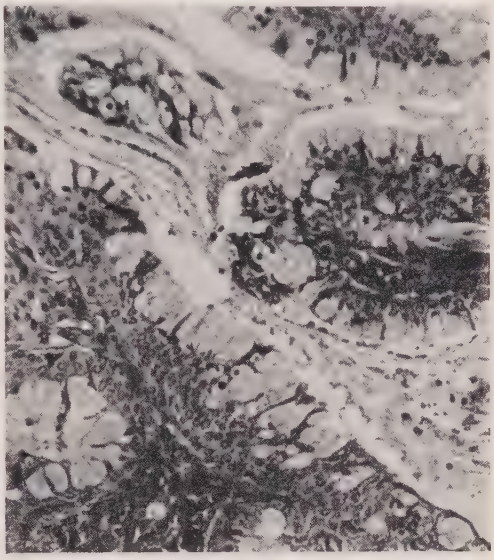

Fig. 671.—Mucoepidermoid tumor of parotid of low-grade malignancy.

Radiating pain is an alarming sign. The tumor is firmly attached to the gland, shows only traces of a capsule, and infiltrates the surrounding nerves and muscles. The microscopic features include islands, cords, and glandular formations of small polymorphic cells with hyperchromatic nuclei, surrounded by a hyaline stroma (Fig. 672). The similarity of some types of this tumor with the adenoacanthoma of the esophagus[77] and the carcinoma of the cardio-esophageal junction[78] has been stressed.

NECK

Ludwig's Angina.—Cellulitis of the floor of the mouth is a not infrequent complication of extractions of infected mandibular molars or premolars, and of mouth floor ulcers. The phlegmonous inflammation usually extends into the upper part of the neck and may spread further along the sternocleidomastoid muscle into the mediastinum.

Enlargement of cervical lymph nodes may be due to a lymphadenitis from infection with

known and unknown agents (Hodgkin's disease, Boeck's sarcoid, infectious mononucleosis, etc.), or to tumors (lymphosarcoma, reticulum-cell sarcoma, lymphatic leukemia), or to tumor metastases.

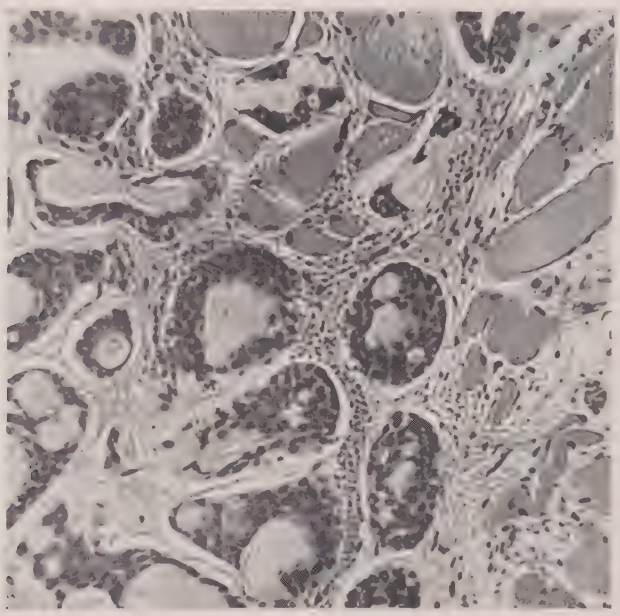

Fig. 672.—Adenocarcinoma of parotid of cylindromatous type invading muscle.

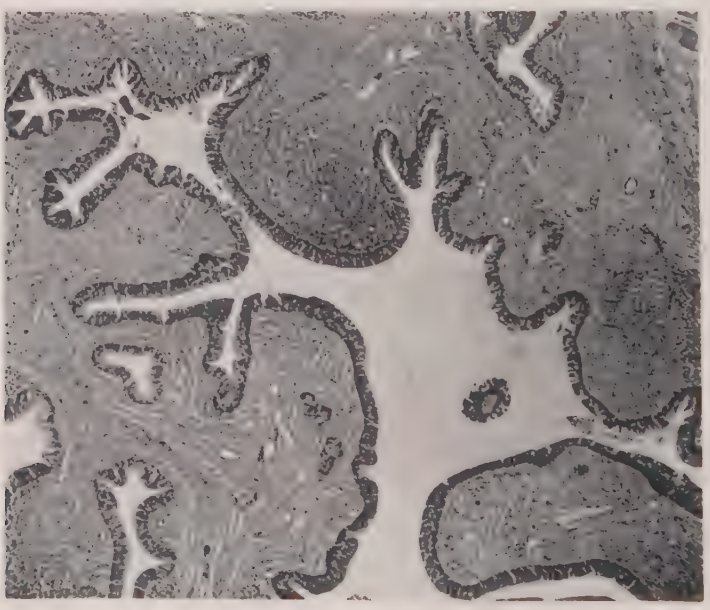

Fig. 673.—Cervical branchial cyst lined with columnar epithelium. Lymphoid tissue in the connective tissue wall.

Lateral cervical branchial cysts of various sizes appear unilaterally in the upper cervical region close to the angle of the mandible and anterior to and along the sternocleidomastoid muscle. Their fatty contents may be sticky and turbid or watery and clear. They grow slowly. The majority rupture, forming a complete fistula which opens externally through the skin and internally into the pharynx close to the tonsils. Less frequently there is only an external opening and, very rarely, only an internal

fistula. When openings develop, this cyst becomes infected. A familial tendency to develop this anomaly has been noted.

Microscopically, the cysts are lined by squamous epithelium or, less frequently, by columnar epithelium. The epithelial layer is surrounded by lymphoid tissue with occasional germinal follicles; the outer loose connective tissue wall may show inflammatory cells.[79]

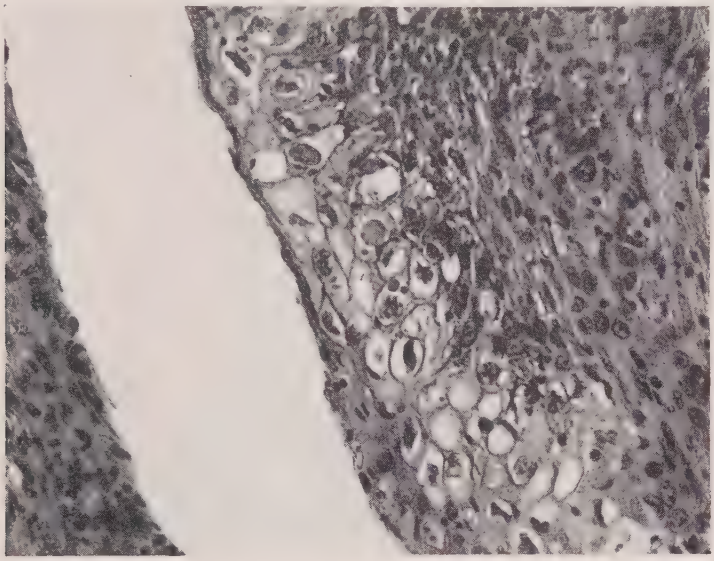

Fig. 674.—Epidermoid carcinoma lining the outer fistular duct of branchial cyst. (Courtesy Armed Forces Institute of Pathology.)

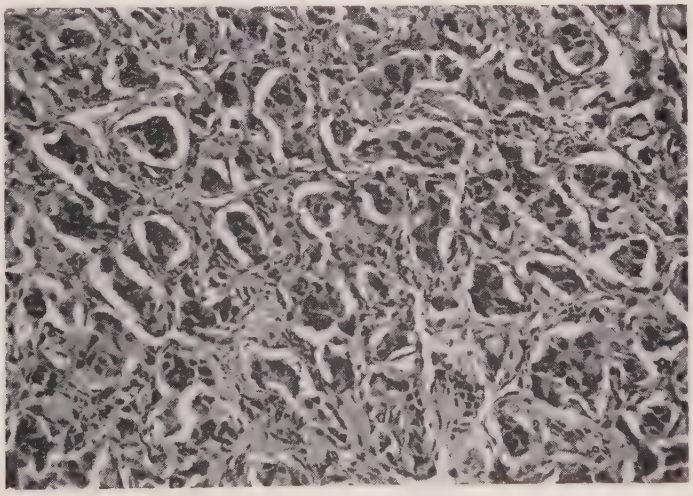

Fig. 675.—Carotid body tumor. Groups of large polyhedral cells with hyperchromatic nuclei.

The development of lateral cervical cysts is still a matter of discussion and various theories have been advanced. It has been held that the cysts arise from the persisting lower part of the thymopharyngeal duct, the upper part of which has become obliterated. Carp and Stout[80] however, favor Rabl's idea, that the abnormal development of the second arch interferes with the normal obliteration of the precervical sinus.

Branchiogenic Carcinoma.—The squamous epithelium of the wall of a cervical (branchial) cyst may give rise to epidermoid carcinoma. The tumor cells line the fistulous duct with an inner keratinized layer of flat epithelial cells above large, vesicular, and occasionally hyalinized epithelial cells. Many multipolar mitoses are usually present.[81] (Fig. 674.)

Chondromas derived from the remains of cartilage of branchial clefts have been observed.

Carotid Body Tumor.—This rare peculiar tumor of the glomus caroticum is found pre-

dominantly in individuals between 20 and 60 years of age. It appears as a slowly growing swelling of variable size in the neck next to the bifurcation of the carotid artery. It is usually unilateral, lobulated, more or less encapsulated, and because of its intimate attachment to the carotid artery, transmits pulsation. It is freely movable horizontally but not vertically. The tumor is relatively benign, yet tends to recur locally and may extend into the adjacent tissue.

Microscopically, a vascular fibrous stroma connected with the capsule traverses the tumor in various directions. The parenchyma is composed of large polyhedral cells clumped together sometimes in an alveolar manner. The cells have a granular, acidophilic, often vacuolated cytoplasm and occasionally hyperchromatic nuclei. (Fig. 675.) They resemble the cells of the carotid body but may display variations in their shape. A few authors[82-84] emphasized the chromaffin type of some of these cells while others[87] questioned it because of the faint chromaffin reaction. Feyrter[90] recently demonstrated by a modified Bielschowsky-Gross impregnation method the presence of cells in the glomus caroticum which resemble the chromaffin and argyrophile cells of the peripheral vegetative nerve tissue.

Congenital Muscular Torticollis.—Congenital muscular torticollis is an entity in which a more or less localized fibrosis of one or the other sternocleidomastoid muscle causes shortening of the muscle. Significantly, other asymmetries of jaws, skull, and external ear are often associated. Either at birth or within the first two weeks a hard immobile swelling develops in a sternocleidomastoid muscle. It may gradually increase in size or disappear within a few months. The head appears inclined toward the involved side while the face points in the opposite direction.

Microscopically, a part of the muscle is replaced by a fibroma-like growth which contains a few degenerated muscle fibers. The study of Chandler and Altenberg[85] conducted on 101 cases showed conclusively that the fibrosis is not preceded by a hematoma. Very little hemosiderin is found even in an early stage.

Various theories concerning etiology have been advanced. The most acceptable conception which can be reconciled with the histologic features is that the fibrosis follows a local ischemic pressure atrophy, which is due to intrauterine pressure in certain positions of the fetus. However, traumatic injury due to difficult childbirth doubtless is the important factor in some cases.

Cystic Hygroma.—Cystic hygroma is a relatively rare, congenital, multilocular cystic tumor of the neck of lymphatic origin. (See discussion on page 548.)

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Chapter 26

THE GASTROINTESTINAL TRACT

John R. Schenken and Edward L. Burns

THE ESOPHAGUS

Congenital Malformations

Atresia is the most common esophageal anomaly. Agenesis, double esophagus, and stenosis are exceedingly rare anomalies.

Atresia may be of various types. In the most common type, the upper portion ends in a blind pouch which is attached to the posterior surface of the trachea. The distal segment communicates with the trachea just above the bifurcation. Unless the lower segment is ligated, feeding these infants through a gastrostomy opening does not save them, because of regurgitation into the trachea.

Circulatory Disturbances

Acute hyperemia and edema are the result of acute bacterial or chemical inflammatory processes. These lesions are discussed elsewhere.

Chronic hyperemia is very common in chronic heart failure but usually does not become of much importance except in cases of venous obstruction. In the rather common disease, portal cirrhosis, and in the rare cases of portal and splenic vein thrombosis, the venous blood flow from the spleen and stomach is obstructed and seeks a new route back to the heart. One of these routes is through the esophageal venous plexus, reaching this structure by way of the coronary and short gastric veins. With prolonged obstruction, the submucosal veins of this plexus become greatly enlarged and bulge into the lumen of the esophagus, covered only by mucosa. These veins rupture not infrequently and lead to massive or even fatal hemorrhage.

Inflammation

Chemical injuries may be due to poisons ingested either accidentally or for suicidal purposes. In general, however, it is often surprising how little damage is done to the esophagus as compared to the stomach. Strong alkalies, usually taken accidentally in solution by children, because of an appearance like milk, uniformly cause lesions. The action is so prompt that the esophagus goes into a spasm and the solution is often regurgitated before it reaches the stomach. The severest lesions are usually located at the levels of natural constrictions, in the following order: (1) level of bifurcation of trachea, (2) upper esophagus, (3) level of hiatus. In the acute phase, there is deep ulceration of the mucosa but rarely perforation. This is followed by healing with fibrosis which, in the course of a few weeks or months, produces stenosis. In our own material, each of the cases showed fibrosis of the muscle coat, and, therefore, we have assumed that the initial lesion must be deep enough to involve muscle before stenosis is likely. All variations may be seen from a narrow fibrous cordlike structure to localized stenoses with dilated segments above. Ingestion of strong acids such as hydrochloric and sulfuric and such corrosives as phenol and mercuric chloride causes surprisingly little damage in the esophagus as compared to the stomach. The lesions are similar to the gastric lesions.

Infective lesions of the esophagus are not common. Acute infectious diseases such as typhoid fever, scarlet fever, and diphtheria are occasionally associated with esophageal inflammation. Among the granulomatous infections, tuberculosis, syphilis, actinomycosis, histoplasmosis, and thrush may produce lesions. The esophagus may be involved primarily or through secondary extension from a contiguous lesion, particularly infected mediastinal lymph nodes. Thrush esophagitis is relatively common among malnourished infants, especially prematures. The lesions may be either superficial erosions or actual pseudomembrane formations, and mycelial threads are found in the tissue sections.

Acute esophagitis with or without "esophagomalacia," which occurs as a rule as a terminal event in aged, debilitated, or seriously ill patients, deserves special mention. For years this condition has been thought to be a postmortem autolysis. The lesion varies from a superficial erosion of the mucous membrane to an extensive necrosis and softening of the lower end of the esophagus with

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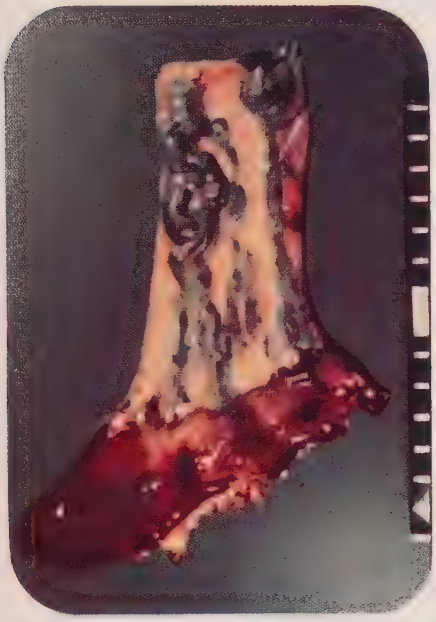
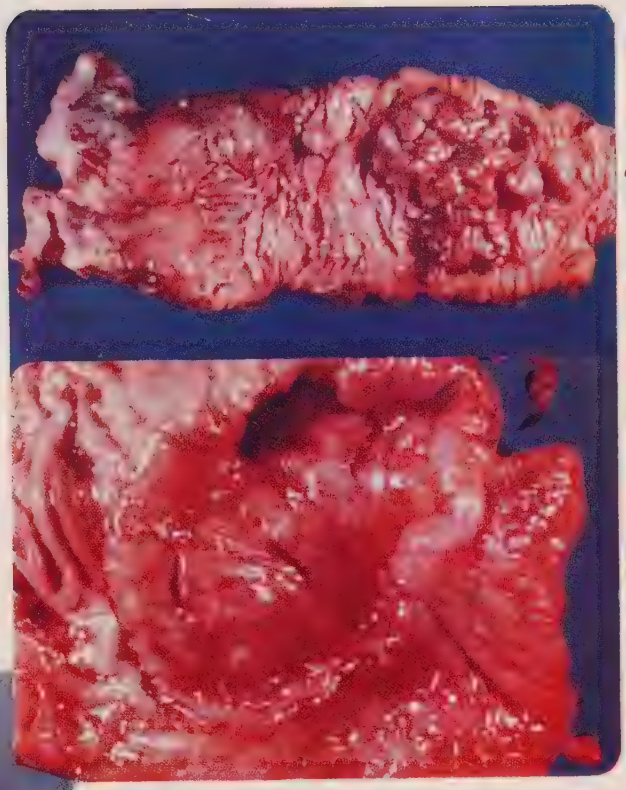
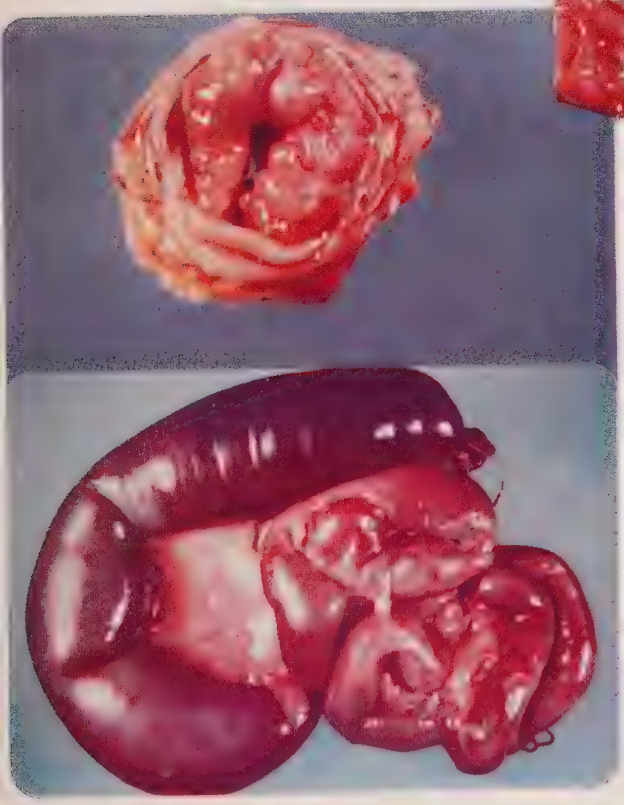
Plate VI.—*1*, Esophageal varices in a case of cirrhosis of the liver. *2*, Mechanical obstruction of small intestine due to old adhesions. Proximal segment is distended and gangrenous. *3*, Annular carcinoma of sigmoid colon showing almost complete encirclement of lumen. *4*, *Enterobius vermicularis* in the cecum of an adult female. *5*, Carcinomatous ulcer of stomach. The margins are rolled and elevated because of carcinomatous invasion beneath the surrounding mucosa. *6*, Polypoid adenocarcinoma of rectum. The anal sphincter is at the left.

1.







4.

PLATE VI. *(For legend see opposite page.)*

perforation into the mediastinum and secondary perforation of regurgitated gastric content into the left pleural cavity. The extensive lesions have a brownish-black appearance due to discoloration by acid hematin created by the hydrochloric acid of the gastric content as it comes in contact with the bleeding denuded surface. Most cases are not suspected clinically but some patients give a history of gurgling in the throat, substernal distress, or vomiting blood.

Peptic ulcer of the esophagus is probably not truly an inflammatory lesion. Most investigators feel that it is due to either a patulous cardiac orifice with constant regurgitation of strong gastric juice or the secretions of ectopic gastric mucosa. These lesions are usually located in the lower 10 cm. of the esophagus. They have the same punched-out appearance as a gastric or duodenal peptic ulcer. Hemorrhage, obstruction, and perforation are the most important complications.

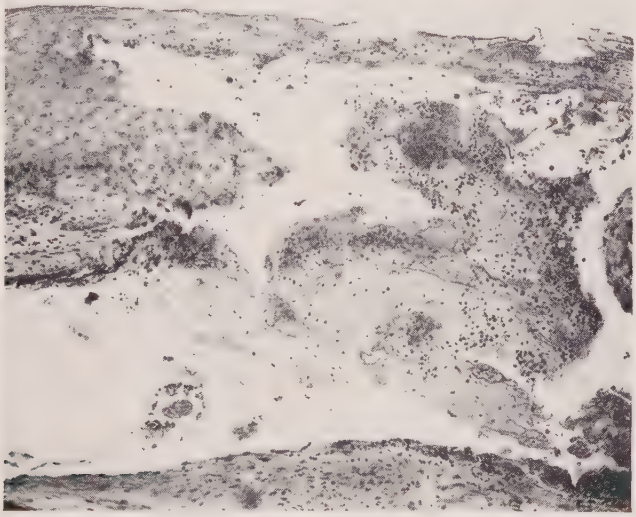


Fig. 676.—Varicose esophageal vein rupturing through mucosa in a case of cirrhosis of the liver.

Neoplasms of the Esophagus

Malignant tumors of the esophagus are much more common than benign tumors. Ninety per cent are squamous cell and 10 per cent are columnar cell or adenocarcinomas. They occur much more frequently in males than females; practically all occur in persons older than 50 years and they are most commonly located at the points of natural constriction. Grossly, they are usually ulcerative or fungating, but may be of the diffuse and scirrhous type. We have seen the ulcerative type most frequently. The lesion begins as an elevated plaque which gradually enlarges in all directions. Within a few months to a year the lesion has practically encircled the lumen and is responsible for symptoms of obstruction. During this period, the surface of the tumor has usually ulcerated and sloughed, giving the lesion its typical appearance of an ulcer with rolled-up margins due to the submucosal growth of the neoplastic tissue. In obtaining a biopsy the esophagoscopist should keep in mind the fact that redundant mucosa, made more redundant by the esophagoscope, may cover the superior margin of the tumor, and hence the inferior margin is more likely to yield neoplastic tissue.

Obstruction, first to solid and then to soft foods, is the first and most outstanding of the complications. Very few diseases are associated with as much emaciation, due mostly to starvation. Hemorrhage and secondary infection are also common complications. Perforation or extension of the lesion into contiguous structures occurs in about half of the cases. Consequently, mediastinitis, empyema, lung abscess, tracheal or bronchial esophageal fistula, or even erosion into the aorta are among the local complicating lesions. Metastasis to the regional lymph nodes is practically always present, but sometimes metastasis to cervical or gastric lymph nodes, to the liver, or generalized metastasis occurs. Carcinomas involving

reveals atrophic glands with an absence of parietal cells and an infiltration of lymphocytes and plasma cells. The absence of the parietal cells accounts for the anacidity commonly present in these patients.

Tuberculosis of the stomach is a rare lesion. Ulcerative lesions are the most common type and are usually located on the lesser curvature near the pyloric end of the stomach.

Syphilis of the stomach is not common; it probably exists as a tertiary lesion more frequently than generally appreciated.

Peptic Ulcers

Ulcers occurring in the stomach and duodenum will be considered together because they follow a similar pathologic course and in all likelihood have a similar etiology. These may be acute or chronic.

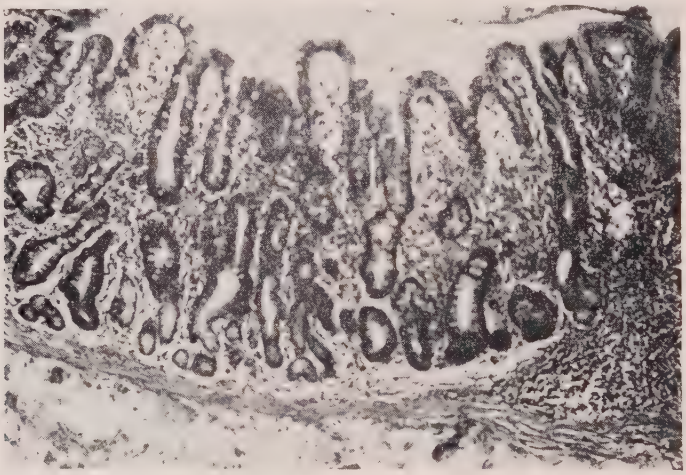


Fig. 677.—Atrophic gastritis. The glandular elements of the mucous membrane are reduced in number.

Acute Ulcer

Most acute peptic ulcers are multiple and occur in the stomach. They are seen in uremia and occasionally in association with lesions of the hypothalamus, and with extensive burns of the skin. The majority, however, bear no constant relationship to other disease processes. Since such ulcers are common at postmortem examination, it seems possible that the failing circulation of the agonal state produces devitalization and autodigestion of the gastric mucosa. In other instances it is also quite possible that there may be a septicemia with multiple localizations in the gastric mucosa with consequent necrosis and autodigestion. The distribution of the multiple small ulcers is rather widespread and seems to bear no relation to the lesser curvature. The ulcer following burns is often referred to as Curling's ulcer, and occurs more frequently in the duodenum. Single acute ulcers occur more frequently in the female than in the male, and apparently are no different from chronic ulcers except for the rapidity of their development. The erosion is rapid, and hence blood vessel destruction may occur prior to thrombosis, so that many of these ulcers bleed rather profusely. Perforation and hemorrhage may occur at the same time, which is very unusual in the case of chronic ulcer.

Chronic Ulcer

Etiology.—Although much is known about the etiology of chronic gastric and duodenal ulcers, the exact cause is still unknown. Chronic peptic ulcer is a very common disease. It has been stated that about 10 per cent of all adult males have or have had an ulcer. It is apparently a disease of civilization. Relatively few gastric ulcers are found among native Malayan tribes in Java and Sumatra; whereas Chinese living in the same area are subject to a high incidence of peptic ulcer. It is primarily a disease of males, but no acceptable reason has been found why this should be true.

There are numerous opinions as to the etiology of peptic ulcer, but, when all of the theories are analyzed, each of them appears to have basic factors to which most of them subscribe. In general peptic ulcers do not occur in patients with achylia gastrica, or in the jejunum or ileum where the reaction is alkaline; therefore, hydrochloric acid and the digestive ferment, pepsin, appear to be necessary for the formation of an ulcer.

Another factor which most people agree must be present is an area of devitalization of tissue which permits the process of autodigestion and ulcer formation. Since Virchow's time, vascular disease, including vascular spasm, has been frequently proposed as the basic cause of an ulcer. The presence of endarteritis obliterans and thrombosed vessels in the base of an ulcer is not proof that vascular disease is of etiological importance, since it is well known that these may be secondary to the ulceration. Cole[30] has proposed that the blood supply to the mucosa in the region of the sulcus angularis is decreased because of the tension placed upon the

PLATE VII.—Chronic ulcer of stomach. (From Dible, The Pathology of Gastric Ulcer, Surgery, November, 1937.)

branches of the left gastric artery going to this area as a result of the upright position of the human being. Wertheimer[53a] pointed out that peptic ulcers are rarely found in quadrupeds, which would support Cole's view. Schindler and Baxmeier[49] noted hemorrhagic erosions in the mucosa of 44 per cent of the patients with gastric ulcer as compared with only 5.6 per cent without gastric ulcer. This observation lends some support to the view that a localized vasospasm with the formation of a tiny ulcer as the initial lesion may be responsible for a chronic peptic ulcer. Little evidence has been found that gastritis is a cause of the ulceration.

The role of the nervous system in the production of a chronic peptic ulcer is still not known. The frequency with which lesions in the diencephalon are followed by a peptic ulcer is ample proof that ulcers as a result of neurogenic lesions may occur. This relationship was first described by Rokitansky[46] in 1841. It was revived by Cushing[32] in 1923 and more recently by Dragstedt,[33, 34] who advocates cutting the left vagus nerve in the treatment of peptic ulcer. Vagal stimulation not only causes an increase in the flow of gastric juice, but also increases the hydrochloric acid and enzyme content. It also increases the tonus of the stomach and causes hyperperistalsis. All of these factors are commonly seen in peptic ulcer. The demonstration of lesions in the diencephalon in most patients with chronic peptic ulcer is still lacking.

Pathologic Anatomy.—About 40 per cent of chronic peptic ulcers are gastric and 60 per cent duodenal. Of the gastric ulcers, about 75 per cent are located in the pyloric region (distal one-third) of the stomach. In the duodenum about 75 per cent are present in the first portion and the remainder in the second portion. Although there are many statements to the contrary, gastric ulcers are not located primarily along the lesser curvature. In our material, those that are present in the pyloric region are distributed in random fashion about the circumference. As a matter of fact, more were found on both the anterior and the posterior walls than along the lesser curvature. Ulcers in the remainder of the stomach tend to be located along the lesser curvature. In the duodenum the majority are located on the anterior wall.

The gross appearance of a chronic peptic ulcer is quite characteristic. It is a rounded, punched-out ulceration, measuring from 1 to 2 cm. in diameter. The wall is either straight, as if a cylinder punch has been used to produce it, or is somewhat terraced with the proximal side wall running in a slanting direction toward the center of the ulcer. There is usually no undermining. Very little heaping up of the margins is present, which is an important differential diagnostic criterion in distinguishing a peptic ulcer from a neoplastic ulcer. The base of the ulcer is red and somewhat granular, and frequently a layer of fibrinous exudate covers it. The depth varies, depending upon how much of the wall is destroyed. Not infrequently the ulcer has eroded through the muscle coats and the base is composed of scar tissue, omentum, or the tissues of a contiguous organ to which the ulcer may be attached. The external surface of the stomach at the site of the ulcer, if not attached to an organ, often shows a puckered appearance with subserosal fibrosis.

Microscopic examination reveals that the base of the ulcer is covered by fibrinous exudate resting upon a chronically inflamed granulation tissue. The tissues beneath show either chronic inflammation with replacement fibrosis of the muscle coat or merely scar tissue. This layer of scar tissue often involves considerable quantities of fat tissue. The cellular infiltration is quite mixed. In the superficial portions of the ulcer, polymorphonuclear leukocytes and macrophages predominate, whereas in the deeper portions, lymphocytes, eosinophiles, and plasma cells predominate. The vessels in the base of the ulcer often show subintimal connective tissue proliferation and occasionally are thrombosed.

Complications.—The common complications of chronic peptic ulcer are perforation, hemorrhage, conversion into carcinoma and pyloric obstruction. Practically every gastric or duodenal ulcer bleeds sometime during its course, but the hemorrhage is usually not fatal. An analysis of our fatal cases consisting of a mixed group of Negro and white individuals showed that about 65 per cent died of perforation, 25 per cent died of hemorrhage, and 10 per cent of other causes. Gastric ulcers have a greater tendency to bleed, whereas duodenal ulcers have a greater tendency to perforate. The majority of those in our series who died of massive hemorrhage had hypertension, and a few showed erosion of the ulcer into the head of the pancreas. Together, this group constitutes about 80 per cent of the hemorrhagic cases. It is our opinion that hypertension

is an important cause of massive fatal hemorrhage, and that its association is often difficult to diagnose clinically because the patient when seen is often in a state of extreme shock. Only follow-up examinations or previous clinic or office records reveal the true state of affairs. Deep erosion of a duodenal ulcer into the pancreas may also cause a mycotic aneurysm of the superior pancreaticoduodenal artery with rupture and fatal hemorrhage. When perforation occurs, occasionally the area is sealed spontaneously by the omentum or by the adherence to surrounding organs. If a peritonitis results, it is primarily a chemical peritonitis for the first few hours, but soon becomes a true infectious peritonitis.

The complication of superimposed carcinoma largely concerns gastric ulcers. Much controversy exists as to the frequency of this condition. The incidence of carcinomatous change in gastric ulcer is probably less than 5 per cent. Pyloric obstruction is a complication which occurs when the ulcer is relatively large and located at the pyloric ring on the gastric or duodenal side. Sometimes it occurs during the active stage of ulceration when spasm is an important factor and at other times it occurs when a relatively large ulcer heals.

Fig. 678.—Chronic peptic ulcer in cardia of stomach. The lower end of the eosphagus is seen above the ulcer. A protruding eroded blood vessel, from which fatal hemorrhage occurred, is evident in the base of the ulcer. (Courtesy Dr. S. B. Pessin.)

Other complications of peptic ulcer may be directly related to treatment. Among these are alkalosis which may occur as a result of excessive administration of sodium bicarbonate. Kretschmer and Brown[39] estimate that about 5 per cent of patients so treated developed urinary calculi. Another is the development of the marginal ulcers, or secondary jejunal ulcers, following gastroenterostomy. This complication is thought to be due to the acidification of the jejunal content, which

is normally alkaline. This complication has made resection of the pyloric end of the stomach a relatively popular procedure at the present time, since this procedure appreciably reduces the acid secretion of the stomach.

The healing of a peptic ulcer is accomplished by organization of granulation tissue at the base of the ulcer with reepithelization of the surface. However, the glands are not reformed, there being only a single layer of columnar epithelium covering the surface.

Neoplasms of the Stomach

Incidence and Etiology.—By far the most common and most important neoplasm of the stomach is carcinoma. Twenty-five to 35 per cent of malignant neoplasms which occur in the male, exclusive of lip and skin cancers, are gastric carcinomas. In the last few years some reviewers claim that primary bronchogenic carcinoma is more common in the male than gastric cancer. No age group is exempt from the disease, although about 80 per cent occur in persons after 40 years of age. We have seen one case in an 18-year-old boy.

There are available some very interesting studies on the incidence of gastric cancer in various races and in various countries. The Caucasian race seems to be more commonly involved than the Orientals. However, in Java the natives show a low incidence of gastric cancer, whereas the Chinese living in the same area show a high incidence. The incidence of gastric cancer in Sweden and Czechoslovakia apparently is about three times that in England. No satisfactory explanation has been offered for these interesting findings.

There is some evidence of an hereditary tendency to gastric cancer. Bockus[54] points out that Napoleon, his father, brother, and two sisters are reputed to have died of gastric carcinoma. Other conditions which are said to predispose to carcinoma are chronic atrophic gastritis, pernicious anemia, and peptic ulcer. There is much controversy as to the relationship between atrophic gastritis and cancer, and the subject does not seem to have been settled. Adenomatous polyps, commonly referred to as gastric polyposis, frequently become carcinomatous, although as a cause of gastric cancer they are negligible because of the relatively few cases of gastric polyps.

Pathologic Anatomy of Carcinoma of the Stomach.—About 50 to 60 per cent of all carcinomas of the stomach occur in the pyloric region of the stomach. Of the remainder, the lesser and greater curvatures constitute the two most common sites. The classification of carcinomas of the stomach is a difficult problem. General agreement exists, if one liberalizes the terminology that is used, but very few papers or textbooks agree on a specific classification. This is a source of considerable confusion to the student, who, being unable to analyze the terminology critically, reaches the conclusion that there must be a wide divergence of opinion with regard to the types of gastric carcinomas. As a matter of fact, the opinion is rather uniform. Microscopically, gastric carcinomas are adenocarcinomas. This helps little as far as classification is concerned, and, hence, most workers have attempted to classify gastric carcinomas on the basis of gross appearance. This seems to be the most sensible method of approach, and certainly from the standpoint of prognosis following resection there seems to be a greater degree of correlation with the gross appearance than with the microscopic. Clinical grading as advocated by Borrman[55] appears to hold considerable promise. This is based upon the extensiveness of the lesion from a macroscopic standpoint.

The first important type of carcinoma of the stomach based upon the gross appearance is the *polypoid* type. This is also commonly referred to as a fungating or papillary type. The lesion projects into the lumen of the stomach as a relatively broad, pedunculated, funguslike mass. The tumors may vary in size from a few centimeters to a large mass almost filling the entire stomach. The external surface is often ulcerated and portions of the tumor are sloughed out. This is the source of hemorrhage from such a tumor. As a rule, the tissue is pinkish-gray in color, soft, and quite friable. In the smaller lesions, invasion may not have occurred through the entire wall of the stomach and, hence, if metastasis has not occurred, resection can lead to a cure.

The second type is the *ulcerative* type. This may begin primarily as an ulcerative lesion or it may be the result of the ulceration of a polypoid lesion. It may also represent a superimposed carcinoma upon a peptic ulcer. In any event, the ulceration which results from any of the three may not be distinguishable one from another. As a rule the ulceration is usually more than 3 cm. in diameter. It is an elevated plateaulike lesion with a central ulceration. The margins may be scalloped

and overhang the surrounding mucous membrane like a pouting lower lip, but often the margins are elevated due to submucosal invasion of neoplastic tissue. The tumor tissue is usually pinkish-gray, granular, firm, and friable, and on section the muscle coat of the gastric wall is frequently obscure or interrupted as a result of replacement by the tumor tissue. Glistening areas are frequently scattered throughout the dull, granular tumor due to localized areas of mucin-secreting cells.

Fig. 679.

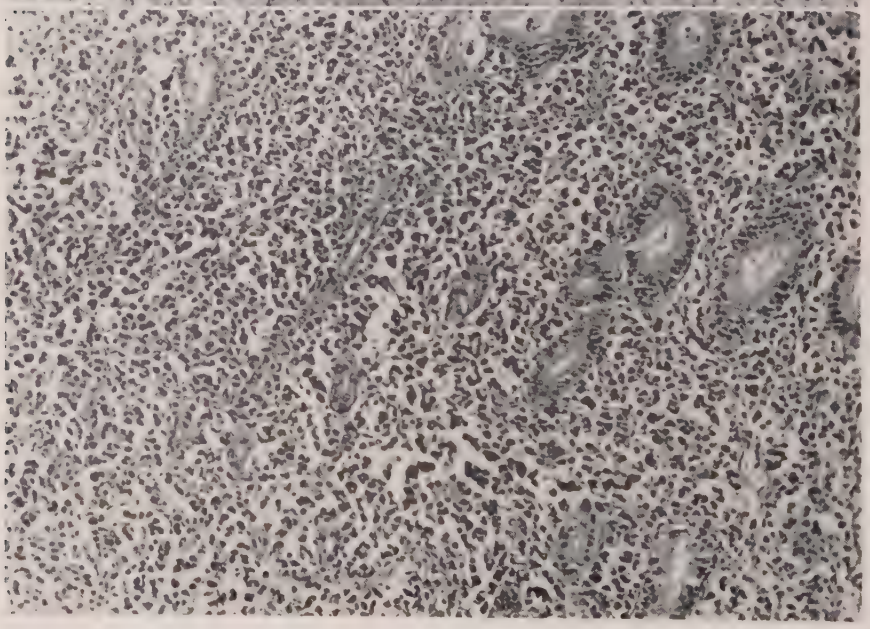


Fig. 680.

Fig. 679.—Base of peptic ulcer in stomach. Fibrinopurulent exudate resting on chronically inflamed granulation tissue.

Fig. 680.—Lymphosarcoma of the stomach. Diffuse infiltration of lymphocytes between the mucosal glands.

The third is the *diffuse* or spreading type. This may be localized to a relatively small portion of the stomach, or it may involve almost the entire stomach. The localized variety is the more common. Here we see a portion of the stomach wall, particularly the pyloric region, in which the mucosal folds are flattened out so that normal markings of the stomach are no longer present. The wall may measure

Fig. 681.

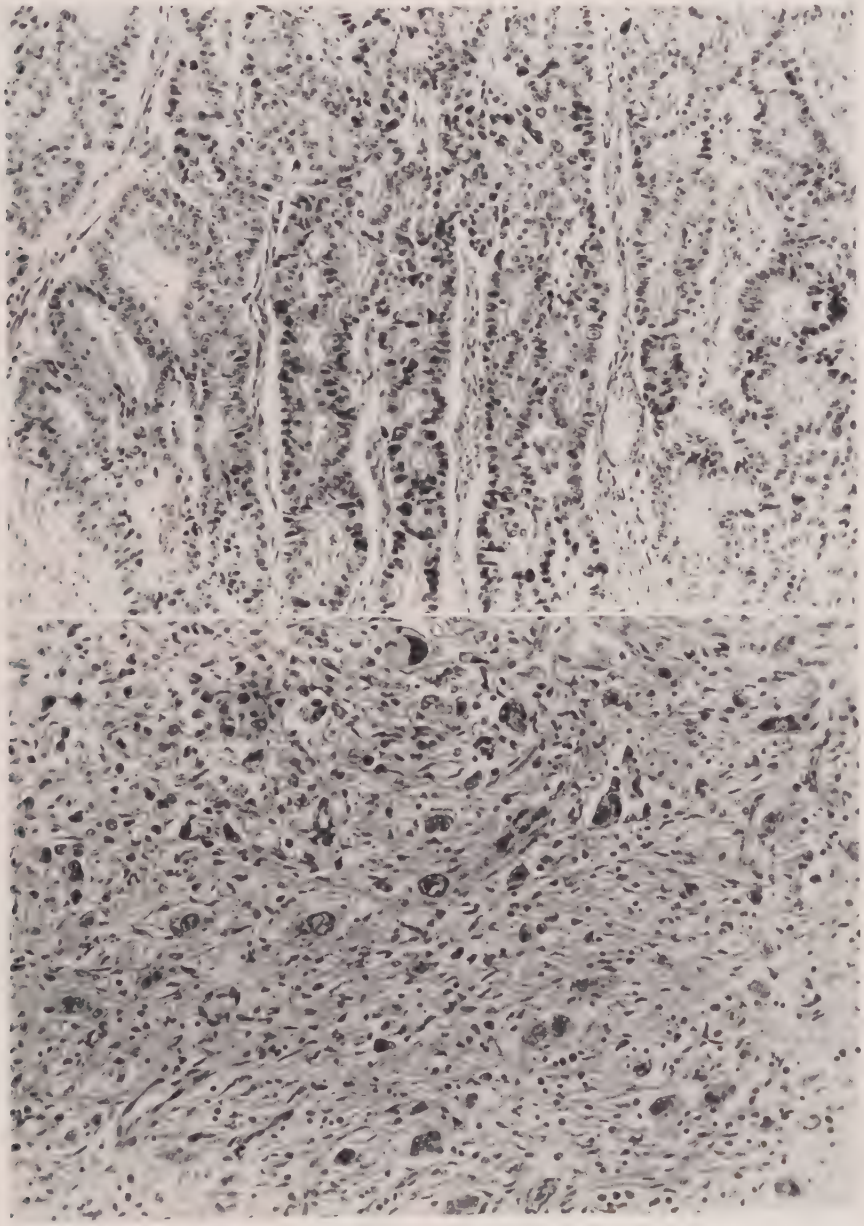


Fig. 682.

Fig. 681.—Adenocarcinoma of the stomach. Irregular acini and solid masses of neoplastic cells invading the wall.

Fig. 682.—Diffuse carcinoma of the stomach. Hyperchromatic, pleomorphic tumor cells are scattered through a dense supporting stroma.

about three to four times the thickness of a normal stomach. On section the muscle coat is still preserved, although glistening gray strands of tissue infiltrate it and cause it to be much thicker than normal. The same type of tissue is found in the serosa and presents gray streaks or diffuse grayish accumulations of tissue beneath the surface. When the entire stomach is involved, the condition is often referred to as a linitis plastica, or the so-called "leather bottle" stomach. In this event the lumen of the stomach has been reduced to a rather small caliber and the walls are rigid.

The fourth type of carcinoma is the *mixed* type, which represents about one-half of all carcinomas of the stomach. In this type, one sees various mixtures of the three types previously described.

Microscopic examination of the more cellular tumors shows the usual acinus-forming epithelial neoplasm. In the non-mucin-secreting types the cells are usually quite hyperchromatic and produce acini of various sizes and shapes. Not infrequently, papillations are formed. Areas of solid sheets of cells are frequently seen. Some tumors show many mucin-secreting cells. In this event, goblet cells are noted and frequently large spaces are formed, filled with mucinous material, the wall of which shows only a few remaining tumor cells, or remnants of tumor cells are present in the center of the mucinous masses. These types of tumors are frequently referred to as "colloid" carcinomas, a bad term since it bears no relationship to colloid as we know it in the thyroid gland. The diffuse type is often referred to as the scirrhous type because of the large quantity of connective tissue stroma. In many cases almost all of the tumor is composed of supporting tissue. The carcinoma cells are scattered throughout this stroma as single cells, as small irregular groups, as solid cordlike structures, or occasionally as small acini. Sometimes it is very difficult to find tumor cells.

Complications.—The complications of gastric carcinoma are numerous. Obstruction is a frequent complication, most commonly of the pyloric end of the stomach, but the cardiac end may also be obstructed. Vomiting, dehydration, weight loss, and alkalosis are the direct results of obstruction. When the cardiac end is involved, the esophageal opening is invaded, the symptoms and signs of esophageal carcinoma are present and may be erroneously diagnosed even after biopsy.

Perforation of the stomach may lead to fatal peritonitis. In other instances the stomach may become attached to contiguous organs such as liver, pancreas, or colon, and perforation may be prevented. Deep carcinomatous excavations are not infrequently seen in the pancreas and in the liver. When perforation occurs through a point of attachment between stomach and colon, a gastrocolic fistula is established which initiates a very characteristic clinical picture of extreme weight loss, diarrhea, and undigested food in the stool. Hemorrhage is another important complication. Bleeding in small amounts probably occurs in practically every carcinoma. A massive hemorrhage occurs when larger blood vessels are eroded. A small carcinoma of the stomach with metastasis to the liver producing an enlarged nodular liver may, with massive hemorrhage, simulate a cirrhotic liver with ruptured esophageal varices.

Anemia which appears in cancer of the stomach is due to a combination of nutritional disturbances and hemorrhage. Occasionally a patient with carcinoma of the stomach develops a macrocytic anemia instead of the normocytic anemia which usually results from hemorrhage. Whether this is due to the lack of intrinsic factor being formed by the stomach, or whether it is due to pernicious anemia in a patient who has carcinoma of the stomach, has not been well established.

Spread.—Metastases from carcinoma of the stomach are extremely common. The spread of carcinoma to other parts of the body may take place from the stomach in a variety of ways. Invasion of the subserous lymphatics producing a mosaic pattern which can be recognized as gray streaks beneath the subserosa is relatively common. Metastases to the regional lymph nodes, particularly along the lesser curvature, to the nodes in the gastrohepatic omentum and to the periaortic lymph nodes are frequently observed. Gastric carcinomas occasionally metastasize to the left supraclavicular lymph nodes by way of the thoracic duct. These are known as Virchow's nodes and for many years were thought to be pathognomonic of gastric carcinoma. However, carcinomas in the lungs, bowel, pancreas, ovaries, or testes may metastasize to these lymph nodes.

When the external surface of the stomach is involved, carcinoma cells may be set free in the peritoneal cavity. These may attach themselves in any portion of the peritoneal cavity, producing a peritoneal carcinomatosis. Occasionally they settle in the lower portions of the

cul-de-sac and produce a firm, shelf-like structure at the reflection of the peritoneum. A rectal examination often reveals this lesion and it may be thought to be a primary carcinoma of the rectum. This condition is referred to as a rectal shelf. When the carcinoma cells gain access to the ovary, they produce either unilateral or bilateral enlargement of these organs, referred to as Krukenberg's tumor of the ovary.

Blood stream metastases commonly occur to the liver through the portal vein. Metastatic lesions of the lung and the bones are less commonly seen.

Malignant neoplasms of the stomach other than carcinoma are very rare. The most common is the malignant lymphoma. Although a few cases have been reported in which the lesion seems to have been localized in the stomach, as a general rule the stomach involvement is merely a part of a general systemic disease. The involvement is characterized by pale gray submucosal infiltrations which elevate the mucosa sufficiently to iron out the gastric folds. Multiple lesions are usually present and they may vary from a few centimeters to large plaques measuring as much as 15 cm. in diameter. The tissue is soft, gray, friable, and the cut surface shows the usual monotonous appearance of lymphoid neoplasms. A few cases of Hodgkin's disease have been described. Both leiomyosarcoma and fibrosarcoma have been described. Their differentiation rests upon minute histologic study.

Benign Gastric Neoplasms.—Benign tumors of the stomach are uncommon. The *leiomyoma* is one of the most common. It arises from the muscle coat and may be located any place in the stomach. It is a submucosal mass which protrudes into the lumen of the stomach, causing thinning out of the mucous membrane, frequently resulting in erosion and hemorrhage. The tumor is firm, rubbery, and its cut surface usually shows bulging, interlacing bundles of grayish-white tissue. *Lipomas* are occasionally seen. These are located in the submucosa as encapsulated masses of fat tissue. *Adenomatous polyps* are likewise unusual. These may be either single or multiple lesions and when multiple, the condition is known as gastric polyposis. The single lesions are usually rounded, pedunculated masses of pinkish-gray tissue which may have a rather long pedicle. Microscopically, they show rather well-differentiated gastric mucosa with some tendency to papillary formation. Invasion at the base is not observed, but sometimes it is a difficult decision to make as to whether these are benign or early polypoid gastric carcinomas. In multiple lesions the polypi may be present for years and often cause great distress to the patient, because several may be located near the pylorus and produce a ball valve obstruction with resulting pylorospasm, pain, and vomiting. These, likewise, have a tendency to become malignant. Other neoplasms which have been described in the stomach, but which are extremely rare, are fibromas, hemangiomas, neurofibromas, and lymphangiomas. Occasionally accessory pancreatic tissue in the gastric mucosa or submucosa may simulate a benign tumor.

Foreign Bodies in the Stomach

Many types of foreign bodies, such as needles, pins, screws, tacks, nails, marbles, coins, buttons, and portions of toys, etc., may be accidentally swallowed, particularly by children. Mentally deranged individuals may swallow enormous numbers of such bizarre things as spoons, nails, and razor blades. In most instances small foreign bodies are passed per anus, but the sharper varieties may cause laceration of the mucous membrane, or even perforation.

Bezoars are foreign bodies which form in the stomach as a result of the conglomeration of small amounts of ingested material. The word bezoar is derived from a Persian word which means "against poison" because some Orientals recover hair balls from stomachs of animals and use them as an antidote against poison. They are of several varieties. The trichobezoar is composed of hair. Most of these are seen in stomachs of nervous youngsters or insane persons. This type of bezoar may weigh as much as 3,000 grams, and may form a cast of the entire stomach including the duodenal cap. The heaviness is apparently due to the fluid caught in the meshes of the closely packed hair, since after a few weeks of drying the entire hair ball loses about 90 per cent of its weight. Phytobezoars are composed of the vegetable fibers and commonly are due to fibers from persimmons, although other fruits and vegetables of high fiber content may be responsible. Bezoars may cause ulceration of the gastric mucosa. Shellac may also produce a foreign body. Gallstones are occasionally seen in the stomach as a result of a cholecystogastric fistula.

Gastric Hemorrhage

A few of the more common causes of gastric hemorrhage are as follows: peptic ulcer, gastric carcinoma, acute esophagitis, acute gastritis, rupture of the esophageal varices as a result of portal obstruction, hemorrhagic diseases of the newborn, primary or secondary thrombocytopenic purpura and other related blood dyscrasias, jaundice, and ulceration of benign tumors of the stomach such as adenomatous polyps.

Unexplained gastric hemorrhage, sometimes of fatal proportion, may occur. Various reports have indicated that 7 to 42 per cent of cases presenting gastric hemorrhage, clinically, have no demonstrable cause. In a few of these cases autopsy still fails to reveal the underlying lesion. When blood remains in the stomach, it turns a brownish color as a result of the formation of methemoglobin by the hydrochloric acid, and when vomited has the appearance of coffee grounds. If the hydrochloric acid content is low, or if vomiting occurs soon after the hemorrhage, the blood is bright red in color.

Gastric Obstruction

A few of the more common causes of gastric obstruction are as follows: gastric carcinoma, peptic ulcer, a pedunculated benign or malignant tumor near the pyloric valve, foreign bodies in the stomach, pressure from an extragastric mass, congenital hypertrophic pyloric stenosis, a congenital mucosal fold of the pylorus, and congenital duodenal atresia. As a result of partial obstruction of the pyloric valve there may be increased thickness in the wall of the stomach due to muscle hypertrophy. Later, with complete obstruction, the lumen might become quite widely dilated.

Postmortem Changes

These are very common in the stomach, as well as in the remainder of the digestive tract. These changes make it almost impossible to obtain good postmortem material for histologic study. The mucosa, particularly in the cardiac end of the stomach, may be partially digested and often shows a brownish or greenish discoloration. Perforation may even occur, and can be differentiated from antemortem perforation on the basis of lack of inflammatory response. Following death, immediate instillation of 10 per cent formalin into the stomach by a gastric lavage is the best way of preserving gastric mucosa. Even then it is quite possible that some of these changes may have occurred in the agonal state.

Retrograde Changes

No doubt the stomach is subject to all of the retrograde changes that other organs have, but most of these changes are difficult to demonstrate, and their importance cannot be properly evaluated. Atrophy is the most common one and is frequently seen in severe anemias, particularly of the Addisonian type. Here the gastric mucosal folds are more or less ironed out and the mucosa is much thinner than normal. Microscopically, the glands are decreased in number and smaller than normal with an absence of the parietal or acid-forming cells.

Acute Dilatation of the Stomach

This is a rare but serious condition which comes on suddenly and is associated with the vomiting of large quantities of fluid. The stomach is enormously dilated, thin walled, and filled with large quantities of watery fluid. This condition usually follows abdominal operation, but may occur in the course of any severe disease or even during convalescence. Its cause is probably neurogenic atony.

THE INTESTINAL TRACT

Congenital Malformations

Except for Meckel's diverticulum, anomalies of the intestinal tract are uncommon. The intestinal tract may be partly or entirely absent. Incomplete rotation of the colon may result in the cecum coming to rest on the left side of the upper abdomen or below the liver. This places the appendix in an unusual location and creates great difficulties in diagnosis. The appendix may be aplastic or even completely absent. Duplications are rare developmental anomalies usually occurring along the small bowel and composed of all the layers of the intestinal wall. They lie within the layers of the mesentery as a tube or pouch of variable size, which may or may not communicate with the true lumen. The condition probably is caused by faulty recanalization of the gut in embryonic life. Occurring most often in infancy and childhood, symptoms result from ulceration or obstruction and usually require surgical intervention. Atresias of the intestine occur as a result of failure in the canalization of the digestive tube, which at one time during embryonic life is represented by a solid cord of cells. They may occur any place in the intestinal tract, but are observed usually in the second portion of the duodenum and in the lower ileum. The intestine above the point of obstruction is dilated and often thick walled because of muscular hypertrophy. The intestine below is collapsed and cordlike, and often so small that one must search carefully to find the lumen. When an atresia of the lower portion of the colon occurs, it is called an imperforate anus. The skin over the anal region may be smooth and intact, or it may show a dimple, or a shallow sinus tract extending upward for a considerable distance into the pelvis. Atresia of the rectum may occur at any level from the rectosigmoid junction to the anus. Sometimes due to failure in the formation of the cloacal membrane there may also be fistulous tracts connecting the rectum and bladder or vagina in the female, and the rectum and bladder or urethra in the male.

Diverticula

Meckel's Diverticulum.—This is a congenital anomaly which represents a persistence of the omphalo-enteric duct. In adults it is located in the ileum about 3 feet above the ileocecal valve, and in children it is about 1½ feet above the ileocecal valve. It is an outpouching which measures from 2 to 8 cm. in length and at its base is only slightly smaller than the lumen of the intestine from which it arises. It usually ends in a blind pouch

and presents a perfectly smooth external surface. In some instances the entire duct may be persistent and a fistulous tract is present between the intestine and the umbilicus. In other instances there may be a cordlike structure which attaches the apex of the diverticulum to the peritoneum in the region of the umbilicus. This may lead to a volvulus. Histologically, the wall shows the same structure as the intestine, but, in addition, islands of gastric mucosa are found in 25 to 35 per cent of the cases. As a result, typical peptic ulcers may form, leading to hemorrhage and perforation. Islands of pancreatic tissue also may be embedded in the wall. Occasionally, the outpocketing becomes diffusely inflamed and the condition is known as diverticulitis. On other occasions there may be an invagination of the diverticulum producing intussusception with bowel obstruction. Stagnation of fecal content in the diverticulum is unusual because the stoma is usually large enough to allow it to empty readily.

Diverticula of the Duodenum.—These may be acquired or congenital. The acquired diverticula apparently occur as a result of healed duodenal ulcers. Congenital types are usually located in the second portion of the duodenum medially, and extend toward the pancreas. The absence of the muscle coat in their walls suggests a process similar to that responsible for diverticulosis of the remainder of the small bowel and colon. Although they are subject to inflammation, duodenal diverticula rarely give rise to symptoms and are most commonly discovered incidentally during x-ray examination of the stomach and duodenum.

Diverticula of the Small Intestine.—These are located largely in the jejunum and ileum. They may number only a few or may occur in profusion. They may vary in size from a few millimeters to several centimeters in diameter. Etiologically, the diverticula are acquired as a result of a weakened area in the bowel wall where the blood vessels and nerves perforate the muscle coat. Hence, the site of formation is typically at the junction of the mesentery and the bowel. In the smaller lesions a vessel can always be seen leading to the apex of the diverticulum. The stoma is relatively large, producing rather free communication with the lumen. Such diverticula rarely cause trouble and are usually found incidentally on x-ray examination or at postmortem.

Fig. 683.—Diverticulosis of the small intestine. The diverticula are located at the mesenteric border and have large stomas.

Diverticula of the Colon.—This is the most common and most important of the diverticula of the bowel. It occurs in about 6 per cent of all patients over 50 years of age and is more common in males than in females. There is some controversy about the cause, but again it is thought that the herniation of the mucosa is permitted as a result of weakness of

the wall created by perforation of blood vessels. The majority on microscopic examination consist of only serosa and mucosa, but in some instances remnants of the muscle coat are present. Such diverticula are rarely found in the rectum but may occur in any portion of the colon, especially the sigmoid colon or in the sigmoid and descending colon. In contrast to small bowel diverticula, these occur at any point around the circumference of the bowel except through the taenia coli. They may even extend into the appendices epiploicae. The diverticula vary in size from 1 to 2 mm. to about 1 cm. They never reach the large size seen in the small bowel. The communication between the diverticulum and the lumen of the bowel is usually much smaller than the diameter of the diverticulum, which leads to the accumulation of fecal material within the diverticulum. Inspissated, rounded, fecal masses are commonly seen in colon diverticula and are responsible for diverticulitis, a not infrequent complication. Perforation may occur with the production of a generalized peritonitis or a pericolonic abscess. Occasionally an abscess may rupture into the bladder, producing a vesicorectal fistula. Repeated episodes of diverticulitis may give rise to multiple small pericolonic abscesses with marked pericolonic fibrosis resulting in stricture formation.

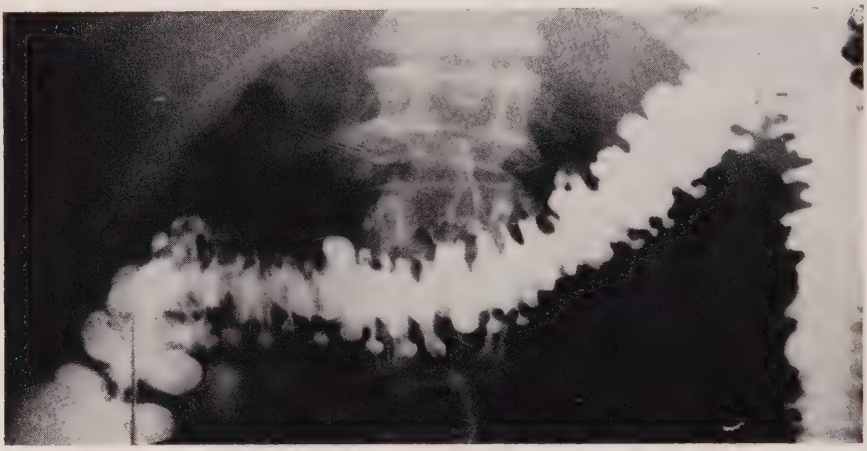


Fig. 684.—X-ray of diverticulosis of colon. The diverticula are small and the stomas are narrow. (Courtesy Drs. Howard Hunt and Ralph Moore.)

Fig. 685.—Diverticulosis of the sigmoid. The diverticula are small with narrow necks.

Primary Megacolon

(Hirschsprung's Disease)

This is a condition in which there is marked dilation and hypertrophy of the wall of the sigmoid colon which at times involves the entire colon. Primary megacolon is a very rare condition which has been observed in all ages from a fetus of 7 months to a patient of 80 years. The majority of cases are children, 1 to 3 years of age. Males are affected more often than females. The etiology is not known, but mechanical causes, inflammatory lesions, and functional derangements of the nervous system have been advanced as contributing factors. The current view is that the musculature at the rectosigmoid junction fails to relax as a result of underactivity of the parasympathetic or hyperactivity of the sympathetic nervous system. Achalasia is the term applied to the unrelaxed state of the musculature. This prevents defecation with a resulting large accumulation of feces in the sigmoid colon. Grossly, in the usual case, the sigmoid colon alone is involved, and is sharply demarcated from the rectum below and the remainder of the colon above. The colon may measure as much as 37 cm. in diameter, and in Lane's[89a] case the colon with its content weighed 54 pounds. Thickening of the mesentery is usually observed and the wall of the involved portion of the bowel is leathery to touch. The mucous membrane is edematous and the folds are sometimes much more prominent than normal. Stercoral ulcers of the mucous membrane frequently develop. The microscopic findings are those of a nonspecific chronic inflammation. The most common complications are volvulus and fecal impaction. The mortality in children is very high, but when the disease occurs in adults, the prognosis is quite good.

Idiopathic Steatorrhea

(Celiac Disease)

This is a nonpancreatic steatorrhea characterized by large, pale, flatulent, foul-smelling stools. When occurring in children it is known as Gee-Herter's disease, and when affecting adults it is referred to as nontropical sprue. Its onset in children is from 1 to 2 years of age. There are no characteristic pathologic changes except those associated with nutritional disturbances, macrocytic anemia, deficient calcium absorption, and avitaminosis. An assay of the enzyme content of the duodenum reveals normal enzymes. This is the distinguishing feature between idiopathic steatorrhea and fibrocystic disease of the pancreas, and others in which there is decreased pancreatic secretion into the duodenum. In nontropical sprue, *Candida albicans* has been repeatedly isolated from the stool but it is not thought to be etiological. **Fibrocystic disease of the pancreas** is a disease of the newborn characterized clinically by steatorrhea similar to that of celiac disease. In this condition, however, there is a deficiency of duodenal enzymes with resulting failure in the digestion of fat. The essential lesion is that of the pancreas where fibrosis and ductal obstruction are present, resulting in the formation of cysts (see page 850).

Intestinal carbohydrate dyspepsia (near-celiac disease) is a condition which should not be confused with celiac disease. The syndrome occurs in children older than 2 years, and is characterized clinically by marked abdominal distention, wasting, and diarrhea, with the passage of voluminous gassy stools. The cause is actually low duodenal amylase which results in an idiosyncrasy to incompletely digested starch.

Tropical Sprue

Tropical sprue is a disease usually occurring in white adults living in the tropics but which may occur in temperate zones. It is characterized by intestinal disorders, mental changes, and usually a macrocytic anemia. The mucosa of the entire gastrointestinal tract may show atrophy and chronic inflammation. Faulty absorption of fats and carbohydrates produces bulky, fatty, foul stools. In the chronic form great emaciation may be present.

Intestinal Obstruction

Intestinal obstruction is a condition in which there is interference with passage of the intestinal contents through the lumen of the bowel.

Causes of Intestinal Obstruction

Perhaps the best classification as to cause of intestinal obstruction is that given by Wangensteen[114] (1937):

I. Mechanical obstruction
  A. Due to narrowing of the lumen
    1. Strictures
      a. Congenital — Atresias, imperforations, inflammation, trauma, neoplasms
      b. Acquired
    2. Obturation
      a. Gallstones
      b. Fecaliths
      c. Foreign bodies
      d. Worms
    3. Compression from without
  B. Due to obstruction, adhesions, or bands
    1. Congenital
    2. Inflammatory
    3. Traumatic
    4. Neoplastic
  C. Due to hernia
  D. Due to volvulus
  E. Due to intussusception
  F. Due to developmental errors
II. Obstruction due to nervous imbalance
  A. Inhibition ileus (adynamic, paralytic)
  B. Spastic ileus (dynamic)
III. Vascular obstruction
  A. Thrombosis
  B. Embolism

The incidence of causes for intestinal obstruction varies from series to series,

depending upon the type of group surveyed. Obstruction in older age groups is likely to include a large percentage of neoplasms. Obstruction in a younger age group is likely to include a large percentage of intussusception. Table IX, as compiled by Tumen,[112] shows the incidence of the various causes of intestinal obstruction as reported by three observers.

TABLE IX

CAUSE	MC IVER[101] (%)	SOUTTAR[108] (%)	VICK[113] (%)
Hernia	44	46	47
Adhesions	30	18	18
Neoplasms	10	11	13
Intussusception	5	21	15
Volvulus	4	2	2.5
Mesenteric thrombosis	3		
Other causes	4		
Gallstones		1	1

Although there was considerable variation in the incidence of causes, this survey shows that in each of the series the leading causes for obstruction were hernias, adhesions, neoplasms, and intussusception.

Hernia.—Hernia may be defined as the protrusion of a viscus or its coverings through the walls of the cavity which normally enclose it. Hernias may be found in any of the body cavities, including the abdominal, thoracic, and cranial.

The great majority of the hernias are abdominal hernias. These may be grouped into two types, external and internal. In the external group, inguinal hernias are the most commonly encountered. These may be of either the indirect or direct type. In the indirect type the herniation occurs along the course of the spermatic cord and follows the inguinal canal into the scrotum. In the direct type the herniation occurs through Hesselbach's triangle and the herniated mass protrudes into the scrotum. Rarer forms of external abdominal hernias are the femoral, perineal, umbilical, and ventral types.

External hernias are caused by two factors: (1) congenital weakness of the abdominal wall, and (2) increased intra-abdominal pressure. Weaknesses in the abdominal wall may be produced by congenital defects, such as failure of obliteration of extensions of peritoneum, which form saclike structures during the development of abdominal organs. Persistence, potential or real, of the pouch of peritoneum which is carried into the scrotum with the descent of the testes is an example of this. Weaknesses in the abdominal wall may be acquired through traumatic injuries or through operative procedures. These weak areas, when acted upon by excess intra-abdominal pressure, often produced by straining or lifting, cause the abdominal viscera to protrude through the wall of the abdominal cavity.

In many instances the mass of tissue which protrudes through the abdominal wall may be pushed back into the cavity; such a hernia is called a reducible hernia. In other instances the hernia may be held in the hernial sac so that it cannot be replaced in the abdominal cavity. This is most commonly due to chronic inflammation which produces adhesions that hold the herniated mass in the interior of the sac. Such a hernia is called an irreducible hernia. In other cases the passage of intestinal contents through the lumen of the bowel may be obstructed, an incarcerated hernia. Finally, the loops of intestine may become compressed by the ringlike opening in the abdominal wall, and obstruction to venous blood flow may occur. Such venous stasis may produce edema of the bowel wall, causing further compression of the intestine in the hernial ring. This produces further obstruction to the blood flow, leading to further edema and swelling and eventually to obstruction of the arterial blood flow to the intestine. Infarction of the intestinal wall then occurs; necrosis may lead to perforation or to spread of infection into the hernial sac, a complication associated with a high mortality. A hernia deprived of its blood supply in this manner is said to be strangulated. With the incarcerated or strangulated hernia, intestinal obstruction occurs and all the signs of this disease are present.

Internal hernias are those which occur within the body cavities. One type is the diaphragmatic hernia in which the abdominal viscera protrude through the diaphragm into the pleural cavities. In some cases these are congenital; in other cases they are acquired and in this instance they are usually due to trauma. The most common form of diaphragmatic hernia occurs about the esophagus. One type is associated with a congenitally short esophagus which causes a portion of the cardia of the stomach to be pulled into the thoracic cavity. A second type is associated with loosening or weakness of the musculature of the diaphragm as it extends about the esophagus. Herniation may also occur about the great vessels as they penetrate the diaphragm. Internal hernias also are found in the retroperitoneal areas of the abdominal cavity, occurring at the junction of the duodenum with the jejunum, about the cecum, about the sigmoid, in the supravesical area, and about the broad ligaments.

Adhesions.—Adhesions are another great cause of intestinal obstruction. They may be classified into congenital, inflammatory, and neoplastic adhesions.

The stage is set for intestinal obstruction when a band or cordlike adhesion extends from one peritoneal surface to another, as between two loops of intestine or between the intestine and the omentum. Under such circumstances loops of intestine may become kinked by, or compressed behind, a fibrous band in such a way that the lumen may be occluded. In many instances, the vascular supply is also occluded because of compression from edema and swelling, much as in the case of the strangulated hernia. In this case the wall of the gut undergoes infarction, with all of the changes described in that condition. The intestine above the point of obstruction is dilated and that below the point of obstruction is collapsed. Such obstructions usually occur in the small intestines because of the greater mobility of this portion of the intestinal tract.

Neoplasms.—Intestinal obstruction due to neoplasms is usually found in the older age groups. The obstruction is produced in the majority of instances by infiltration of the neoplastic tissue into the wall of the gut with complete or almost complete encirclement. This leads to constriction and stenosis of the bowel with complete or partial obstruction of the lumen. Since primary tumors of the small intestine are rare, this type of lesion does not account for a large percentage of obstructions in the small bowel. The most usual site is in the sigmoid colon and rectum where the infiltrating types of carcinomas are found. Secondary neoplasms of the intestines or peritoneum may produce obstruction but are more rare in this role than the primary neoplasms.

Intussusception.—Intussusception is the telescoping of one portion of intestine into the portion ahead. This is most frequently found in children. In a series of cases analyzed by Fitzwilliams[95] it was found that 71 per cent of the cases occurred in infants of less than 1 year. In Perrin and Lindsay's[104] survey, 78.5 per cent occurred before the age of 2 years. The disease, however, does occur in adults, where it is usually associated with some pathologic lesion in the intestinal wall.

The most common locations of the intussusception are in the region of the ileocecal valve, and in the small intestine. The less frequently involved sites are the colon and the cecum. In the region of the ileocecal valve, the ileum may be invaginated into the colon and the ileocecal valve may remain in essentially its normal position, or the ileum may be invaginated into the colon and carry along with it a portion of the colon itself. In this latter case the head of the intussusception is formed by the ileocecal valve.

Fig. 686.—Intussusception of the small intestine. Hemorrhage of the mucosa with bleeding into the bowel.

In children the etiology of intussusception is obscure but it has been attributed to imbalance of intestinal muscular contraction, to the presence of lymphoid tissue about the ileum and the region of the cecum, and to the varying directions of peristaltic waves in the region of the ileum and cecum where the antiperistalsis of the colon meets the peristalsis of the ileum. In adults the condition is associated with a pedunculated lesion, often a neoplasm, which protrudes into the lumen of the intestines. This apparently is caught by the peristaltic waves and in the attempt of the intestine to move the mass along the intestinal lumen, a portion of the gut is pulled into the lumen ahead.

The gross appearance of the intussusception is quite characteristic. The seg-

ment of gut which is telescoped into the lumen of the intestine is called the intussusceptum. The portion of gut which forms the sheath for the intussusceptum is called the intussuscipiens. The mesentery of the intussusceptum is pulled along into the gut as the apex of the intussusceptum is carried forward. At the point where the mesentery enters into the intussuscipiens it is compressed, and consequently there may be vascular occlusion with edema, congestion, necrosis, ulceration of the surface, and eventually strangulation of the portion of gut invaginated. The portion then becomes dark red and hemorrhagic in appearance. The wall is thickened and filled with blood. In some cases necrosis permits the intussusceptum to drop off in the lumen of the gut.

These lesions may lead to complete or incomplete intestinal obstruction. They characteristically produce pain, vomiting, and the passage of blood and mucus in the stool. The examination of the abdomen may not be associated with much tenderness but usually an abdominal mass can be palpated.

The mortality from intussusception depends upon the duration of the condition. Ladd and Cutler[97] reported a mortality of less than 10 per cent in patients operated upon less than twelve hours after the onset of symptoms, whereas in those operated on later than seventy-two hours after the onset, the mortality was 60 per cent.

Postmortem Intussusception.—Postmortem intussusception commonly occurs in the small intestine of children. The invaginations may be multiple. They are unassociated with inflammatory reaction or circulatory disturbances in the invaginated gut and may be distinguished in this manner from the antemortem intussusception.

Volvulus of the Intestine.—Volvulus is a twisting of the intestine on its mesentery, the twist varying from 180 through 360 degrees or more. Volvulus occurs most frequently in the sigmoid portion of colon, next most frequently in the small intestine, and more rarely about the cecum and in other portions of the intestine. According to Braun,[114a] the incidence of the disease in these various locations is 54 per cent, 30 per cent, and 7 per cent, respectively.

A long mesentery, coupled with approximation of the two limbs of the loop, is a predisposing factor for volvulus of the sigmoid. This is thought to be the result of a congenital defect by some authorities and by others it is considered to be the result of chronic constipation. Chronic constipation is common in persons who develop volvulus of the sigmoid. Unequal weight of fecal masses in the two limbs of the redundant sigmoid and pressure on the outside such as may occur from a tumor mass are immediate factors in causing volvulus.

In volvulus of the small intestine, congenital defects, particularly with long mesenteries, are commonly found. The condition may also result from tumors of the gut wall or of the mesentery. The lowermost portion of the ileum is the segment of intestine most frequently involved. Volvulus of the small intestine may occur in the walls of hernial sacs.

In volvulus of both the cecum and small intestine the degree of twisting and the tightness of the twist are factors which govern the appearance of the bowel. In cases where the blood vessels are compressed, the wall of the bowel very quickly undergoes congestion and distention. The pressure of the distention may complete the occlusion of the blood vessels in the twisted loop, and infarction and gangrene may occur. Rupture and peritonitis as a result of gangrene may occur. The loop of bowel is commonly filled with bloody fluid.

The disease is more common in men than in women in a relation of 3 or 4 to 1. The mortality depends upon the duration of the volvulus but in general is rather high. Various reports show the mortality to vary from 16 to 60 per cent.[102]

Obturation Obstruction.—Obturation obstruction is produced by plugging the lumen of the intestine by a foreign body. Many types of material, such as gallstones, intestinal parasites, fecaliths, enteroliths, bezoars, food boli, and miscellaneous objects such as buttons, glass, stones, etc., are described as producing this type of obstruction. In most cases, however, the obstruction is due to a gallstone. These may enter the intestinal tract either through the common bile duct or through a fistula between the gall bladder and the intestine, most commonly the duodenum. The stones may be large enough in themselves to produce obstruction, they may produce obstruction through spasm and irritation, or they may form a

nucleus about which other foreign material collects to produce obstruction. The condition is most commonly seen in elderly women.

Adynamic or Paralytic Ileus.—In this condition, intestinal obstruction occurs due to failure of the muscle to propel the contents properly. It occurs when muscular activity is inhibited or paralyzed.[103] Some of the causal factors are peritoneal irritation due to trauma, bacteria, or chemicals, extraperitoneal irritation due to hemorrhage, infection or diseases of the renal tract, vascular changes such as mesenteric thrombosis and strangulation of the intestine, and toxic factors such as those found in pneumonia, uremia, and systemic infection. Other causes appear to be neurogenous in origin.

In a mild form this is perhaps the most common type of intestinal obstruction which is observed clinically. It frequently follows laparotomies when the intestines are handled roughly, exposed to the air, or otherwise irritated. The intestines are distended with a mixture of gas and fluid. The wall is thin. The dilatation may be limited to a single loop of intestine or may involve almost the entire intestinal tract. Patients with this disease show distention of the abdomen, dull pain, absence of peristaltic sounds, and, on x-ray examination, multiple fluid layers in the intestinal tract. In extreme cases respiratory embarrassment may follow elevation of the diaphragms and compression of the lungs. In many cases, adynamic ileus may be associated with mechanical obstruction and in some instances mechanical obstructions too slight to produce complete obstruction by themselves may produce serious intestinal obstruction when combined with adynamic ileus. Thus, in acute peritonitis, fibrinous adhesions which ordinarily would be broken up by peristaltic movements may become effective in producing intestinal obstruction when there is severe adynamic ileus of the intestine above the fibrinous exudate.

Effects of Intestinal Obstruction

The effects of intestinal obstruction are complicated and not completely understood. They depend upon a variety of factors. The level of intestinal obstruction is of some importance. In general, high intestinal obstruction, that is, intestinal obstruction involving the jejunum or upper ileum, is more likely to cause death than low intestinal obstruction, that is, obstruction involving the colon, particularly the lower portions of the colon. The rate of obstruction is also of some importance. Intestinal obstruction which develops rapidly is more likely to produce serious effects than that which develops slowly.

In order to understand the pathologic effects of intestinal obstruction, it is necessary to study the anatomic changes in the intestinal wall in obstruction. In many cases there is interference, directly or indirectly, with the blood supply of the intestine. When the arterial supply is occluded, there may be ischemic necrosis of the bowel wall with ensuing gangrene. In the majority of instances, however, the interference is with the venous circulation, and under these circumstances there is marked congestion of the veins with hemorrhage and exudation of fluids, both into the wall and into the lumen of the bowel.

As the circulation and nutrition become impaired, infectious agents in the lumen invade the bowel wall and produce inflammatory changes. These lead to loss of the epithelial covering of the intestine and to accumulation of leukocytes in the wall of the gut. Extension of the infectious agents through the wall may lead to peritonitis, which in some cases remains localized and in other cases becomes generalized. In rather rare instances, the loop of bowel ruptures and there is a massive discharge of intestinal contents into the peritoneal cavity.

If the intestinal obstruction is in the upper portions of the alimentary tract, that is, in the duodenum or upper jejunum, the fluids which accumulate above the point of obstruction are relatively easily vomited and, consequently, distention is not an important factor. When the lower ileum or the large bowel is obstructed, however, distention of the bowel lumen becomes a prominent and important factor causing injury. The lumen of the bowel above the point of obstruction becomes markedly distended, often reaching a diameter two or three times that of the normal intestine. The lumen is distended by both gas and fluid. The fluid is derived from the blood and digestive juices; the gas is said to be generated by the activity of bacteria on the intestinal contents and by the swallowing of air. The fluid content in the fully developed case is usually bloody, foul smelling, and swarming with numerous bacteria.

Attempts to correlate the changes with symptoms and signs have led to several theories as to the cause of injury and death in intestinal obstruction. It has been proposed, particularly by Sperling and Wangensteen,[109] that the damaged bowel wall is more permeable to noxious agents and that absorption of these toxic products produces serious injury. Among things which have been proposed as toxic

substances are the secretions of the intestinal mucosa and digestive organs, autolyzed intestinal wall, partially digested material in the lumen of the gut and products of bacterial growth, particularly those of *Clostridium welchii.*

It has also been emphasized[106, 107] that loss of blood and fluid into the lumen and into the intestinal wall may be an important factor in the production of shock. This may be fatal in cases of intestinal obstruction. Likewise loss of plasma has been mentioned as a factor in causing shock. When the changes in the bowel wall are so severe that generalized peritonitis results, there is little question as to the mechanism of injury and the cause of death.

In high intestinal obstruction where distention and damage to the bowel wall may be at a minimum, injury to the body seems to be accomplished by additional means. In these instances the loss of electrolytes due to vomiting is a prominent factor in the causation of injury. There is a decrease in the blood chloride and sodium ions, and a rise in the blood nonprotein nitrogen. Prolongation of life in these circumstances has been made possible through the administration of sodium chloride and it has been proposed that it is particularly the sodium ion which is of great importance in producing this beneficial effect. In most cases of intestinal obstruction it is probable that injury and death are due to a combination of these many factors.

Occlusion of the Mesenteric Vessels

Because occlusion of the mesenteric vessels leads to paralysis of the muscular wall and presents symptoms and effects much like intestinal obstruction, this subject is considered with intestinal obstruction. Occlusion of the mesenteric vessels may involve either the artery or the vein.

Arterial occlusion is said to be more frequent, accounting for approximately 60 per cent of the cases in some series. Usually the superior mesenteric vessel is affected, and, consequently, the jejunum or upper ileum is the portion of the intestinal tract involved. The cause for the occlusion is usually embolism, although thrombosis, usually associated with an atherosclerotic plaque, is also causative. Venous occlusion occurs particularly following appendicitis, pelvic inflammation, and hernias.

Both arterial and venous occlusion of the mesenteric vessels lead to infarction of the intestine. The segment of infarction is often large, although it varies in length, depending upon the level at which the vessel is occluded and the degree of anastomotic circulation. Shortly after the occlusion of the vessel the bowel becomes a deep purple color due to congestion. There is hemorrhage into, and necrosis of, the bowel wall. Bacteria, which are present in the lumen of the intestine, invade the wall of the gut and produce changes in addition to those that are produced by the lack of blood supply. Peritonitis develops and the peritoneal cavity may contain bloody fluid. The lumen of the intestine is filled with foul-smelling bloody fluid. Paralysis of the muscular wall due to insufficient nutrition results in intestinal obstruction and further complicates the anatomic and clinical pictures.

Inflammatory Lesions of the Intestines

Tuberculosis of the Intestines

Two forms of intestinal tuberculosis are encountered. The first is primary intestinal tuberculosis in which tubercle bacilli gain entrance to the body by way of the intestinal tract following the ingestion of contaminated food. This is rare in the United States. The second is the most common form, and in this country almost the only form. It complicates pulmonary tuberculosis and, consequently, is referred to as secondary intestinal tuberculosis.

Primary Tuberculosis.—Primary intestinal tuberculosis occurs through the ingestion of infected foods which are almost invariably dairy products that carry the bovine type of tubercle bacillus. The disease exists in two forms, the hyperplastic and the ulcerative types.

Hyperplastic Type.—Most of the lesions appear in the region of the ileocecal valve. The lesion is usually localized. It involves the mucosa and submucosa and projects in a nodular, tumor-like fashion into the lumen of the gut producing obstruction. The regional lymph nodes are usually enlarged, and the lesion is not uncommonly mistaken for carcinoma.

Ulcerative Type.—This type of infection is likewise very rare in the United States. It occurs most commonly in children. The portal of entry is through the mucous membrane of the

ileum, where either a small ulcer or no gross lesion is found. The striking feature is marked enlargement and caseation of the mesenteric lymph nodes.

Secondary Tuberculosis.—Infection in secondary tuberculosis occurs as a complication of pulmonary tuberculosis with cavitation. In such cases, tubercle bacilli are present in the sputum, and the intestinal tract is infected through the swallowing of sputum. Because of this mode of infection, the human type of tubercle bacilli is causative in the great majority of cases. At autopsy, involvement of the intestine is present in from 50 to 80 per cent of cases of pulmonary tuberculosis.

Pathologic Anatomy.—The terminal ileum and cecum are most commonly involved. Here the Peyer's patches and the solitary lymph follicles are attacked, probably because the organisms are phagocytosed in these structures. From these sites spread may be in either direction up or down the intestinal tract. In rare cases the entire intestinal tract may be involved including the stomach and esophagus. The involved lymphoid structures first become enlarged and somewhat gray and translucent. Later, the areas become softer and more yellow as caseation occurs, and with softening there is sloughing and ulcer formation. The infection tends to spread by way of the lymphatics which encircle the gut; consequently, it is usual to find the ulcers running transversely about the intestine. However, ulcerations extending in the longitudinal axis of the intestine are by no means rare. The base of the ulcer is covered with necrotic material in the fully developed case, and the edge is slightly undermined and overhanging. In some cases gray tubercles may be found in the base of the ulcers. The margins are usually irregular. The size of the ulcer varies greatly. Sometimes complete encirclement of the gut is noted. Very characteristic is the appearance of the ulcer from the serosal surface where minute gray nodules extending along the course of lymphatics may be seen. Very often the diagnosis is more easily made from the serosal than from the mucosal surface. Microscopically, the base of the ulcer often shows a nonspecific inflammatory reaction due to the invasion of bacteria in the intestinal lumen. Deeper in the wall, however, and particularly beneath the serosa, there are typical tubercles with epithelioid cells, caseous necrosis, giant cells, and lymphocytes.

Among the complications, obstruction of the intestine may occur, although this is not common. In some cases this is due to constriction of the lumen by scar tissue, but in others it may be due to kinking of the intestine due to the formation of adhesions between two loops of bowel. Perforation may occur in the ileum or in the appendix. Hemorrhage from tuberculous ulcers is uncommon. Spread of infection from the tuberculous ulcers to the mesenteric lymph nodes occurs in approximately 50 per cent of the cases.

Tuberculous Fistula in Ano.—Fistulous tracts frequently develop in the region of the anus. These are thought to be due to infection in the crypts of Morgagni of the rectum, with penetration of the bowel wall and extension into the surrounding tissue. About 10 per cent of these, as seen in general practice, are tuberculous in nature. The remainder are probably pyogenic infections in which, in some cases, the reaction simulates tuberculosis because of the foreign-body giant-cell reaction which occurs as a result of the passage of fecal material through the fistulous tract.

Lymphogranuloma Venereum

Lymphogranuloma venereum is essentially a venereal disease which involves the rectum as a complication. The primary lesion in lymphogranuloma venereum involves the external genitalia of the male, and usually the cervix or vagina of the female. In the male the lymphatic drainage from the infected area is primarily to the inguinal lymph nodes, whereas in the female the perirectal and pelvic lymph nodes are primarily involved. The disease as it affects the colon, therefore, usually occurs in females. The perirectal fat tissue becomes secondarily involved, producing a variable degree of external constriction. This process usually ends abruptly at the junction of the sigmoid colon and rectum. Very often the degree of constriction is such that the lumen may measure no more than 1 cm. in diameter. The mucous membrane may be intact, but in other instances ulcerations are present from which sinus tracts extend into the perirectal tissues. In some instances also, fistulous tracts appear in the perineum. (See also page 291.)

Typhoid Fever

The general aspects of this disease have been discussed in the chapter on infectious diseases (page 219). In the intestinal tract, the important lesions are located in the lower portion of the ileum. From here they extend frequently into the cecum and occasionally they spread upward in the intestinal tract, sometimes to involve even the jejunum. The appendix is sometimes involved and may give rise to symptoms of acute appendicitis.

Early in the course of the disease the Peyer's patches and solitary lymph follicles of the ileum become hyperemic and hyperplastic. This change persists into the second week of the disease, at which time necrosis of the lymphoid tissue occurs giving the central portions of the involved structures a ragged, roughened, yellowish-gray appearance. Sometimes cracks and fissures appear which give the surface a convoluted appearance. The central necrotic tissue sloughs away, leaving an ulcer. The ulcers which involve the Peyer's patches take the outline of these structures, and are usually oval with the long axis extending parallel to that of the gut. Other ulcers, however, may extend transversely about the gut or may be distributed without reference to the axis of the intestine. The margins of the ulcer are elevated due to peripheral remnants of the swollen lymphoid structures. The base extends to the submucosa or muscularis and is covered by a varying amount of necrotic greenish-yellow material.

Microscopically, there is great stimulation of the reticulo-endothelial cells with the production

of large actively phagocytic macrophages. These cells infiltrate the lymphoid structures of the intestine in large numbers. Their presence produces vascular occlusion which contributes to the necrosis of the lymphoid structures. The cytoplasm of many of these cells contains phagocytosed red blood cells, lymphocytes, and necrotic cellular debris. In the early stages this reaction is limited almost entirely to the lymphoid tissue, but as the disease progresses the cells penetrate through the muscularis and are frequently seen in the muscle coat and in the subserosal tissues.

With ulceration, the surface becomes covered with a relatively thin layer of fibrin, polymorphonuclear leukocytes, and necrotic material. The ulcer may extend only to the submucosa or it may extend deep into or through the muscle coat.

Healing occurs with granulation tissue replacement of defects, followed by regeneration of the epithelium over the surface. It is almost impossible to find the site of a previous typhoid ulcer in a patient who has recovered and lived for a number of years. Scarring with stricture is extremely rare.

The two important complications of typhoid fever are perforation and hemorrhage. These, along with toxemia, account for most of the deaths in this disease. Hemorrhage usually occurs during the second week of illness and perforation during the third. Hemorrhage occurs, with deep ulceration when the necrotic tissue is first sloughed out. It arises from vessels with incomplete or dislodged thrombi. The hemorrhage into the intestinal tract is often massive and death may ensue rapidly.

Perforation may occur in any location and is independent of the number and size of ulcers or the severity of the disease. It occurs when the ulceration is deep and extends through the muscular coat. Secondary infection plays an important role in producing perforation. Following perforation, the intestinal contents are discharged into the peritoneal cavity and fatal peritonitis often ensues.

Death may occur from toxemia alone during the first week of illness, even before well-defined ulcers are formed.

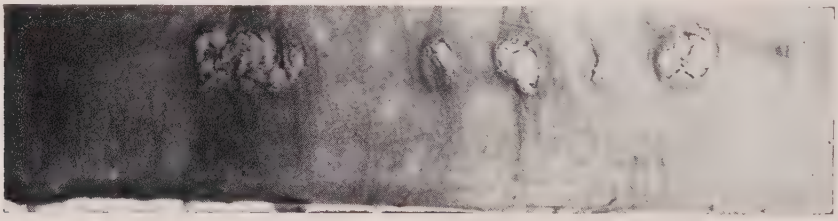


Fig. 687.—Typhoid ulcers of the ileum. The ulcers are sharply defined and show unsloughed necrotic debris in their centers.

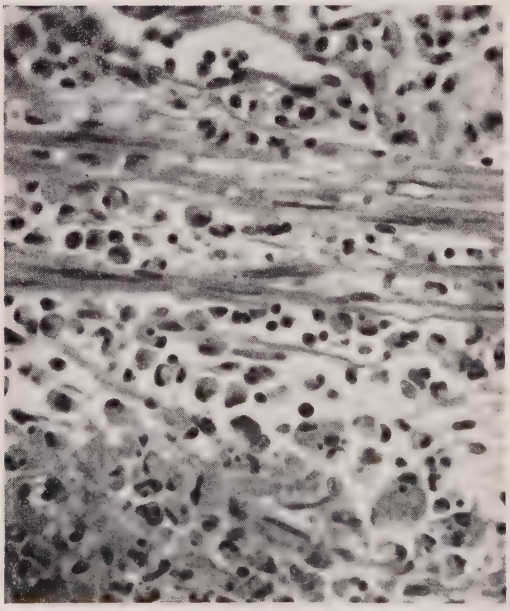


Fig. 688.—Base of typhoid fever ulcer in ileum. The macrophages (Mallory cells) are characteristic.

Amebiasis

Amebiasis must be distinguished from amebic dysentery. The first term denotes any infection of human tissues with *Endamoeba histolytica,* whereas the second term denotes infection of the intestinal tract severe enough to produce diarrhea. It is extremely important to differentiate between these two terms because many patients infected with ameba show no signs of dysentery or diarrhea. It has been estimated that from 5 to 10 per cent of all persons in the United States are infected with ameba. (See discussion in Chapter 16.)

The lesions, almost invariably located in the large intestine, are quite variable in extent. The regions of the cecum and the rectum are most commonly involved. In severe cases the entire length of the large intestine is involved, particularly in patients who die of amebic dysentery.

The lesions may be divided into two groups, an early and a late lesion. The early lesion may be small, pin point, and

hemorrhagic. As it enlarges, an area of roughened, elevated, opaque necrosis is produced on the mucosa of the intestine. These lesions, when incised, often show a liquefied area in the center which contains the *Endamoeba histolytica.*

Histologic examination of these early lesions shows a necrotic area which may be flask-shaped in contour. The infected site shows coagulation necrosis with very little cellular reaction. Such dilated blood vessels as appear in the region may contain polymorphonuclear leukocytes in their lumina, but these cells do not migrate actively into the area of injury. The trophozoites are often present in great numbers. This type of lesion is usually limited by the muscularis mucosa.

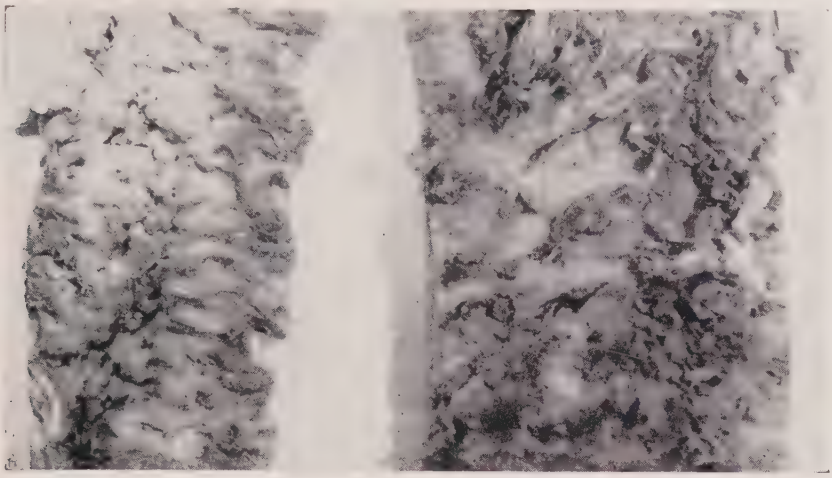


Fig. 689.—Amebic colitis. The specimen on the left shows typical irregular undermined ulcers with intact mucosa between them. Specimen on the right shows the ragged mucosa of a fulminating process.

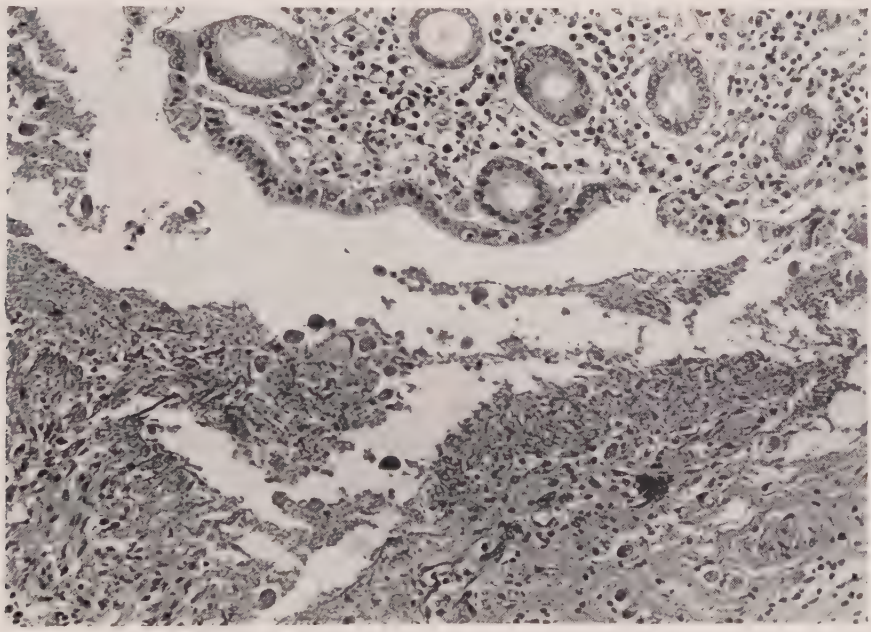


Fig. 690.—Amebic colitis. The large rounded bodies are trophozoites embedded in tissue showing characteristic coagulation necrosis

The late type of lesion is dependent upon progression of the early lesion. In this case the necrotic area becomes large, often showing an elevated, sharply outlined, yellowish-gray granular zone. When this material sloughs out, an ulcer is formed which may be sharp and punched out in appearance or may have irregular undermined edges. The base of the ulcer may extend below the muscularis mucosa and expose the muscle fibers of the muscularis coat. In advanced cases there is undermining of the edges of the ulcer, with sinus formation between adjoining ulcerated areas. The margins of the ulcers often present a ragged, shredded appearance. In general, the intervening areas of mucous membrane between ulcerated areas are relatively normal in appearance. The wall of the intestine in long-standing cases is often thickened and occasionally the omentum is plastered over areas where deep ulcers are located. It is well to remember that the majority of cases of amebiasis have lesions in the rectosigmoid area which are available for direct study.

Microscopically, the same cellular reaction is found in the deeper layers of the ulcers as is noted in the early lesions. However, with the loss of the surface of the ulcer and infection with intestinal bacteria, there is a secondary inflammatory reaction with the production of a polymorphonuclear exudate. This type of reaction, however, is never characteristic of the amebic infection alone.

Liver abscess is one of the more frequent complications. Its incidence is said to vary from 1.8 to 17.4 per cent of the cases. It is important to point out that the lesions in the intestinal tract may be fairly extensive without producing signs of diarrhea and that it is not uncommon for patients with minimal intestinal lesions to present amebic abscess of the liver. Subdiaphragmatic abscess and empyema, abscess of the lung, and bronchopleural fistula are the result of extension of infection from a liver abscess. Primary abscess of the lung is rare.

Perforation of the intestine is said to occur in from 4 to 19 per cent of the autopsied cases. Peritonitis may result from rupture of an intestinal ulcer or from rupture of a liver abscess. Appendicitis has been reported in from 7 to 40 per cent of fatal cases of amebiasis, but we saw very few cases in our material at Charity Hospital in New Orleans. Other complications are hemorrhage into the intestinal tract, infection of the pericardium, brain, gall bladder, urinary tract, and spleen.

Balantidiasis is a rare infection in man, but may produce ulcerations of the colon similar to those of amebiasis (see page 378).

Asiatic Cholera

This is an acute infectious disease of the intestines produced by *Vibrio cholerae,* which usually occurs endemically and epidemically in tropical countries. An epidemic in Hamburg, Germany, in 1892, with 17,000 cases and 8,600 deaths, emphasizes that it may occur in temperate zones. Contaminated drinking water is the chief source of infection. Mild cases may have only a severe diarrhea, but in the fulminating cases, death may occur within a few hours with symptoms of expulsive diarrhea, collapse, delirium, coma, dehydration, and acidosis. The striking features at postmortem examination are the presence of an extreme degree of rigor mortis and inelasticity of the skin, which has a peculiar leaden color. The serosal surfaces of the cavities are dry and sticky. The blood is dark and viscid because of marked dehydration. The recti muscles are occasionally ruptured because of the violent contractions attending the expulsive diarrhea. The heart is flabby, and occasionally cholecystitis and cholangitis are present. The intestinal lesions begin at the duodenum and extend throughout the entire length of the intestinal tract, the small intestine being most severely involved. The intestinal content is a turbid, viscous, grayish fluid which looks like thin barley soup in which white flecks are present, consisting of a mixture of desquamated epithelial cells, mucus, and bacteria. The mucous membrane is smooth, translucent, and has a peculiar reddish color due to the congested submucosal vessels which are readily visible. There is some hyperplasia of the solitary follicles and Peyer's patches. No ulcerations are present. Hemorrhages may be seen. Microscopically, there is almost a complete loss of mucosal epithelium except that which is present in the crypts. The villi are preserved. Necrosis may be present in the sinuses of the mesenteric lymph nodes (see also page 223).

Bacillary Dysentery

This is the term used for an infectious disease due to the Shigella group of organisms. The term is as much a misnomer for this infection as amebic dysentery is for amebiasis, inasmuch as many infections are unassociated with dysentery, which implies the passage of frequent stools containing blood and mucus.

There is some lack of agreement about the classification of the organisms causing the disease. However, three main groups may be recognized, first, the *Shigella dysenteriae,* or the Shiga type; second, *Shigella paradysenteriae,* or the Flexner type, and third, *Shigella sonnei.* These organisms all resemble the intestinal bacteria in that they are gram-negative rods. They are to be distinguished from the *Escherichia coli* and the typhoid organisms because they are nonmotile. The various groups are distinguished by their fermen-

tation reactions with lactose and mannitol. The first group ferments neither lactose nor mannitol; the second group ferments mannitol but not lactose; and the third group ferments both mannitol and lactose.

Infection with the *Shigella dysenteriae* produces the most severe infection, probably because this organism elaborates both an exotoxin and endotoxin. The latter two groups apparently produce only an endotoxin. The organisms remain localized in the intestinal tract, as a rule, and do not spread to distant organs although occasionally they may be isolated from the mesenteric lymph nodes. Specific antibodies against the organisms are produced in the serum of infected patients as manifested by the agglutination test. These appear from the seventh to the tenth day, and reach their height in about three weeks. They are consequently not of great value in diagnosis of acute cases. The best method of diagnosis is probably through stool culture.

The lesions are predominantly found in the large intestine, although involvement of the lower portion of the ileum is sometimes seen. The appendix is not uncommonly affected. It is said that the sigmoid portion of the colon and the rectum are likely to be more severely involved by the inflammatory reaction. In one case studied by the authors, in which death occurred within forty-eight hours after the onset of symptoms, there were only edema and hyperemia of the mucosa and submucosa of the intestine with moderate infiltration of polymorphonuclear leukocytes. No necrosis of the epithelial lining was present. In this case the organisms were recovered from both intestine and mesenteric lymph nodes.

More severe lesions are associated with hemorrhage into the intestinal wall and with necrosis of the epithelial lining, pseudomembrane formation, and even suppuration. As the disease progresses, ulcers occur, these at first being small and limited to the mucous membrane. In more severe or protracted infections the ulcers enlarge, become irregular in size, and sometimes almost completely destroy the mucous membrane. The margins of the ulcers are frequently sharp and they may be undermined. The base is often covered by a necrotic inflammatory exudate and may be brown in color. The intervening mucous membrane is often damaged and sometimes is covered by a pseudomembrane which is yellowish-brown or green in color. Occasionally, polypoid structures may form due to edema and hyperplasia of the nonulcerated areas of the mucous membrane.

The microscopic lesions are those of a nonspecific pyogenic inflammatory process with necrosis, polymorphonuclear cell infiltration, and fibrin deposition over the areas of necrosis. These lesions are more pronounced in the mucous membrane but may involve the submucosa and muscularis coat. As the lesions persist, granulation tissue forms at the margins of the inflammatory areas and production of scar tissue in these areas may lead to contraction and stenosis of the bowel lumen.

The lesions in other parts of the body consist of enlargement of the mesenteric lymph nodes which are moist and soft. The liver and kidneys show albuminous degeneration. Coagulation necrosis of the cortex of the adrenal glands has been described by Remlinger and Dumas.[134a] The spleen may show enlargement, with a soft dark-red pulp tissue. In acute cases, marked dehydration may occur.

Complications of the disease include inflammation of the anus and perianal regions due to the irritating material in the stool. Prolapse of the rectum may occur, particularly in children. Perforation and hemorrhage of the intestine are not common. The joints are occasionally involved with a nonsuppurative arthritis. This appears suddenly, sometimes several months after the acute disease, and commonly involves the knee joint. Involvement of the nervous tissues, due to the exotoxin of the *Shigella dysenteriae* is said to be common, particularly in the tropics (see also page 221).

Chronic Ulcerative Colitis

Chronic ulcerative colitis is a disease entity of unknown etiology, characterized by ulceration of the intestinal tract, particularly of the large bowel. It is a condition which persists for many years and is marked by remissions and exacerbations. When all attempts to ascribe an etiological agent have been exhausted in a patient with chronic diarrhea with ulceration of the colon, the condition is pigeonholed as one of chronic ulcerative colitis.

The Shigella group of organisms has been thought by many investigators to be the etiological agent. The failure to isolate the organism regularly from these cases, the irregularity of the presence of agglutinins in the blood serum, and the lack of contagion are all factors which do not support this view. Another organism, the diplobacillus of Bargen, has also been considered to be causative. Most investigators view this organism as a secondary invader, and believe that it is a variant of one of the enterococci. The *Bacterium necrophorum*, an anaerobic nonspore-bearing bacillus, is thought by Dragstedt and his co-workers to be causative. Its presence in nonulcerative lesions of the bowel and the fact that it has been occasionally isolated

from the bowel in other ulcerative lesions also make it questionable that this organism is causative. Many other organisms also have been held to be causative in this disease including viruses, but none can be proved to be important. Disturbances of the autonomic nervous system, psychogenic states, and vitamin deficiencies have all been supported as being factors in the production of colitis. The disease as it occurs in man has never been reproduced experimentally in animals and, therefore, the problem of assigning these various etiological factors to their proper roles seems quite difficult.

In the majority of cases, the disease starts in the rectosigmoid region, and the remainder of the colon is involved by a retrograde extension of the process. A few cases of localized involvement elsewhere in the colon, known as segmental colitis, do occur, and these may be in association with lesions in the terminal ileum. Grossly, the appearance depends entirely upon the duration of the lesion. In the early cases, during the acute phases of development, there is marked hyperemia and edema of the mucous membrane, with shallow, small, irregular ulcerations often associated with pseudomembrane formation. In the later stages of the disease, the ulcers tend to become confluent and have a tendency to follow along the course of the taenia coli, producing typical longitudinal furrows and ridges. In others the ulcerations are quite irregular. Islands of mucosa remain between the ulcers and have the appearance of polyps. In some instances the ulcers are deep and the walls are correspondingly thin, whereas, in others, stimulation of connective tissue with replacement fibrosis of the muscle coat produces rigidity of the wall with stricture formation. Microscopically, there are no characteristic findings, the inflammatory reaction being that of an infiltration with cells associated with chronic inflammation and fibroblastic proliferation. The student should be reminded repeatedly that all cases of ulcerative colitis, despite the gross appearance, should be investigated thoroughly for bacterial agents and amebae, as well as other causes for ulcerative colitis, and, hence, the establishment of the diagnosis of chronic ulcerative colitis rests largely upon the elimination of all known etiological agents which produce ulcerative lesions in the colon.

The most common complications are perforation with peritonitis or perforations of the rectum with perirectal abscess or fistulous tract formation. Localized stricture may occur, but more commonly there is a generalized reduction in the lumen of the bowel. Polyposis is often emphasized as a complication, but these are not true polyps in the sense of a neoplastic lesion like an adenomatous polyp. Carcinoma occasionally occurs, probably in higher percentage than is expected in the general population. Gangrenous pyoderma has been reported as a rare complication. We have seen one case. It is difficult to determine by survey of the literature whether a true relationship exists or whether this is merely an incidental lesion. In any event, such gangrenous ulcers of the skin have occurred with enough frequency for correlation to be suggested by some observers. Secondary changes in the body as a whole as the result of vitamin deficiencies are very common.

Regional Ileitis

Regional ileitis is the term which was originally used to describe a condition associated with signs of intestinal obstruction and diarrhea, abdominal pain, and generalized symptoms such as loss of weight and anemia. Other terms which have been proposed for the disease are regional enteritis, regional enterocolitis, and chronic stenosing regional enteritis.

The disease appears to be on the increase. It is commonly seen in people between the ages of 20 and 40 years. The incidence in the two sexes is approximately equal. It has been said to be more common in the Jewish race and among the offspring of emigrants from southern Russia and Italy.

The cause is unknown. Lymphatic obstruction due to low-grade infection of the bowel wall which, according to some investigators, comes from the serosal and not the mucosal surface, has been suggested. It has also been linked with bacillary dysentery, with primary mesenteric lymphadenitis, and with appendicitis, as well as disturbance in the blood supply and trauma. Histologically, the lesion may be much like Boeck's sarcoid. Tubercle bacilli have not been found in the lesions.

The condition is most commonly found to involve the terminal portion of the ileum where it stops at the ileocecal valve. In a moderate number of cases, however, extension occurs into the cecum and into the large intestine, sometimes extending to the junction of the rectosigmoid. The upper portions of the small intestines are sometimes involved.

The involvement is segmented and the demarcation from the uninvolved portion is sometimes fairly sharp. The bowel wall becomes thickened, firm, and has been compared to a garden hose. The serosal fat

extends from the mesentery over the surface of the intestine, and tends to surround the involved portion of the intestine. The mesenteric lymph nodes are usually enlarged, up to 2 cm. in diameter, and the mesentery draining the involved portion is thick and rubbery in consistency. The inner surface of the intestine shows disruption of the usual intestinal folds, the areas being replaced by a nodular mucous membrane in which there are ulcerations and fistulous tracts. The wall of the intestine is thickened, the involved areas corresponding to the area of fat tissue distribution over the surface of the gut. The ulcers may be superficial or deep and they are the basis for the formation of fistulas between various loops of intestines or communications with other organs in the region. They are also the cause for perforation of the intestine, either into the mesentery or into the peritoneal cavity.

The microscopic lesion is characterized by a prominent thickening of the submucosa due to edema, fibrosis, and infiltration with lymphocytes. The muscular wall is involved to varying degrees, showing fibrosis and infiltration with giant cells, which may be located in nodules resembling tubercles with epithelioid cells at the periphery or which may be found in the tissues in isolated form. Similar types of cells and arrangements are noted in the mesenteric lymph nodes. Caseous necrosis and acid-fast organisms are not present.

The lesion results in obstruction of the intestinal lumen due to thickening of the bowel wall with corresponding narrowing of the lumen. This causes the so-called "string sign" observed by the radiologist. There may also be loss of blood from the ulcerated areas, leading to secondary anemias. Bowel perforations may lead to abscesses, fistulous tracts, or peritonitis. Fever, abdominal pain, and diarrhea are common accompaniments.

Mycotic Infections of the Intestinal Tract

Actinomycosis infection either involves the appendix or the cecum in the region of the appendix. (See page 343.) *Histoplasmosis* may involve the intestinal tract as an ulcerative process which may involve any part from the mouth to the anus. The lesions have no particular site of election, and are composed of irregular ulcerations which at first show a caseation type of necrosis (see page 346).

Chemical Enteritis and Colitis

The two most common chemicals producing lesions in the intestines are mercury and arsenic.

The colon is affected in *mercurial poisoning* because the chemical is concentrated at the points of excretion, and the kidney and colon are the two organs which excrete the mercury in the largest quantity. In the milder cases the mucous membrane is edematous and congested, but in the more severe cases there are large, irregular areas of necrosis, with yellowish-gray shreds of necrotic tissue hanging from the mucous membrane. In some instances local gangrene is present. The small intestines are rarely involved.

In *arsenical poisoning*, the lesions are not only found in the stomach if some of the inorganic arsenical compounds such as Paris green or London purple are swallowed, but also appear at the points of excretion. In contrast to mercury, the small and large intestines are both involved in arsenical poisoning. The mucous membrane is edematous and congested, and often fibrinous exudate is deposited upon the surface in the form of a pseudomembrane. Large quantities of thin, gray, turbid fluid may be present in the lumen of the intestines. Ulceration occurs if the patient lives several days after the ingestion.

Uremic Colitis

In some patients who die of renal insufficiency there is an acute terminal inflammation of the gastrointestinal tract. The small intestine is rarely involved, the stomach may be affected, and the colon is most frequently involved. The lesions are nonspecific, and vary a great deal in their appearance from merely edema and congestion to a necrotizing type of ulcerative colitis, indistinguishable from some of the other types of acute infection. Bacteriologic studies should be carried out on all such cases in order to avoid overlooking a coincidental infectious type of colitis.

Appendicitis

Acute appendicitis is the most common surgical emergency of the abdomen. The number and seriousness of the complications of acute appendicitis in contrast to the rapid recovery after surgical removal makes it one of the most clear-cut indications for surgical intervention. Clinically, it may simulate, or be simulated by, such a large number of conditions that it must be considered in the differential diagnosis of practically every disease process producing acute abdominal pain.

Acute appendicitis is an uncommon disease before 5 and after 50 years of age; the majority of cases occur in relatively young individuals, but no age is exempt. Those cases which occur in the very young and the very old present very bizarre clinical findings which probably need more emphasis than is usually given. The disease occurs with equal incidence in both sexes and has no racial distribution. Studies have shown that uncivilized natives

living on a high cellulose diet have a very low incidence of appendicitis. When placed on a diet common to civilized people, however, the incidence of appendicitis increased.

The two most important factors in the production of appendicitis are infection and obstruction of the lumen. In human beings infection is present in all cases, although experimentally in the dog, appendicitis without infection can be produced. *Escherichia coli* (80 per cent) and nonhemolytic streptococci (25 per cent) are the two most common aerobic organisms found in the acutely inflamed appendix; Bacterium melaninogenicum (90 per cent) and nonhemolytic streptococci (50 per cent) are the two most common anaerobic organisms found. These organisms are commonly found in the intestinal content and, therefore, it is unlikely that they are brought to the appendix by way of the blood stream.

Although obstruction is not demonstrable in all cases of acute appendicitis, particularly in the mild acute inflammations, it is present in practically all of the severe inflammations such as gangrene. This indicates that it plays a very important role in the production of necrosis of the wall of the appendix. The causes of obstruction are numerous, and, of these, fecaliths are probably the most common. These consist of single or multiple inspissated masses of firm fecal material which are rarely opaque by x-ray, but which occasionally contain calcium and then should be more correctly referred to as fecal calculi. Foreign bodies in the lumen, stenosis, external bands and adhesions, usually the result of previous acute inflammation, hyperplasia of the appendiceal lymphoid tissues in the submucosa, sphincteric action of the muscle of the appendiceal-cecal junction, and tumors of the appendix, most commonly carcinoids (argentaffinomas) are other causes of obstruction. There is considerable controversy regarding the existence of an appendiceal sphincter, but Wangensteen and Bowers[156] found that the intraluminal pressure of the normal appendix in situ could be increased to 40 cm. of water before any fluid appeared in the cecum. It seems quite possible that this sphincteric action and the obstruction caused by lymphoid hyperplasia seen most commonly in young people may account for many of the cases of mild acute appendicitis in which none of the other more obvious obstructive mechanisms are present. The mechanism by which obstruction produces severe damage to the appendiceal wall is fundamentally one of interference in the circulation. When obstruction occurs, secretions accumulate and distend the lumen. The distention causes compression of capillaries and venules without arterial obstruction, and thus passive congestion and edema of the wall occur. As a result of the edema, more fluid pours into the appendiceal lumen, the distention becomes greater, and finally the arterial blood supply is cut off. This occurs first along the antimesenteric portion of the wall, the region farthest from the origin of the blood supply. Meantime, while this mechanism is in progress, organisms readily invade the mucosa due to decreased resistance, and a diffuse infection of the wall occurs. Thus, when complete infarction occurs as a result of arterial occlusion, both the liquefaction as a result of the infection and the infarction are responsible for perforation. The observation of Bowers and Wangensteen that 100 per cent of all gangrenous appendices showed obstruction emphasizes the importance of this mechanism in the inflamed appendix.

In our classification of appendicitis outlined below, we have attempted to classify the anatomical changes observed in the appendix. It does not necessarily follow that all of these types of appendiceal involvement have a counterpart in the way of clear-cut clinical findings. If we accept this premise, a good deal of the present-day controversy about "chronic appendicitis" can be eliminated.

Classification of Appendicitis

- I. Acute Appendicitis
  - A. Focal
  - B. Diffuse
    - 1. Nonsuppurative
      - a. With obstruction
      - b. Without obstruction
    - 2. Suppurative
      - a. Pyogenic
        - (1) With obstruction
        - (2) Without obstruction
      - b. Amebiasis (with secondary infection)
      - c. Typhoid (with secondary infection)
    - 3. Gangrenous
  - C. Traumatic (operative)
- II. Lymphoid hyperplasia
- III. Chronic appendicitis
  - A. Focal
    - 1. With foreign body (fecalith)
    - 2. With fibrosis (stenosis)
  - B. Diffuse
    - 1. Nongranulomatous
      - a. Obliterative
      - b. Nonobliterative
    - 2. Granulomatous
      - a. Tuberculosis
      - b. Actinomycosis
- IV. Parasitic infection
  - A. *Enterobius vermicularis*
    - 1. Intraluminal
    - 2. Focal granulomatous
  - B. *Trichuris trichiura*
    - 1. Intraluminal
  - C. *Ascaris lumbricoides*
    - 1. Intraluminal
    - 2. Obstructive with acute inflammation
- V. Protozoal infection
  - A. Amebiasis
  - B. Balantidiasis

Acute Appendicitis

Focal.—Grossly, the appendix appears normal, or shows some congestion of the serosal vessels. The lumen may contain a small amount of purulent material in

the distal third, but often no exudate and no gross mucosal lesions are present. Microscopic examination, however, reveals small quantities of purulent exudate in the appendiceal lumen, particularly in the distal portion. Multiple sections not infrequently show a small ulceration of the mucosa from which the purulent exudate arises. Since serial sections are often necessary to demonstrate this lesion, it becomes an impractical procedure in routine examinations. It is much simpler to search for the purulent exudate in the lumen. In order to demonstrate this exudate, however, the appendiceal lumen must not be opened, otherwise the exudate is lost. Fixation should first be carried out, following which careful longitudinal or cross sections of the gross specimens are made, taking care to cause minimal disturbance of the luminal content. This is the type of appendix frequently removed from patients who are clinically diagnosed as having chronic recurrent appendicitis.

Acute Diffuse Nonsuppurative Appendicitis.—Acute diffuse nonsuppurative appendicitis may or may not have an associated obstructive mechanism. Grossly the appendix is swollen, measuring as much as 1 cm. in diameter instead of the usual 0.5 to 0.7 cm. The blood vessels are markedly congested, and often petechiae are present. The lumen is often small and contains practically no exudate. The mucosa shows little ulceration. Microscopically, there is a diffuse inflammatory cell infiltration. The wall is diffusely infiltrated with inflammatory cells consisting largely of neutrophiles and a few macrophages.

Acute Diffuse Suppurative Appendicitis.—An acute diffuse suppurative type may also be present with or without obstruction, but in the majority of cases some obstructive lesion is present. Grossly the appendix is enlarged, the blood vessels are congested, petechiae are present, the mesoappendix is swollen and often hemorrhagic, and sheets of fibrinous exudate are present upon the surface. The exudate is friable and can be readily removed, which distinguishes it from fibrous adhesions. When obstruction is present, the portion of the appendix distal to the point of obstruction is usually the only region showing inflammation. The lumen of the appendix contains a purulent exudate which is gray or reddish-gray in color, due to hemorrhage into the exudate. Obstruction is usually due to a fecalith. The mucosa may be completely ulcerated or show irregular ulcerated areas. The wall is usually thin, as a result of marked distention by exudate and secretions within the lumen. Microscopically, ulceration of the mucosa and submucosa with diffuse infiltration of the

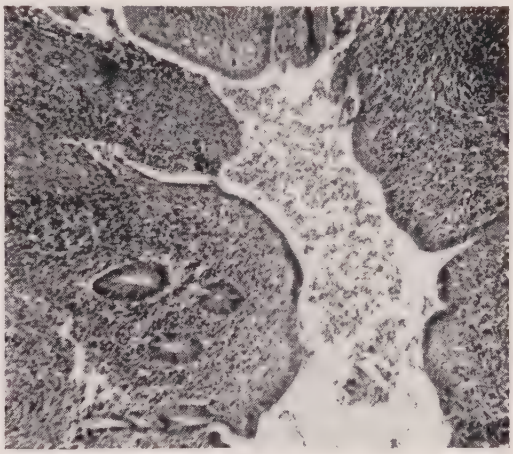


Fig. 691.—Acute focal appendicitis. Pus cells pouring into the lumen from a small mucosal ulcer.

entire wall, and an exudate consisting largely of polymorphonuclear leukocytes, are the outstanding features. This type of appendicitis is often accompanied by fluid in the abdomen which is sometimes turbid and may or may not contain organisms. In the suppurative appendicitis of amebiasis or typhoid fever, the lesion is largely one of superimposed pyogenic infection, and the appearance grossly that of acute suppurative appendicitis. Microscopically, however, both types of pathologic change are present. Vegetative forms of the ameba are demonstrated in the tissues in amebiasis, and in typhoid fever the wall is diffusely infiltrated with large phagocytic macrophages, the so-called Mallory cells.

Gangrenous Appendicitis.—This is merely an extension of the acute diffuse suppurative process. In addition to the lesions seen in suppuration, areas of gangrene, frequently associated with perforation, are present. Congestion, hemorrhage, areas of greenish-gray, purple, or almost blackish discoloration are present. Here

again the involved region of the appendix is very likely to be that portion distal to the obstruction of the lumen. Perforation is likely to be along the antimesenteric border, the point farthest from the origin of blood supply.

Acute Traumatic Appendicitis.—Acute traumatic appendicitis is seen in appendices removed by the surgeon or the gynecologist as an incidental part of another operation such as a hysterectomy or a hernioplasty. During the course of the operation the appendix is traumatized. Grossly it is congested, and microscopically there is an infiltration with polymorphonuclear leukocytes in the subserosal tissues. The wall and the lumen show no exudate.

Lymphoid Hyperplasia of the Appendix

Lymphoid hyperplasia of the appendix, as a rule, occurs in persons less than 20 years of age. Grossly, the appendix may appear quite normal. On section, the lumen is difficult to see because of marked hyperplasia of the lymphoid tissues. If the lumen is opened longitudinally, the mucosa presents a cobblestone appearance because of mounds of hyperplastic lymphoid tissue protruding into the lumen. Occasionally, small amounts of purulent exudate are present microscopically in the lumen. In other cases no exudate is present. It seems possible that in some cases the hyperplastic lymphoid tissue produces obstruction with symptoms of acute appendicitis but without actual inflammation of the wall of the appendix. In measles lymphoid hyperplasia is associated with the presence of multinucleated giant cells. (See Fig. 217.)

Chronic Appendicitis

As a clinical entity, chronic appendicitis is not a common disease, but lesions commonly found in the appendix such as scarring and infiltration with chronic inflammatory cells indicate the residuum of previous inflammation or a low-grade chronic inflammation.

Chronic Focal Appendicitis.—In this type, only localized areas of the walls are involved. Very often these are at the site of a fecalith which is not responsible for an acute attack at the moment. Sometimes one sees an area of annular fibrosis producing stenosis of the lumen. Grossly, the appendix may show nothing but enlargement and some increased firmness. Microscopically, fibrosis of the wall with infiltration of lymphocytes and eosinophiles in the muscle and subserosal tissues are outstanding features.

Chronic Diffuse Appendicitis.—In this type the lumen of the appendix may be obliterated. Usually this involves only the distal portion. This obliteration has led to considerable speculation as to whether this is a process which develops with age or is a residuum of previous acute inflammation. The absence of obliteration in the newborn and in children and the frequency of its association with acute inflammation speak strongly in favor of an inflammatory lesion. Periappendiceal adhesions are present in some of these cases, which also indicates a previous acute inflammation. Masson reports proliferation of nerve fibers in the connective tissue of the obliterated portion of appendices. He calls the lesion a neuroma. The overgrowth is probably regenerative, similar to an amputation neuroma. It is not a common lesion and it is difficult to evaluate its importance from a clinical standpoint. In the nonobliterative type, not infrequently the wall of the appendix shows a diffuse chronic inflammatory cell infiltration. Here many lymphocytes, plasma cells, and eosinophiles are present, both in the muscle and in the subserosal tissues. The mucosa is intact and the lumen contains no exudate. This lesion, although not common, is a true instance of chronic appendicitis because not infrequently the patient gives no clinical history of an acute attack.

Chronic diffuse appendicitis may also be due to tuberculosis or to actinomycosis. Tuberculosis of the appendix is usually a part of an intestinal tuberculosis and is rarely primary in the appendix. Ulceration of the mucosa with tubercles in the ulcer as well as in the subserosal tissues is the only important finding.

Actinomycosis of the appendix may be primary or a part of involvement of the cecum. The disease is chronic and may first attract attention by the presence of a mass in the right lower quadrant. It is characterized by the formation of many abscesses and the stimulation of large quantities of dense connective tissue. Grossly one may see sulfur granules, and microscopically the characteristic finding is the presence of colonies of organisms (ray fungi) in the centers of the abscesses. Postoperative fistulous tracts are commonly a complication of actinomycosis.

Parasitic Infection

Enterobius Vermicularis.—*Enterobius vermicularis* is the most common of the parasitic infections of the appendix. It is probably a very important cause of appendiceal pain in children, but it is questionable whether it causes acute appendicitis in many cases. The infection may occur at any age, but the highest incidence occurs in the ages between 10 and 15 years. Males and females are almost equally involved, although many papers in the literature indicate that females are more frequently infected than males. Our data do not substantiate this statement. Most of the data in the literature relative to the incidence of this condition are unreliable because the methods employed in determining the presence of the parasite are not sound. Examination of the content of the appendix by parasitological methods is the only way by which an accurate determination can be made. We found that about 25 per cent of all appendices removed at Charity Hospital in New Orleans were infected with pinworms. Our data also strongly indicate that the incidence is equally as high in other parts of the country.

Grossly, the appendix shows little or no change externally. The lumen may contain from a few to several hundred adult worms. Those that are readily seen by the naked eye are gravid females. A male worm is difficult to see without the use of a hand lens or a microscope. Microscopically, the findings are very disappointing. The wall may be perfectly normal not even revealing an increase in eosinophiles. Not uncommonly a pinworm can be seen imbedded in the lymphoid tissue, but with no cellular reaction around it. This invasion obviously occurs after the appendix has been removed. Occasionally the worms invade through the mucosa and set up an inflammatory response. Usually this is a typical granulomatous lesion with a central area of liquefaction surrounded by a zone of chronic inflammatory cells containing many eosinophiles and a peripheral zone of epithelioid cells and connective tissue. It has been suggested that with the entrance of these worms into the wall of the appendix, pyogenic organisms may be carried in mechanically and set up a typical acute appendicitis. From our own studies it seems very unlikely that this is a very common cause of acute appendicitis.

Trichuris Trichiura.—Infection with *Trichuris trichiura* (whipworms; threadworms) is much less common. They are practically always associated with pinworm infection of the appendix, and, hence, it is difficult to evaluate their importance. (See page 403.)

Ascaris Lumbricoides.—*Ascaris lumbricoides* (roundworms) may also be present in the appendix. Most commonly they are found in the lumen and cause no difficulty, but occasionally they may produce obstruction leading to acute inflammation. (See page 391.)

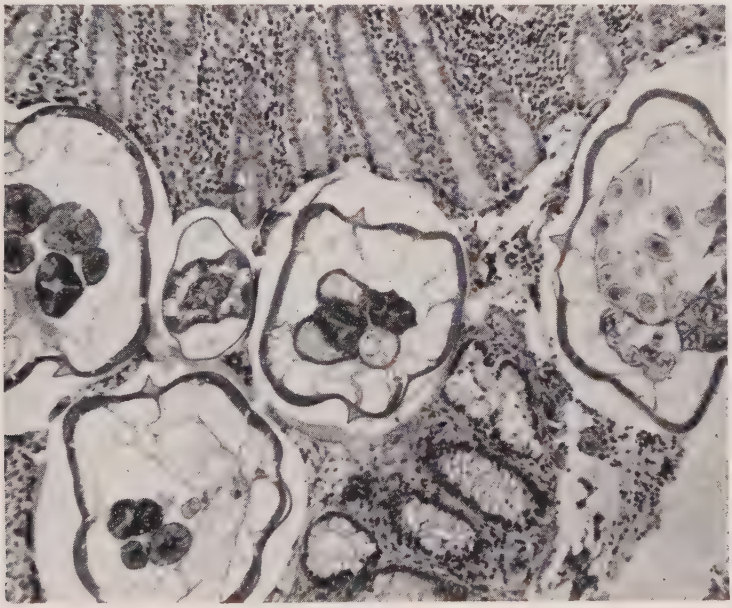


Fig. 692.—*Enterobius vermicularis* (pinworms) in the lumen of the appendix. (From Anderson, Synopsis of Pathology.)

Complications of Acute Appendicitis

The complications of acute appendicitis are many and serious, although many have been eliminated by the use of sulfonamides and penicillin. With perforation of the appendix a periappendiceal abscess or a localized peritonitis may be formed. This may be walled off with the aid of the omentum. If not, a generalized

peritonitis may occur. If the appendix is located retrocecally, a retroperitoneal abscess may be formed which may dissect upward or downward. In one instance we traced such an abscess upward through the diaphragm into the lung where a bronchial fistula was produced. Infected material may be present in the cul-de-sacs and, due to adherence of intestines at the pelvic inlet, produces a localized pelvic abscess. As a result of a generalized peritonitis, a subdiaphragmatic abscess may be produced, either on the left or on the right side, or loculated abscesses may occur between loops of intestines. If an appendiceal abscess is formed and drainage is not instituted, it may rupture into another viscus, producing an appendiceal fistula, or may extend externally and produce an abdominal fecal fistula. Localized thrombophlebitis in the region of the cecum may also complicate appendicitis. This may lead to the discharge of septic emboli with the production of multiple abscesses in the liver and in the lungs. Occasionally the portal vein is the seat of a thrombophlebitis, a serious condition known as a pylephlebitis. Such thrombi often show suppuration. Septicemia occasionally complicates an appendicitis.

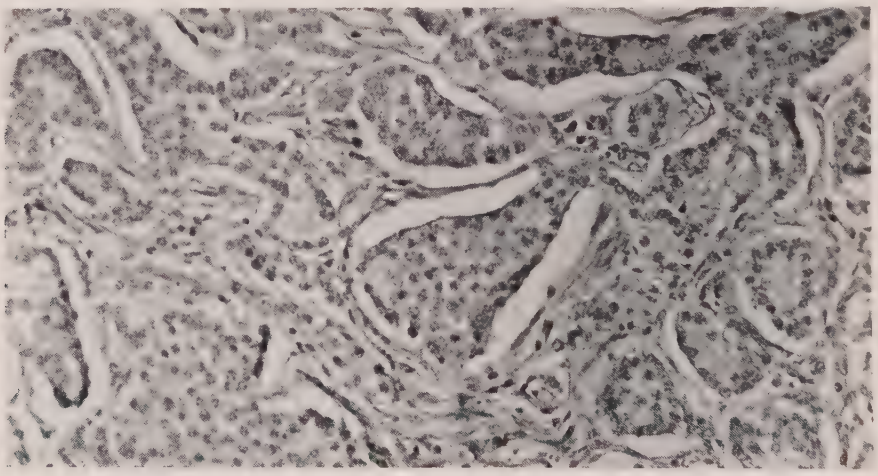


Fig. 693.—Argentaffinoma (carcinoid) in the appendix.

Tumors of the Appendix

Carcinoma.—This rarely affects the appendix, but when it occurs it has the appearance of an adenocarcinoma of the large bowel.

Argentaffinoma (Carcinoid).—This is a rather common tumor found in the appendix, which apparently arises, according to Masson,[153] from the chromaffin cells in the mucosa known as Kulchitsky cells. It is usually found incidentally in the routine examination of the appendix and occasionally may produce obstruction with resulting acute appendicitis. Argentaffinomas are usually located in the tip of the appendix and, hence, the appendix often shows a bulbous distal portion measuring 1 cm. or more in diameter. Here a firm nodule can be palpated, which on cross section shows that the normal markings of the appendix have been replaced by a firm, rubbery, pale yellow tumor. Sometimes this is a small lesion, and sometimes it produces a solid, large mass replacing all of the structures in this region. Microscopically, small, irregular, solid masses of cells are scattered throughout, supported by a scant amount of stroma. These cells show poorly defined cytoplasmic borders and dark-staining nuclei. Many of the cells show vacuolated cytoplasm which apparently contains a lipoid substance similar to the material in the adrenal cortex. This lipoid substance is responsible for the yellowish color. The tumor is not well encapsulated, invasion occurring in the mucosa, through the muscle, and often into the subserosal tissues. Despite this extensive invasion the prognosis in the vast majority of cases is good. A few have been seen to metastasize to the regional lymph nodes, and even to the liver. The demonstration of the relationship of this tumor to chromaffin cells depends on a special stain by silver impregnation.

Other tumors of the appendix are extremely rare. Lymphosarcoma may occasionally involve the appendix as part of a general involvement of the intestinal tract. Lipomas, myomas, and angiomas have been described in the literature. All are extremely rare.

Mucocele of the Appendix

This condition results from the accumulation of sterile mucin within the lumen of the appendix as a result of obstruction of the proxi-

mal end produced by an inflammatory stenosis. Occasionally, the mucus-secreting cells of the mucosa are forced through the wall of the appendix and implanted upon the peritoneum where they continue to grow and produce mucinous secretions. This condition is known as pseudomyxoma peritonei. It is not a true neoplasm, but may closely resemble neoplastic implantations upon the peritoneum from a pseudomucinous cystadenocarcinoma of the ovary. We observed one case in which the obstruction of the proximal end was caused by a lipoma of the cecum at the appendiceal orifice.

Tumors of the Intestines

Carcinoma of the Large Intestine

The majority of the malignant tumors of the intestinal tract are carcinomas, of which approximately 98 per cent are found in the large intestine.

Carcinoma of the large bowel takes a large toll of life each year, accounting for about 15 per cent of all cancer deaths. When the tumors are discovered, 80 to 90 per cent of the patients are over 40 years of age. About 5 per cent, however, occur in persons under the age of 30 years. It is generally stated that carcinoma of the large bowel is more common in males than females by a ratio of about 2 to 1. Other observers, however, show that carcinoma of the colon is more frequent in females, and carcinoma of the rectum more common in males.

Probably the most important of *etiological factors* in the causation of carcinoma of the large bowel is the adenomatous polyp. The frequency with which these undergo malignant change has been somewhat controversial. Most figures range from 5 to 84 per cent, although some observers believe that all the carcinomas of the colon arise from preexisting adenomatous polyps. Among other factors which have a suggested etiological bearing is a predisposition of the colonic mucosa to develop epithelial hyperplasia leading to further proliferation and carcinoma. Inflammatory lesions associated with chronic ulcerative colitis, diverticulitis, intestinal parasites, and lesions about the anus do not commonly undergo malignant change. Hereditary predisposition probably plays a significant role. Almost 25 per cent of patients with large bowel cancer give a significant family history of malignant disease.

Figures regarding the *location* of carcinomas of the large bowel are somewhat variable, but it is probably fair to state that about two-thirds of such lesions are found in the left colon and one-third in the right colon. Of those present in the left colon, the great majority are found in the rectum and sigmoid portions. The cecum is the next most frequent location, with the hepatic and splenic flexures least commonly involved.

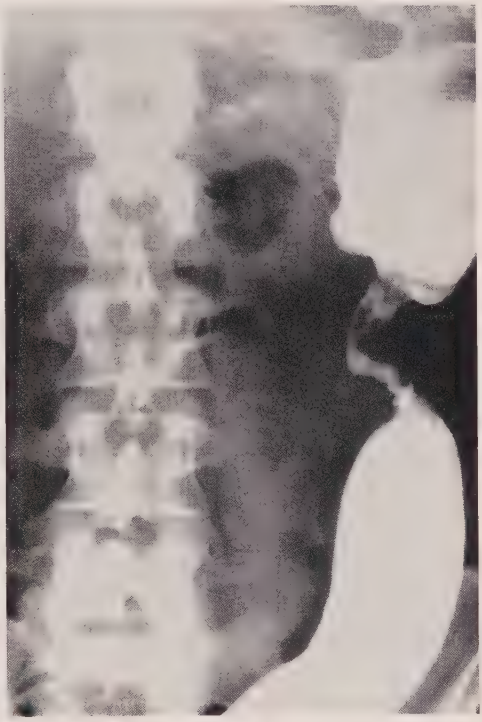


Fig. 694.—X-ray film of constricting annular carcinoma of the sigmoid colon.

Grossly, the majority of carcinomas of the large bowel appear to start as rather sessile, buttonlike nodules which are elevated above the mucosal surface. It is this appearance of the early lesion which suggests its origin from an adenomatous polyp. The tissue is pinkish-gray, firm, granular, and friable. As the lesion progresses, invasion of the muscular wall occurs, and the tumor tends to encircle the bowel. Miles states that it requires about one year for the tumor to encircle three-fourths of the circumference of the bowel. Ulceration of the mass occurs relatively early, and deep excavating lesions are produced. The margins of such ulcers are firm, nodular, and

elevated. The base is covered by necrotic tissue and fecal matter.

With complete, or almost complete, encirclement of the bowel, the intestinal lumen becomes narrowed and obstruction occurs. Proximal to the point of obstruction, the intestine becomes dilated and the wall sometimes hypertrophies. After obstruction has existed for some time, the proximal elevated margin tends to become flattened and the distal margin more elevated, producing an everted liplike structure which overhangs the mucosa. This forms a structural mechanism whereby the intestinal content can pass downward, despite narrowing of the lumen, whereas barium sulfate solution, when given per enema and viewed by x-ray, shows almost complete obstruction in its upward passage. The distal liplike margin is lifted up by the solution and acts as a ball valve. In some instances the accumulation of feces above the obstruction leads to the production of so-called stercoral ulcers.

The peritoneal surface over the lesion is often puckered and finely nodular, due to invasion of carcinomatous tissue into the subserosal tissue. If extension into the surrounding fatty structures has occurred, these tissues are likewise firm and contracted.

When the tumor mass remains small and is associated with the formation of a large amount of connective tissue, a sharp constriction of the intestinal lumen is produced, and the lesion is often referred to as a "napkin ring" type of carcinoma. Another type of lesion is the colloid or mucinous type of tumor. Tumors of the large bowel quite commonly display mucinous change in small areas, although changes extensive enough to produce grossly gelatinous tumors are not common. In another form of tumor there is a warty, papillary, funguslike projection into the lumen of the bowel with rather shallow ulcerations of the surface.

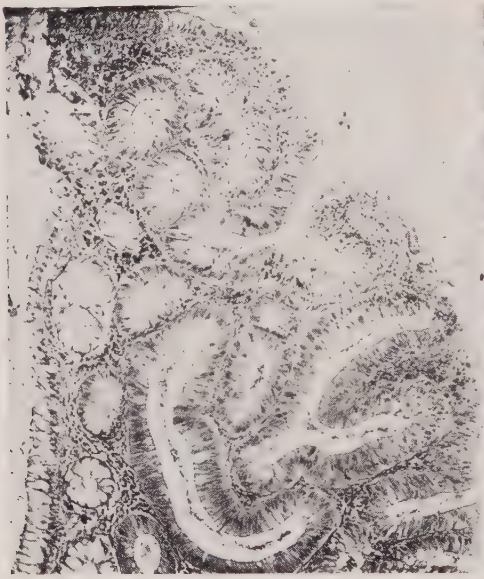


Fig. 695.

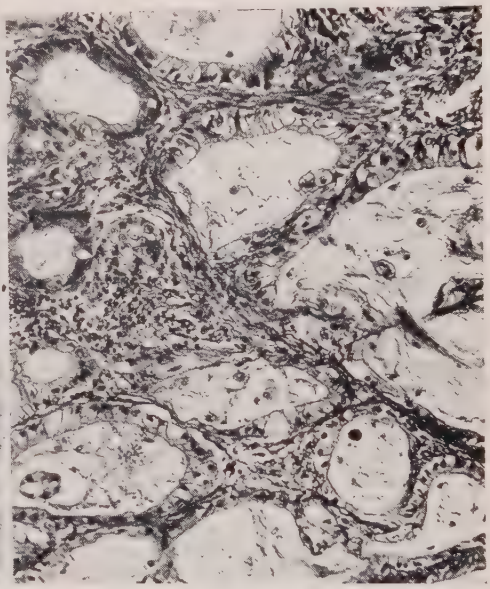


Fig. 696.

Fig. 695.—Rectal adenomatous polyp. The acini are only slightly atypical, and hence have not become carcinomatous.

Fig. 696.—Adenocarcinoma of the colon. Many mucus-secreting cells are present in this area.

It is said that carcinomatous lesions of the ascending colon tend to project into the lumen as fungating growths with a lower incidence of obstruction, whereas in the descending colon they tend more to invade the wall of the bowel and produce constriction, with a higher incidence of obstruction. The larger size of the lumen and the liquidity of the fecal content are also factors in the lower inci-

dence of obstruction in the right side of the colon. We have, however, seen several examples of a constricting lesion with early obstruction in the ascending colon.

Microscopically, nearly all tumors of the large bowel are adenocarcinomas. They produce irregular acini or strands or nests of cells which are surrounded by varying amounts of fibrous tissue stroma. In some instances a sharp transition from normal to carcinomatous epithelium may be seen at the margin.

The cells in the neoplasm exhibit basophilic cytoplasms and have large hyperchromatic nuclei which frequently show abnormal mitotic figures. The ability of such carcinomatous cells to secrete normal mucin is frequently lost. Invasion of neoplastic tissue through the bowel wall into the subperitoneal tissue may be seen. A different cell composition is seen in the small areas of mucinous change which are often seen in large bowel tumors. Here the cells show a cytoplasm distended with vacuoles of mucin which have pushed the nucleus to one side. In some cases when mucinous change is pronounced, the nucleus may be almost crescentic in shape, the so-called signet ring cell.

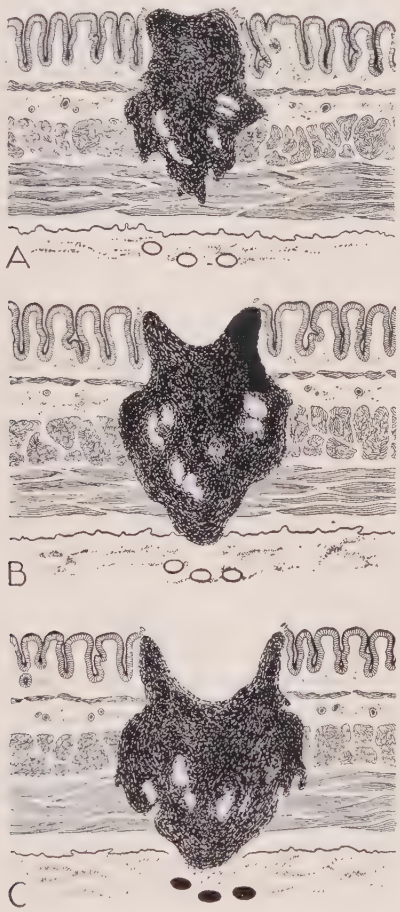


Fig. 697.—Duke's classification of carcinoma of the large bowel. *A*, Invasion of muscle only; *B*, invasion to the serosa; and *C*, invasion through the serosa and involvement of the regional lymph nodes. (From Ackerman and Regato, Cancer, The C. V. Mosby Co.)

Tumors arising in the lower portion of the rectum close to the anal margins may be of the squamous cell type.

The *spread* of the tumor directly through the wall to involve the serosal coat is common. Spread through the lymphatic channels has been found to

occur early and frequently. The regional lymph nodes are involved in 60 to 70 per cent of all cases of carcinoma of the large bowel. Blood stream metastases are common in late cases and the organs most commonly involved are the liver, which shows lesions in more than one-half the cases, and the lungs. Recurrent carcinoma of an abdominal or perineal wound several years after an apparently successful resection is an occasional distressing complication.

Complications of carcinoma of the colon are many. Ulceration and obstruction developing in cases of carcinoma of the colon have been previously described. Perforation is relatively common, and generalized peritonitis or localized abscess may develop as a result. Gastrocolic fistula formation is not an uncommon occurrence in carcinoma of the transverse colon, and a vesicocolic fistula may complicate carcinoma of the sigmoid colon. In carcinoma of the rectum, rectovaginal and rectovesical fistulas may occur. Occasionally the ureters are infiltrated or surrounded to produce urinary obstruction. Hemorrhage into the bowel occurs in all cases, but occasionally it may be massive and fatal.

Carcinoma of the Small Intestine

Approximately 3 per cent of all malignant tumors of the gastrointestinal tract are said to occur in the small intestine. Approximately one-half of these occur in the duodenum and the other half in the jejunum and ileum, where the most frequent site is the lower end of the ileum. The lesion may project into the lumen of the bowel as an ulcerated nodule or may produce a "napkin ring" constriction due to invasion of the wall. The microscopic picture is that of adenocarcinoma. The same predominance of the tumor in the male sex is noted as is found in carcinomas of the large bowel; the age incidence is somewhat younger than that for either the large bowel or the stomach.

The tumors bleed easily. They may produce obstruction by causing kinking of the small intestine and by initiating intussusception, particularly when a pedunculated carcinoma is present. Very rarely, perforation may occur. Carcinoma of the duodenum is described elsewhere (see page 859).

Malignant Lymphoma of the Large and Small Intestine

Lymphosarcoma of the intestinal tract is of considerable interest because an increasing number of cases are being reported. Males are more frequently affected than females, and although the disease may occur at any age, it is most frequently encountered between the ages of 20 and 50 years. The colon is involved about twice as frequently as the small bowel, about one-third of the colonic lesions appearing in the rectum and about two-thirds in the cecum. Enlarged lymphoid masses in the submucosa (solitary follicles or Peyer's patches) are the first signs of neoplastic involvement. Very soon there is a diffuse invasion of all coats, which may completely encircle the intestine for a considerable distance producing the so-called "garden-hose" appearance. Very little stroma is present, hence the absence of constriction. Large, fungating masses with ulceration of the mucosa are present in about 25 per cent of the cases. The regional lymph nodes are usually involved. The tissue is firm but not hard, yellowish-gray or whitish-gray, friable, and presents a homogeneous appearance on cut section. Histologically, the small and large round cell lymphomas, the reticulum cell sarcoma, and the giant follicle types have been observed. Hodgkin's disease rarely involves the intestine.

Some cases have been resected successfully, but the majority of patients die as a result of a progressive generalized lymphoma. Some terminate with leukemia. When treated with heavy doses of x-ray, disastrous results may occur. The bowel wall may slough because of the rapid destruction of the lymphoid tissue.

Miscellaneous Malignant Neoplasms

Malignant melanomas occasionally occur in the rectum in the region of the anorectal junction. They are highly malignant tumors which have the same gross and microscopic appearance as those which arise in the skin.

Leiomyosarcoma may arise from the muscle coats. They may ulcerate rapidly or may be as well circumscribed as a leiomyoma. Histologically, many cells are undifferentiated and bizarre mitoses are present.

Neurogenic sarcomas have been described arising in the intestine. They are usually edematous-appearing nodular tumors which histologically show the characteristics of a neurogenic sarcoma arising in the skin or nervous system.

Kaposi's sarcoma (angiosarcoma) may involve the intestines, in addition to the skin and subcutaneous tissue.

A few liposarcomas have been reported. These may occur in the submucosa or subserosal tissues. When submucosal they may be pedunculated and produce intestinal obstruction.

Benign Tumors of the Intestines

Adenomatous Polyps.—Many lesions of the colon have been termed polyps and many classifications have been made in an effort to subdivide the types of polyps seen. It is important to distinguish between the inflammatory polyps, or pseudopolyps, and neoplastic or adenomatous polyps. Inflammatory polyps are less important than neoplastic polyps because the latter are intimately concerned with the development of carcinoma. Inflammatory polyps are seen most commonly in association with chronic ulcerative colitis and chronic bacillary dysentery.

The neoplastic or adenomatous polyp is by far the most important and most common lesion of the colon. It is said to comprise from one-half to two-thirds of the benign tumors of the intestinal tract, and, although the figures vary in different surveys, it has been stated that polypoid lesions are found in approximately half of the individuals who are over 30 years of age.

Although adenomatous polyps may be present in any portion of the intestinal tract, they are more common in the large bowel, especially in the sigmoid and the rectum. The neoplasms may be single, but in one-third to one-half of the cases these tumors are multiple.

Factors which have been considered etiological in the genesis of adenomatous polyps are inflammation, chronic irritation, epithelial disorders, embryonal rests, and hereditary predisposition. The problem of etiology of neoplastic polypi appears to be the same as for neoplasms in general. There appears to be a rather strong hereditary tendency toward the development of these neoplasms.

The gross appearance of the neoplasms varies quite widely. Some of the lesions are pedunculated and attached to the mucosa by stalks of varying lengths; others are broad sessile masses and should actually not be classified as polypoid lesions. This type is often observed in cases where the polyps are innumerable. The surfaces of the larger lesions are usually roughened and wartlike. Ulceration is seen frequently and the tumor masses may be hemorrhagic. Their diameter is usually between 0.5 and 2.0 cm.; however, variations outside these limits are not uncommon. The tissue is soft, gray and very friable.

The microscopic structure, as suggested by the gross description, varies considerably. In the fully developed polyp, there is a stalklike connective tissue central structure surrounded at the base by relatively normal-appearing epithelium. The widened tip is covered by epithelium which usually shows some irregularity in its arrangement. In the benign neoplasm the cells lining the surface are mucus-secreting and form glands similar to those seen in normal mucosa. Edematous vascularized connective tissue and usually some mononuclear cells are seen beneath the epithelium.

Atypical hyperplasia is quite commonly present in the polypoid lesions, particularly in those which have given rise to clinical symptoms. These hyperplastic reactions manifest themselves by irregular proliferation of cells with a tendency to extend into the connective tissue portions of the polyp and by a loss of mucous secretion in the cytoplasm of the cells. The cytoplasm becomes more basophilic and the nuclei hyperchromatic. As the process progresses toward malignant neoplasia, the cells become more atypical and invade into the deeper layers of the connective tissue center. In the evaluation of the progress made by adenomatous polyps toward carcinoma, it is important to examine the stalk of the polyp to determine whether or not the base and underlying bowel have been invaded. Most observers believe a close relationship exists between adenomatous polyps and carcinoma of the rectum and colon.

The tumors, as previously described, are sometimes complicated by inflammation and ulceration, and under these circumstances bleeding from the rectum may be noted. This may take the form of gross blood or may be in the occult form. It has been stated that approximately two-thirds of all patients with polyps, whether symptomatic or asymptomatic, show a positive test for occult blood if the stool is examined at regular intervals. This offers definite possibilities for early diagnosis of these lesions. Intestinal obstruction sometimes complicates intestinal polyps, in both the large and the small bowel. Sometimes the tumor mass itself becomes large enough to cause obstruction but more often the tumor is the head of an intussusception.

Other benign tumors of the large intestine are lipomas which usually develop in the submucosa and form sessile or pedunculated tumors showing yellow, fatty tissue on cut section. Myomas arise from the muscular coat and may protrude into the lumen or into the serosal surface of the bowel. Fibromas usually arise in the mucosa or submucosa and are encapsulated. Angiomas tend to arise in the submucosa and extend around the circumference of the bowel.

Fig. 698.—Pedunculated benign polyp of the large bowel. (From Ackerman and Regato, Cancer, The C. V. Mosby Co.)

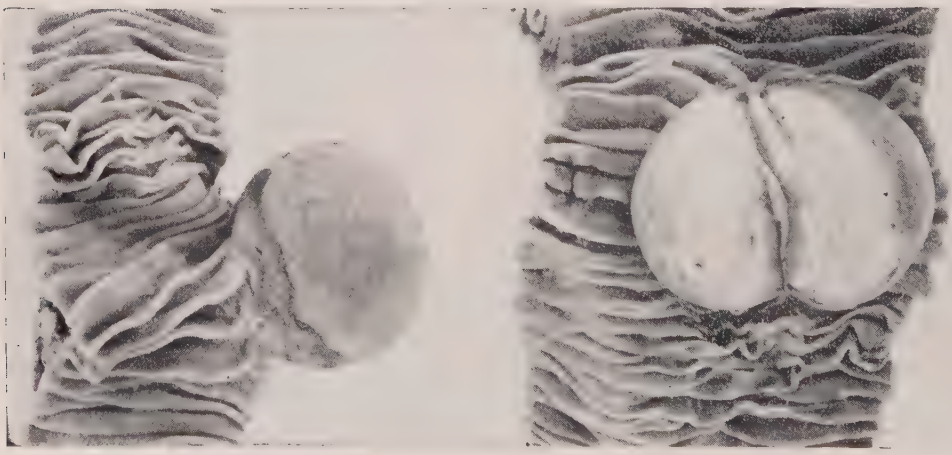


Fig. 699.—Polypoid myoma of small bowel. (Courtesy Dr. R. S. Haukohl.)

Benign Tumors of the Small Intestine.—Benign tumors of the small intestines are rare. They are most frequently present in the duodenum and ileum. The most common is the argentaffinoma, which appears more often in the lower ileum as a submucosal nodule. Occasionally this tumor invades through the muscle coat, metastasizes to the regional lymph nodes and may even metastasize by way of the blood stream. (See page 792 for further description of the tumor.)

Other tumors are adenomas, myomas, neurofibromas, lipomas, and angiomas, appearing in frequency in the order named.

THE PERITONEUM

Congenital Anomalies

These rarely occur and consist usually of peritoneal pouches into which a herniation such as paraduodenal and retromesocolic hernia may occur. Occasionally, congenital bands are formed which may produce intestinal obstruction.

Circulatory Disturbances

Active congestion is present in all cases of acute inflammation of the peritoneum. Passive congestion occurs as the result of venous obstruction, of which heart failure and portal cirrhosis are the two most common causes. Portal thrombosis or lesions such as neoplasms compressing the portal vein externally may also produce passive congestion. Tumor thrombosis of the inferior vena cava occurs most commonly as the result of renal carcinomas, primary liver cell carcinomas, and malignant teratomas of the testicle. Portal obstruction is associated with the abnormal accumulation of fluid in the peritoneal cavity known as ascites. This fluid is a true transudate and should be differentiated from an exudate. As a rule, it is a clear, straw-colored fluid with a specific gravity of less than 1.015 and a total protein content of less than 3 per cent. The cellular content is scanty. When the fluid has a milky appearance with a high-fat content, it is known as chylous ascites and is caused by obstruction of the thoracic duct. The obstruction is usually neoplastic, but occasionally tuberculosis may be the cause.

Hemorrhage Into the Peritoneal Cavity

Hemorrhage may occur into the peritoneal cavity and produce enough irritation to cause pain, leukocytosis, and fever. Penetrating wounds obviously cause hemorrhage. Nonpenetrating blows may rupture a hollow viscus such as the urinary bladder or gastrointestinal tract, with resulting hemorrhage. Rupture of the spleen or liver, however, is more commonly the cause of hemorrhage following such a blow. Nontraumatic causes of hemorrhage are ectopic pregnancy which is usually tubal, rupture of a graafian follicle or corpus luteum of the ovary, rupture of an intra-abdominal aneurysm, and rupture of a varicose ovarian vein. Occasionally, peritoneal carcinomatosis, peritoneal tuberculosis, and hemorrhagic pancreatitis are associated with an appreciable amount of hemorrhage.

Peritonitis

Acute peritonitis is a common disease process. With the advent of sulfonamides and the antibiotic drugs the mortality from this condition has been markedly reduced. Peritonitis usually occurs as the result of disease in some abdominal organ or abdominal surgery directed toward the eradication of this disease. Postoperative peritonitis occurs to some extent in every operative procedure in which the gastrointestinal tract is opened, although occasionally enough bacteria are introduced at the time of operation to cause a peritonitis.

Inflammation of the appendix is a common source of peritonitis. Here infection may gain access to the peritoneal cavity either by rupture or by invasion through an intact wall where a portion has been devitalized but not actually ruptured.

Conditions in which an inflamed but otherwise intact organ is the source of peritonitis are acute cholecystitis, puerperal endometritis, hemorrhagic pancreatitis, and infarction of the bowel as a result of strangulated hernia or mesenteric thrombosis.

A ruptured viscus is a relatively common cause of peritonitis. This is seen most commonly as the result of perforation of a benign gastric or duodenal ulcer, but the rupture of an ulcer of typhoid fever, bacillary dysentery, amebic dysentery, and chronic ulcerative colitis occasionally occurs. A carcinomatous ulcer anywhere in the gastrointestinal tract may rupture and lead to peritonitis. An abscess in the liver or spleen rarely may lead to peritonitis.

Disease of the fallopian tubes is commonly complicated by peritonitis. It is likely that in all cases of acute gonorrheal salpingitis there is an associated pelvic peritonitis due to soiling of the pelvic peritoneum from purulent exudate being discharged from the fimbriated ends of the tubes.

Occasionally, peritonitis is blood borne since no diseased abdominal viscera are present, and organisms are present in the blood stream. Abdominal injuries as a result of penetrating wounds are also causes of peritonitis. Nonpenetrating injuries may cause a rupture of a viscus, which in turn may be responsible for inflammation of the peritoneum.

Any of the organisms which are found in the gastrointestinal tract may be responsible for peritonitis. The most common, however, are *Escherichia coli,* aerobic and anaerobic streptococci and anaerobic bacilli, among which *Bacterium melanogenicum* seems to be a common contaminant. Enterococci and spore-bearing anaerobic bacilli such as *Clostridium welchii* are also occasionally seen.

Acute peritonitis may be either localized or generalized. When large areas of the peritoneal cavity are contaminated by the spilling of large quantities of stomach or intestinal content, or when a large segment of bowel becomes gangrenous, the peritonitis is more likely to be generalized. When a suture line leaks or an appendix ruptures, the peritonitis is more likely to be localized because the peritoneum reacts very rapidly in localizing infections to one portion of the peritoneal cavity. The first response is that of marked congestion and edema, with a granular, dull serosal surface replacing the normal shiny, translucent appearance. When the peritoneum is contaminated with gastric content, the reaction for the first two or three hours is largely chemical. Very soon a yellowish, friable exudate appears, which is composed of fibrin and can be readily peeled away from the peritoneal surface. The type and quantity of fluid associated with the exudate are quite variable, depending upon the type of the infectious agent. Virulent organisms such as hemolytic streptococci may be associated with relatively thin, only slightly turbid fluid, whereas less virulent organisms such as staphylococci, many strains of streptococci, and colon bacilli are often associated with frank purulent fluid. The fibrinous exudate causes loops of intestine to be glued together, and frequently this phenomenon is most marked at the source of the infection, evidently an attempt to localize the infection in one area of the peritoneum. The omentum also responds promptly and is frequently found sealed by exudate to the site of the infection. Frequently, as in perforating lesions of the stomach, duodenum, and appendix, the omentum effectively prevents generalized peritonitis by sealing the perforation.

Fig. 700.—Acute peritonitis. Large quantities of fibrinous exudate cover the serosa.

If the peritonitis continues, there is a tendency for accumulations of purulent

exudate to occur. This may be in the cul-de-sacs, which may be sealed off from the remainder of the peritoneal cavity by loops of intestine adhering together over the brim of the pelvis. Accumulations of purulent material between loops of bowel or in one or both lumbar gutters are commonly seen. Subphrenic and subhepatic abscesses may occur and remain as a problem after the generalized peritonitis has subsided. Most of these are due to appendicitis or disease in the stomach, duodenum, or gall bladder. In subphrenic abscesses the exudate accumulates beneath the diaphragm and is sealed off from the remainder of the peritoneal cavity by fibrinous adhesions.

During the course of acute peritonitis one of the most important and serious complications is the development of a paralytic ileus. When loops of bowel are bathed in a peritoneal exudate which contains toxic products of bacterial growth, dilatation may result with loss of peristalsis. Intestinal obstruction is thus produced, since the bowel content cannot pass the dilated segment. It is in this type of obstruction that the Miller-Abbott tube has found its greatest usefulness.

If healing of a peritonitis occurs, evidently most of the fibrinous exudate is absorbed and leaves a normal, smooth peritoneal surface. If the exudate is not absorbed, it undergoes organization beginning about the sixth to the tenth day following the onset of the disease. This results in dense fibrous adhesions which may later lead to serious difficulty in the form of intestinal obstruction. Microscopically, the acute inflammatory exudate consists mostly of fibrin, polymorphonuclear leukocytes, and macrophages. During the stage of organization lymphocytes make their appearance and macrophages are increased in number. Young fibroblasts are present with newly formed capillaries.

Special Types of Peritonitis

Gonococcal Peritonitis.—Gonococcal peritonitis is particularly prone to produce severe pelvic adhesions. It is probable that in many instances there is a secondary infection. Frequently the adhesions are so marked that all the organs in the pelvis and adjoining loops of bowel are firmly adhered by dense fibrous adhesions. This is referred to as a "frozen pelvis." The gonococcus does not seem to survive very well in the general peritoneal cavity since few adhesions are found outside of the pelvis. However, one almost pathognomonic sign of previous gonorrheal infection is the presence of "violin string" adhesions between the diaphragm and the right lobe of the liver.

Tuberculous Peritonitis.—This may occur as a primary infection by the hematogenous route or may be secondary to tuberculosis in the mesenteric lymph nodes, intestines, and fallopian tubes. In tuberculosis sanatoriums, by far the most common of these is intestinal tuberculosis because of the high incidence of intestinal involvement among far-advanced cases of pulmonary tuberculosis.

There are two types of inflammatory response: One is the wet or moist form in which large accumulations of fluid occur in the peritoneal cavity. In this type, scattered, glistening tubercles are found upon the peritoneal surface but very little fibrinous exudate is present. The fluid presents the characteristics of an exudate having a specific gravity of more than 1.015 and a protein content above 3 per cent. Sometimes the exudate is blood tinged, suggesting carcinomatosis. The omentum is often studded with tubercles and is occasionally rolled up in a thick sausagelike mass in the upper abdomen.

The other is the dry type, which is characterized by the exudation of large quantities of fibrinous exudate, the formation of many tubercles upon the peritoneal surfaces with caseous necrosis, and the formation of numerous adhesions. In the more severe cases the viscera are so firmly united by exudate and adhesions that they appear to be encased in another peritoneal cavity. Fistulous tracts between loops of intestine and abdominal wall may occur.

Bile Peritonitis.—This rare but important condition may occasionally occur as a result of a pinpoint perforation of an apparently normal gall bladder, but, in some instances, although the gall bladder wall is suffused with bile, no perforation is demonstrated. In the majority of cases, however, bile peritonitis occurs as the result of disease in the gall bladder and extrahepatic bile ducts following either a spontaneous rupture or a postoperative complication. The most common cause is a stone impacted in the common bile duct which was overlooked at operation. In some cases, bile leakage apparently takes place from untied accessory bile ducts. It has also been suggested that bile capillaries drain directly from the liver into the gall bladder, in some cases, and that when they are severed during cholecystectomy, leakage may occur. We have observed several postoperative cholecystectomy cases with bile peritonitis in which we could find no cause for the bile leakage and which may represent bile capillary drainage into the peritoneum. The initial reaction to bile peritonitis is extreme shock which accompanies the exudation of large quantities of fluid into the peritoneal cavity as a result of the irritant action of the bile. Hemoconcentration of the blood is present. The subsequent reaction is apparently dependent upon the bacterial content of the bile, which in a majority of cases is infected, producing an ordinary type of acute peritonitis accompanied by bile. Very rarely, sterile bile may be poured into the peritoneal

cavity in large quantities over a long period of time and cause difficulty only as the result of the loss of bile and its absence in the digestive tract.

Talc and Lycopodium Peritonitis.—A curious type of peritonitis is that in which the peritoneum is studded with small tubercle-like lesions following a previous operation.

Parasitic Peritonitis.—Occasionally *Enterobius vermicularis* gain access to the peritoneal cavity by way of the uterus and Fallopian tubes and produce granulomatous nodules on the peritoneal surface which resemble tuberculosis or carcinoma.

Primary Idiopathic Peritonitis.—This usually occurs in children, often in girls, and most cases are associated with an upper respiratory tract infection. We have seen one case in which peritonitis occurred in a 55-year-old woman following otitis media and mastoiditis. Most of the cases are due to streptococci or pneumococci. In addition to the hematogenous route of infection, contamination of the peritoneal cavity from the fallopian tubes or from the pleural cavity through the diaphragm has been suggested as a possible source of infection. The acute pneumococcal peritonitis which occasionally complicates the nephrotic stage of glomerulonephritis is probably blood borne.

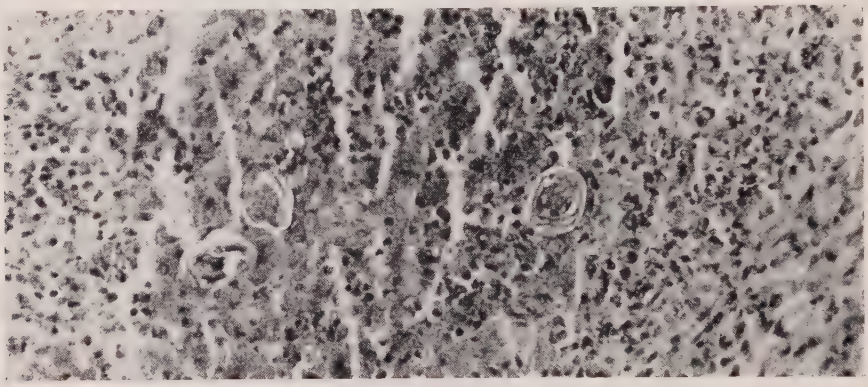


Fig. 701.—Parasitic granuloma of peritoneum. Portions of *Enterobius vermicularis* embedded in necrotic tissue and surrounded by inflammatory and epithelioid cells.

Tumors of the Peritoneum

Primary tumors of the peritoneum are extremely rare, and are referred to as mesotheliomas or endotheliomas. Characteristically, they produce a spreading tumor mass covering large areas of serosal surface with a gray, granular, firm tissue which on microscopic examination often shows some of the characteristics of epithelium in that acinous and papillary formations are present.

Secondary tumors of the peritoneum are very common and usually are carcinomas. The majority arise from the stomach, large bowel, or ovary, although the gall bladder, pancreas, and uterus are occasional intra-abdominal sources. We have seen several instances of peritoneal carcinomatosis arising apparently by hematogenous spread from carcinoma of the breast. The carcinomatous nodules consist of firm, shotty, gray granular masses as small as 1 mm. in diameter, which may be scattered throughout the peritoneum. They have a tendency, however, to be most numerous at the site of the tumor, in the cul-de-sacs, and along the junction of the mesentery and small intestine. Peritoneal carcinomatosis is usually associated with ascites and the fluid is frequently bloody. The surgeon must learn to differentiate the nodules of carcinoma from tubercles and areas of fat necrosis. Carcinomatous nodules are elevated, gray, and opaque. Tubercles are elevated, yellowish, and translucent, and areas of fat necrosis are flattened, yellowish, opaque, and often have a halo of hemorrhage or congestion. The ascitic fluid may contain tumor cells, but unless groups of cells are present it is very often dangerous to make a diagnosis of carcinoma from ascitic fluid by the study of single cells. Huge, swollen peritoneal cells are often seen in portal obstruction which on cursory examination closely resemble tumor cells.

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Chapter 27

THE LIVER

W. A. D. Anderson

The liver is the largest single organ in the body and is surpassed by none in the multiplicity and importance of its various physiologic activities. Accordingly, the state of the liver and the level of its functional efficiency are of great significance to the general bodily economy both in health and in disease.

Structure and Circulation

Structure.—The gross anatomic division of the liver into a large right lobe and a smaller left lobe is recognizable at an early stage of development; the caudate and quadrate lobes make their appearance somewhat later. Between these two lobes lies the porta hepatis, or gateway to the liver, through which enter the hepatic artery and portal vein and from which emerge the hepatic duct and a number of lymphatic vessels. In the porta hepatis the blood vessels and hepatic duct divide into right and left branches. In their subsequent ramifications through the liver the branches of the artery, vein, and hepatic duct lie always together and are enclosed with the lymphatic channels in a common sheath of connective tissue (Glisson's capsule). The spaces occupied by these structures are termed the portal canals. The hepatic veins, on the contrary, are not enclosed in any sheath and course through the liver as naked vessels in direct contact with the liver tissue. These veins commence with the intralobular (central) veins which receive blood from the sinusoids of the liver lobules. The intralobular veins open into sublobular veins. These in turn unite to form several large hepatic veins which open separately into the inferior vena cava.

The parenchyma of the liver, as may be seen with the naked eye or more clearly with the microscope, is composed of innumerable small lobules, each of a diameter of 0.5 to 2 mm. and having the shape of an irregular, somewhat pyramidal hexahedron. At the center of each lobule is the intralobular or central efferent vein, while around the periphery four or five portal spaces are arranged at regular intervals, each containing a small branch of the hepatic artery, portal vein, and hepatic duct. Each lobule is made up of anastomosing cords of liver cells which radiate from the central vein. Between these cell columns is a labyrinth of wide blood sinusoids through which the mixed blood coming from the terminations of the hepatic artery and portal vein flows to the central intralobular vein and so into the hepatic veins. The sinusoids are lined by flat endothelial cells and in part by the stellate phagocytic Kupffer cells which hang loosely in the blood stream. The latter form a part of the reticuloendothelial system. Between the lining cells of the sinusoids and the cords of liver cells is a rich network of reticular fibers which provides a supporting framework for the liver parenchyma.

In their simplest form the liver cell columns could be pictured as tubular glands of one cell thickness and of the shape of a test tube with the blind ends directed toward the center of the lobule. In the long axis of each is the bile capillary or canaliculus, closed at the central end and opening at the periphery into the interlobular bile ducts in the portal canals, through which the bile is conducted into the larger hepatic ducts and so to the gall bladder or duodenum.

Circulation.—During rest the liver contains about one-fourth of the total blood volume. The blood supply is a double one, partly arterial and partly venous. The hepatic artery is much smaller than the portal vein, but, by reason of higher pressure, it delivers about one-fifth of the total blood flow to the liver and its arterial blood provides about one-third of the oxygen requirement. Nevertheless, the liver is largely dependent on portal blood, poor in oxygen (40-60 per cent saturated) and delivered at low pressure (6-12 mm. Hg), so that its oxygen supply is probably always rather precarious and it is thus particularly vulnerable to conditions of chronic anoxia, such as chronic anemia and chronic passive hyperemia.

The portal blood comes to the liver in two more or less separate streams, one from the small intestine and ascending colon through the superior mesenteric vein which flows largely to the right side of the liver, and one from the descending colon and gastrosplenic area by way of the splenic vein which flows mostly to the left side of the liver. The division of the liver as regards this bilaterality of the portal circulation does not correspond with the anatomical division into right and left lobes but is along a plane passing through the middle of the gall bladder fossa and the point of entrance of the hepatic veins into the inferior vena cava (Cantlie's line). There is no evidence of a corresponding difference in the function of the two sides of the liver, but the streamline flow has an obvious bearing on the destination of substances absorbed in different parts of the gastrointestinal tract and on the hepatic localization of blood-borne infections and tumor metastases originating in the area of portal drainage.

Liver Function

The various known functions of the liver can be grouped under the following general headings:

1. The secretion of bile.
2. Metabolism and nutrition.
   (a) The assimilation and preparation of foodstuffs for distribution to the tissues.
   (b) The storage of foodstuffs and vitamins for maintenance and emergency.
3. Blood formation and coagulation.
4. Purification of the blood of useless and toxic substances, bacteria, and other particulate matter.
5. Regulation of blood volume by action of the liver as a blood depot.
6. Mineral metabolism, especially that of iron.
7. Regulation of acid-base equilibrium.

Tests of Liver Function

In considering the possibility of testing clinically the functional capacity of the liver, a number of limiting factors must be kept in mind:

(1) In common with other vital organs, the liver has a functional capacity far in excess of ordinary physiologic needs. Hence, there is difficulty in devising tests sufficiently sensitive to detect deterioration of liver function before the functional reserve has disappeared. (2) The liver has a great capacity for regeneration after partial removal or partial destruction. Thus, unless the damage to the liver is extensive and rapid, the simultaneous regenerative processes may compensate for and mask the destructive changes. (3) The liver is a dynamic and not a static organ. Hence, there is need for repeated testing in order to follow the upward or downward trend of hepatic function. (4) The liver has manifold functions which cannot be measured by testing a single function because there is a dissociation of the various functional activities. Thus, the necessity of testing more than a single function of the liver when attempting to estimate the degree of hepatic insufficiency. (5) Most of the functions of the liver are so intimately associated and correlated with the physiologic activities of other organs and tissues that it is difficult to demarcate precisely the hepatic factor.

Certain laboratory determinations, though not actually "tests" of liver function, are of great value in some forms of hepatic disease. Thus, in the jaundiced patient, it is evident that quantitative estimations of serum bilirubin, the van den Bergh reaction, the determination of bile in the urine and of urobilinogen in the urine and feces, all provide valuable information. Serum phosphatase and differential protein estimations also are important.[14b]

Among the various tests of hepatic insufficiency the following appear to have met more or less general approval: Galactose tolerance test, bromsulfalein clearance test, hippuric acid synthesis, blood prothrombin level and response to vitamin K, and the cephalin-cholesterol flocculation test.

The theoretical bases and the techniques of a great number of tests of liver function are described in detail by Lichtman.[1] Greene[12] discusses the employment and interpretation of a limited number of tests that they regard as especially valuable. The question of the relative sensitivity and reliability of some of the newer tests of liver function is dealt with by Mateer et al.[13] The correlation of biochemical and histologic changes in hepatic disease have been carefully studied by Sherlock.[14b]

Postmortem Changes

Postmortem autolytic changes develop quite rapidly in the liver. Portions of the liver adjacent to the transverse colon often develop a bluish-black discoloration. The most striking postmortem change is the so-called "foamy liver," which is due to postmortem growth in the liver of anaerobic gas-producing organisms from the intestinal tract. The liver becomes soft and spongy, the bubbles of gas produced honeycombing the hepatic tissue. Microscopically, the cells appear autolysed, with loss of cellular and nuclear detail. Numerous bacilli may be evident, particularly in blood vessels.

Congenital and Acquired Abnormalities of Form and Position

Congenital abnormalities of the liver are not common or important. Reidel's lobe is a downward projection of the right lobe, which may be mistaken for a tumor or thought to be a displaced kidney. The liver may be displaced in position in association with a congenital diaphragmatic hernia.

Acquired abnormalities of position are mainly downward or upward displacement by some extrahepatic cause, such as a subdiaphragmatic abscess or abdominal tumor. Abnormalities of form may be the result of contraction of scar tissue (e.g., hepar lobatum, see page 820) or nodularity from irregular regenerative hyperplasia or neoplastic growth. Transverse, oblique, or sagittal grooves on the upper or anterior surface of the liver are quite common. They have been attributed to pressure of the ribs, to folds of the diaphragm, and to tight clothing. The capsule is thickened at the depths of the folds, and adjacent hepatic parenchyma may show slight atrophic changes. Such grooving does not appear to be of any functional significance.

Traumatic Injury

Hematomas of small or large size are occasionally found beneath the capsule of the liver in newborn infants. While some appear to be on a traumatic basis, they may also be seen in blood dyscrasias, such as erythroblastosis fetalis, even when there has been no apparent trauma. More severe traumatic injury or rupture of the liver occurs on rare occasions incident to parturition. In adults, the liver may be severely injured or ruptured by crushing injuries of the upper abdomen, or by penetrating wounds. Severe hemorrhage and shock may accompany such traumatic injury. Leakage of bile may

cause sterile peritonitis. Necrosis in the liver as a result of trauma may result in the so-called "hepatorenal syndrome." Blunt injuries of the abdomen, even though the liver is only indirectly affected, may cause areas of necrosis in the liver. The convexity of the right lobe is particularly prone to such indirect traumatic injury. (See Fig. 84, page 122.)

Liver Death and the Hepatorenal Syndrome

More than twenty years ago, Heyd called attention to the fact, now generally recognized, that unexplained death may follow surgical operations on the biliary tract. Similar deaths have since been noted following traumatic injury of the liver and in association with various intoxications.[15, 16] The so-called "liver death" occurs within one to three days, with stupor increasing to coma and with extreme hyperpyrexia. In another group of cases, coma and hyperpyrexia are not features, but there is instead the delayed development of vasomotor collapse and oliguria, increasing to anuria with death in uremia a week or more after operation. This is referred to as the "hepatorenal syndrome." Pathologic findings are meager, consisting only of severe degenerative changes in the liver parenchyma and sometimes necrosis of small groups of liver cells, especially at the centers of the lobules. The kidneys present cloudy swelling of the epithelium of the convoluted tubules, varying in degree from slight in the cases of rapid liver death to severe degeneration or even necrosis of tubular epithelium in the cases exhibiting the hepatorenal syndrome. Other pathologic lesions are generally insufficient to account for death. Heyd[15] attributes these disturbances to failure of the liver to detoxify the products of disintegration of its own cells following injury to the liver. He regards the early deaths as the result of massive intoxication; the later deaths with renal insufficiency he interprets as due to the effects of smaller quantities of the hepatic toxin on the renal epithelium. Wilensky[16] believes that the early "liver deaths" may be attributable to overwhelming infection and he points out that the hepatorenal syndrome could be caused by the action on the kidney of any one of a variety of toxic substances detoxified by the normal liver but not effectively dealt with by the damaged liver. The subject is fully dealt with by Boyce.[2]

Degenerations

Cloudy Swelling.—Cloudy swelling is common in the liver as a result of acute infections. The liver is enlarged, has a tense capsule, softer consistency, and a paler, more opaque appearance than normal. Microscopically, the liver cells are swollen, have distinct margins and a pale granular cytoplasm.

Glycogen Infiltration.—Glycogen is normally quite abundant in the cytoplasm of liver cells, but is much depleted by the wasting which precedes death from many diseases, or during fasting or starvation. In autopsied cases a correlation may be shown between the amount of glycogen present and the elapsed time between food intake and death.[18] When abundant glycogen is present, as in cases of sudden unexpected death or in biopsied hepatic tissue, the cytoplasm of hepatic cells has a pale and fluffy appearance in contrast with the more homogeneous appearance usually seen. When glycogen is abundant, it may be quite evenly distributed in all parts of the lobule, but when present in lesser amount it is found mainly in periportal or peripheral parts of the lobule. The amount of cytoplasmic glycogen is also reduced in diabetes mellitus.

The glycogen content of the cytoplasm of hepatic cells may be abnormally increased in *von Gierke's glycogen storage disease.* This appears to be a congenital defect of glycogen mobilization, whereas normally glycogen is a very labile substance readily converted into glucose. It is seen as a rare condition in infants and children, and enlargement due to the excess glycogen accumulation may involve the heart or spleen as well as the liver.

The nuclei of hepatic cells normally do not contain glycogen. However, it is frequently present in the nuclei in diabetes mellitus and also in some other cases in which its causation and significance are unknown. The presence of glycogen in the nuclei of hepatic cells gives them a glassy, vacuolated, or empty appearance with ordinary stains. The chromatin is arranged about the periphery of the enlarged nuclei, and the central areas are clear.[18]

While glycogen often is dissolved out by the ordinary methods of fixation and preparation of tissues, it may be preserved by fixation of the tissue in absolute alcohol or Carnoy's fluid, and stained by Best's carmine. (See Fig. 761.)

Hyaline Change.—Intracellular droplets or irregular masses of hyaline material may be found in hepatic cells in portal cirrhosis. It apparently represents an early degenerative change, and by some has been considered a specific type of degeneration in cirrhosis. Connective tissue hyalin is observed in areas of fibrosis of the capsule or in the liver substance.

Amyloid Infiltration.—Amyloid infiltration is common in the liver as well as in the spleen and kidney in cases of tuberculosis, leprosy, and chronic suppuration.

The liver is enlarged, firm, has a tense capsule, rounded edges, and a pale color. The cut surface is abnormally translucent in the areas of amyloid accumulation. The amyloid appears as a hyaline material between the lining cells of the sinusoids and the liver cells. Its continued accumulation causes compression, atrophy, and disappearance of the cords of liver cells.

Fatty Change.—Fatty change in the liver is a common event, perhaps more frequent than in any other organ, and it may be of severe degree. The fat tends to accumulate at the periphery of the lobules, where, when abundant, it forms large globules which distend the hepatic cells. Nearer the centers of the lobules the globules tend to be smaller and only partially fill the hepatic cells. In prolonged passive congestion the fatty change may be most marked at the centers of the lobules. With marked fatty accumulation the liver is increased in size, is pale, with a tense capsule, and rounded margins. The cut surface bulges slightly, is pale or definitely yellowish, and usual markings tend to be obscured.

Distinctions between fatty degeneration and fatty infiltration in the liver are unreliable. Experimental evidence has indicated that the fat which is seen in the hepatic cells is transported metabolic fat derived from food or from fat depots of the body, rather than from an unmasking of fat held in the hepatic cells in some other form. The fat accumulation may be the result either of excessive mobilization of fat to the liver, or of injury to hepatic cells causing defective utilization or metabolism of fat brought to the liver in normal amount. Fatty livers are found in association with obesity, chronic alcoholism, malnutrition and wasting diseases (e.g., tuberculosis and malignant tumors), and in some cases of diabetes mellitus. Certain poisons, such as phlorhizin, carbon tetrachloride, chloroform, and ether, may cause fatty change. In experimental animals, marked fatty change in the liver may be produced by deficiency of choline (dietary) or of lipocaic (in depancreatized dogs). The role of such deficiencies in the pathogenesis of the common fatty change of the liver in human pathology is not yet estab-

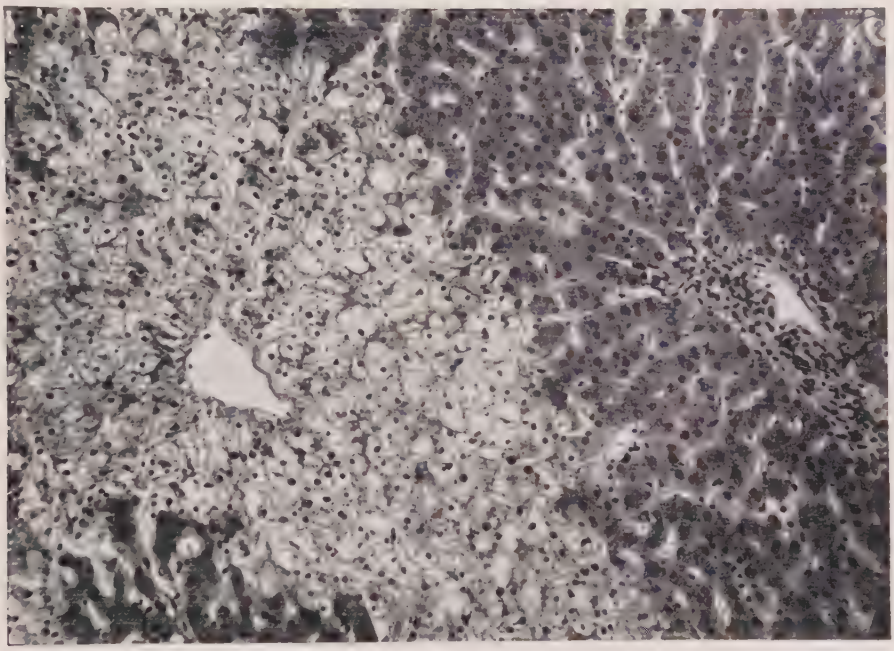


Fig. 702.—Fatty degeneration and atrophy around the central vein area in chronic passive congestion of liver.

lished. Very severe degrees of fatty change may be present in chronic alcoholism and may proceed to fibrosis (fatty cirrhosis) and eventually to portal cirrhosis, with disappearance of the fat in late stages. The relative importance of dietary deficiency and of a direct metabolic effect of the alcohol on the hepatic cells cannot be assessed at present.

In some cases of sudden death in young adults, marked fatty change in the liver has been the only finding.[20]

Pigmentation of the Liver

Hemosiderin accumulation in the liver is very common. In chronic passive congestion of the liver the hemosiderin is most prominent about central parts of the lobules. In hemolytic anemias the hemosiderin tends to be distributed diffusely. The pigment is found in both the hepatic cells and the phagocytic Kupffer cells of the sinusoids.

In hemochromatosis the pigment is largely hemosiderin, but hemofuscin is present as well. The pigment tends to appear first in the periphery of the lobules, and fibrosis (cirrhosis) develops (see page 818).

In malaria, hematin pigment may accumulate in large amount, mainly in the Kupffer cells of the sinusoids. It may be sufficient to give the liver a dark grayish-brown color. A similar pigment may be found in the liver in schistosomiasis.

Bile pigmentation of the liver is seen in any variety of jaundice. When seen fresh, the liver is yellowish, but soon changes to green as a result of oxidation of the bilirubin to biliverdin. Masses of pigment may be seen distending the bile capillaries and small ducts, and also within the hepatic cells.

Anthracotic pigment may be carried to the liver by the blood stream following rupture into the pulmonary veins of a thoracic lymph node containing carbon pigment. The carbon particles are phagocytized by the Kupffer cells and tend to be carried to portal spaces, where they accumulate.

Silver pigment may be found under the sinusoidal endothelial cells of the liver in argyria.

Circulatory Disturbances

Passive Hyperemia.—Passive hyperemia of the liver is most often the result of cardiac disease with congestive failure, but may also result from compression and obstruction of the inferior vena cava or obstructions of the pulmonary circulation leading to right-sided cardiac failure. Increased pressure in the venous system affects the liver severely because of the short distance between the point of entry of hepatic veins into the vena cava and the latter's entry into the right auricle.

In early or acute phases, the liver is large, dark red or purple in color, soft, and oozes blood on being cut. The central zones of the lobules are congested and red, the periphery of the lobules light brown. The liver may appear smaller at postmortem examination than it actually was during life because some of the blood may drain out into other areas after death. When the congestion has been more prolonged, lobular markings are pronounced, with reddish areas of congestion and contrasting yellowish areas of fatty degeneration. This gives the cut surface the so-called "nutmeg" appearance.

Microscopically there are dilatation and congestion of the central vein and adjacent central parts of the sinusoids. The hepatic cells in the central zone appear atrophic or may show pronounced fatty degeneration. Actual central necrosis may occur. The effects on the hepatic cells appear to be mainly the result of anoxemia. Hemosiderin pigment accumulates in Kupffer cells. Accompanying the central atrophy of hepatic cells there are a condensation and relative increase of connective tissue (see cardiac cirrhosis, page 819).

Edema.—Edema in the liver is manifested by a separation of the cords of liver cells from the endothelial and Kupffer cells lining the sinusoids. The widened space around the hepatic cells is occupied by a fine web of pink-staining granular debris which appears to be precipitated protein material. This change has also been referred to as "serous hepatitis."

Infarction.—Aseptic infarction in the liver is uncommon, presumably because of the abundant anastomoses in the double blood supply. When it occurs it is most often due to blockage of intrahepatic branches of the portal vein, although some infarcts have developed after blockage of the hepatic artery. The infarct is usually hemorrhagic. The so-called Zahn's infarct (atrophic red infarct) is not a true infarct. It is an area of hyperemia with atrophy of hepatic cells but without actual necrosis.

Obstruction of Hepatic Arteries.—Occlusion of the main hepatic artery may result in massive necrosis. Obstruction of intrahepatic branches may cause a Zahn's infarct or a true infarct, but often causes no recognizable change in the liver.

Obstruction of Portal Veins.—Acute complete obstruction of the portal vein, as by rapid thrombosis or ligation, results in early death. There may be an associated infarction of the small intestine. According to Boyce,[2] the chief cause of death is not loss of blood into the

Fig. 703.

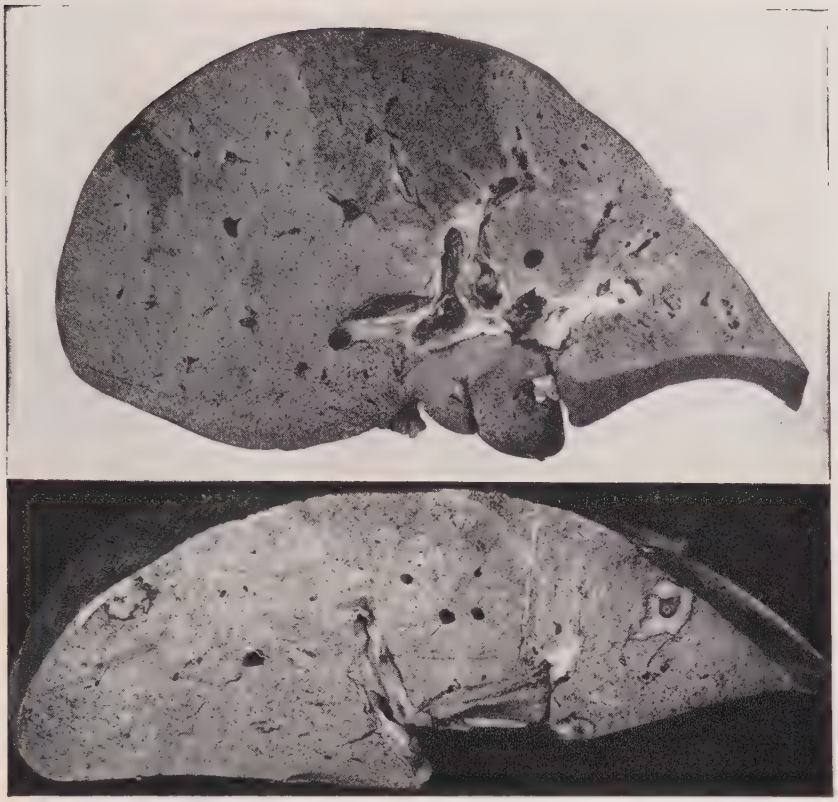


Fig. 704.

Fig. 703.—Liver. Thrombosis of intrahepatic portal veins with Zahn infarcts.

Fig. 704.—True infarcts of liver due to embolism from mural thrombi complicating cardiac infarction. (Courtesy Dr. G. L. Duff.)

Fig. 705.—Infarcts of the liver in a case of polyarteritis nodosa. (Courtesy Dr. J. F. Kuzma.)

gastrointestinal tract, but abrupt fall of blood pressure due to a neurogenic factor, the decrease of blood pressure being maintained by gradual withdrawal of blood from the circulation, decreased blood volume, and stagnation of blood in the gastrointestinal area. A more gradual or chronic occlusion of the portal vein may be found associated with a variety of hepatic and extrahepatic conditions. Cirrhosis and carcinoma of the liver may be complicated by portal thrombosis, as may also carcinoma of the pancreas. Changes in the vein wall itself (portal phlebosclerosis) may predispose to thrombosis, and such phlebosclerosis tends to result from the prolonged portal congestion which accompanies hepatic cirrhosis. Organization and canalization of the thrombus results in a chronic obstruction in the portal flow. Collateral circulatory channels develop which tend to by-pass the liver, in a fashion similar to that which occurs in portal cirrhosis, and the spleen becomes enlarged. Ascites and esophageal varices may occur. Thrombosis of hepatic veins (Chiari's syndrome) is discussed on page 545.

hepatic cells from injurious influences (see discussion also on page 816).

Hepatic necroses may be classified roughly according to their distribution as of the following types: (1) focal necrosis, i.e., small necrotic foci distributed without any constant relationship to particular areas of the liver lobules; (2) zonal necrosis, in which the involved areas are in fairly constant relationship to a particular part of the liver lobules, and referred to as central, midzonal, and peripheral; and (3) diffuse necrosis, such as occurs in acute yellow atrophy and fatal infectious hepatitis, in which hepatic parenchyma is destroyed over massive areas.

Focal Necrosis.—Focal necroses, which have no special or constant site in the liver lobules, occur in a variety of severe

Fig. 706.—Liver. Portal cirrhosis and thrombosis of portal vein. (Courtesy Dr. G. L. Duff.)

Necrosis

Hepatic cells are injured sufficiently to undergo necrosis by a wide variety of poisons of chemical, infectious, and metabolic origin, and by local disturbances of circulation. Resistance of the hepatic cells probably may vary with their metabolic or nutritional state. Adequate stores of glycogen in the liver cells appear to give them some protection. Certain dietary factors, particularly choline and methionine or other components of the vitamin B complex when adequate in amount, appear to protect the

infections, but particularly in typhoid fever, tularemia, and poliomyelitis. They are not usually large enough to be prominent grossly. Microscopically they are small areas, not always sharply circumscribed, in which the hepatic cells are in various stages of degeneration, necrosis, and autolysis. At a somewhat later stage the necrotic cells may be largely removed, and the area infiltrated by inflammatory cells, predominantly mononuclear. In typhoid fever there appears to be a local blockage of sinusoids by large mononuclear cells, the destruction of hepatic cells

being due to a combination of ischemia and toxic injury.

Central Necrosis.—Central necrosis is the commonest type of zonal necrosis. It is most often due to ischemia, and may be seen when there is severe chronic passive congestion. Sometimes an infective factor is added, particularly from streptococci. The central parts of the liver lobule, being farthest from well-aerated blood, are most subject to injury from anoxia. The hepatic cells around the central vein areas show degeneration, atrophy, and necrosis, and the sinusoids are dilated and congested. Various infectious diseases may show central necrosis. A variety of chemical poisons, such as chloroform, carbon tetrachloride (Fig. 117, page 158), and trinitrotoluene, produce central necrosis. Severe hyperthyroidism may be associated with central necrosis.

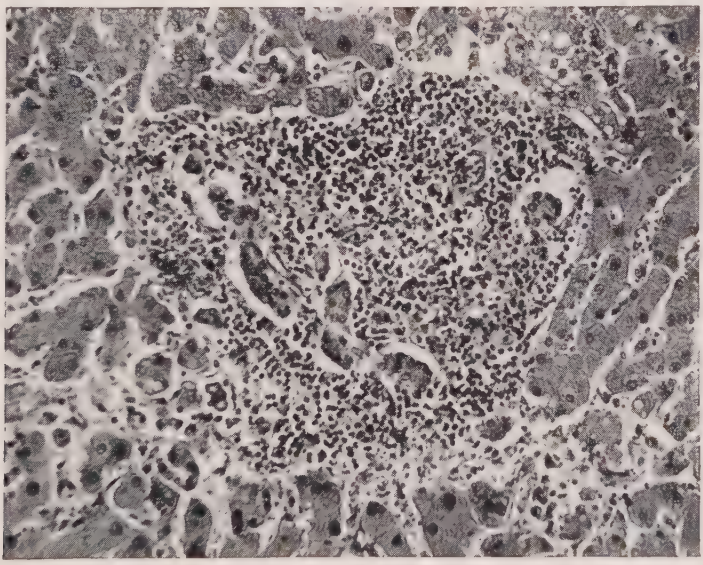


Fig. 707.—Liver. Focal necrosis in tularemia.

Midzonal Necrosis.—Midzonal necrosis is particularly characteristic of yellow fever, but may be seen in other infective conditions. The lesions in yellow fever may be rather sharply and regularly found in the midzonal areas of the liver lobules (Fig. 218, page 333), and are characterized by rounded hyaline cytoplasmic change (Councilman bodies) and intranuclear inclusions. The Councilman bodies are not specific for yellow fever as they are also found in some cases of infectious hepatitis and of fatal burns. Although Belt[25] has described the hepatic lesions in fatal burns as simulating those of yellow fever, hepatic changes are more commonly in a central zone, and appear to be due to tannic acid treatment rather than to the burn itself.

Peripheral Necrosis.—Peripheral necrosis occurs in phosphorus poisoning, and also in eclampsia. However, in eclampsia the necroses are by no means constant in position, but are often focal in distribution and hemorrhagic in character.

The Liver in Eclampsia.—Hepatic lesions often form the most prominent pathologic changes found in eclampsia, although they are not readily correlated with the severity of the condition and probably are of less importance than the renal and cerebral lesions. In the eclamptic toxemia of late pregnancy the hepatic changes may be varying combinations and degrees of hyperemia, fatty degeneration, necrosis, infarction, and hemorrhage. Patchily scattered through the hepatic substance, they give the liver a grossly mottled appearance. Irregular hemorrhagic areas beneath the capsule and throughout the liver often result in a striking gross appearance.

Microscopically there is edema, hemorrhagic necroses, most often about peripheral parts of the lobules, and fibrinous thrombi in small branches of the portal vein. Fibrin appears in portal capillaries, with capillary stasis, formation of blood spaces and hemorrhages accompanied by cell destruction. None of the changes in the liver in eclampsia appear to be constant or pathognomonic.

Diffuse Necrosis of the Liver.—Widespread or diffuse necrosis involving the liver has commonly been called *acute yellow atrophy* of the liver. Milder or more prolonged cases in which there has been opportunity for removal of some necrotic cells and regenerative hyperplasia from remaining liver tissue have been called *subacute yellow atrophy,* postnecrotic cirrhosis, and toxic cirrhosis. In most such nonfatal cases, however, a progressive fibrosis does not occur, complete regeneration and healing may be achieved, and a true cirrhosis does not develop.

A variety of causal agents may produce widespread hepatic necrosis. Certain acute infections, such as scarlet fever, on rare occasions may be complicated by hepatic necrosis. The more important chemical agents are chloroform, arsenicals, cinchophen, phosphorus, carbon tetrachloride, and sulfonamides. It may occur in severe hyperthyroidism, particularly the so-called thyroid crisis or thyroid storm. The hepatic necrosis in eclampsia occasionally becomes diffuse. A distinctive type of acute yellow atrophy has been described in pregnant women,[23] and in obstetric practice delayed chloroform poisoning may produce hepatic necrosis. A large group of cases of acute yellow atrophy of the liver, formerly considered of idiopathic origin, now seem to be accounted for as cases of infectious hepatitis. The hepatic changes in acute and subacute yellow atrophy of the liver are essentially the same as those described in acute and subacute fatal cases of infectious hepatitis (see page 823). The acute form is fatal after a short duration with fever, gastrointestinal upset, disturbances of hepatic and renal functions, jaundice, crystals of leucine and tyrosine in the urine, and coma.

Associated with the destruction of hepatic parenchyma the liver is small, soft, wrinkled, and mottled with red, yellow, and greenish areas. The liver may be shrunken to half its normal size. In areas where there is extensive destruction of hepatic cells the red color predominates, the yellowish and pale areas representing areas of fatty degeneration or, in the more subacute cases, areas of regenerative hyperplasia. The microscopic changes are similar to those of infectious hepatitis (page 824).

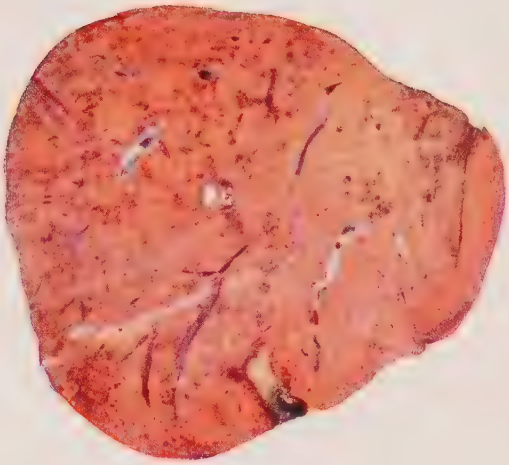
Cirrhosis

Cirrhosis is a chronic, diffuse, progressive inflammation of the liver characterized by fibrosis or scarring, degeneration and destruction of hepatic parenchymal cells, and attempted regenerative proliferation of remaining cells. In a broader sense the term is often applied to any widespread fibrosis or scarring of the liver, in which loss of hepatic cells is associated with actual or relative increase of connective tissue. Localized limited inflammatory processes and scarring are usually excluded. Although the term "cirrhosis," derived from the Greek word *kirrhos,* meaning tawny or orange-colored, was applied originally because of color changes, it is fibrosis rather than any distinctive color which forms a constant feature of the condition.

Cirrhosis of the liver occurs in several forms, only some of which are of known or distinctive etiology. Cirrhoses due to variable and distinctive etiological factors may produce similar clinical pictures and indistinguishable anatomic changes, particularly in their late phases. Hence, the most satisfactory classification of cirrhosis at present appears to be one in which both etiological factors and anatomic changes receive consideration.

1. Diffuse nodular, portal or Laennec's cirrhosis, which is of variable and often undetermined etiology.
2. Biliary cirrhosis, which is of chologenic origin, and associated with obstruction of bile ducts, either within the liver or extrahepatic.
3. Congestive or central cirrhosis, usually the result of prolonged congestive cardiac failure.
4. Parasitic cirrhosis, due to infection by schistosomes or the liver fluke, *Clonorchis sinensis.*

1.



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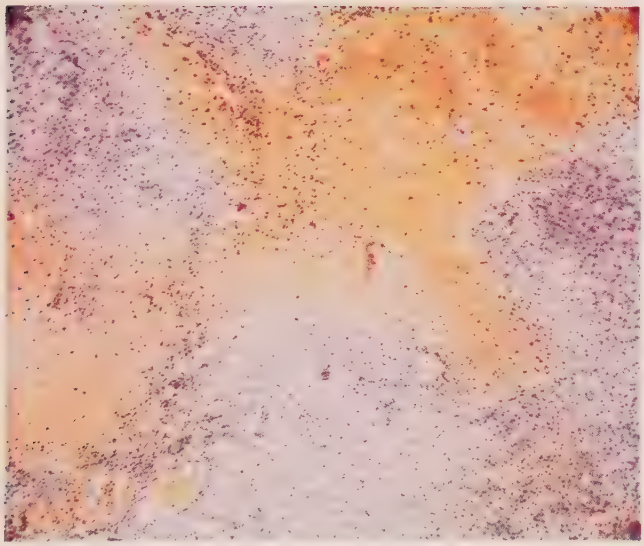

3.

PLATE VIII.—The liver in eclamptic toxemia of pregnancy. *1* and *2* show the anterior surface and a cross section of the liver. Note that the lesions are predominantly in the right lobe. *3* shows the extensive periportal hemorrhage in the microscopic section. (From Dieckmann, The Toxemias of Pregnancy, The C. V. Mosby Co.)

5. Syphilitic cirrhosis, a diffuse fibrosis or extensive scarring resulting from syphilitic infection.

Within these classes are subvarieties which are distinguishable on an etiological or morphologic basis.

Portal Cirrhosis

Portal cirrhosis (Laennec's cirrhosis, diffuse nodular cirrhosis, atrophic cirrhosis, hobnailed liver, alcoholic cirrhosis) is the commonest variety of cirrhosis. Few of the multitude of names by which it has been called are without some objectionable feature. The term, atrophic cirrhosis, is not acceptable, as in not all cases is the liver smaller than normal, particularly before late stages. To call it alcoholic cirrhosis is not always possible because alcohol may sometimes be excluded as a causative factor. As in many cases the etiology is unknown or incompletely understood, no etiological designation is generally applicable to this type of cirrhosis.

Portal cirrhosis is characterized by marked alteration of the architectural pattern of the liver. The normal lobular arrangement of the liver becomes diffusely and completely distorted by irregular degeneration and destruction of hepatic cells, accompanied by fibrosis and irregular regenerative hyperplasia of hepatic cells and bile ducts. In addition to disturbances of various functions of the liver, there is obstruction of portal blood channels in the liver, with chronic passive hyperemia of tissues drained by the portal circulation. This results in distension of collateral channels of venous return which by-pass the liver, some of which may rupture and result in fatal hemorrhage. The obstruction to portal flow is the main factor in causation of ascites in cases of cirrhosis.

Incidence.—Portal cirrhosis is a common disease in most parts of the world, forming a very large proportion of all types of cirrhosis. The reported autopsy incidence of cirrhosis has varied from 0.3 per cent (Moscow) to 12 per cent (Zurich, China). In the United States, the autopsy incidence in various centers has been reported from 1.6 to 9 per cent, with an average of about 3 per cent. It may occur at any age, but the peak incidence is in late middle life (50 to 55 years) and most cases are between 40 and 65 years of age. Cases in juveniles have been reported to constitute from 0.5 to 4.4 per cent of cases of cirrhosis. It appears to be more than twice as frequent in males as in females, and in women the peak age incidence is about a decade earlier than in men. It appears to be more common among Italians and Irish, but there is little accurate data concerning the influence of race and nationality on the incidence of portal cirrhosis.

Etiology.—A complete understanding of the etiology and pathogenesis of portal cirrhosis has not yet been reached. It is apparent that it is due to chronic or repeated injuries of hepatic cells. Experimentally, many hepatotoxic agents have been found capable of causing the changes characteristic of portal cirrhosis. The hepatotoxic substances include arsenic, lead, copper, phosphorus, silica, manganese, tar, carbon tetrachloride, and chloroform. Except for isolated examples, such substances have not been incriminated as factors in the usual cases of portal cirrhosis of man. The clinical evidence points to alcohol as a hepatotoxic agent of importance in human portal cirrhosis. Among chronic addicts of alcohol, 5 to 8 per cent eventually develop portal cirrhosis. Among cases of portal cirrhosis, a history of excessive use of alcohol has been found in 30 to 60 per cent in various series. Among cases selected by certain anatomic criteria, 80 per cent have been in patients with chronic alcoholism.[40] Although the overwhelming clinical evidence indicates that alcoholism is of marked etiological importance, alcohol alone has failed experimentally to produce cirrhosis. It seems clear that the relationship of alcohol to cirrhosis is not a direct one, and that other complementary factors are essential. This led to a search for contaminating substances in alcoholic beverages which could be incriminated. Lead, copper, and phosphorus have been under suspicion in this regard, but without evidence that they are commonly of importance.

The experimental administration of alcohol to animals has resulted in production of cirrhosis when combined with a high-fat diet in a prolonged experiment.[39] The changes so produced in the liver proceed through a stage of enlargement and marked fatty change (fatty cirrhosis), a finding common in alcoholism, although the late or final stage was that of an atrophic liver containing little fat. Although a direct metabolic effect of alcohol has been postulated, in the nature of an interference with oxidation in hepatic cells and leading to their excessive accumulation of fat, it appears probable that other factors, such as deficiency of certain dietary elements, are of equal or greater importance.

The probable importance of dietary deficiency has been shown by experiments in which cirrhosis was produced by deficiency of dietary factors without the addition of known hepatotoxic agents. Brewer's yeast has been shown to contain an unidentified factor which prevents cirrhosis in animals on a diet deficient in the vitamin B complex.[32] In other experiments with rats, the addition of choline or methionine to a deficient diet low in casein tends to protect the liver from fatty change and cirrhosis, whereas the addition of cystine alone appears to accentuate the hepatic injury.[35] The experimental dietary cirrhosis appears essentially similar to portal cirrhosis in man except for the presence in experimental dietary cirrhosis of a pigment termed "ceroid." This is a greenish-yellow pigment, observed mainly in the periportal connective tissue, but also in hepatic and Kupffer cells. The pigment, although insoluble in lipoid solvents, has an affinity for fat stains, basic aniline dyes (especially methyl green), is acid-fast when stained with the Ziehl-Neelsen method, and is fluorescent. While the nature and significance of this pigment is unknown, evidence has been presented suggesting a relationship to vitamin E deficiency.[38] Clinical success in arresting human cirrhosis by dietary means and by methionine and choline supports the importance of these factors.[33, 34]

The evidence from experimental studies and clinical observations points to dietary deficiency as being of marked importance in many cases of portal cirrhosis. Deficiencies in dietary intake in alcoholic addicts are common, and appear to be the important factor added to any specific injurious effect of alcohol or its contaminants on the liver cells. It is obvious that in a minority of cases hepatotoxic agents other than alcohol may be etiologically important, and dietary deficiency here likewise may be responsible for failure of the liver to be protected from injury. Chronic ulcerative colitis is sometimes complicated by hepatic cirrhosis, probably chiefly as a result of nutritional deficiency.[40a]

Pathologic Anatomy.—The liver affected by portal cirrhosis is variable in size. While usually reduced in size and weight (often below 1,800 grams), the organ may be of normal size or even considerably larger than normal, and weights up to 3,000 grams or even more are not uncommon. The most characteristic feature is the diffuse development of small brownish-yellow nodules, usually between a millimeter and a centimeter in diameter, separated by irregular thick bands of connective tissue of pale gray color. The surface is markedly roughened by the projecting nodules. The consistency of the liver is very firm, and its normal shape usually is well maintained.

Microscopically, bands of connective tissue divide the hepatic cells into irregular lobules of variable size. The normal architectural arrangement of lobules with a central vein and peripheral portal areas is markedly distorted or completely lost. Hepatic cells show variable degrees of albuminous, fatty, and hyaline degeneration, and necrosis. Various inflammatory cells, lymphocytes, plasma cells, and some neutrophilic leukocytes infiltrate the excess connective tissue and are often abundant. The connective tissue is young, loose, edematous, cellular and actively proliferating, except in latent or healed stages. Irregular attempts at regeneration of hepatic cells may be evident. Small bile ducts appear numerous and prominent, and appear to be due to active proliferation.

The early changes in portal cirrhosis consist of an increase in perilobular connective tissue. Proliferating fibrous tissue around the portal spaces extends irregularly between injured hepatic cells at the periphery of the lobule. In some cases a marked fatty change is prominent during early phases, the great degree of fatty change overshadowing the increase of connective tissue (fatty cirrhosis). Disappearance of the fat, largely or completely, often occurs in late stages, and is accompanied by marked decrease in the size of the liver. The so-called healed or latent stages are characterized by sharply outlined nodules, dense collagenous connective tissue with few inflammatory cells, absence of marked degeneration or necrosis of remaining hepatic cells, and lesser prominence of small bile ducts.

Effects of Portal Cirrhosis.—Although the various functions of the liver are disturbed to variable degrees by cirrhosis, the most prominent effects are the result of obstruction in the portal circulation. This results in a chronic passive hyperemia of the tissues drained by the portal veins, the spleen, and much of the intestinal tract. The bowel appears congested and edematous. The spleen is enlarged, firm, and dark red in color.

The obstruction with increase in pressure in the portal circulation appears to

be the most important factor leading to ascites. A second factor promoting accumulation of peritoneal fluid is a decrease of plasma albumin as a consequence of the extensive hepatic damage, with a corresponding lowering of the osmotic pressure of the blood. Some evidence suggests that this hypoproteinemia may not be of major importance.[48, 49] Unexplained hydrothorax sometimes occurs.[49a]

Collateral communications between the portal vein and inferior vena become enlarged when obstruction develops in the portal flow, and may result in a large amount of the portal blood by-passing the liver. Cutaneous vessels over the abdomen and back become distended and prominent. Varices of esophageal veins commonly develop, the anastomoses with these from the portal circulation being composed of

Fig. 708.

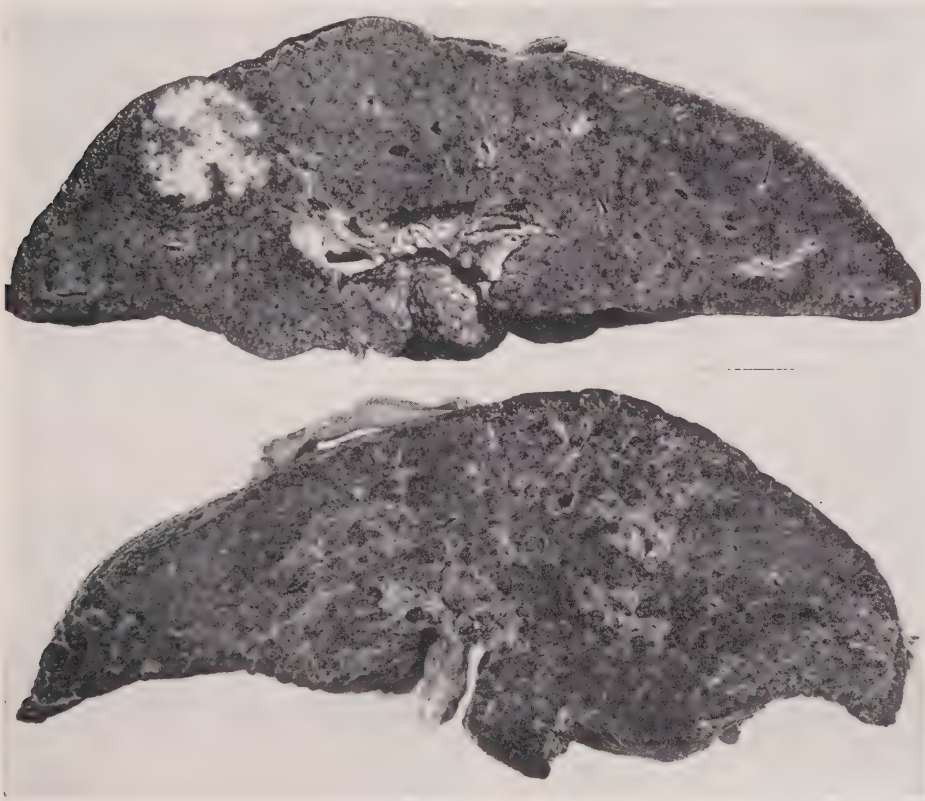

Fig. 709.

Fig. 708.—Portal cirrhosis and primary carcinoma of liver.
Fig. 709.—Portal cirrhosis of liver. (Courtesy Dr. G. L. Duff.)

Injection studies have shown a marked diminution in the total vascular bed in cirrhotic livers.[50] Another factor in the portal obstruction has been suggested by in vitro perfusion studies which suggest abnormal communications between hepatic arteries and portal veins in cirrhotic livers. As a result, the higher pressure in the hepatic arteries is transmitted to the portal veins, which hinders drainage by the portal system.[41]

vessels from the coronary veins and from the left gastroepiploic veins and vasa brevia. In the lower third of the esophagus the rich anastomoses of submucosal veins are poorly supported. This is a frequent site for varices and venous rupture with massive hemorrhage in cases of cirrhosis. Varices of hemorrhoidal veins are much less common in association with cirrhosis.

Testicular atrophy is a common accompaniment of cirrhosis.[44] Alteration or in-

activation of circulating estrogens appears to be a normal function of the liver which is disturbed when the liver is extensively damaged in cirrhosis. Urinary excretion of estrogens is increased and of androgens decreased.[46] The testis is susceptible to excess of the circulating estrogens. Other common phenomena in cirrhosis which are probably related to the estrogenic excess are gynecomastia, arterial spider nevi, and palmar erythema.[45] There is considerable recent evidence that members of the vitamin B complex are important in protecting the liver from agents which interfere with its normal function of inactivation of estrogenic substances.

Fig. 710.—Varicose veins at lower end of esophagus. From a case of portal cirrhosis of the liver. (Courtesy Dr. H. C. Schmeisser.)

In active cirrhosis, depression of the serum albumin and lengthening of the galactose time show some correlation with the severity of the hepatic changes. Other tests of hepatic function show abnormalities which appear to have no close correlation with the degree of histologic change.[14b] Occasional patients with cirrhosis develop a macrocytic anemia, with findings in the blood and hemopoietic tissues similar to those of pernicious anemia. Mild leukopenia with a relative monocytosis also may occur.

Banti's Syndrome.—Banti's syndrome is a condition in which splenomegaly and anemia dominate the clinical picture, even though there is a portal cirrhosis of the liver. The hepatic changes are similar to those in other cases of portal cirrhosis (see page 918).

Hepatolenticular Degeneration (Wilson's Disease).—Hepatolenticular degeneration is a rare, progressive, fatal disease characterized by portal cirrhosis of the liver, degenerative changes in the basal ganglia (often with gross degeneration of lenticular nuclei), extrapyramidal signs, and pigmentation of Descemet's membrane at the limbus of the cornea (Kayser-Fleischer ring). It usually begins before the age of 30 and is sometimes familial. Some evidence suggests that the liver is primarily involved, and the cephalin flocculation test usually shows disturbance of hepatic function.[53] The hepatic changes do not differ from those of other cases of portal cirrhosis (see also page 1315).

Pigmentary Cirrhosis.—Pigmentary cirrhosis, a regular occurrence in hemochromatosis, is morphologically similar to the ordinary portal cirrhosis except for the addition of abundant pigment. The pigment, mainly hemosiderin but with lesser amounts of hemofuscin, is abundant in the connective tissue, hepatic cells, and Kupffer cells, and gives the organ grossly a dark brownish color. It is probable that the accumulation of pigment is primary, and injures or destroys hepatic cells. The presence of the pigment around portal spaces stimulates proliferation of connective tissue, as occurs also in other organs of the body where the pigment accumulates. The destruction of hepatic cells probably is a factor also in promoting fibrosis (see also page 82).

Cirrhotic livers apart from hemochromatosis often show an excess accumulation of hemosiderin pigment, a change sometimes referred to as "pigmented cirrhosis." There is no evidence in these cases that the hemosiderosis has been a cause of the cirrhosis, and in hemolytic conditions hemosiderosis of the liver is often marked without the development of any cirrhosis.

Biliary Cirrhosis

Obstructive biliary cirrhosis is the result of a prolonged obstruction of bile ducts. Commonly it is the extrahepatic ducts which are affected, but sometimes the site of obstruction is in the intrahepatic ducts. Experimentally and in man the prolonged biliary obstruction results in dilatation and tortuosity of biliary channels, which become filled by inspissated bile. Also, there occur proliferation of terminal bile ducts, atrophy and necrosis of hepatic cells, and proliferation of connective tissue about portal areas at the periphery of the lobules.

The biliary obstruction in infants may be congenital, due to congenital stenosis

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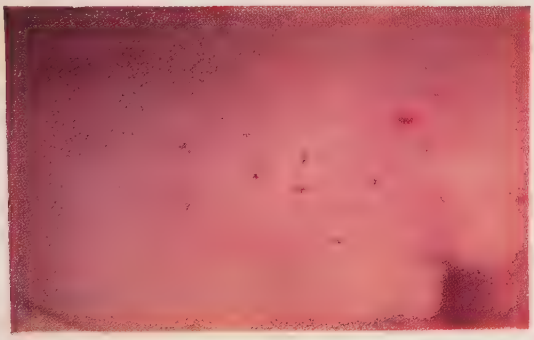


4.

PLATE IX.—*1*, Hepatic cirrhosis. Ascites, congested veins, pimented male nipple, axillary alopecia, absence of striae. *2*, Hepatic cirrhosis. Palmar erythema and vascular spider. *3*, Hepatic cirrhosis. Vascular spiders. *4*, Jaundice and biliary cirrhosis following ligation of common bile duct. (From Wiener, Skin Manifestations of Internal Disorders, The C. V. Mosby Co.)

or atresia of extrahepatic bile ducts. Acquired biliary obstructions in adults may be due to a variety of causes, of which gallstones, tumors of the head of the pancreas or at the ampulla of Vater, and inflammatory stenosis are most frequent.

The liver is of normal or moderately decreased size, with a smooth or slightly granular surface and deep bile pigmentation. Microscopically, there is perilobular fibrosis, the bile ducts are distended with inspissated masses of yellowish-brown bile, and an infiltration of lymphocytes, plasma cells, and sometimes neutrophilic leukocytes occurs around the proliferating and distended small bile ducts. The marked degrees of architectural distortion, fibrosis, and nodularity such as occur in portal cirrhosis are not usually seen in obstructive biliary cirrhosis.

There is evidence that an intrahepatic biliary obstruction of inflammatory origin occurs, and gives rise to a form of obstructive biliary cirrhosis. This has been referred to as "chronic intrahepatic obliterating cholangitis"[58] or as "cholangiolitic cirrhosis," and it has been suggested that the rare hypertrophic biliary cirrhosis described by Hanot (Hanot's cirrhosis) is of this type. Certain cases of prolonged hepatitis appear to undergo a transition to a cholangiolitic cirrhosis.[59] In such cases there occurs regurgitation jaundice with pruritis, hypercholesterolemia, and hyperphosphatasemia, but ascites is absent. In late or end stages, the changes in the liver progress to give an appearance similar to that of portal cirrhosis.

Cirrhosis due to *Clonorchis sinensis* (see page 820) and xanthomatous cirrhosis in the lipidoses[46b] (see page 950) are due essentially to intrahepatic biliary obstruction. Xanthomatous (pericholangiolitic) biliary cirrhosis is characterized by chronic inflammation about the smallest bile ducts in portal areas, with duct blockage and intralobular bile stasis. Observed mainly in females, it is associated with high cholesterol and lecithin values of the serum and xanthomas of the skin. It has been evident in some cases that the cirrhosis preceded the xanthomatosis.

Fig. 711.—Liver, cardiac cirrhosis. (Courtesy Dr. G. L. Duff.)

Cardiac Cirrhosis

Cardiac or congestive cirrhosis is a fibrosis and alteration of architecture of the liver associated with severe and prolonged passive hyperemia of that organ in cases of congestive cardiac failure. It is preceded by centrolobular congestion and necrosis. In the most severe degree it occurs in cases of constrictive pericarditis and rheumatic heart disease, and less commonly with hypertension or other forms of cardiac disease. Repeated bouts of decompensation appear to favor development of congestive cirrhosis. Hypertension of

the portal circulation over a sufficiently long period appears to be an essential factor.[57a] There is some doubt that congestive cirrhosis is a truly progressive disease apart from repeated episodes of cardiac decompensation.

Fig. 712.—Echinococcus cyst of liver. Note the convoluted membranous content.

In congestive cirrhosis the liver is of normal or slightly reduced size, firm in consistency, and dark reddish-brown or purplish-red in color. The surface is only slightly nodular, and the capsule is thickened. The cut surface shows a mottling of gray or yellowish-gray areas separated by brownish-red zones of variable size and shape. Microscopically, fibrosis may be evident in portal zones as well as centrally. Cellular infiltration in areas of fibrosis is scanty. Some alteration of lobular architecture may occur (see also page 107).

A type of congestive cirrhosis occurring in cases of diffuse toxic goiter has been described by Moschcowitz.[57a] Predominantly in the subcapsular zone of the liver, it is characterized by fibrosis in the interlobular septa, apparently due to altered circulatory dynamics.

Syphilitic Cirrhosis

The liver is frequently affected in both congenital and late acquired syphilis. In congenital syphilis excess mesoblastic tissue and chronic inflammatory cells are present in enlarged portal areas, but it probably does not progress to a true cirrhosis. Acquired syphilis, however, may produce very marked scarring and distortion of the liver. This may be in the form of coarse bands of connective tissue which traverse the liver and produce linear depressions of the surface[31] or there may be deep retracted scars as a result of healing of multiple gummas (hepar lobatum). Hepar lobatum has been found in 16 per cent of cases of late acquired syphilis, and predominantly between the ages of 30 and 60 years. Jaundice, ascites, esophageal varices, and splenomegaly may occur separately or in various combinations in some cases.

Parasitic Cirrhosis

Fibrosis in the liver may result from infection with the liver fluke, *Clonorchis sinensis,* or with schistosomes.

Clonorchis sinensis, prevalent in the Far East and in India, lodges in the biliary system, where it may at times cause sufficient obstruction to result in a cholangitic biliary cirrhosis (see page 378).

Schistosomiasis results in hepatic fibrosis due to the lodgment of ova in the liver. Cirrhosis occurs particularly with *Schistosoma mansoni* and less frequently with *S. japonicum* and *S. haematobium.* The liver is nodular, firm, and shows on the cut surface pale gray fibrotic areas. The fibrosis is particularly about portal areas, where ova or their remnants may be seen. Broad bands of fibrous tissue may be formed, with considerable architectural distortion. In late stages, clinical manifestations may be similar to those of portal cirrhosis, with ascites, splenomegaly, anemia, and esophageal varices (see page 384 and Fig. 278).

Infections of the Liver

A great variety of organisms, including many bacteria, spirochetes, viruses, fungi, protozoa, and helminths may involve the liver. Pyogenic organisms quite commonly involve the liver, producing abscesses. Certain bacteria, such as those of typhoid fever and tularemia, quite constantly and characteristically involve the liver, producing small areas of necrosis (see page 220). In tuberculosis and leprosy the liver is often infected, but usually hepatic involvement is overshadowed by lesions elsewhere. Among spirochetal infections, Weil's disease, due to *Leptospira icterohaemorrhagiae,* is characterized by severe hepatic involvement. Syphilis may involve the liver in either the congenital or the acquired form (see page 277). Certain viral infections involve the liver

severely and characteristically. Yellow fever produces characteristic hepatic lesions (see page 333). Infectious hepatitis and homologous serum jaundice appear to be of viral origin with primary involvement of the liver. Among the fungi, actinomycosis frequently produces hepatic abscesses. Blastomycosis and coccidioidomycosis may occasionally produce small hepatic lesions. Histoplasmosis often involves the liver, the encapsulated organisms being found in large numbers in the Kupffer cells. Among the protozoa, *Endamoeba histolytica* frequently produces abscess in the liver due to metastatic spread of the organisms from the bowel. Malaria commonly produces heavy accumulation of hematin pigment in the phagocytic Kupffer cells. Several helminths commonly or characteristically produce lesions in the liver. The larval form of the dog tapeworm, *Taenia echinococcus,* often lodges in the liver, producing there a hydatid cyst (see page 390). Schistosomal infection produces hepatic lesions due to ova which are carried to the liver in the portal blood and produce irritation (see page 384). The liver fluke, *Clonorchis sinensis,* and *Fasciola hepatica* lodge in the bile ducts, which they tend to obstruct (see page 378).

Abscess of the Liver.—Abscesses of the liver are usually of pyogenic, amebic, or actinomycotic origin.

Pyogenic abscesses may result from: (a) spread of organisms to the liver by way of the portal vein (pylephlebitis) from the appendix, rectum, or other parts of the bowel; (b) extension of organisms to the liver by way of the bile ducts (cholangitis) from the gall bladder; (c) spread to the liver from contiguous infected tissue, e.g., a subphrenic abscess; (d) infection carried to the liver by hepatic arteries in septicemia; and (e) penetrating traumatic injuries. The bacteria most commonly found are colon bacilli, staphylococci, and streptococci.

Pylephlebitis with multiple liver abscesses most frequently is an extension from an acute suppurative appendicitis. Infected emboli from small inflamed veins in the infected area are carried by portal venous channels to the liver, and produce small abscesses at their site of lodgment. The abscesses tend to be more abundant in the right lobe. The areas of necrosis vary from microscopic size to a diameter of several centimeters, and by coalescence can form large cavities. Necrosis, cellular disintegration, and leukocyte accumulation are found in the areas of abscess. Occasionally there is the complication of rupture or spread of the infection to adjacent tissues.

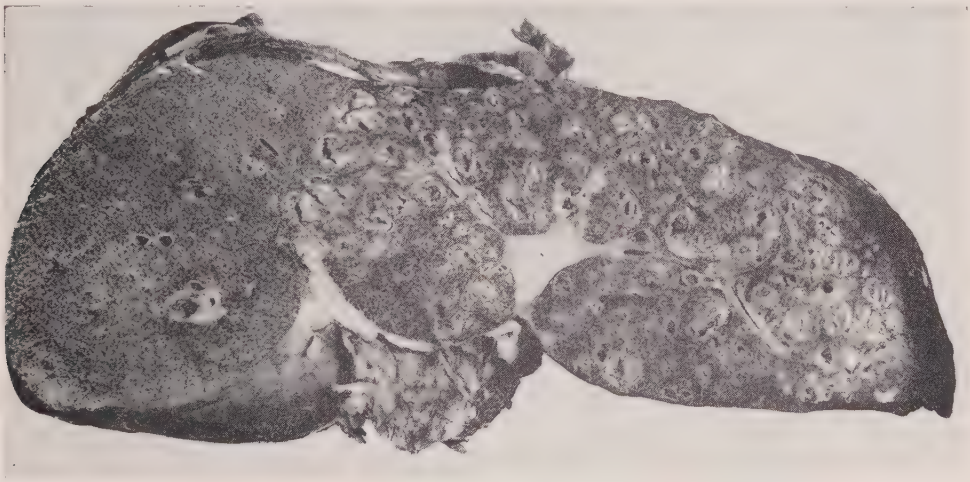


Fig. 713.—Liver. Multiple cholangitic abscesses associated with obstruction of left hepatic duct by gallstone. (Courtesy Dr. G. L. Duff.)

Pyogenic hepatic abscesses due to spread of organisms to the liver by hepatic arteries are usually but part of a general septicemia

and pyemia, with abscesses present in other organs as well.

Actinomycotic abscesses of the liver usually have a pathogenesis similar to the pyogenic pylephlebitic abscesses. Spread to the liver from intestinal lesions is by the portal venous channels. Multiple small ragged abscess cavities are produced, in which the actinomycotic colonies can be found (see Fig. 714).

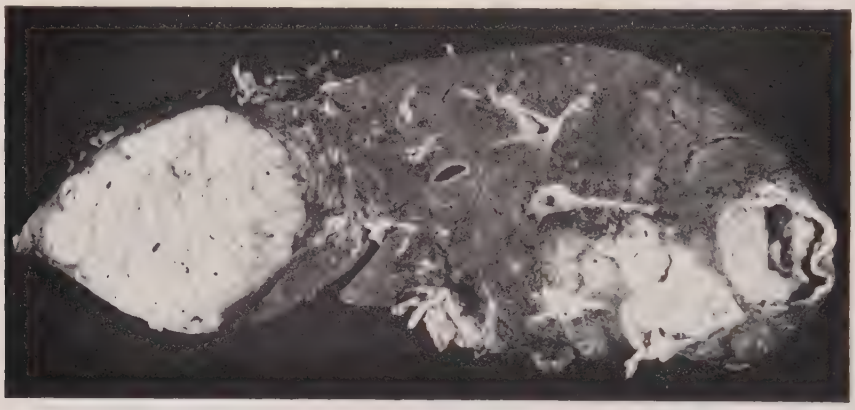


Fig. 714.—Actinomycosis of liver. (Courtesy Dr. G. L. Duff.)

Fig. 715.—Amebic abscess of liver. (Courtesy Dr. G. L. Duff.)

Amebiasis and amebic abscess of the liver are due to spread of *Endamoeba histolytica* from intestinal lesions by way of the portal vein. The lesion begins in the portal areas, with lysis of tissue and but little accompanying inflammatory reaction. Adjacent abscesses coalesce to produce lesions of considerable size. The larger abscesses tend to become walled off by connective tissue (see also page 359).

Tuberculosis.—Tuberculosis of the liver may occur in miliary form as part of a generalized miliary tuberculosis, as a few conglomerate tubercles secondary to pulmonary or abdominal tuberculosis, or as a tuberculous cholangitis. The last form, which is uncommon, is due to spread of tuberculous infection by biliary passages, either as an ascending infection of extrahepatic bile ducts, or as involvement of intrahepatic bile ducts by caseation with intrahepatic spread. Localized tuberculous hepatic lesions are more commonly due to infections of portal veins from tuberculous ulcers of the bowel. A portal area or interlobular tissue is usually involved. Solitary tuberculoma is rare.

Syphilis.—Syphilis may involve the liver in either the congenital or the acquired form. In congenital syphilis spirochetes are often abundant in the liver. The liver may be enlarged,

grayish-yellow in color, and with diminution of normal markings. Microscopically, there is increase of mesoblastic and more mature connective tissue in both perilobular and intralobular areas. Lymphocytic and plasma cell infiltration may be present. There occur variable degrees of loss or distortion of parenchyma. Gummatous necrosis of greater than miliary size is unusual.

Acquired syphilis may produce a diffuse hepatitis, gumma formation, or, in healing of multiple gummas, a severe scarring with gross distortion of the liver (hepar lobatum, see page 820).

Weil's Disease.—Weil's disease, or spirochetal jaundice, is a severe prostrating infection due to a spirochete, *Leptospira icterohemorrhagiae.* It is sometimes confused with infectious hepatitis. It is characterized by sudden onset, fever, jaundice, hemorrhagic tendencies, muscular pain, and renal injuries. Spread occurs to man from rats. The organism is excreted in the rat's urine, and human infection occurs through the skin. It occurs mainly in crowded communities living under damp, unhygienic conditions, as in trenches during war. Laboratory diagnosis is most easily made by inoculation of blood into guinea pigs. Generalized jaundice is usually but not invariably present. Damage to capillaries is shown by widely distributed minute hemorrhages. The kidneys exhibit degeneration and necrosis in convoluted tubules and interstitial lymphocytic infiltration. Degenerative changes are common in muscle fibers, particularly those of the calf or pectoral region.

The liver may be of normal size but is usually slightly enlarged, and is bile stained. Microscopically, bile stasis may be prominent, particularly in central parts of the hepatic lobules. Areas of degeneration and necrosis of hepatic cells may be slight and focal, or so severe and extensive as to simulate acute yellow atrophy. There may be active proliferation of hepatic cells, and occasionally mitoses are prominent. In cases without jaundice, hepatic changes may be absent or slight (see also page 284).

Infectious Hepatitis

Although not a new condition, infectious hepatitis was the outstanding disease of World War II, and was the only pandemic disease of this war. Until recently, this disease has been rather poorly defined, but great advances in knowledge have occurred in the past decade. No universally accepted term for the condition has yet come into general usage, and infectious hepatitis is also referred to as infective hepatitis, virus hepatitis, epidemic hepatitis, catarrhal jaundice, infectious hepatic jaundice, nonspirochetal infectious jaundice, inoculation hepatitis, and homologous serum jaundice.

The sporadic form of infectious hepatitis has long been known as catarrhal jaundice. This term originated from the etiological concept, promoted by Virchow, that it was an extrahepatic obstructive jaundice due to a catarrhal inflammation of the common bile duct or adjacent duodenum, with a plug of mucus in the ampulla of Vater. Although the primary involvement of the liver was recognized by certain individuals,[69] the disease was confused for a time with hepatitis due to *Leptospira icterohaemorrhagiae* (Weil's disease). The opportunities for study of the disease during the past decade have confirmed that it is primarily a hepatitis, apparently of virus etiology, and that in fatal cases the pathologic changes in the liver correspond with those which have long been known as acute yellow atrophy of the liver.

Incidence and Epidemiology.—Although it may occur at any age, infectious hepatitis has its highest incidence in children and young adults. The sexes are equally affected. The disease tends to be more severe in adults than in children, and is more serious during pregnancy or in association with some other hepatotoxic agent. The mortality is low, and was about 0.2 or 0.3 per cent in the pandemic of the war period. More recently there appears to have been some enhancement of virulence, and the mortality, particularly from inoculation hepatitis, seems to have been considerably greater. It is world-wide in distribution, and occurs in both sporadic and epidemic form. Epidemic outbreaks, which have tended to occur particularly under artificial conditions of crowding, such as in time of war, occur at any season but most often during the summer and autumn months.

Etiology and Transmission.—The infective agent appears to be a filtrable virus. Although a susceptible experimental animal has not been found, transmission to human volunteers has been achieved by injection of infective serum, oral ingestion of infective serum and material from feces, and nasopharyngeal spraying of infective material. The virus is capable of passing the finest filters, is unusually resistant to heat, drying, and chlorination of water, and is detectable in the blood and feces in the acute active stage of the disease.

While the natural method of spread of the virus has not been established with certainty, the evidence suggests that it is most probably by the intestinal route, and may at times be water borne. Artificially, the disease may be transmitted by inoculation of the infective agent from blood of an infected individual in transfusion of blood or plasma, injection of vaccines containing human serum, or from contaminated needles or syringes (postarsphenamine hepatitis, hepatitis following insulin injections, etc.). Infectious hepatitis artificially spread by inoculation is termed "homologous serum jaundice." The disease so produced is similar clinically and pathologically to the naturally occurring in-

fectious hepatitis, although there appears to be a difference in incubation periods. In naturally occurring infectious hepatitis the incubation period is relatively short (20 to 40 days), whereas homologous serum jaundice has a long incubation period, usually about 100 days. In the latter condition, virus is recoverable from the serum of the apparently healthy individual during the latter part of the long incubation period.

Immunity of some degree appears to be conferred by an attack of infectious hepatitis, although recurrences sometimes occur. Passive immunization may be conferred by the injection of gamma globulin during the incubation period.[75]

In the clinical course there is usually a preicteric phase of several days, a period of jaundice of one to three weeks, and a prolonged convalescence of one or two months. In some cases the course may be very prolonged. Gastrointestinal symptoms, fever, and headache are common. Approaching jaundice is heralded by the appearance of bile in the urine and a yellowish tint of the scleras. In the unusual fatal cases, death may occur in less than ten days or as long as six weeks after the onset.

serum proteins, the serum cholesterol, and the urine Ehrlich reaction; and (3) in the defervescent stage, the serum bilirubin, the urine Ehrlich reaction, the Hanger and Maclagan tests, the bromsulfalein tests, and the twenty-four-hour urinary urobilinogen and coproporphyrin.

Pathologic Anatomy.—Biopsy studies of the liver in nonfatal cases have indicated that well-advanced lesions may be present at the time symptoms become manifest. The changes in the liver are essentially a degeneration and destruction of hepatic cells with an associated inflammatory reaction. There may be destruction of scattered hepatic cells, or actual focal areas of necrosis, most often in central parts of the lobules. Degenerative changes may take the form of a hyalinization of hepatic cells, similar to the Councilman bodies seen in yellow fever.[71] The inflammatory reaction may

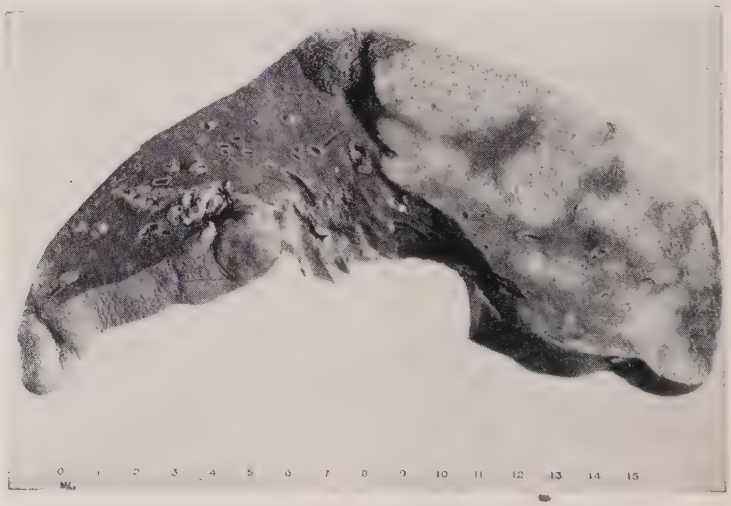


Fig. 716.—Epidemic hepatitis, nineteenth day. Regenerating tissue is evident on the right. (From Lucké, Am. J. Path. 20: 1944.)

According to Sherlock[14b] the extent of the hepatic damage in acute hepatitis is reflected in the serum bilirubin and serum albumin levels. Galactose tolerance is impaired only in severe degrees of damage. The hippuric acid test gives inconstant results which do not always agree with the extent of the hepatic lesion. Rapid recovery of the liver after hepatitis is reflected in a rapid fall of serum bilirubin and galactose time.

Watson and Hoffbauer[79b] have found the liver function tests of most value in hepatitis to be: (1) in the preicteric phase, the serum bilirubin, the urine bilirubin, the urine Ehrlich test for urobilinogen; (2) in the icteric phase, the Hanger and Maclagen tests for abnormal

be perilobular or intralobular, with a predominance of mononuclear cells mixed with neutrophilic and eosinophilic leukocytes.

In fatal cases that have run an acute course with early death, the liver is usually moderately reduced in size, very soft in consistency, has a slightly wrinkled capsule, and is dark reddish-brown in color. The cut surface may be mottled but without any distinct pattern, and purplish-red and congested in appearance. Microscopically, there is massive destruction of

hepatic cells but with preservation of the supporting architectural framework. The preserved sinusoids are congested and the bile ducts unaffected, although the smaller bile ducts may show proliferative changes. Infiltration of inflammatory cells is most marked about the peripheral parts of lobules, and is chiefly by mononuclear cells, lymphocytes, and plasma cells, with fewer neutrophiles and eosinophiles.

In fatal cases which have had a more prolonged course or are subacute, the liver is markedly reduced in size and weight, sometimes to half normal, and severely deformed. The surface is irregular, with wrinkling and irregular projecting coarse nodules. The cut surface shows a variegated appearance, with dark red spleenlike areas of destruction of hepatic parenchyma, and irregular nodular areas of pale or greenish color due to regenerative hyperplasia of hepatic cells. Microscopically, there are destruction of hepatic cells and inflammatory infiltration similar to the more acute cases, and irregular areas of formation of new parenchymal cells. The hyperplastic hepatic cells are often arranged in atypical fashion, with poor lobular architecture.

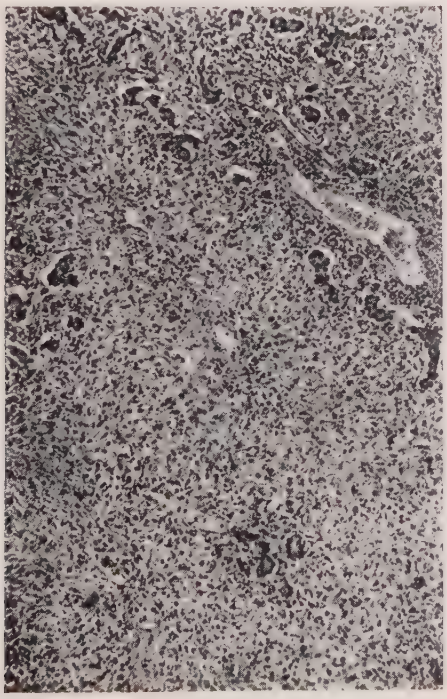


Fig. 717.—Epidemic hepatitis. Microscopic appearance of the liver shown in Fig. 716. (Courtesy Dr. B. Lucké.)

The severity of the jaundice observed clinically does not correlate with the degree of the hepatic destruction. The jaundice appears to be due mainly to obstruction of small intralobular bile canaliculi, in which plugs of bile often may be evident.

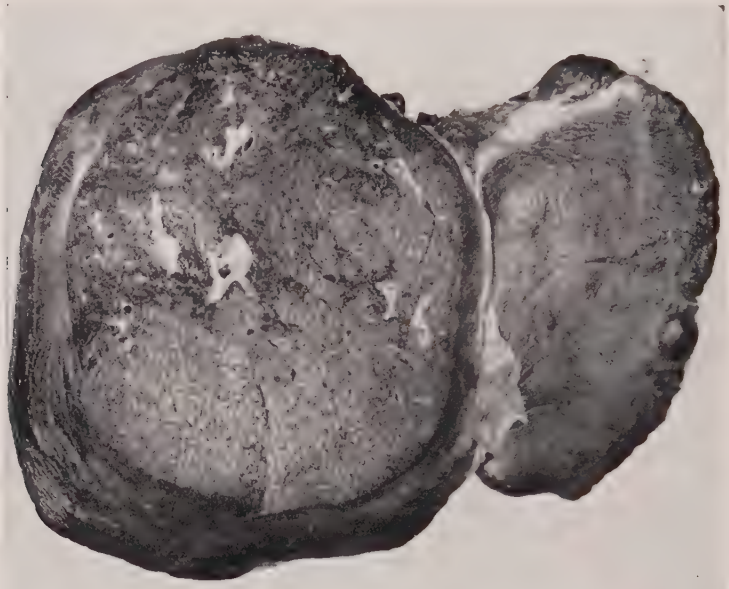
Fig. 718.—Epidemic hepatitis, ninety-third day, showing regenerating nodule of liver parenchyma. (From Lucké, Am. J. Path. 20: 1944.)

Extrahepatic changes in fatal cases include ascites, and sometimes pleural effusion and peripheral edema. The regional lymph nodes and spleen are enlarged. The gastrointestinal tract shows edema and sometimes erosions or phlegmonous inflammation. Hemorrhagic phenomena may be seen in various tissues due to disturbances of prothrombin and vitamin K as a result of hepatic destruction. The kidneys may show fatty degeneration or cholemic nephrosis varying from mild to severe degrees. The brain may have mild nonspecific degenerative changes in ganglion cells and slight inflammatory infiltrations about blood vessels or in meninges.[71]

Lucké has studied the liver in recovered cases in which death resulted from some

unrelated cause. No gross abnormality of the liver was found. A month after recovery, but slight traces of injury were left, and later there was complete restoration to a normal appearance. Although complete restoration of the hepatic parenchyma without significant scarring appears to occur in almost all cases, there is evidence that some prolonged cases may proceed to cholangiolitic cirrhosis[79b] (see page 819). However, even in individuals with late residual symptoms following infectious hepatitis there is little evidence of progression to cirrhosis.[79a]

Fig. 719.



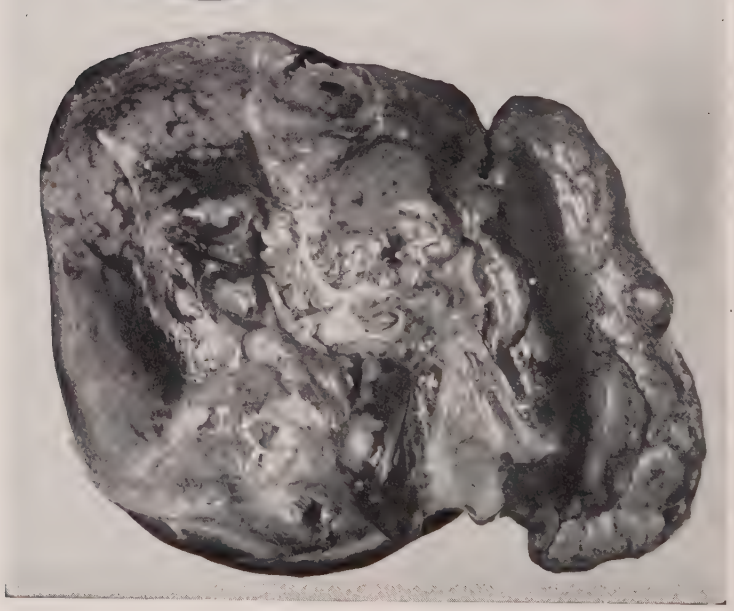


Fig. 720.

Fig. 719.—Liver. Necrosis and nodular regeneration in epidemic hepatitis.
Fig. 720.—Liver. Epidemic hepatitis, showing necrosis and nodular regeneration. (Courtesy Dr. G. L. Duff.)

Cysts of the Liver

Cysts in the liver are commonly of the following types: (1) congenital cysts; (2) cystic distention of ducts (hydrohepatosis); and (3) hydatid (echinococcus) cysts.

Congenital cysts are not common, but sometimes are found associated with congenital cystic disease of the kidneys or other organs. They are usually small and cause no disturbance, but cysts of large size have been reported. They tend to be most common just under the capsule, contain clear fluid, and are lined by flattened or cylindrical epithelium.

Cystic distention of bile ducts (hydrohepatosis) is the result of obstruction of bile passages, particularly if such obstruction is intermittent, incomplete, or slow in development.

Fig. 721.—Liver, showing dilatation of intrahepatic biliary channels (upper) due to obstruction by primary carcinoma of common hepatic duct (lumen indicated by black thread).

Hydatid cysts are due to the lodgment in the liver of the larval form of the dog tapeworm, *Taenia echinococcus*. The liver is a commonly involved organ. The cyst wall is composed of concentric hyaline laminae lined by germinal cells from which grow "daughter" cysts. Scolices and hooklets of the worm may be identified in the cyst wall or its contents by microscopic examination (see Figs. 283, 284, and 712).

Old cysts, in which the parasites are dead, contain a yellowish-gray puttylike material (see page 391).

Tumors of the Liver

Primary tumors of the liver, either benign or malignant, are relatively uncommon. Among the benign neoplasms, hemangiomas are most common, but hamartomas, adenomas and fibromas also occur.

Cavernous hemangioma, similar to those occurring elsewhere, is often encountered at autopsy as an incidental finding. It grows very slowly or remains stationary in size. When large and near the surface of the liver it may be palpable clinically as a nodule, and rupture with intraperitoneal hemorrhage may occur. It usually appears as a circumscribed dark-blue area, from a few millimeters to several centimeters in diameter, which bleeds freely and has a somewhat spongy appearance. Microscopically, it is composed of large, blood-filled, endothelium-lined spaces separated by dense connective tissue. In rare cases it may become malignant and invasive. It is probably of congenital origin.

A primary hemorrhagic endothelial-cell sarcoma of the liver has been reported to have followed the use of thorotrast for diagnostic visualization of the liver.[97]

Peliosis hepatis is a rare diffuse angiomatoid change of the liver. Minute angiomatoid spaces of hemorrhagic appearance are distributed throughout a congested liver. The pathogenesis is uncertain, but it possibly follows severe passive congestion and miliary necrosis.

Adenoma of the liver is relatively infrequent. It is a circumscribed mass of well-formed liver cells which grows expansively, compressing the surrounding liver substance. Veins are not invaded. Bile-duct adenoma also occurs, and tends to be cystic. Adrenal inclusions sometimes occur beneath the capsule of the liver and may give rise to neoplasms.

Hamartoma of the liver is a benign tumorlike malformation of a portion of the liver. It consists of both proliferating hepatic cells and bile ducts (mixed adenoma of liver). Most cases occur in infants and children. The histologic appearance may resemble cirrhosis of the liver.

Primary Carcinoma

Primary malignant tumors of the liver are relatively very uncommon in comparison with the frequent incidence there

of metastatic tumors. Although rare instances of primary sarcoma of the liver have been reported, almost all primary malignancies of the liver are carcinomas. In most instances they can be classified as of liver-cell type or as bile-duct type. Clinical features most commonly observed are an abdominal mass, abdominal pain, jaundice, ascites, weight loss, and edema of the legs.[82]

Incidence.—Primary carcinoma of the liver has a peculiar variability of incidence geographically, racially, sexually, and according to age. The average incidence in reported series of necropsies has been about 0.2 per cent[1] with variations from 0.1 to 0.7 per cent. However, among the Bantus of South Africa, primary carcinoma of the liver has been reported to compose as much as 37 per cent of all cancer. Likewise in Orientals, and particularly among the natives of South China, primary cancer of the liver has been found to be a relatively frequent disease.

South Africa has not been evaluated with finality. That proper diet may be important as a protective factor has been suggested by experimental studies. Sufficient casein and riboflavin in the diet of mice and rats has been found to prevent the development of the hepatic cancer which can be induced by a diet containing azo dyes such as butter yellow.[84] Rice and fat in the diet seems to favor the production of hepatic tumors by butter yellow.[91] Thus, certain dietary factors appear to predispose the liver to cancerous change, although the actual carcinogenic agent is unknown.[84] The relationship to cirrhosis is of particular interest. Among adults, there is an associated cirrhosis of the liver with about 90 per cent of hepatic carcinomas of the liver-cell type, and with 37 to 50 per cent of those of the bile-duct type. Cirrhosis is usually present with the primary hepatic carcinomas in Orientals and South African Bantus. Among cases of cirrhosis, 3 to 7 per cent eventually are complicated by the development of hepatic carcinoma. In experimental production of hepatic carcinoma by selenium, cirrhosis has been found to precede development of the cancer.[92] Primary carcinoma of the liver has been found in about 7 per cent of cases of hemochromatosis. Pigment is absent from the tumor cells.[89]

Fig. 722.—Liver, multiple primary hepatomas. (Courtesy Dr. G. L. Duff.)

Primary carcinoma of the liver may be found at any age, but most cases occur in individuals between the ages of 45 and 60 years. However, a group of cases occur in infants and children, particularly under the age of 2 years.[83] Unlike the adult cases, there is not usually a concomitant cirrhosis. In childhood, about two-thirds occur in males, but in adults primary carcinoma of the liver shows a preponderance in males in a ratio of 6:1.[80] The sexual incidence is perhaps related to etiological factors, and particularly to the occurrence of cirrhosis.

Etiology.—The importance of racial factors, dietary habits, and parasitic infestation with the liver fluke *(Clonorchis sinensis)* in influencing the higher incidence in Orientals and in Bantus of

Pathologic Anatomy.—The liver tends to be considerably enlarged, weighs more than 3,000 grams, and usually shows the nodularity and firmness of portal cirrhosis. The primary tumor is seen in three gross forms: (1) nodular, in which various circumscribed tumor nodules are present throughout the liver; (2) massive, in which a single large tumor occupies one of the lobes; and (3) diffuse, in which tumor cells are found extensively invading every

part of the liver. The nodules of tumor tissue tend to be pale gray or pinkish-gray in color, but reddish areas of hemorrhage or opaque regions of degeneration and necrosis often may be seen. In the nodular varieties, some of the small masses of tumor may be contained within veins, and appear sharply circumscribed.

may be difficult to classify into either of these groups. The **hepatocarcinomas,** which far outnumber the cholangiocarcinomas, are composed of columns and solid masses of tumor cells resembling the parenchymatous cells of the liver. Atypical lobules may be formed, and there is often some evidence of bile

Fig. 723.

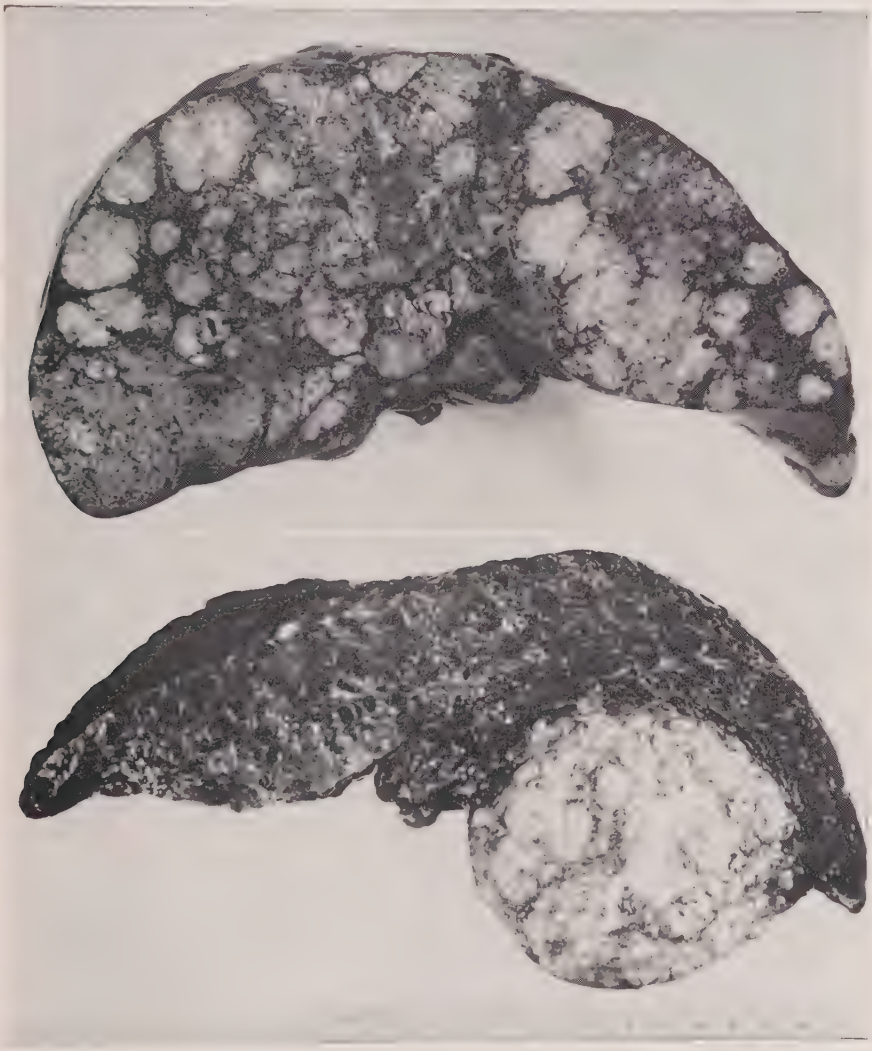


Fig. 724.

Fig. 723.—Liver, metastatic carcinoma (primary in colon).
Fig. 724.—Liver, portal cirrhosis and primary carcinoma. (Courtesy Dr. G. L. Duff.)

Histologically there are two main varieties, a liver-cell type (hepatocarcinoma) and a bile-duct type (cholangiocarcinoma), but some highly undifferentiated tumors

secretion. Some of the tumor cells frequently are hyperchromatic and multinucleated or of giant size. A delicate network of capillaries is found in the

stroma. Small groups of tumor cells are frequently found within portal veins. **Cholangiocarcinomas** are glandular carcinomas arising from bile ducts. They compose less than 20 per cent of primary hepatic cancers. The tumor cells are columnar or cuboidal, and attempt to form tubules or glandlike structures. The connective tissue stroma is abundant, dense, and contains but relatively few capillaries. The course tends to be more rapid than with the liver-cell type.

Metastasis.—Primary hepatic carcinoma tends to spread readily within the liver, often by way of portal veins. While a multicentric origin seems to have been proved in rare cases, the evidence suggests that it is usually unicentric in origin, the multiple and seemingly independent nodules being due to intrahepatic venous spread. Extrahepatic metastasis occurs in about 40 to 50 per cent of cases, mainly to the lungs and regional lymph

Fig. 725.

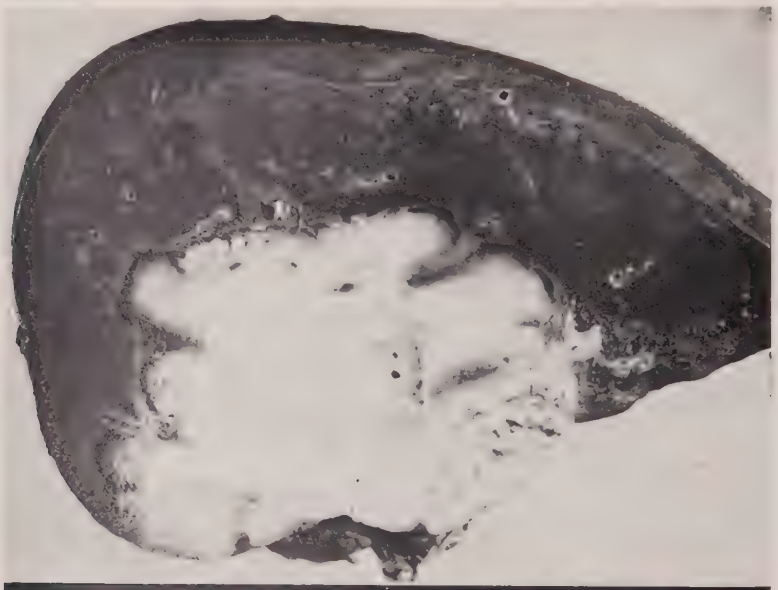


Fig. 726.

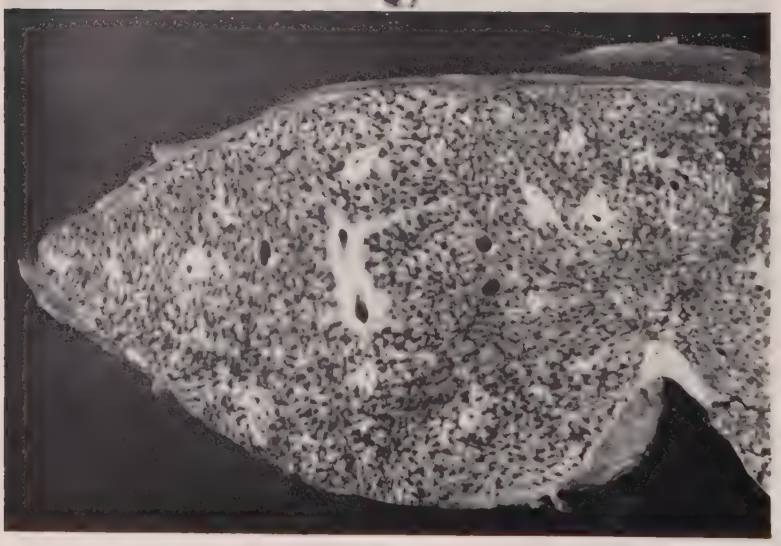


Fig. 725.—Liver, showing nodular mass of secondary lymphosarcoma.
Fig. 726.—Liver, showing infiltration by lymphosarcoma. (Courtesy Dr. G. L. Duff.)

nodes. Carcinomatous invasion of larger portal veins with gross or massive hemorrhage into the peritoneal cavity is quite frequent, and often is the final cause of death.

Metastatic Tumors of the Liver

The liver is one of the most frequent sites for metastatic tumors. These may vary from single nodules of small to massive size, to innumerable growths studding the liver and producing marked distortion. The liver in such cases may be greatly enlarged. The masses of metastatic tumor are usually irregular in shape, pale in color, and, if near the sur-

Fig. 727.—Liver, lymphatic leukemia. (From Ackerman and Regato, Cancer, The C. V. Mosby Co.)

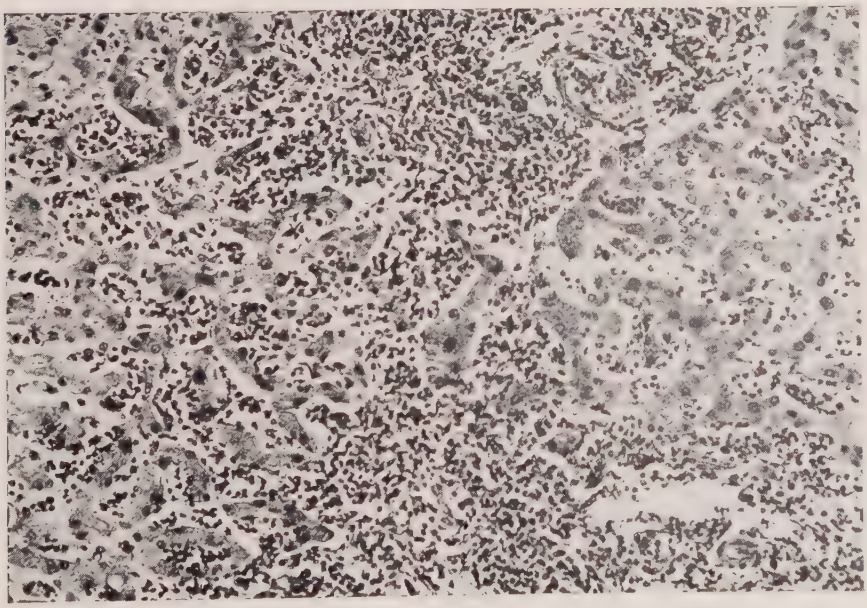


Fig. 728.—Liver, leukemic infiltration.

face, project as nodular elevations. The nodules often show depressed centers (umbilication). Yellowish areas of necrosis are often present in the centers of the tumor masses.

The multiplicity of tumor nodules within the liver is often due to invasion of portal veins within the liver and intrahepatic spread by such channels, even though the original metastasis reached the liver by tumor emboli in hepatic arteries.[95]

Satterlee[96] has given tables indicating the frequency of metastatic tumors in the liver, and the probabilities regarding the original site. According to his figures, metastasis to the liver occurs in 36 per cent of all cancers, in 50 per cent of cancers of portal areas, in 48 per cent of breast cancers, and in 44 per cent of gastric cancers. In a given case of cancer of the liver in a man, the probabilities are 26 per cent that it is from the stomach, 20 per cent from the intestine, 14 per cent from other digestive organs, and 14 per cent from the genitourinary tract. In a given cancer of the liver in a woman, the probabilities are 20 per cent that it is from the breast, 18 per cent from the intestine, 16 per cent from the uterus, 13 per cent from other digestive organs, 12 per cent from stomach, and 7 per cent from other genitourinary organs.

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Chapter 28

THE GALL BLADDER AND THE BILIARY DUCTS

BÉLA HALPERT

Structure and Function

The right and left hepatic ducts as they reach the porta hepatis join at an obtuse angle to form the common hepatic duct. This continues as the common bile duct after giving off the cystic duct at an acute angle. The cystic duct gradually widens into the S-shaped neck of the gall bladder, while the common bile duct terminates in the duodenum at the papilla of Vater.

The biliary ducts, as well as the gall bladder, are lined by tall columnar epithelium. Acinous glands producing a mucinous secretion open into the ducts and into the neck of the gall bladder but are absent in its body and fundus. Beneath the epithelium the lamina propria is delicate and contains the capillaries. The mucosal surface of the gall bladder is immensely enlarged by deep polygonal spaces bordered by ridges of varying heights. The ridges examined microscopically are richly branching, delicate, connective tissue stalks covered by tall columnar epithelium (Fig. 729). External to the lamina propria is a fairly dense, fibrous, connective tissue making up the wall of the extrahepatic biliary ducts. In the gall bladder external to the lamina propria there are smooth muscle bundles arranged longitudinally, then obliquely or circularly. The muscular coat is surrounded by the perimuscular layer composed of a loose narrow zone of connective tissue sometimes interspersed with adipose tissue cells. Serosa covers the perimuscular layer over the peritoneal surface of the gall bladder. The opposite surface is attached to the liver. Particularly on the surface toward the liver aberrant bile ducts (Luschka ducts) frequently occur in the perimuscular layer.

The closeness of the lining epithelium to the muscular layer and the absence of a submucosa suggest that the muscular coat of the gall bladder is genetically a muscularis mucosae. This is further supported by the observation that the glands in the neck of the gall bladder penetrate the muscular coat just as Brunner's glands traverse the muscularis mucosae of the duodenum.[1] Furthermore, in the course of development the muscular coat of the gall bladder appears simultaneously with that of the muscularis mucosae and later than the muscular coats of the intestine.[2] This derivation would explain why direct mechanical, chemical, and electrical stimuli that cause an immediate and powerful contraction of the intestines have no demonstrable effect on the gall bladder.

The blood for the extrahepatic biliary ducts is derived from the hepatic arteries, the right supplying the cystic artery to the gall bladder. The return from the gall bladder is through the cystic vein that empties into the portal vein.

The network of lymph channels in the wall of the gall bladder drains into the lymph node at the neck of the viscus. From here the flow is toward the porta hepatis and to the peripancreatic lymph nodes. Enlargement of the nodes within the hepatoduodenal ligament may impede or obstruct the flow of bile through the common bile duct.

The nerve supply is parasympathetic and sympathetic. Whether the pattern of distribution in the gall bladder is that of the myenteric plexus (Auerbach) or that of the submucous plexus (Meissner) is as yet undetermined.

The function of the extrahepatic biliary ducts is to provide passage of bile into the duodenum. Bile is the product of the liver cells and is a complex liquid. It is apparently produced continually with its quantity and composition subject to wide variations. According to a conservative estimate, about 0.6 c.c. of bile is produced per hour per kilogram of body weight in man,[3] in rabbits about 3 c.c.[4] Bile contains an average of 3 per cent solids; the rest is water.[5] The substances it contains are alkali salts of the bile acids, bile pigments, cholesterol, mucoprotein, and the electrolytes common to all body fluids: sodium, calcium, potassium, and magnesium, as chlorides, bicarbonates, carbonates, and phosphates.[3] The pH of the bile is between 7.1 and 7.3.[6]

A mechanism at the choledochoduodenal junction regulates the flow of bile into the duodenum. It has long been postulated that an anatomic sphincter exists here and that it has a reciprocal innervation with the gall bladder so that when the sphincter relaxes the gall bladder contracts and evacuates its content.[7] Clinical tests assuming the existence of this mechanism are still in use.[8] It is, however, not fully established that an *anatomic sphincter* exists at the choledochoduodenal junction.[9, 10] There is also doubt whether the anatomic arrangement of the biliary ducts and the gall bladder, and the distribution and strength of the muscular coat of the viscus permit complete evacuation of the gall bladder by muscular contraction. Occasionally in man and frequently in animals (rhesus monkey) the gall bladder is completely or almost completely imbedded in the liver without obvious interference with its function.[11]

The function of the gall bladder is to receive and dispose of the overflow of bile while its passage into the duodenum is being negotiated. The bile reaches the gall bladder through the funnel-shaped cystic duct that widens toward the gall bladder. The course of the duct appears

somewhat twisted because its lumen is ridged by a series of folds, the valves of Heister. The last of these narrows the lumen toward the gall bladder offering interference to the flow of bile from the gall bladder. The main force driving the bile into the gall bladder is the pressure on the liver during inspiration.[12] The muscular coat of the gall bladder adjusts the size of the viscus to the change in its content.[13, 14] Overdistention is prevented by the ability of the gall bladder to resorb half the volume of its content per hour.[15] According to one concept, mainly water is resorbed while another contends that the mucosa of the gall bladder can resorb all constituents of the bile.[16, 17] Accordingly, the increased concentration of the bile in the gall bladder is due to the variation in the rate of resorption, some constituents being resorbed more slowly than others.

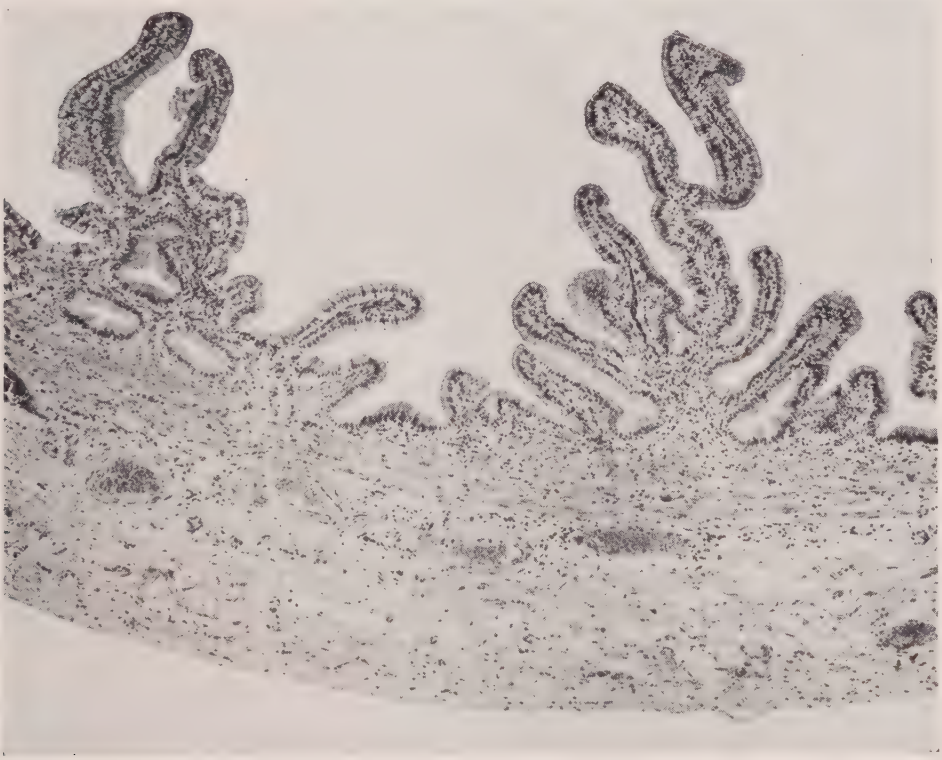

Fig. 729.—Normal gall bladder from a 33-year-old woman. In cross section of the mid-portion, delicate connective tissue stalks are covered by tall columnar epithelium. Beneath the tunica propria is the muscular coat with the smooth muscle bundles arranged longitudinally, then obliquely or circularly. External to the muscular coat is the perimuscular layer. (×40.)

Certain substances when injected intravenously or given by mouth appear in the bile and reach the gall bladder.[18] Some substances so administered accumulate in the gall bladder in concentrations not attained in the bile coming from the liver.[12] Cholecystography, the visualization of the gall bladder roentgenographically, is based on this selective resorbing ability of the gall bladder. Radiopaque substances like sodium tetraiodophenolphthalein and Priodax[19] after reaching the gall bladder are resorbed slower than the bile, eventually attaining a concentration sufficient to cast a shadow on an x-ray film. The shadow becomes smaller following a fatty meal.[20] This has been interpreted as being due to evacuation of the viscus. Diminution of the shadow may as well be accomplished by selective resorption of the content.[21]

Lesions of the Extrahepatic Biliary Ducts and the Gall Bladder

Inflammations, concretions, neoplasms, and anomalies are the important lesions affecting the extrahepatic biliary ducts and the gall bladder. Acute cholecystitis, chronic cholecystitis, and acute cholecystitis superimposed on a chronic cholecystitis are the common inflammatory processes involving the gall bladder. Tuberculous, syphilitic, actinomycotic, and parasitic lesions are rarely encountered and are usually associated with similar changes in the intrahepatic biliary ducts and in the liver.

Cholecystitis

Acute Cholecystitis.—This is a nonspecific inflammation caused by streptococci, staphylococci, or by the enteric groups of microorganisms. These may reach the viscus in the bile, in the blood, through the lymphatics, or by direct extension from neighboring organs. In the latter instance the process extends from the outer layers inward and may barely reach the mucosa—pericholecystitis. A temporary increase in bile salt content in the gall bladder also may cause acute cholecystitis as has been shown experimentally.[22] Enzyme action from reflux of pancreatic secretion into the gall bladder may induce inflammation of the viscus.[23] The gall bladder may become involved in an inflammatory process as a part of an allergic reaction, in polyarteritis nodosa, in endarteritis obliterans, and also in terminal uremia. Chemical, enzymatic, and perhaps allergic factors probably excite or play a contributory role in exciting cholecystitis more often than suspected. Vascular obstruction may result in hemorrhagic infarction of the gall bladder with subsequent acute cholecystitis and may terminate in acute diffuse peritonitis. The exact mechanism by which acute inflammation of the gall bladder is initiated is, as yet, unknown; however, in acute cholecystitis from whatever cause, the involvement usually commences within the mucosa and extends outward.

Grossly, the viscus is enlarged, firm, and discolored red brown, with an increase in thickness of its wall up to tenfold. This is produced by spreading of the tissue elements and filling of the tissue spaces with edema fluid and extravasated blood. The lumen usually contains a mixture of bile, blood, and pus. Gallstones usually are not present.

Microscopically, the epithelium may be preserved over extensive areas, elsewhere it is either shed or missing. All the layers are spread apart and are densely infiltrated with erythrocytes and neutrophilic granulocytes within a network of fibrin or an amorphous pink substance. In the distended capillaries margination of white blood cells is conspicuous. The changes are more marked about blood vessels and involve all the layers including the perimuscular layer and the serosa.

Commensurate with the intensity of the inflammatory process the clinical signs and symptoms, too, are severe. There are intense pain in the right upper abdomen radiating toward the right shoulder, abdominal rigidity, malaise, nausea, and other signs of beginning peritonitis. The acute process is usually progressive and may end in perforation of the gall bladder with focal abscess or diffuse peritonitis. In rare instances the inflammation may subside.

Chronic Cholecystitis.—Various conditions may induce chronic cholecystitis. It is usually assumed to be the sequel of an acute inflammation of the gall bladder, that is, the healing state of a subsiding acute cholecystitis. In other instances the chronic cholecystitis is due to the presence in the viscus of pure gallstones or of the mulberry-shaped mixed gallstones. Chronic cholecystitis may also be induced by intermittent or continuous abnormal composition of the bile. Attenuated or usually nonpathogenic enteric organisms may also produce chronic cholecystitis. Since so many variables operate in the production of the chronic inflammatory reaction, practically no two gall bladders with chronic cholecystitis are exactly alike though they have certain features in common. The most important of these is the almost invariable presence of gallstones in the gall bladder. In some instances the gallstones are the cause of and in others are the sequel to the chronic inflammatory state of the gall bladder. Familiarity with the chemical composition and structure of gallstones aids therefore in interpreting their role in the inflammatory process.

Grossly, the wall of the gall bladder with chronic cholecystitis is increased to several times its usual thickness. The folds are coarse and in advanced stages obliterated or absent with trabeculations of the mucosal surface. Occasionally the wall may become impregnated with calcium so that a crackling sound (porcelain gall bladder) may be elicited on touch. The lumen of the cystic duct is invariably increased to several times its usual diameter, permitting the passage of calculi into the common bile duct.

Microscopically, the epithelium is usually intact and is mounted on coarse folds. At intervals it dips down to line outpouchings of the mucosa toward the external layers. These outpouchings, the Rokitansky-Aschoff sinuses,[24] usually form along

blood vessels and penetrate the thickened muscular coat to varying depths. Their fundi frequently reach the perimuscular layer (Fig. 730). They are more numerous in the body and fundus than about the neck of the viscus. The muscular coat is hypertrophied, being increased to several times its usual thickness. The perimuscular layer becomes dense with many coarse collagenous bundles. It may increase to a thickness greater than that of the entire wall of the normal gall bladder. There is also an increase of connective tissue in the lamina propria and between the muscle bundles. All the connective tissue is infiltrated with lymphocytes, plasma cells, large mononuclear cells, and eosinophilic granulocytes. Rarely there is prominence of lymphocytic infiltration in all the layers with the formation of lymph follicles, many of which have large germinal centers—cholecystitis lymphfollicularis[25] (Fig. 731). Sometimes the Salmonella group of organisms appears to be responsible[26]; at others the cause remains uncertain.

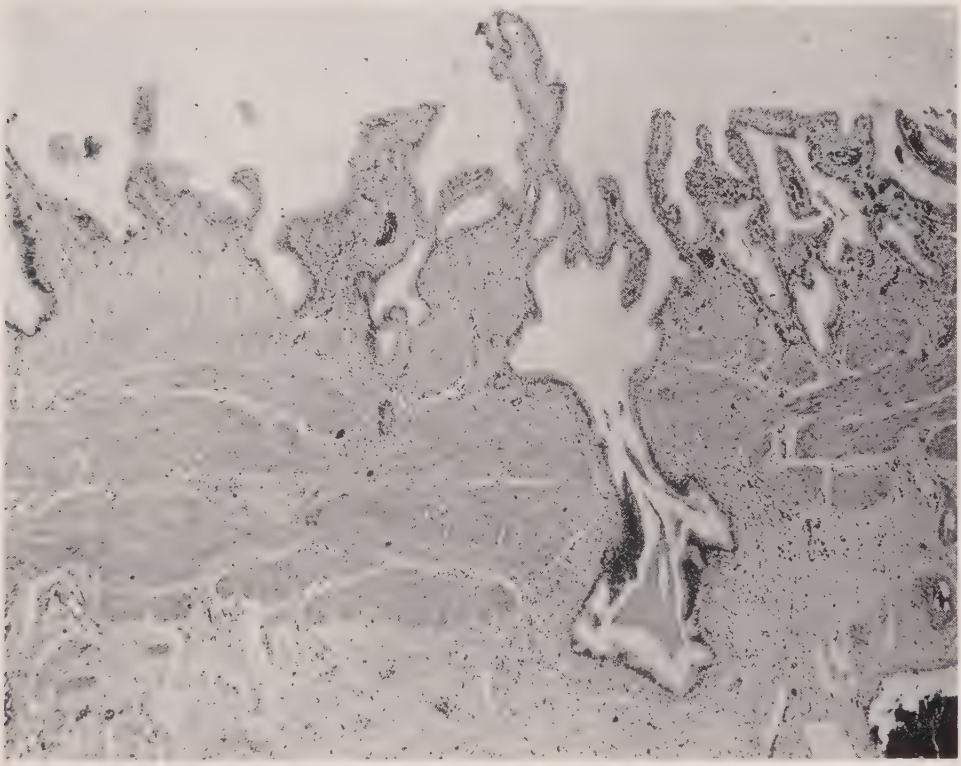

Fig. 730.—Gall bladder with chronic cholecystitis and cholelithiasis (mixed gallstones) from a 57-year-old woman. In a longitudinal section from the body of the viscus the folds of the mucosa are fairly delicate. A Rokitansky-Aschoff sinus extends through the entire thickness of the markedly hypertrophied muscular coat. There is an increase in the connective tissue of the tunica propria and between the muscle bundles. The perimuscular layer is broad. In all the layers there is a slight infiltration with lymphocytes, plasma cells, large mononuclear cells, and some eosinophilic granulocytes. (×32.)

Chronic cholecystitis usually produces vague right upper abdominal distress and distaste for fatty foods. The calculous content of the viscus may occasionally be felt by bimanual palpation. Usually the gallstones may be visualized roentgenographically. The presence of biliary calculi within the viscus lends clinical importance to chronic cholecystitis. Gallstones may pass through the dilated cystic duct and obstruct the common bile duct, producing jaundice. They also predispose to the development of an acute cholecystitis that becomes grafted on the chronic process.

Chronic Cholecystitis With Superimposed Acute Cholecystitis.—Acute cholecystitis more frequently occurs in a gall bladder with chronic cholecystitis containing biliary calculi than in an intact

gall bladder. Chronic and acute cholecystitis in the same gall bladder is often referred to as an acute exacerbation of the chronic process though actually the acute inflammation is superimposed on the chronic inflammatory process. Grossly, such a gall bladder differs little from one with acute cholecystitis except for the presence of calculi within the viscus. Red, brown, or creamy pus fills the lumen. The calculi may be of any variety though mixed gallstones of the faceted type are most common. The mucosa is angry red, velvety, ragged with frequent erosions. The waterlogged wall is many times the usual thickness and the serosa is discolored red and brown with flakes of fibrin giving the peritoneal surface a ground glass opacity.

Microscopically, the effects of the chronic inflammatory process are in evidence. The mucosal folds are coarse, low, or absent. The epithelium is preserved only in the depths of the numerous Rokitansky-Aschoff sinuses. Elsewhere the epithelium varies in height and is shed over extensive areas. The muscular coat is markedly hypertrophied with an increase of the intermuscular connective tissue and thickening of the perimuscular layer. There is in all the layers a scattering of lymphocytes, plasma cells, and large mononuclear cells. In addition, a hemorrhagic fibrinopurulent exudate covers denuded areas of the mucosa. All the layers are markedly spread apart by inflammatory edema and are infiltrated with freshly extravasated erythrocytes and neutrophilic granulocytes. The serosal surface is covered by fibrin.

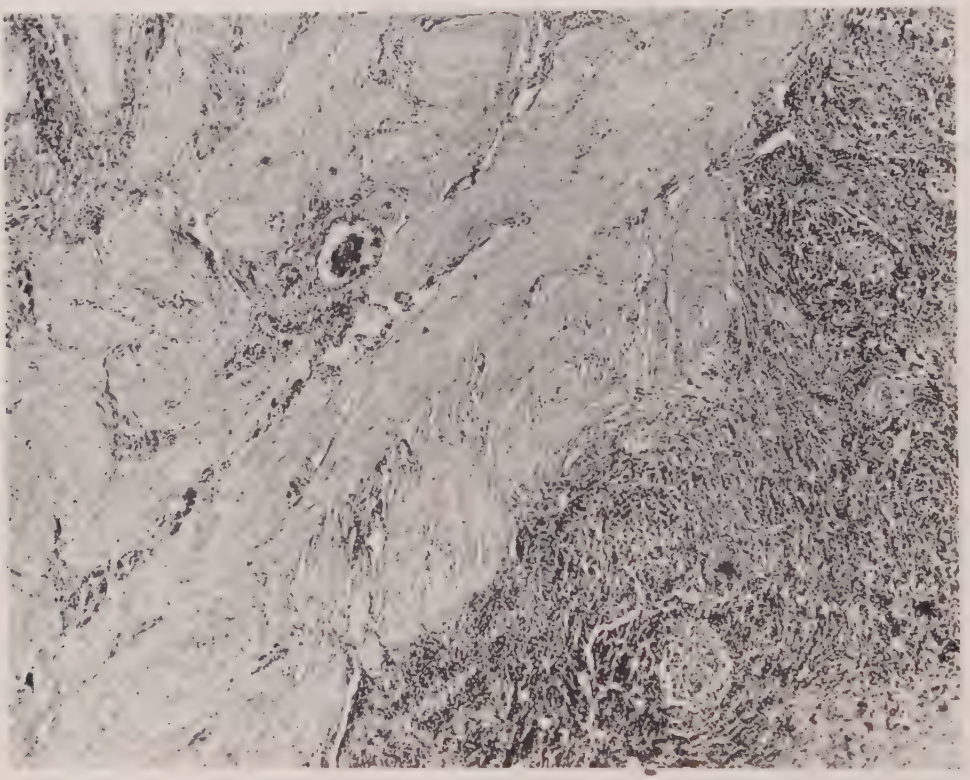

Fig. 731.—Gall bladder with cholecystitis lymphfollicularis, cholelithiasis (calcium bilirubinate calculi), and acute cholecystitis from a 52-year-old man. There is a dense lymphocytic infiltration with a tendency to form lymph follicles that have germinal centers. The lymphocytic infiltration is mostly in the intermuscular connective tissue and in the perimuscular layer. Superimposed are evidences of an acute reaction such as edema, extravasation of erythrocytes, and infiltrations with neutrophilic granulocytes. (×60.)

Chronic cholecystitis with superimposed acute cholecystitis is a well-known entity. This is the lesion that most commonly necessitates surgical intervention and removal of the gall bladder.

The clinical signs and symptoms are those of acute cholecystitis. Because of the presence of biliary calculi, obstruction of the common bile duct may occur and jaundice may accompany the process. In acute cholecystitis without cholelithiasis jaundice does not occur unless there is concomitant hepatitis or cholangitis. Perforation of the gall bladder with subsequent focal or diffuse peritonitis is a common sequel of acute cholecystitis superimposed on a chronic cholecystitis with cholelithiasis.

Cholelithiasis

Gallstones usually form in the gall bladder and only occasionally in the biliary ducts. The presence of biliary calculi or gallstones in the gall bladder or in the biliary ducts is called cholelithiasis. The roles played in the formation of gallstones by faulty composition of the bile, stagnation of bile in the gall bladder, and inflammation of the gall bladder and biliary ducts are, as yet, not definitely determined.[27] Gallstones are best grouped according to their composition. Chemical analyses reveal that three normal constituents of the bile—cholesterol, calcium bilirubinate, and calcium carbonate—are the principal stone-forming substances.[28] Gallstones may be composed almost entirely of one of these substances—pure gallstones—or of a mixture of them in varying proportions—mixed gallstones—or of a combination in which one kind of gallstone forms the nucleus and another the shell—combined gallstones.

Pure Gallstones.—About 10 per cent of biliary calculi are pure gallstones. Pure gallstones form when the bile contains intermittently or continually an excess of one of the stone-forming substances. This excess is due to disturbances of metabolism or of liver function rather than to an inflammatory reaction of the gall bladder or of the biliary ducts. Pure gallstones are composed almost entirely of cholesterol or of calcium bilirubinate and rarely of calcium carbonate.

Fig. 732.

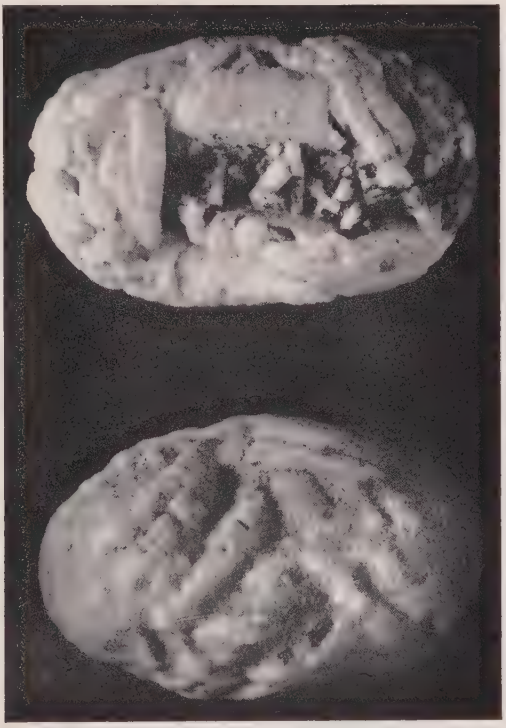

Fig. 733.

Figs. 732 and 733.—Crystalline cholesterol stones of varying sizes, each from a different gall bladder. (×2.) (Courtesy Dr. Malcolm A. Hyman, Brooklyn, N. Y.)

The *crystalline cholesterol stone* is the most common and is always solitary and remains so, as long as its surface is crystalline (Figs. 732 and 733). It may vary from 0.5 to 5 cm. in diameter.

The smaller ones are spherical, the larger ones ovoid. Eventually the crystalline surface becomes obscured, the crevices are filled in, and the entire calculus becomes permeated with calcium carbonate so as to cast a faint radiographic shadow. Yet the cut surfaces remain crystalline with a glistening radiating pattern. A metabolic disturbance causing an increased cholesterol content of the bile results in the formation of the crystalline cholesterol stone.[29] The gall bladder containing such a stone usually presents no other changes than a delicate network of yellow-white lines corresponding to the slightly broadened ridges of the primary and secondary folds of the mucosa. Microscopically (Fig. 734), in the connective tissue stalks of the folds there are many large mononuclear cells with doubly refractile lipoidal substances (cholesterol esters) in their cytoplasm (cholesterolosis, see page 843).

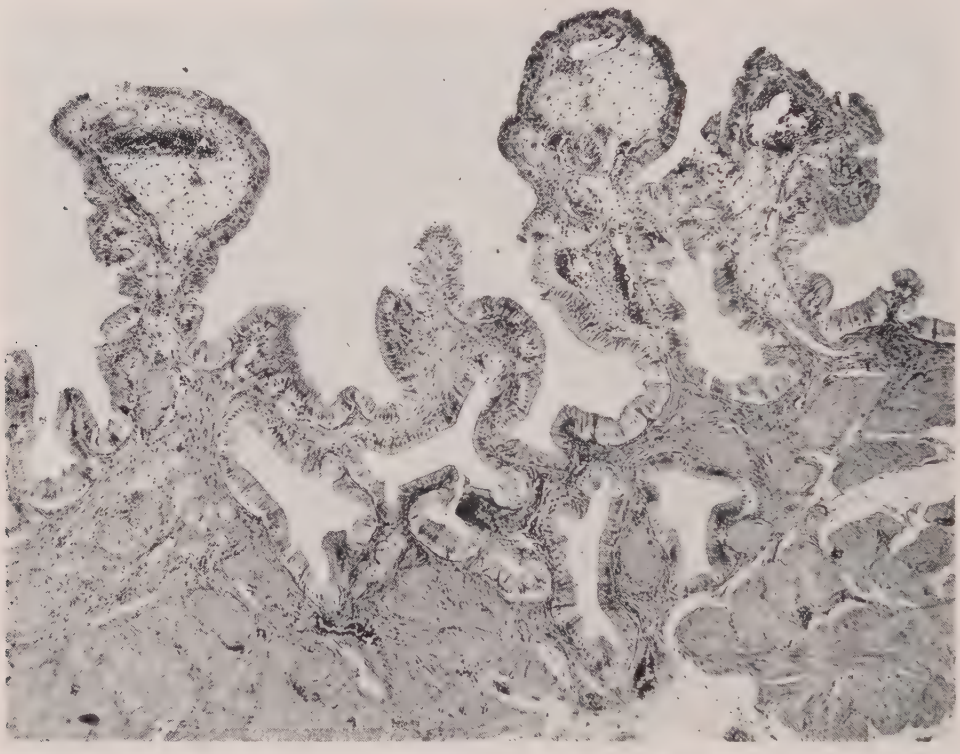

Fig. 734.—Gall bladder with cholesterolosis of the mucosa and cholelithiasis (crystalline cholesterol stone) from a 46-year-old woman. In a cross section from near the neck, the folds are enlarged and rounded. The connective tissue stalks contain many large mononuclear cells with light stained cytoplasm and eccentric nuclei. These cells contain anisotropic lipoidal substances that can be demonstrated by fat stains. (×60.)

The *calcium bilirubinate stones* are less frequently encountered than the crystalline cholesterol stone. Usually they are multiple, jet black, with the shape of jackstones, and are rarely over 1 cm. in diameter (Fig. 735). Some are firm and preserve their shape. Others are fragile and readily crumble into small fragments. Their calcium content renders them radiopaque. The principal factor in the production of calcium bilirubinate calculi appears to be an intermittent or continuous increase in the bilirubin content of the blood serum due to hemolysis from whatever cause.[30] Hereditary defects in the erythrocytes such as are assumed to occur in hemolytic icterus and sickle cell anemia[31] probably play a role in some instances. In others, the hemolysis may be due to hemolysins (antibodies or chemicals) or to infections (malaria).

The *calcium carbonate stone* is the rarest of the pure gallstones. It is usually gray-white and amorphous.[32] The source of the calcium is undetermined, and the appearance of such calculous material in the bile is not related to any known disturbance of calcium metabolism. Its precipitation may be due to changes in the pH of the gall bladder content. The relation between the amorphous calcium carbonate calculus and the precipitation of a paste of lime salts, "milk of calcium bile,"[33] still remains to be investigated.

Mixed Gallstones.—About 80 per cent of the biliary calculi are mixed gallstones, that is, they are composed in varying proportions of all three of the stone-forming constituents of the bile. They form when

the function of the gall bladder is so altered that the solvents—bile acids—are resorbed faster than the stone-forming substances they hold in solution. This creates opportunities in the gall bladder for further concentration, precipitation, and crystallization of these substances. Mixed gallstones have the greatest variety in size, number, external appearance, and structure. They vary from 0.1 to 2 cm.

Fig. 735.—Calcium bilirubinate stones in the gall bladder of a 64-year-old Negro. They are multiple, jet black, with the shape of jack stones.

in diameter, are always multiple, and when they are small, several thousands of them may be contained in a single gall bladder.[34] Their surfaces are usually faceted with adjacent stones articulating. Some mixed gallstones have a lobulated surface with the contour of a mulberry. These are twisted, petrified, and broken-off polypoid projections of the gall bladder mucosa that contained lipoidal substances (Figs. 736 and 737). They usually are about 0.5 cm. in diameter and rarely reach the size of 1 cm.

The appearance and structure of mixed gallstones depend largely on their chemical composition. Cholesterol lends a yellow, calcium bilirubinate a black, and calcium carbonate a white hue. Predominance of the color is a fair indication of the chemical composition. Accordingly, mixed gallstones may be grouped as having a predominant content of cholesterol and calcium bilirubinate (yellow black), cholesterol and calcium carbonate (yellow white), calcium bilirubinate and calcium carbonate (gray black), cholesterol, calcium bilirubinate, and calcium carbonate (yellow, black, and white).

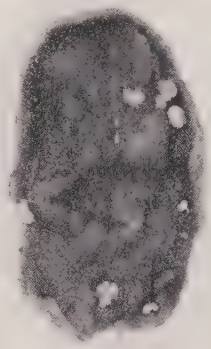

Fig. 736.—Mixed gallstones, mulberry type, in the gall bladder of a 46-year-old man. The petrified polypoid projections are attached to the mucosa (natural size).

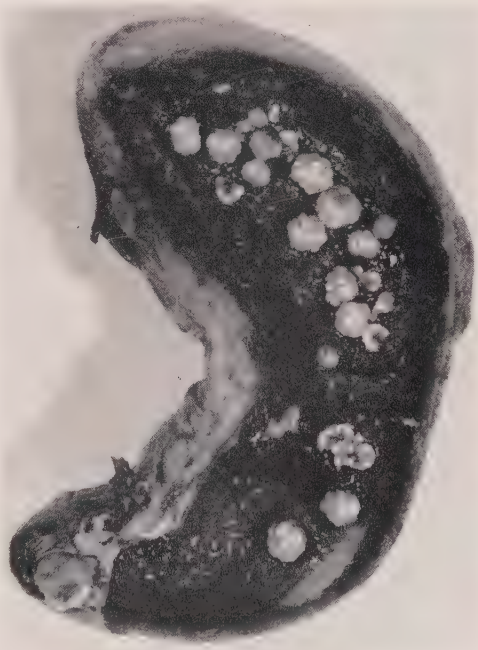

Fig. 737.—Mixed gallstones, mulberry type, in the gall bladder of a 42-year-old white man. The slightly larger calculi have the same appearance and composition as the polypoid projections in Fig. 736.

Radiopacity of mixed gallstones depends on their calcium content in the form of calcium bilirubinate, calcium carbonate, or both. When the calcium content is high and the calculi are large enough or numerous enough, they cast a shadow without the aid of cholecystography.

The mode of the formation of mixed gallstones appears to be more complicated than that of the pure gallstones. It seems certain that disturbance of the resorptive activity of the gall bladder plays a leading part. Whether this disturbance that allows resorption of the solvents faster than of the stone-forming constituents is alone responsible for the formation of mixed gallstones is uncertain. A coincidental increase in stone-forming substances in the bile would certainly accelerate the formation of mixed gallstones and would determine the relative amounts of the various components. It is also uncertain whether the process that caused the mixed gallstones to form is also the cause of the chronic cholecystitis that is almost always observed in a gall bladder containing mixed gallstones. It is, however, more likely that chronic cholecystitis itself is the principal cause of the formation of mixed gallstones.

Combined Gallstones.—About 10 per cent of the biliary calculi are combined gallstones; that is, they are composed of a combination of the ingredients of pure and mixed gallstones, with the one forming the nucleus, the other the shell. They form when the two principal conditions favorable to the formation of gallstones prevail in one or the other sequence. Most commonly the combined gallstone is solitary and its nucleus is a pure cholesterol stone, the shell any one of the mixed gallstones. In some instances, in addition to the large combined stone, a crop of smaller mixed gallstones having the same composition as the shell of the large stone is present in the same gall bladder. Calcium bilirubinate stones may acquire a shell of mixed stone. Conversely, mixed gallstones may acquire shells composed of cholesterol or of calcium bilirubinate or of calcium carbonate. A solitary combined gallstone attains the largest size, sometimes filling the entire lumen of the viscus. The gall bladder containing a combined gallstone or combined gallstones always discloses evidences of chronic cholecystitis, not unlike gall bladders containing mixed gallstones.

Incidence of Cholelithiasis.—It is rarely observed in the first and second decades of life.[35] Mixed gallstones occur about four times more frequently in women than in men. The childbearing period in its second half appears to be the most frequent age. Combined gallstones occur more frequently in the older age groups.[36]

Effects of Cholelithiasis.—Calculi within the gall bladder need not produce clinical manifestations. This is true particularly of the pure gallstones, namely, the crystalline cholesterol stone and the calcium bilirubinate stones. Their presence, however, may induce a chronic cholecystitis or there may occur in such a gall bladder an acute cholecystitis with clinical signs and symptoms appropriate to that condition.

A solitary cholesterol stone may float in the bile and become imprisoned in the neck of the gall bladder between the proximal folds of Heister. This situation cannot develop until the cystic duct has become dilated to at least five times its usual diameter. This dilatation is brought about by intermittent prolonged closure of the opening of the common bile duct into the duodenum. After the extrahepatic biliary ducts have reached a state of distention the valvelike action of the stone permits the bile to enter the gall bladder. Because of the increased pressure in the biliary ducts, white bile that contains little or no coloring matter is intermittently produced and fills the distended thin-walled gall bladder (hydrops of the gall bladder). A predisposition to the formation of white bile exists in a patient whose cystic duct has a low insertion and whose common bile duct therefore is short. A pure gallstone imprisoned in the neck of the gall bladder producing intermittent distention of the viscus by its ball valve action may cause only transient discomfort in the right upper abdomen. Later a chronic inflammatory reaction develops, interfering with the resorptive function of the viscus. Thereafter, three clinical courses are possible: the gall bladder becomes nonfunctioning and no signs and symptoms of cholecystic disease appear; or signs and symptoms of chronic cholecystitis develop; or, if bacterial invasion occurs, empyema of the gall bladder develops.

Calcium bilirubinate stones and calcium carbonate precipitates are usually silent, that is, they produce no clinical manifestations whatsoever.[37]

Mixed gallstones are contained in gall bladders with chronic cholecystitis. The cystic duct of such a gall bladder is always distended to several times its usual

diameter. This occurs because of intermittent increased intravesical pressure. As a result of this intravesical hypertension, there develops hypertrophy of the muscular coat with outpouchings of the mucosa toward the external layers producing the Rokitansky-Aschoff sinuses. The dilatation of the cystic duct with eventual incompetence of its folds at times allows the passage of the mixed calculi from the gall bladder into the common bile duct, causing obstruction of the flow of bile into the duodenum. The clinical manifestations produced by the passage of gallstones are intense pain in the right upper abdomen often radiating to the right shoulder; sometimes there are associated mild fever and leukocytosis. A gradually deepening jaundice with clay-colored stools follows obstruction of the common bile duct.

Combined gallstone, or gallstones, like the mixed gallstones, are contained in gall bladders with chronic cholecystitis. A gall bladder with a large combined gallstone may become fused with the duodenum or with the transverse colon, causing a communication between the gall bladder and the duodenum or the colon. Through a cholecystoduodenal fistula the calculus may pass from the gall bladder into the duodenum and onward through the jejunum; and, if of sufficient size, it may cause obstruction in the narrow portion of the ileum. Communication with the colon opens a way for retrograde infection of the gall bladder and biliary ducts.

Table X

Classification of Gallstones

TYPE	COMPOSITION	APPEARANCE	FACTORS IN ORIGIN	CHANGES IN GALLBLADDER
Pure gallstones, 10 per cent	Cholesterol (crystalline)	Solitary, crystalline surface	Hypercholesterolemia	Cholesterolosis
	Calcium bilirubinate	Multiple, jet black, crystalline or amorphous	Hyperbilirubinemia	No change
	Calcium carbonate	Gray-white amorphous	Unknown	No change
Mixed gallstones, 80 per cent	Cholesterol and calcium bilirubinate Cholesterol and calcium carbonate Calcium bilirubinate and calcium carbonate Cholesterol, calcium bilirubinate, and calcium carbonate	Multiple, faceted, or lobulated, laminated and crystalline on cut surfaces; hue depends on content: cholesterol, yellow—calcium bilirubinate, black—calcium carbonate, white	Chronic cholecystitis plus increased content in bile of cholesterol, calcium bilirubinate, or calcium carbonate	Chronic cholecystitis
Combined gallstones, 10 per cent	Pure gallstone nucleus with mixed gallstone shell	Largest of gallstones, when single. Hue depends on composition of shell	As in pure gallstones followed by chronic cholecystitis	Chronic cholecystitis
	Mixed gallstone nuclei with pure gallstone shells		As in mixed gallstones followed by increased content in bile of cholesterol, calcium bilirubinate, or calcium carbonate	Chronic cholecystitis

The presence of gallstones in the gall bladder, though at times silent, constitutes a reasonable indication for surgical removal of the gall bladder. Mixed and combined gallstones are a pending threat in that they predispose to acute cholecystitis and also to the passage of the calculi, resulting in obstruction either of the common bile duct or of the small intestine.

Cholesterolosis

When the cholesterol content of the bile is within physiologic limits, resorption of

the cholesterol apparently leaves no demonstrable trace in the mucosa of the gall bladder. When there is an increased cholesterol content, the folds of the mucosa of the gall bladder become yellow streaked with the pattern of the surface of a ripe strawberry—"strawberry gall bladder."[38, 39] This condition precedes and is usually concomitant with the presence of the crystalline cholesterol stone and is usually seen with mixed gallstones having high cholesterol content. This cholesterolosis may be seen in otherwise normal gall bladders containing no calculi, in gall bladders containing a crystalline cholesterol stone, and in gall bladders with chronic cholecystitis containing mixed or combined gallstones. Up to 20 per cent of all gall bladders removed surgically disclose some degree of cholesterolosis.

Cholecystography

Visualization of the gall bladder by means of radiopaque substances may reveal whether the resorptive function of the viscus is intact or impaired. Occasionally the Rokitansky-Aschoff sinuses may be visualized.[40] Cholecystography may also disclose anomalies in the shape and position of the gall bladder and the presence of gallstones and occasionally of neoplasms.[41]

Among the biliary calculi the crystalline cholesterol stone is nonopaque. It may occasionally visualize as a negative shadow in the opaque medium filling the viscus. Calcium bilirubinate stones are radiopaque and, if of sufficient size and number, may cast a shadow without the contrast medium. The radiopacity of mixed gallstones depends on their calcium content. Their visualization with the aid of a contrast medium may be unsuccessful because of the usually impaired resorptive function of the gall bladder. Combined gallstones usually visualize without the aid of cholecystography (scout film).

Neoplasms

In the extrahepatic biliary ducts neoplasms are infrequently encountered. They are seen more often in the gall bladder.

Papilloma, Adenoma, and Adenomyoma.—Soft projections on the mucosa of the gall bladder, papillomas,[42, 43] may occur singly or in groups or may be scattered over a large part of the surface. The cauliflower or seaweed-like, readily movable projection is composed microscopically of delicate or coarse connective tissue stalks covered by columnar epithelium like that of the rest of the mucosa. In the connective tissue stalks there may be infiltrations with large mononuclear cells filled with doubly refractile lipoidal substances. Sometimes these projections may become inspissated, petrified, twisted, or broken off and form the center or framework of berrylike mixed calculi. The papillomas are not precursors of, nor do they predispose to, carcinoma of the gall bladder.

Adenomas are low flat elevations on the mucosal surface, usually of the body of the gall bladder, causing some thickening of the wall. Microscopically, acinar tubular structures lined by cuboidal or columnar epithelium are within a scanty connective tissue stroma. Some of the acini may open into the lumen of the viscus. They do not usually extend into the muscular coat. An adenoma is not a precursor of a carcinoma.

Adenomyoma is the most common neoplasm of this group. It occurs almost invariably on or near the fundus, causing slight thickening in that region. Microscopically, a system of acinar tubular structures lined by cuboidal or columnar cells in a scanty connective tissue stroma is seen between interlacing smooth muscle bundles (Fig. 738). An adenomyoma is probably a hamartoma, that is, the anlage either of a part of the fundus that did not develop or of the fundus, of an undeveloped bifid or bilobed gall bladder.

Carcinoma.—*Carcinoma of the extrahepatic biliary ducts* usually arises in either of the hepatic ducts near their junction, or in the common hepatic or common bile ducts where the cystic duct branches off, or at the papilla of Vater. When the carcinoma involves the intraduodenal portion of the common bile duct, it is frequently difficult or impossible to determine whether the growth originated in the common bile duct, in the papilla of Vater, in the pancreas, or in the duodenum proper.[44] While carcinoma of the head of the pancreas usually obstructs the common bile duct, possible origin of the carcinoma in the other sites is to be considered. Carcinomas of the biliary ducts produce a local stiffening, thickening, distortion, and gradual obstruction of the lumen of the duct without necessarily involving its entire circumference. The growth usually enlarges by direct extension and spreads to regional lymph nodes. After obstruction of the common bile duct occurs, jaundice appears. When the obstruction is gradual, the proximal tributaries, including the intrahepatic biliary ducts, become dilated with the eventual production of "white bile"—hydrohepatosis.[47] While still small, these carcinomas cause obstruction, and the patient develops jaundice early and usually dies of cachexia. Practically all carcinomas of the extrahepatic biliary ducts, like those of the intrahepatic biliary

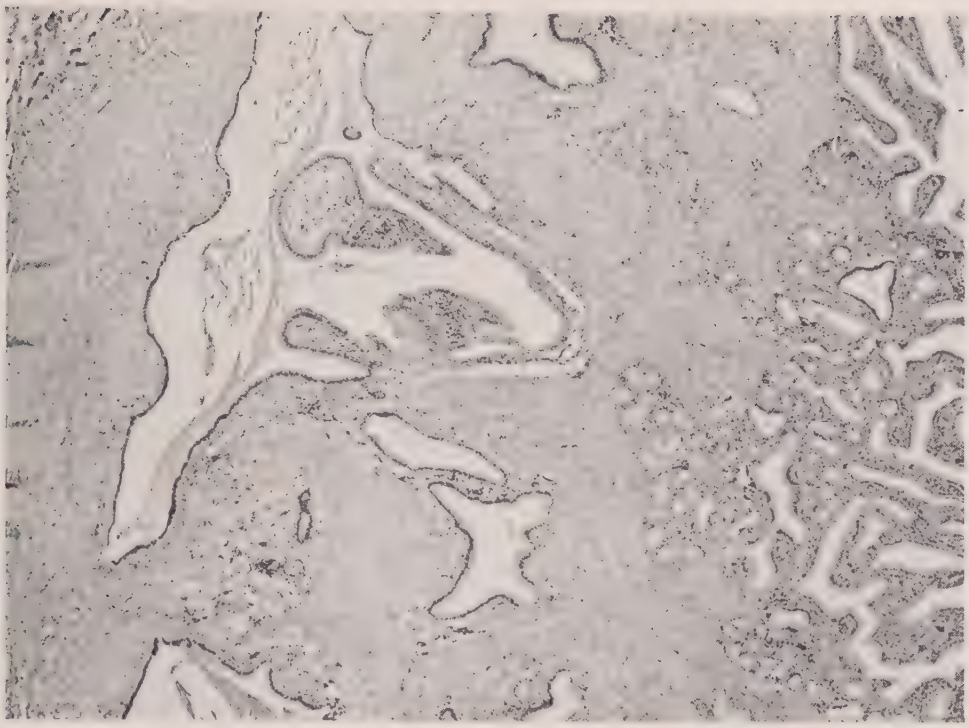

Fig. 738.—Adenomyoma of the gall bladder from a 56-year-old woman. A system of acinar tubular structures lined by cuboidal or columnar cells in a scanty connective tissue stroma is seen between interlacing smooth muscle bundles. (×32.) (Courtesy Dr. Malcolm A. Hyman.)

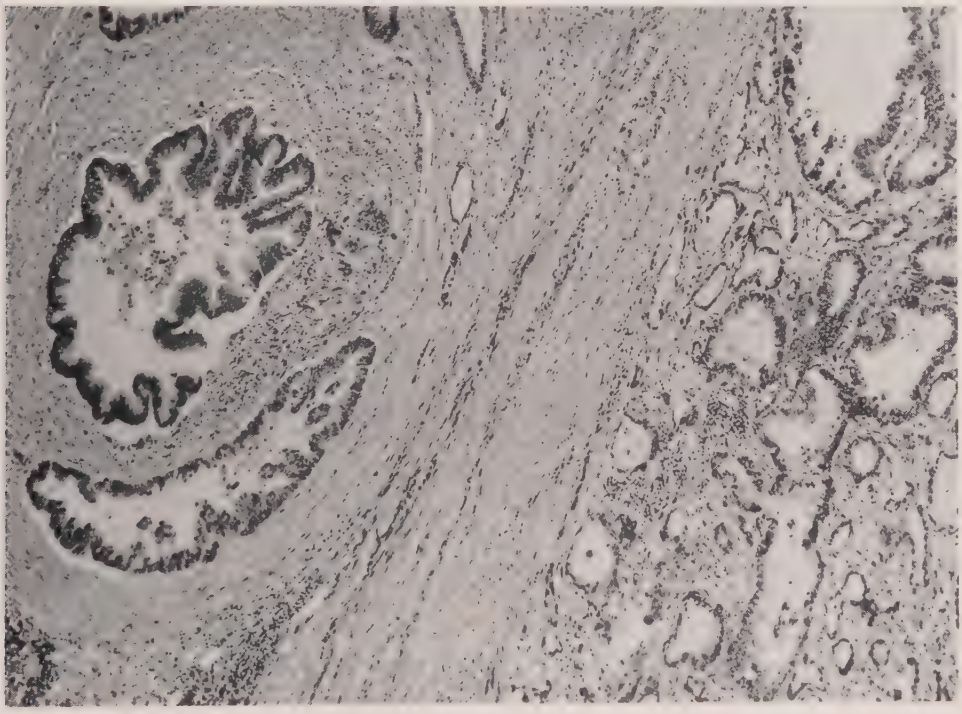

Fig. 739.—Carcinoma of the common bile duct from an 83-year-old man. Neoplastic cuboidal and columnar cells form acinar tubular structures or are mounted on delicate connective tissue stalks. Neoplastic cells are seen within the sheath of a nerve. There was complete obstruction of the common bile duct. There was no involvement of the regional lymph nodes and no distant metastasis. (×60.)

ducts, are columnar cell carcinomas.[45] They exhibit considerable variation in the height of the cells lining the acinar tubular structures or covering the papillary projections (Fig. 739). The degree of differentiation of the cells, the number of cells in a state of division, and the amount and character of the stroma also vary in the individual growths.

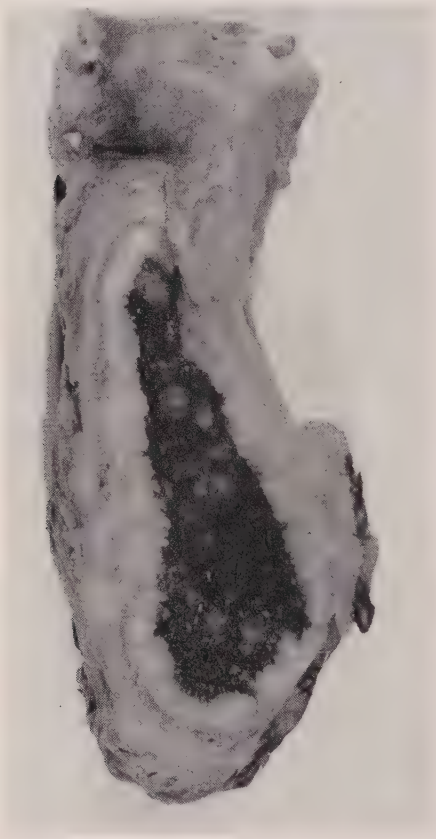

Fig. 740.—Carcinoma of the gall bladder from a 39-year-old white man. The entire wall is diffusely involved with multiple areas of ulceration in the mucosa. The viscus contained no calculi.

Carcinoma of the gall bladder[46, 47, 48, 49] usually originates in the fundus or neck of the viscus and occasionally in the cystic duct. It infiltrates the viscus locally, causing thickening and stiffening of the wall at the site of involvement. It may involve the entire gall bladder (Fig. 740). Some growths protrude into the lumen as irregular, small or bulky, firm or soft masses. More frequently the growth infiltrates the entire viscus and by direct extension involves the liver about the fossa of the gall bladder, forming a crust, several centimeters thick, of solid neoplastic tissue (Fig. 741). In rare instances where the entire wall is diffusely involved with multiple areas of ulceration in the mucosa the extension of the growth is toward the porta hepatis and down the course of the common bile duct involving the pancreas and duodenum as well. It is estimated that in about 90 per cent of carcinomas of the gall bladder there is cholelithiasis. This has led to the assertion that cholelithiasis predisposes to the development of carcinoma of the gall bladder.

Microscopically, over 90 per cent of carcinomas of the gall bladder are columnar cell carcinomas with pattern and structure similar to those that occur in the biliary ducts. Neoplastic columnar cells of varying heights are mounted on delicate connective tissue stalks or form acinar tubular structures in a scanty or more abundant, loose or dense, fibrous, connective tissue stroma (Fig. 742). Occasionally the columnar cells produce mucin in abundance. In rare instances the mucin-producing cells have a signet-ring appearance. Occasionally a squamous cell carcinoma is encountered in the

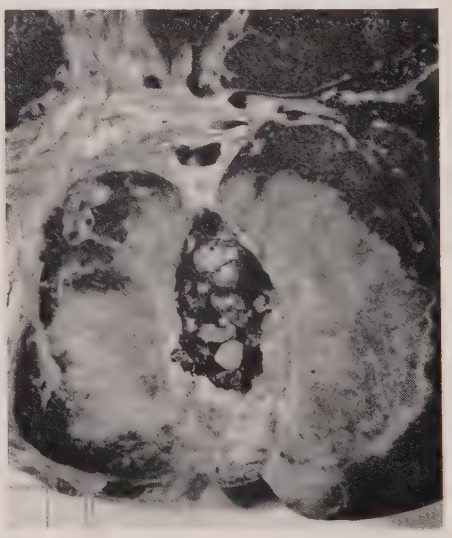

Fig. 741.—Carcinoma of the gall bladder from a 55-year-old man. The lumen is filled with mixed gallstones that are faceted. The wall of the viscus blends with the neoplastic tissue that forms a crust about the gall bladder several centimeters thick.

gall bladder and quite rarely the growth may be a columnar cell and squamous cell carcinoma (adenoacanthoma).

Anomalies

Some of the anomalies of the extrahepatic biliary ducts[50] are incompatible with extrauterine existence. Anomalies of the gall bladder usually do not interfere with its function. Hypoplasia to the degree of stenosis or atresia of the lumen of the common bile duct is sometimes seen in the newborn. A large cystlike outpouching of the common bile duct (idiopathic cyst) has been observed and, in some instances, successfully removed.[51] Variations occur in the number of the hepatic ducts and in the manner of their junction with one another, and with the cystic duct. Variations occur also in the manner of distribution of the arteries.[52]

There may be no anlage for the gall bladder, resulting in absence (agenesis) of the viscus, or there may be a double anlage, resulting in partial or complete duplication. Both conditions are rare. Bilobed, double, and septate fundi appear in man but are more common in animals, particularly cats.[53] A "stocking cap" reflection with a septum protruding into the lumen is observed in about 10 per cent of the gall bladders. Sometimes the septum is near the center, giving the viscus the shape of a dumb-bell. Variations in form, size, and peritoneal relations are frequent. The gall bladder may be small and end several centimeters short of the inferior margin of the liver—hypoplasia. In such instances the cystic duct is usually short, while the common bile duct is long. The reverse is usually true of large gall bladders. The cystic duct runs parallel with the common bile duct sometimes for a distance of several centimeters, and is fused with it, being separated only by a septum. Usually about half of the surface of the human gall bladder is covered by peritoneum. Rarely the entire circumference is surrounded by liver tissue. Occasionally the viscus is covered by peritoneum with a mesentery-like peritoneal attachment. All transitions between these two extremes may be observed. In rare instances a small accessory lobe completely detached from the liver is encountered on the surface of the gall bladder.[54] It has been inferred that there was a relation between such an accessory lobe and aberrant biliary ducts in the perimuscular layer (Luschka ducts).[24]

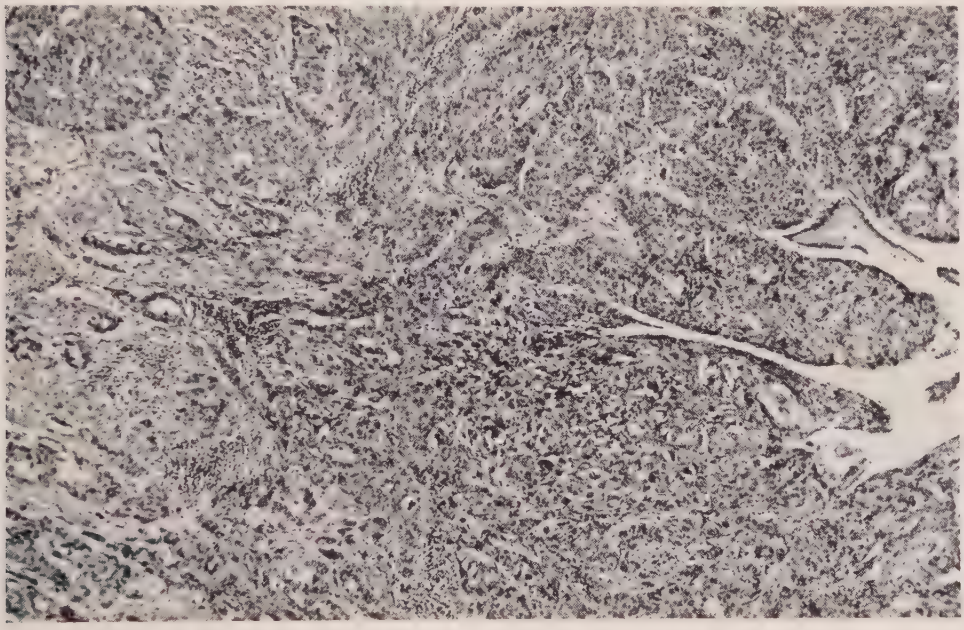

Fig. 742.—Microscopic appearance of the growth in the gall bladder shown in Fig. 740. Sheets of neoplastic epithelial cells in places in acinar tubular or papillary pattern permeate the entire thickness of the wall. (×60.)

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Chapter 29

THE PANCREAS

W. A. D. Anderson

The pancreas is an elongated yellowish organ situated in the posterior part of the upper abdominal cavity. It is composed of acinar tissue, which produces a secretion containing digestive enzymes carried to the duodenum by ducts, and localized areas of specialized tissue (islets of Langerhans), which produce a hormonal internal secretion (insulin) concerned with carbohydrate metabolism. The pancreas averages about 15 cm. in length, 3 cm. in thickness, and weighs 65 to 125 grams. The acinar cells, which form the main mass of the gland, contain refractile zymogenic granules in varying numbers according to their stage of secretory activity. The acinar lumina are normally small and not prominent. The larger ducts are lined by columnar epithelium, with some goblet cells and shallow mucus glands. Small ducts are lined by cuboidal or flattened cells.

Pancreatic extracts have been shown to contain a substance, lipocaic, which is active in the control of fat accumulation in the liver.

Heterotopia.—The presence of heterotopic pancreatic tissue apart from its normal and usual location and without anatomic connection with the pancreas proper is not rare, and may give rise to clinical disturbances. The incidence in routine autopsy studies has been variously reported between 0.6 and 5.6 per cent. The most common locations of the heterotopic pancreatic tissue are in the duodenum, stomach, jejunum, and Meckel's diverticulum. Situated usually in the submucosa but sometimes extending into the muscular wall, it appears grossly as a single, pale yellow or white lobulated nodule, and is easily mistaken for a neoplasm. The microscopic morphology is usually that of normal pancreatic tissue, and includes islets of Langerhans. Digestive disturbances simulating peptic ulcer or cholecystitis may accompany pancreatic heterotopia in the stomach or duodenum. Inflammatory changes and fat necrosis are sometimes found in associated tissue. Islet cell tumors giving rise to hyperinsulinism may originate in heterotopic pancreatic tissue, as also may pancreatic carcinoma.

Annular Pancreas.—Annular pancreas is a congenital pancreatic maldevelopment which, although rare, may be of clinical importance. From the head of the pancreas in its normal position in the bend of the duodenum, a band of pancreatic tissue encircles the second part of the duodenum. Usually the encirclement is complete, but there is sometimes a gap anteriorly. It is probably due to a maldevelopment involving the ventral pancreatic anlage, the tip of which fails to rotate with the duodenum. Other congenital abnormalities of development are a frequent accompaniment. The pancreatic tissue ordinarily is of normal microscopic structure. The duct draining the annular tissue usually passes around the entire duodenum to enter the main duct or opens separately into the common bile duct.

Somewhat more than fifty cases have been reported, most of which were without symptoms. In a few cases annular pancreas has given rise to duodenal obstruction or has been associated with acute pancreatitis.

Fatty Infiltration of the Pancreas.—A fatty infiltration of the pancreas, with increase in the amount of interstitial fat, is common in cases of obesity. When extreme, there may be some corresponding atrophy of acinar tissue.

Tuberculosis.—The pancreas is not commonly involved by tuberculosis, even in the generalized miliary form.

Syphilis.—A fibrosis, or retarded development of the pancreas, with abundant fine cellular connective tissue and many spirochetes, is not uncommon in congenital syphilis. Acquired syphilitic lesions of the pancreas are rare.

Cysts of the Pancreas

Several varieties of cystic change occur in the pancreas, none with great frequency. Most cases can be classified into the following groups: (1) retention cysts, due to dilatation behind a duct obstruction, and including congenital fibrocystic disease of the pancreas; (2) neoplastic cysts, including cystadenomas, and dermoid cysts; (3) pseudocysts—cysts resulting from hemorrhage or necrosis; (4) parasitic cysts, such as due to Echinococcus; (5) angiocystic disease (Lindau); and (6) congenital cyst, often associated with cystic disease elsewhere (e.g., polycystic kidney).

Retention cysts have been considered to be the result of some blockage of pancreatic ducts, sometimes by a gallstone impacted in the ampulla of Vater. Attacks of biliary colic or pancreatitis have frequently been observed to precede the development of pancreatic cysts. The cysts are most often in the distal part of the body or the tail, vary from minute to very large size, and usually are unilocular, though sometimes divided by thin septa into several loculations which may or may not communicate. A communication between the cyst cavity and the larger ducts usually is not demonstrable. The cyst walls are of dense fibrous tissue. A lining epithelium varying from tall columnar to low flat cells is usually present.

Pseudocysts are mainly encapsulated collections of fluid in or about the pancreas, usually resulting from trauma, with hemorrhage, pancreatic inflammation, or suppurative necrosis. The walls

are composed of elevated peritoneum or adherent omentum. The pseudocyst is often adherent to adjacent peripancreatic structures. The cavity is single, may be quite large, and contains cloudy or brownish fluid. The wall is composed of vascular fibrous tissue, and often contains blood pigment and fat cells or foam cells. An epithelial lining is lacking.

Parasitic cysts of the pancreas are infrequent. Echinococcus cysts of the pancreas have the same character as elsewhere. Amebic abscess of the pancreas is rare.

Angiocystic lesions of the pancreas have been reported in association with the vascular cerebellar cysts of Lindau and the angiomatosis of the retina of von Hippel. However, progressive, destructive angiomatous and cystic disease of the pancreas, differing from that described by Lindau, has been reported.[19]

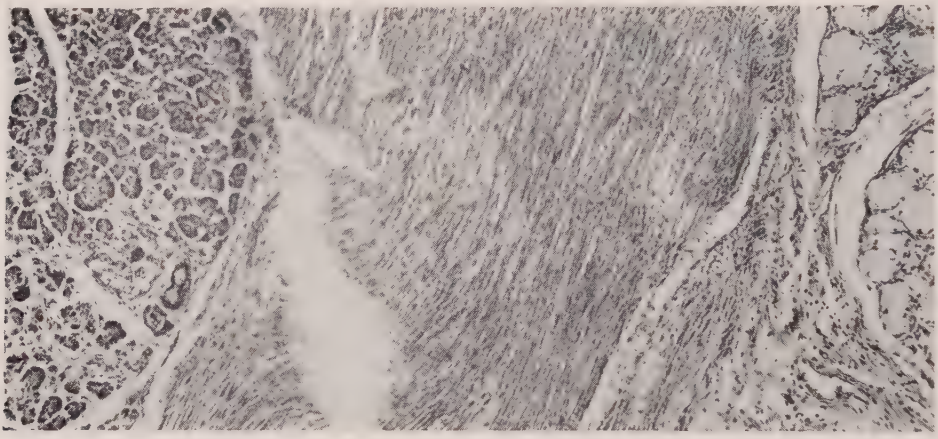


Fig. 743.—Pancreatic heterotopia. A small focus of pancreatic tissue in the muscular wall of the stomach is seen on the left. Gastric mucosa is evident on the right.

Fibrocystic Disease of the Pancreas.—Fibrocystic disease of the pancreas is a congenital and often familial abnormality of the pancreas in which there is cystic distention of the ducts, which are filled with inspissated material. There are associated atrophy and fibrosis of the exocrine parenchyma. The condition is often fatal in infancy or early childhood. Pancreatic achylia, with lack of absorption of fat-soluble vitamins A and D, and poor absorption of calcium, is an important feature. Death may occur in the neonatal period as a result of intestinal obstruction due to this inspissated meconium (meconium ileus). At later periods, chronic respiratory infection is a prominent feature, and there may be evidence of the celiac syndrome, with bulky, fatty, offensive stools (steatorrhea), abdominal distention, and failure of proper growth. Vitamin A deficiency may be evident, due to deficient digestion and absorption of fat-soluble vitamins. In autopsied cases which have presented the celiac syndrome about one out of four have shown microscopic evidence of cystic fibrosis of the pancreas.[25]

The pancreas may show little gross change except to be firmer and thinner than normal. Infiltration with fat, increased fibrous tissue between the lobules, and unevenness in the size of the lobules have been described. The pancreatic duct is usually patent. Microscopically, there are dilated ducts and acini containing coagulated eosinophilic material. The pancreatic parenchyma is atrophic and scanty in advanced cases, with relative increase of the fibrous stroma. The stroma may be infiltrated by some lymphocytes and mononuclear cells. The ductal epithelial cells are flattened and may be squamous in appearance. The inspissated material in the lumina may be laminated and is usually acidophilic, but may become calcified. In the dilated acini the material may in part stain similarly to mucus, and in part resemble fibrin. The islets of Langerhans appear relatively unaffected.

Except in early cases the respiratory tract is affected. Common respiratory lesions are purulent bronchitis and bronchiectasis, abscesses, and patches of bronchopneumonia. Bronchiolar lining epithelium is often flattened and has a squamous appearance.

The etiology and pathogenesis are undetermined, but the evidence suggests that it is a congenital and sometimes familial anomaly of development, such as a congenital atresia of the ducts.[23] Farber[22] has presented evidence that the condition is systemic, the primary fault being an alteration of the character of the secretions within glandular structures. Evidence of disturbed secretion may be found also in the respiratory tract, upper intestinal tract, liver, and gall bladder.

A somewhat similar picture of dilatation of pancreatic acini with slight fibrosis and minimal inflammation may be seen in adults who have suffered from uremia, hepatic disease, high intestinal obstruction, or chronic ulcerative colitis. The change probably is due to an abnormal secretion of the exocrine parenchyma, which, being unusually thick and viscid, causes obstruction of acini and ducts with dilatation of the lumens. The altered secretion in turn may be due to altered protein metabolism. Acinar dilatation may be an early change in chronic pancreatitis, and also may precede the occurrence of acute pancreatitis precipitated by other factors.

Pancreatitis

Acute pancreatitis may occur as an acute interstitial inflammation or as an acute hemorrhagic and necrotizing inflammation. The pathologic changes and prognoses are radically different in the two forms.

Blood amylase activity of moderate or marked degree is almost always associated with disease of the pancreas. Pancreatic involvement secondary to other pathologic changes, such as duodenal ulcer or mesenteric thrombosis, may be indicated by a slightly increased blood amylase.

Acute Interstitial Pancreatitis.—Acute interstitial pancreatitis occurs mainly in young adults, and may produce abdominal signs and symptoms, including epigastric pain, tenderness, nausea, vomiting, and prostration. Serum amylase activity is increased, particularly in early stages. The pancreas appears enlarged, firm, edematous, and whiter than normal. Microscopically there is edema of the interstitial tissue of the pancreas and peripancreatic tissues. There may be some infiltration by neutrophilic leukocytes. Occasionally, small areas of fat necrosis are present. Recovery usually occurs with conservative treatment, but recurrence is common. Mumps and other infectious diseases also may have an associated interstitial pancreatitis.

Acute Hemorrhagic Pancreatitis.—Acute hemorrhagic and necrotizing inflammation of the pancreas is associated with severe symptoms of abdominal pain, nausea, rigidity, prostration, shock, and toxicity. Serum calcium often is low (below 9 mg. per 100 c.c. of blood) and in fatal cases may be below 7 mg.[32a] Most cases are in middle adult life, and the frequency in women is somewhat greater than in men.

Pathogenesis.—The pathologic changes are related to the release and activation of enzymes, particularly trypsin and lipase, from the pancreatic acini and ducts. The trypsin affects especially the walls of blood vessels, producing hyaline degeneration and necrosis, with resulting rupture and hemorrhagic changes. Lipase activity results particularly in fat necrosis. In any individual case the pathologic picture depends upon the relative degree of involvement of blood vessels and of fatty tissue.

The etiological factors leading to release of pancreatic enzymes are variable, and in many cases are difficult to determine. Opie,[30] and others, demonstrated that a gallstone lodged in the ampulla of Vater might cause reflux of bile into the pancreatic duct, and lead to pancreatitis. While this seems anatomically possible in about 18 per cent of individuals,[27] this mechanism has been demonstrated to have occurred in but few cases. However, cholelithiasis has been shown to occur with greater frequency in individuals with acute pancreatitis than in the general population of the same sex and age groups.[29] Biliary tract disease and calculi are associated in a high proportion of cases.[33b] It is evident, however, that other explanations of pathogenesis are necessary in many cases, and obstructions by other methods, including spasm of the sphincter of Oddi, have been postulated. Obstruction to the outflow of pancreatic secretion may result in distention and rupture of acini and small ducts, with release of the damaging enzymes. Rich and Duff[32] have emphasized that such obstruction may be due to metaplasia of the epithelium of small ducts. Ingestion of alcohol or a heavy meal appears to promote acinar rupture, apparently by stimulation of secretion. No doubt other mechanisms are important in some cases, including spread of infection from adjacent tissues. Vascular occlusions and vascular lesions appear to be important quite frequently. Pancreatic arterioles are involved commonly and severely by hyaline arteriolosclerosis in hypertensive individuals, and areas of pancreatic necrosis appear to be a not infrequent complication of hypertensive arteriolosclerosis and arteriolonecrosis. The pancreatic lesions in such cases are usually overshadowed by the severe renal involvement. Periarteritis nodosa also may cause areas of localized pancreatic necrosis. Pancreatitis due to infection or vascular interference is usually of a mild or subclinical grade, and leads to recovery with scarring or chronic pancreatitis.

Pathologic Appearance.—The pancreas is enlarged and firm, with softer friable areas of necrosis. Various degrees of hemorrhagic and gangrenous changes

may involve portions of the pancreas or the whole organ. The gangrenous changes progress rapidly post mortem. Areas of fat necrosis affect the fat of the pancreas, mesentery, and omentum. There is evidence that disseminated areas of fat necrosis are due to lipase transmitted by lymph channels.[37a] These appear as firm, dry, opaque yellow or gray nodules. The necrotic areas of fatty tissue are surrounded by a zone of hyperemia and leukocytes. The tissue is edematous and infiltrated by erythrocytes but relatively few leukocytes. Blood vessels may show necrosis of their walls and thrombi in their lumina. Inspissated secretion may be found in pancreatic ducts. Metaplasia of duct epithelium with associated acinar dilatation was found in 13 of 24 cases described by Rich and Duff.[32] Complications include development of multiple suppurative abscesses or sinus tracts which may open back into the duodenum, and pseudocysts.

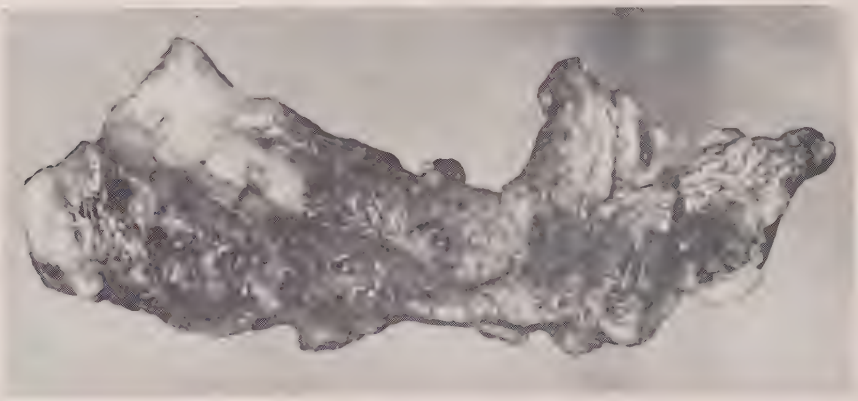


Fig. 744.—Acute hemorrhagic necrosis of the pancreas. (Courtesy Dr. G. L. Duff.)

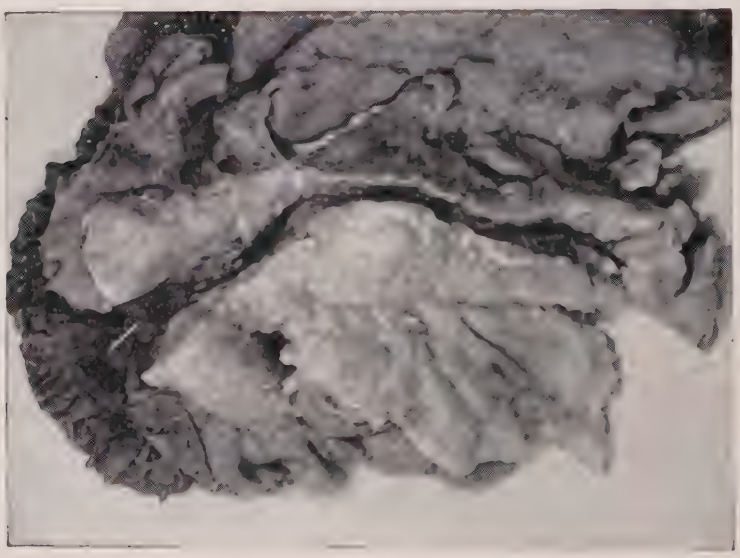


Fig. 745.—Fat necrosis and acute pancreatitis. The white opaque areas represent fat necrosis. A small white rod is in the duct opening into the duodenum. (Courtesy Dr. H. C. Schmeisser.)

Chronic Pancreatitis.—Localized pancreatitis of the head of the pancreas may obstruct the common bile duct and hence produce jaundice. Such lesions may be very difficult to distinguish from carcinoma of the head of the pancreas without biopsy of the area. Diffuse chronic

sclerosing pancreatitis is rarer, and may lead to permanent stenosis of the common bile duct in addition to atrophy of pancreatic glandular tissue. Fibrosis of the pancreas is seen in hemochromatosis (see page 82).

Pancreatic Calculi

Pancreatic stones are not common, the autopsy incidence being about one in 1,500 to 2,000 autopsies. Alcoholism and diabetes mellitus are common associated conditions.[44] True pancreatic calculi are found in ducts, and apparently result from infection and inflammation, with stasis and altered pancreatic secretion. Calcifications in the parenchyma of the pancreas are sometimes referred to as false stones; such calcification may occur in areas of pancreatitis or of fat necrosis. In rare cases such calcification is diffuse.[40]

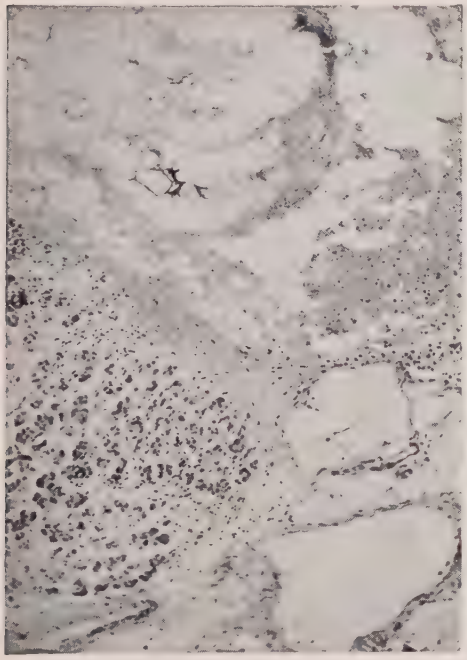


Fig. 746.—Fat necrosis of the pancreas.

Pancreatic calculi are grayish-white, firm or friable, and vary up to one or more centimeters in diameter. They are usually rough or irregular in outline, and often multiple. Calcium carbonate and calcium phosphate are the main constituents.

Epigastric pain, either dull or colicky, is the only common symptom. Associated with calculi there is often a chronic pancreatitis with fibrosis, and parenchymal atrophy in late stages may result in steatorrhea and mild diabetes mellitus. In disseminated or diffuse calcification there is marked calcification of the parenchyma of the gland, associated with atrophy of acinar tissue and marked interlobular fibrosis.[40, 44a]

Tumors of the Pancreas

Neoplasms of the pancreas are mainly adenomas and carcinomas which may be cystic or solid, and of ductal, acinar, or islet cell type. Rarer tumors of angioblastic or sarcomatous nature also occur. Included with the consideration of pancreatic tumors are the neoplasms of the duodenum arising from the ampulla of

Fig. 747.—Squamous metaplasia of the lining of a pancreatic duct.

Vater or adjacent ductal tissue, and from aberrant pancreatic tissue. Carcinomas of the region of the head of the pancreas have obstruction of the common bile duct and jaundice as a prominent feature. Carcinomas of the body and tail of the pancreas are associated with different clinical features, with massive local and distant metastasis and often widespread venous thrombosis. Tumors of islet cell tissue frequently are characterized by excessive insulin production and clinical manifestations of hypoglycemia.

Cystadenoma of the Pancreas.—Cystadenomas of the pancreas are uncommon tumors, rounded, coarsely lobulated, with a definite capsule and cystic consistency, usually 2 to 8 cm. in di-

ameter, and somewhat more frequent in the tail of the organ than in other parts. They are composed of many cystic spaces lined by flattened or cuboidal epithelium, and separated by fibrous septa or bands of varying width. Occasionally there is some papillary infolding of the lining epithelium. They grow slowly and by expansion.

Cystadenocarcinoma of the Pancreas.—Cystadenocarcinomas of the pancreas are similar to the cystadenomas, but with cystic spaces lined by cuboidal or columnar hyperchromatic epithelial cells, frequent papillary infoldings, and infiltration of surrounding tissue. Solid areas of adenocarcinomatous appearance occur.

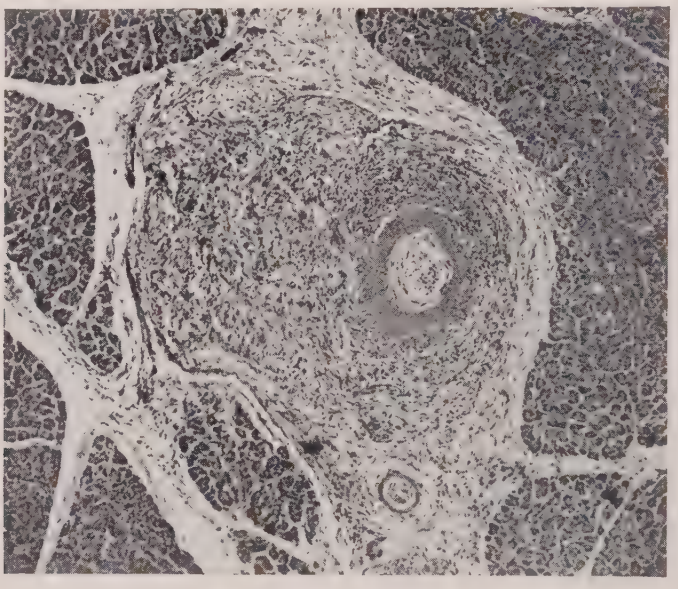


Fig. 748.—Periarteritis nodosa of pancreas.

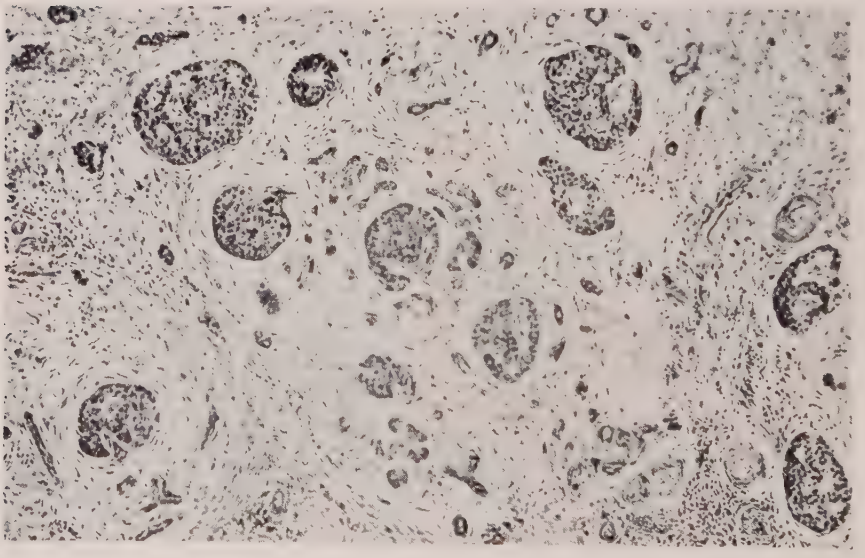


Fig. 749.—Pancreas. Acinar atrophy following duct obstruction. The islet tissue is left relatively intact.

Carcinoma of the Pancreas.—Adenocarcinoma is the most common neoplasm of the pancreas, and is estimated to account for 2 to 4 per cent of deaths from

cancer. About 60 per cent occur in the head of the pancreas. Most cases occur in middle or late age periods, and with greater frequency (3 to 1) in men than in women. Jaundice, epigastric pain, backache, and digestive disturbances are the most frequent clinical manifestations, with anorexia, weight loss, cachexia, and weakness becoming prominent in later stages.

Fig. 750.—Arteriosclerosis and atrophy of pancreas. Lower: Roentgenogram of the specimen showing the severe calcification of blood vessel wall.

The cancer forms a hard nodular mass within the pancreatic tissue, firmer than the normal parenchyma, but difficult to distinguish grossly from localized areas of chronic inflammation and fibrosis. There is marked variation in size (usually between 1 and 10 cm.), and in shape. Although sometimes ovoid and well demarcated, many fuse with surrounding parenchyma and have no definite gross margin. They may be entirely within the substance of the organ, or bulge from the surface. Multiple nodules of tumor tissue are not uncommon.

Microscopically, most of the tumors are cylindrical cell adenocarcinomas appearing to be of ductal origin, and less frequently are of acinar cell type resembling the parenchyma of the pancreas. The duct cell type is composed of irregular ductal or glandlike structures lined by one or several layers of anaplastic columnar or cuboidal cells. Papillary projections are common. The individual cells have well-defined margins and vesic-

Fig. 751.—Cystadenoma of the pancreas. The coarse porous surface is typical. (From Brunschwig, Surgery of Pancreatic Tumors, The C. V. Mosby Co.)

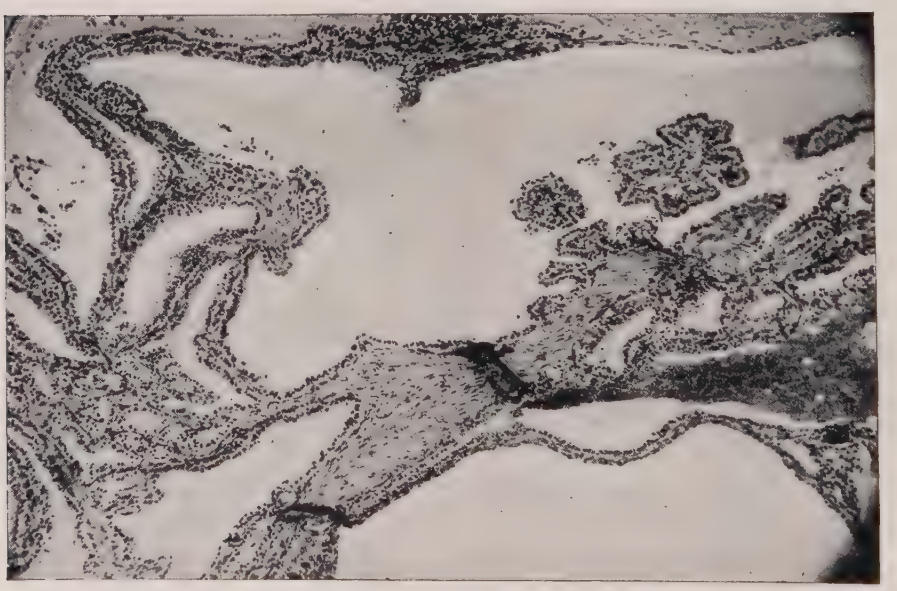


Fig. 752.—Cystadenoma of pancreas. (From Brunschwig, Surgery of Pancreatic Tumors, The C. V. Mosby Co.)

ular nuclei, usually with a single nucleolus. Fibrous stroma is often abundant.

The acinar cell carcinoma consists of irregular or lobular masses of tumor cells having poorly defined margins and large hyperchromatic nuclei with inconspicuous or absent nucleoli. Occasionally small clusters of the cells resemble pancreatic acini. Marked pleomorphism may be evident, with cells of elongated or bizarre shapes and large or multiple nuclei. In rare instances of well-differentiated acinar carcinomas, fat necrosis may be present not only about the pancreas, but around distant metastases or even in areas devoid of metastasis.[50a, 50b]

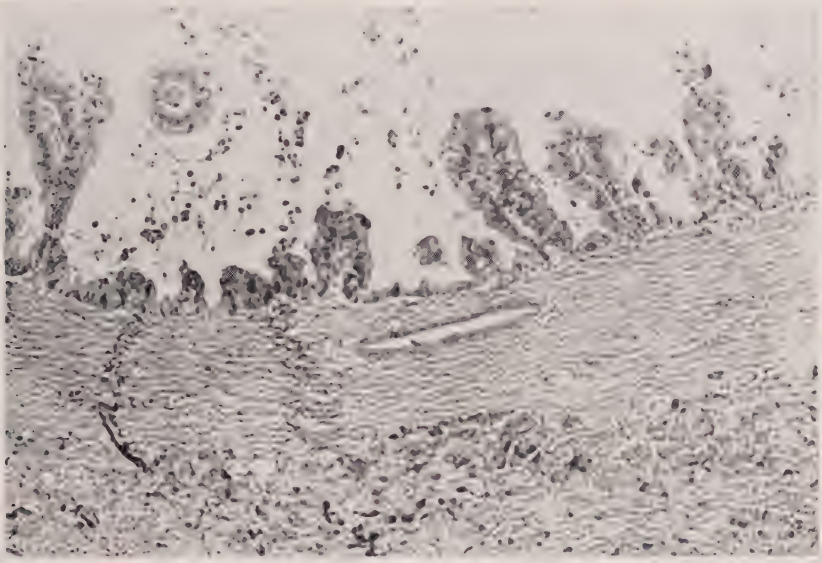


Fig. 753.—Mucoid papillary cystadenocarcinoma of pancreas.

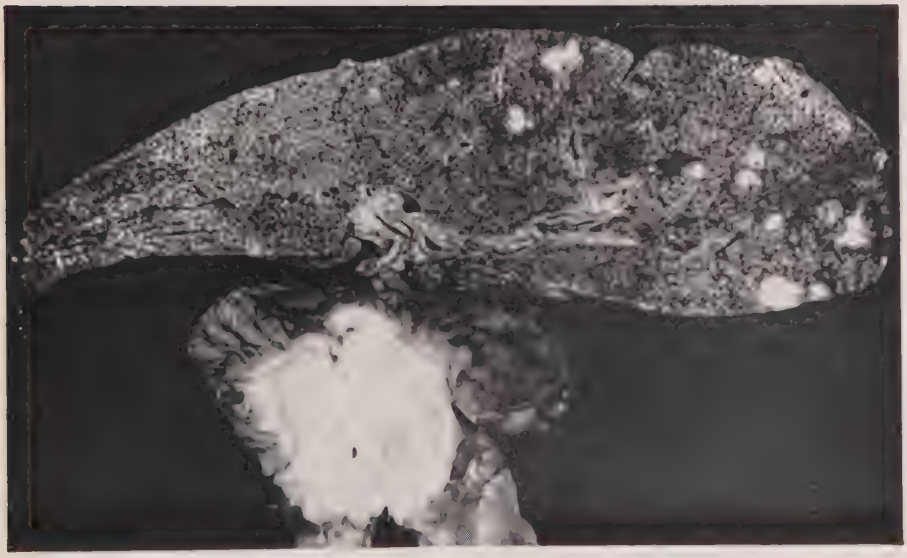
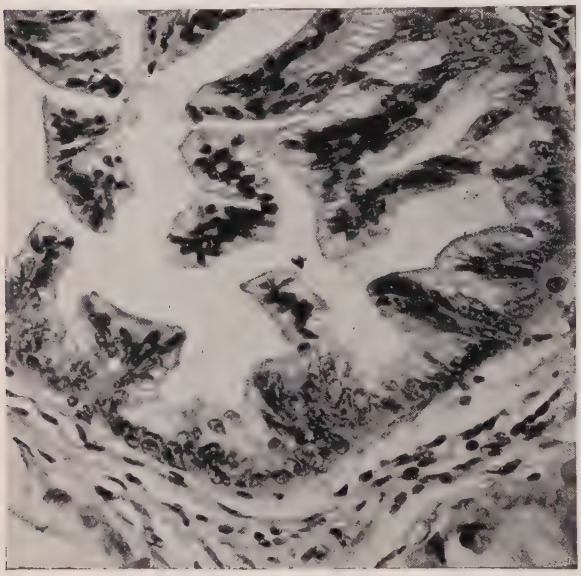


Fig. 754.—Primary carcinoma of head of pancreas with direct invasion of duodenal wall and metastases in liver. (Courtesy Dr. G. L. Duff.)

Obstruction of the common bile duct by cancer of the head of the pancreas

leads to progressive jaundice. There is usually an actual invasion of the duct wall by cancer cells, rather than simply mechanical compression of the duct by the adjacent tumor.[51] The gall bladder and the extrahepatic and intrahepatic biliary tract above the obstructed area become dilated.

Cancer of the head of the pancreas is fatal within a relatively short period of time, the average survival being only about nine months after onset of symp-



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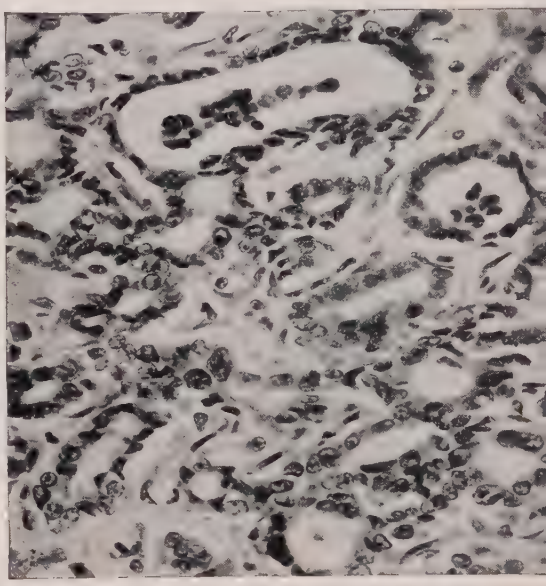

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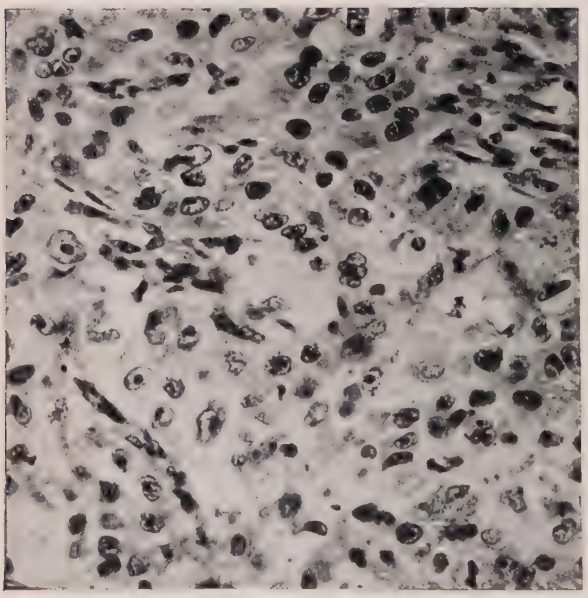

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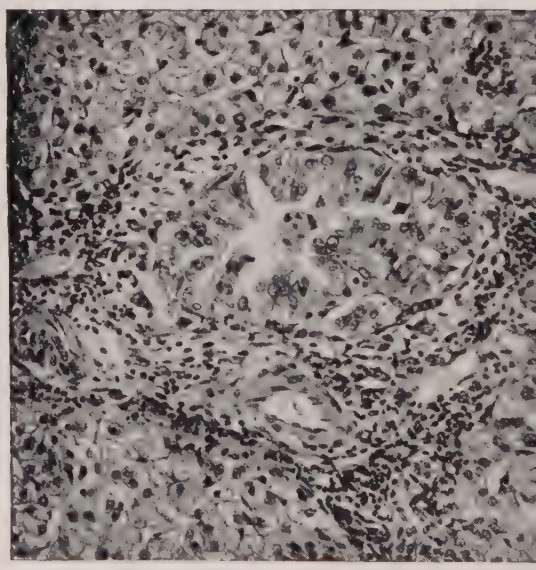

D.

Fig. 755.—Histologic types of carcinoma of the pancreas. *A*, Papillary cystic. *B*, Adenocarcinoma reproducing small ducts. *C*, Medullary carcinoma, composed of large anaplastic cells. *D*, Metastatic duct cell carcinoma of pancreas in liver. (From Brunschwig, Surgery of Pancreatic Tumors, The C. V. Mosby Co.)

toms. Metastases occur most often in regional para-aortic and mesenteric lymph nodes, liver, and lung.

Carcinoma of the body and tail of the pancreas constitutes nearly one-third of pancreatic cancers, but is difficult to recognize clinically because of a paucity of distinctive signs or symptoms. Abdominal pain and severe loss of weight occur most constantly; ascites and hematemesis are common; hepatomegaly, splenomegaly and terminal jaundice sometimes occur, but a wide variety of signs and symptoms may occur as a result of metastases which are relatively widespread and massive as compared with carcinomas of the head of the pancreas. Extensive invasion of venous radicles may be present around the tumor and in the portal vein within the liver. About one-third of the carcinomas of the body and tail of the pancreas are associated with multiple venous thrombosis of considerable extent, a feature which may dominate the clinical history. An adequate explanation is lacking for the tendency to marked venous thrombosis, which does not occur with cancers of the head of the pancreas. The gross and microscopic character of the cancers of the body and tail of the pancreas do not differ from those of the head of the organ.

Fig. 756.—Primary carcinoma of head of pancreas, penetrating duodenum with deep ulceration, and metastases in liver. (Courtesy Dr. G. L. Duff.)

Tumors of the Ampulla of Vater.—Neoplasms of the ampulla and papilla of Vater include adenomas, papillomas, and carcinomas. Such tumors of biliary tract origin, while uncommon, compose the large proportion of tumors of the duodenum. Carcinomas of the ampullary region may be papillary or ulcerative, and are composed of glandlike or ductlike spaces lined by cuboidal or columnar epithelium, often with papillary irregularities. Mucus production may occur. Solid cords or masses of cells are not uncommon. Infiltration occurs into the duodenal wall and adjacent areas of the head of the pancreas. Biliary obstruction and jaundice develop early in the course of the neoplasm. Metastases occur late and often only locally. Some of the carcinomas of the duodenum other than in the ampullary region have been shown to arise from aberrant pancreatic tissue.[56]

Islet Cell Tumors of the Pancreas.—Pancreatic tumors resembling tissue of islets of Langerhans have been known for many years. It was not until 1927, a few years after the discovery of insulin, that it was recognized that such tumors

may have secretory activity and produce a clinical syndrome of hyperinsulinism and hypoglycemia. The clinical syndrome is characterized by paroxysmal attacks similar to insulin shock, which occur particularly during fasting or an overfatigued state, are accompanied by blood sugar concentrations of 50 mg. per cent or less, and are usually promptly relieved by ingestion of glucose. Central nervous system disturbances are common. It has been estimated that hypoglycemic symptoms occur with about 20 per cent of islet cell tumors. Surgical removal of such tumors has resulted in relief of symptoms. The functional activity of the tumor bears little relation to its size, but is probably related to the type and differentiation of the cells which compose the tumor.

Islet cell tumors occur at any age, but with greatest frequency between 30 and 50 years. Those in the lower age groups are more frequently associated with hypoglycemic manifestations. The incidence is slightly greater in males. The most frequent location is in the tail of the pancreas, but the body and head of the organ may be involved. In about 12 per cent of cases more than one tumor is present.[59]

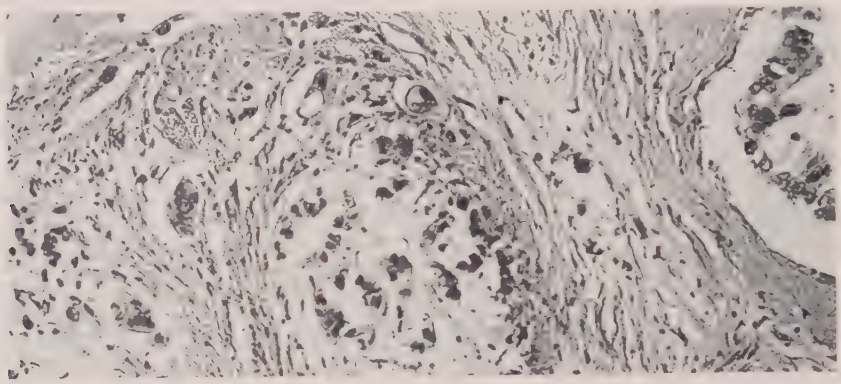

Fig. 757.—Well-differentiated adenocarcinoma of pancreas invading adjacent nerve.

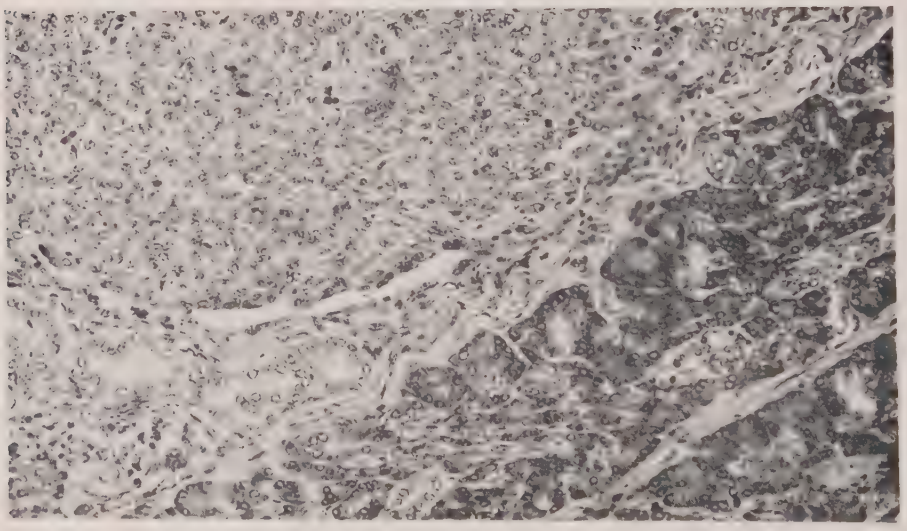

Fig. 758.—Islet cell adenoma of pancreas. The margin is shown, with adjacent pancreatic acinar tissue at lower right.

The size of reported islet cell tumors has varied from diameters of 1.2 mm. up to 15 cm., but the majority are between 1 and 2 cm. in diameter. They are usually circumscribed and sometimes

encapsulated, of reddish-gray color, and homogeneous in appearance, lacking the fine lobulation characteristic of normal pancreatic tissue. Rich vascularity is often a marked feature. The tumor is firmer than the surrounding pancreatic tissue.

Histologically, the tumor cells have a morphology and arrangement resembling those of the islets of Langerhans. The cells are arranged in short anastomosing cords of varying thickness, sometimes with broader bands or masses of cells. Occasionally, rosettelike clusters of cells around a tiny lumen may be found. The individual cells are often very similar to those of normal islets, of polyhedral, cuboidal, or columnar shape and most frequently with central spherical or ovoid nuclei. The cytoplasm is eosinophilic. By special methods of fixation and staining, alpha and beta granules have been demonstrated in the tumor cells, and it has been suggested that the severity of symptoms may be related to the degree of similarity of the majority of cells to the beta cells of normal islets. A functionally inactive tumor composed almost exclusively of the delta type islet cells has been reported.[67] Degenerative changes such as fibrosis, hyalinization, and calcification, which commonly affect islets, may also be found in the tumor.

The large majority of islet cell tumors are benign adenomas. However, a small proportion progress rapidly and metastasize early and widely by lymphatics and blood stream. The hypoglycemic syndrome may or may not be present in such cases. There also occurs a group of islet cell tumors in which certain histologic features, such as incompleteness of the capsule, or invasion of the capsule, adjacent pancreatic tissue, or blood vessels, suggest a malignant nature, but which behave in benign fashion.

Hemorrhagic and degenerative changes have been described in the central nervous system in fatal cases of hypoglycemia. Small petechial perivascular hemorrhages may be found in any portion of the brain, and have been interpreted as the result of convulsive seizures. Acute degenerative changes occur in nerve cells of the cerebral cortex and basal ganglia.

Much evidence has indicated that islet cell tumors, like the epithelium of normal islets, are derived by differentiation from epithelium of pancreatic ducts.[59, 65] Rare cases of islet cell tumors developing in aberrant pancreatic tissue have been observed. There is some indication that alloxan may have a destructive effect on the cells of an islet cell tumor, in a fashion similar to its specific action on normal islet tissue[68, 69] (see page 864). This presents an interesting problem for future exploration.

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Chapter 30

DIABETES MELLITUS

Shields Warren

Diabetes mellitus is a protracted disturbance in utilization of carbohydrate, evidenced by glycosuria and an increase in blood sugar.

Etiology

Etiology is unknown, although relative insulin insufficiency is basic in all forms of the disease. Heredity has been established as an important factor. Similar twins have diabetes in a high proportion (63 per cent) of cases. The incidence of the disease is appreciably higher in blood relatives of diabetics than in the general population. Another factor is obesity. Almost 80 per cent of all adult diabetics were obese prior to the development of the disease. Trauma is not a factor except in those rare instances where all or nearly all of the pancreas has been destroyed.

Incidence

At least half a million diabetics are alive in the United States today, their condition varying in severity from cases that can be controlled by reduction of carbohydrate in their diet alone to those that require 100 or more units of insulin daily to utilize properly their carbohydrate. The disease is half again as frequent in women as in men. While it may occur at any age, it develops most frequently in the fifth and sixth decades. In general, diabetes is milder in older patients, more severe in young. This seems to be paralleled by a lesser insulin content in the pancreas of the young severe diabetic. Possibly extrapancreatic factors are more important in the older group. Experimental diabetes may be produced in animals by total pancreatectomy, by partial pancreatectomy with high carbohydrate diet, or administration of thyroid hormone, or by injury to the islands of Langerhans secondary to injection of crude anterior pituitary extract, growth hormone, alloxan, or massive parenteral administration of glucose.

Pathologic Anatomy

The primary pathologic change usually is found in the islands of Langerhans of the pancreas. However, in approximately 20 per cent of the cases there is no anatomic pancreatic change demonstrable by usual histologic methods. Frequently the changes present may be slight and cannot be closely correlated with the clinical severity of the disease. When present in mild degree they are not pathognomonic of the disease. Arteriosclerosis of the pancreatic vessels has been considered as a precursor of diabetes, but is probably merely a manifestation of its presence. By study of the clinical course of the patient it is impossible to say whether or not any lesion will be found in the islands after death, or what the character of such a lesion may be if present. If more than five-sixths of the pancreas has been destroyed by other disease processes, such as carcinoma or acute pancreatitis, diabetes may be produced. However, the bulk of the islands of Langerhans are situated in the tail of the pancreas and consequently extensive destruction of the other portions of the gland will do relatively little harm to them. Since the islands of Langerhans have structure and blood supply independent of the acini, there is frequently, even in advanced carcinoma, almost no destruction of insular tissue.

Gross Pathologic Changes.—Gross evidence of the disease is not common. Occasionally the pancreas may be small, under 35 grams. Gross fibrosis may be related; lipomatosis is not significant. Pancreatic lithiasis may or may not be associated with diabetes. If hemochromatosis is sufficiently well advanced to cause impairment of sugar tolerance, the pancreas appears a rusty-brown color due to deposition of hemosiderin.

Microscopic Lesions.—The pancreas as a whole may show an appreciable degree of fibrosis, either interacinar, interlobular, or both. Since insulin is produced by the beta cells of the islands, it is natural that changes in them should most frequently be associated with the development of diabetes. There is a wide range of normal variation in the number of islands, estimates based on moderately complete counts ranging from 750,000 to 3,750,000.

Sometimes there is a distinct quantitative reduction. It is possible that this quantitative variation might explain the hereditary aspect of diabetes, as a pancreas with fewer islands might well predispose to development of the disease. It has been suggested that alpha-cell counts may prove helpful. On the other hand, Gomori finds this method of little service.

Hyalinization.—Hyalinization is the commonest insular change. Hyalin is laid down between the epithelial cells and the endothelium of the sinusoids. This hyalin frequently gives a staining reaction for amyloid and may rarely become calcified. The hyalin merely encases the sinusoids, rarely occluding them, but it ultimately replaces nearly all the epithelial elements of the islands. Sometimes the peripheral cells of the islands attempt to proliferate and the hyalin continues to encroach upon the new cells so that masses of hyalinized material much larger than the original island may be produced. Ninety-seven per cent of the cases of hyalinization of the islands are found in those over 40 years of age. Hyalinization of the islands is not restricted to diabetics. It is seen to a minor degree in about 2 per cent of nondiabetic persons. It is very frequently present in functioning insular adenomas and carcinomas. (See Fig. 64.)

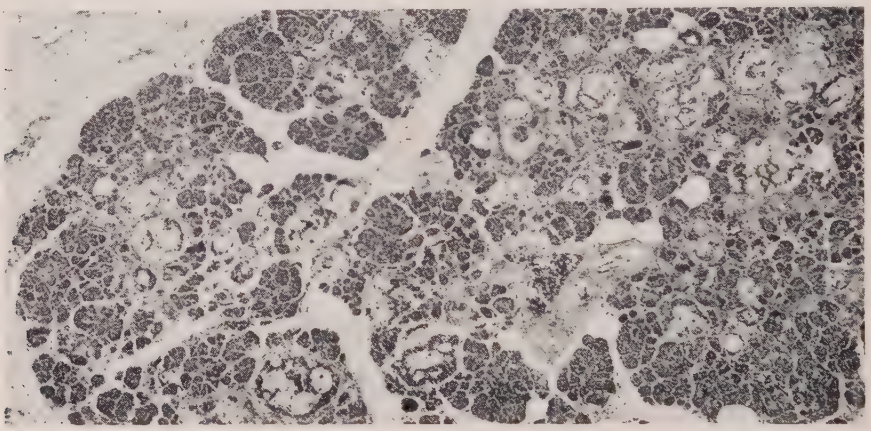

Fig. 759.—Low-power view of a sectioned pancreas showing numerous hyalinized islands of Langerhans. (×48.)

Hydropic Change.—Hydropic change, first described by Weichselbaum, is occasionally seen at present in some of the untreated or poorly treated cases of diabetes. In cases adequately treated with insulin it is almost never seen. The cytoplasm of the beta cells first becomes vacuolated and later disappears, leaving nuclei and cell membrane alone visible. Histochemical study indicates that the vacuoles are filled by glycogen or a related material. The theoretical implications of this finding, if confirmed, are important. This lesion has been produced experimentally by partial removal of the pancreas and overfeeding of carbohydrate, by administration of aqueous extract of anterior pituitary gland, and by administering alloxan. In dogs and cats this change may be followed by fibrosis and occasionally by hyalinization. Hydropic change is usually restricted to the beta cells. In the experimental animal its appearance may be reversible. Superficially similar vacuoles (not glycogen-containing) may appear as a stage in postmortem degeneration.

Necrosis.—Necrosis of the islands occurs rarely and to a mild degree in a number of the bacterial toxemias and may account for the transient glycosuria occasionally seen in such diseases as lobar pneumonia and streptococcal sepsis. The administration of alloxan to the experimental animal produces necrosis of the beta cells alone. These cells disappear through autolysis without leukocytic infiltration. This high degree of specificity is one of the remarkable features of alloxan poisoning.

Lymphocytic Infiltration.—Lymphocytic infiltration, chiefly seen in diabetes of short duration in children and in young

adults, is probably an intermediate, though not constantly present, step between necrosis of the islands and fibrosis. Usually in involved islands there is complete, or almost complete, disappearance of epithelial cells with scattered lymphocytes taking their place. This change occurs in approximately 2 per cent of cases. The lymphocytic infiltration is probably a short-lived lesion and is replaced by fibrosis as a rule.

Fibrosis.—Fibrosis may develop directly following hydropic degeneration or necrosis of the insular epithelium, as well as following lymphocytic infiltration. The fibrous tissue is usually laid down roughly parallel to the sinusoids and varies in amount from a few extra fibrocytes with a slight amount of collagen to an almost complete replacement of the island by dense collagen. In the slighter degrees of change there may be little more than exaggeration of the capsule of the island. Even in the more advanced cases there is very little extension of fibrosis into the adjacent acinar tissue. Fibrosis may exist alone, or combined with other types of pancreatic lesions such as chronic pancreatitis. Occasionally, the pancreas of a diabetic will be encountered in which all of the island cells appear somewhat columnar with hyperchromatic nuclei which give a ladderlike or "cobra" appearance to the insular cells. Regeneration of island tissue can occur to some degree even in adult life, but it is usually not sufficient to result in amelioration of diabetes. Transition between acinar cells and island cells probably does not occur.

Hemochromatosis.—In this disturbance of iron metabolism, sufficient iron may be deposited in the beta cells of the islands of Langerhans to produce diabetes. In such instances, injury to the adrenal has usually occurred also. This is perhaps related to the melanin pigmentation of the skin. Hence the symptom complex is frequently known as "bronze diabetes." (See also pages 82 and 818.)

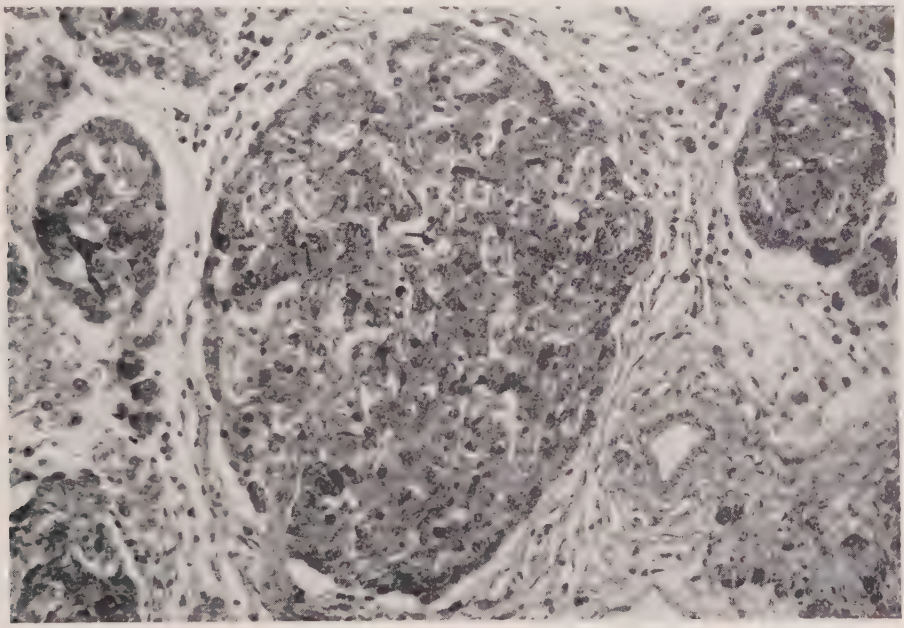

Fig. 760.—Hyperplasia of islands of Langerhans in infant of diabetic mother. (×155.)

Kidneys.—In cases of adequately treated diabetes there may be no gross evidence of renal changes. In untreated cases of diabetes with the development of acidosis and coma there is severe tubular epithelial damage. Grossly, the kidneys are soft and enlarged, even reaching a combined weight of 500 grams. The capsule is stripped away readily, leaving a smooth reddish-brown surface. The cut surface of the kidney bulges a little above the capsule and shows a yellower, more opaque tint than is usual. Microscopically, there may be albuminous damage of the proximal convoluted tubules and some fatty degeneration. If serious glycosuria is present, there is glycogenic infiltration of the epithelium of the proximal convoluted tubules and Henle's loops. This is indicated in routine sections by

vacuolated cells, the so-called Armanni-Ebstein change.

About one-fourth of the cases of diabetes, particularly those with hypertension or albuminuria, develop a nephrotic syndrome and show glomerulosclerosis. This lesion is not recognizable on gross examination. Hyaline acellular material is deposited about the capillary loops, most characteristically as spheroid masses which are often situated toward the periphery of the tuft (see Fig. 448, page 569). The exact site in relation to the capillary wall has not been clearly established. Some believe it to be intramural, others intercapillary. Both afferent and efferent arterioles show hyaline thickening of their walls.

Chronic pyelonephritis is a frequent complication of diabetes. (See page 582.) Necrotizing renal papillitis is most often seen as a complication of diabetes.

Liver.—There is no characteristic change in the liver of the diabetic patient. In those poorly controlled it may be enlarged and yellow due to fatty infiltration (12 per cent or more fat). In severe lipemia the Kupffer cells may be distended with lipoid. The water content of the liver may increase appreciably above the normal in diabetic coma and acidosis. The normal store of glycogen in a poorly controlled or uncontrolled diabetic is depleted from the cytoplasm of the liver cells, and frequently there is no cytoplasmic glycogen. In such cases, how-

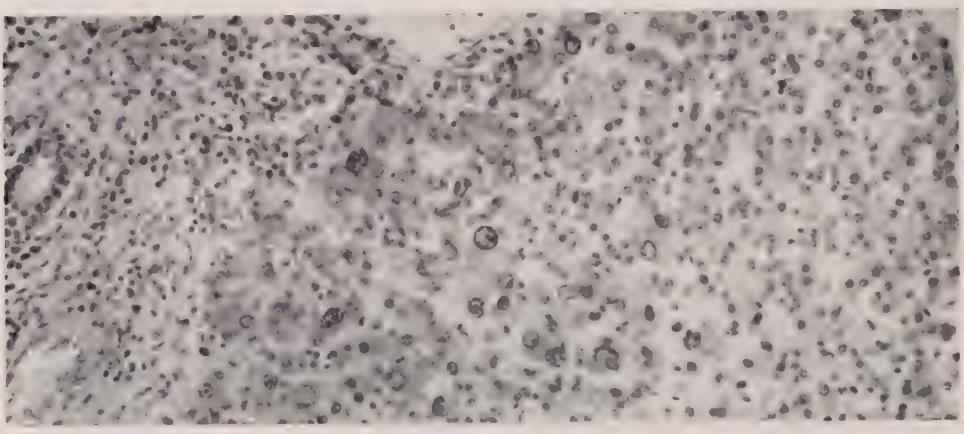

Fig. 761.—Liver from patient with diabetes showing glycogenic vacuolization of liver cell nuclei. (×200. Best's carmine stain.)

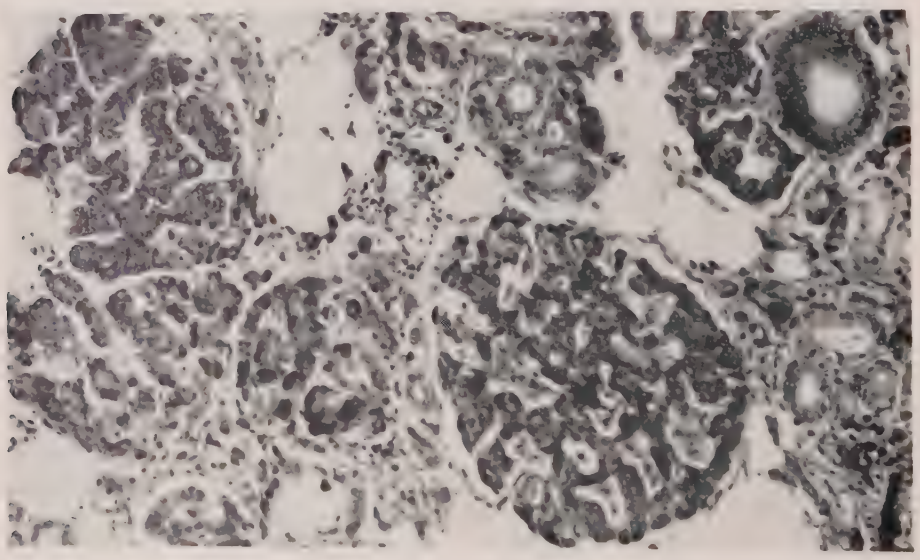

Fig. 762.—Pancreas showing deposition of hemosiderin in some island cells and some acinar cells in hemochromatosis. (×170.)

ever, there is usually vacuolar enlargement of the nucleus due to glycogen deposition. This latter change occurs not only in diabetics, but also in approximately 20 per cent of nondiabetic persons. Extensive liver damage from hemochromatosis or cirrhosis may lead to insulin resistance.

Gall Bladder.—Cholesterosis and cholesterol gallstones occur more frequently in diabetics than in nondiabetics.

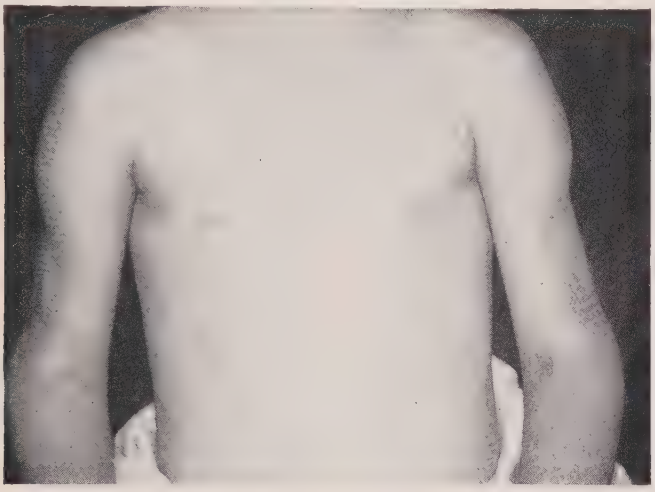

Fig. 763.—Insulin atrophy of subcutaneous tissue in a diabetic boy.

Skin.—In severe diabetics whose diet has been inadequately regulated there may develop yellow, raised plaques, particularly about the joints or on the eyelids. The xanthoma diabeticorum is due to accumulations of lipoid filled macrophages in the corium. Adequate insulin and dietary control may lead to their disappearance. Some diabetic patients are careless in proper placing of their injections of insulin and they may develop atrophy of the subcutaneous fat in the sites of repeated injections. This may be accompanied by sufficient fibrosis to interfere with prompt absorption of insulin injected into the area. Sometimes when diabetic patients have been for a long time on diets high in carotene such as carrots, squash, and yellow turnip, they may show a distinct diffuse yellow pigmentation which clears following reduction of the carotene intake. Necrobiosis lipoidica diabeticorum (Fig. 999) is discussed on page 1148.

Arteries.—Severe and premature development of arteriosclerosis is frequent in diabetics and presents one of the most dangerous complications of the disease. As a rule, the degree of arteriosclerosis is roughly proportionate to the duration of the diabetes and to the inadequacy of its control. There is no distinct diabetic type of arteriosclerosis. However, atheromatosis is much more common in the peripheral arteries in diabetes than in other conditions. Whereas for the nondiabetic population sclerosis of the vessels of the heart, of the kidneys, and of the brain are of major importance, for the diabetic the vessels of the heart and of the legs are chiefly involved. Medial calcification is as frequent in those suffering from diabetes as in those free from the disease.

Eye.—The most characteristic late lesion seen in the eyes of diabetics is retinitis proliferans, associated with vascular damage and hemorrhage. Capillary microaneurysms are more common in the retinas of diabetics than normal persons. In the past they have not been

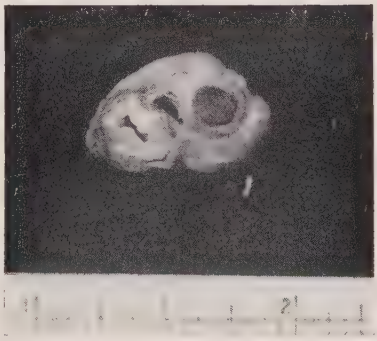

Fig. 764.—Almost complete obliteration of lumen of femoral artery by atheromatous arteriosclerosis in diabetic patient 68 years of age.

recognized as aneurysms, but were called punctate hemorrhages. Repeated hemorrhages and organization occurring about them are an important factor in the development of retinitis proliferans. Cataract apparently develops at an earlier age and more frequently than in the nondiabetic, but it is a rarer lesion than is retinitis. Accumulation of glycogen in the pigmented epithelium of the iris may be extensive, and may lead to escape of pigment into the vitreous during ophthalmic surgery.

Nervous System.—There is no characteristic change in the brain, even in coma. In poorly controlled diabetics patchy demyelinization and

fibrosis may be found in the cord and peripheral nerves. While this may be due to sclerotic changes in their small arteries, the evidence is not convincing and similar neuropathy is not seen in hypertensives. Frequently, neuritis may occur without anatomic change present in the nerve to account for it. Cerebral edema is induced by hyperinsulinism, and may progress to degenerative changes in nerve cells.

Pituitary.—No constant changes occur in the pituitary gland of patients with diabetes. However, diabetes mellitus is frequently found in acromegalic individuals (see discussion on page 987).

Elementary Pathologic Physiology

The diabetic patient cannot utilize sugar normally. Overproduction of carbohydrate by the liver from fat and protein has been suggested, but failure of adequate utilization of sugar by the tissues appears more likely. The key is insulin deficiency which may rarely be absolute and is usually relative. Either failure of adequate production or excessive demand may create this imbalance. Thus the obese diabetic may sometimes be cured by dieting sufficiently to reduce the metabolic demand on the islets. Of course, as Stetten has shown, carbohydrate oxidation is not alone involved, the metabolic pathways of carbohydrates, fat, and protein tend to overlap.

The pathologic climax of untreated diabetes is coma. In diabetes mellitus there is inadequate oxidation of fat with resulting tendency to develop acidosis. Coma follows ketosis and leads inevitably to death unless drastically treated with insulin.

Of great importance clinically, but entirely unexplained, is the extreme susceptibility of the diabetic patient to bacterial infection. Minor infections and relatively nonpathogenic organisms may assume major importance in the diabetic. This susceptibility is not restricted to the pyogenic organisms, but extends to tuberculosis and others as well. Owing to the high sugar content of tissues of a poorly controlled diabetic, infections due to *Escherichia coli* may lead to simulation of gas gangrene.

As a result of the failure to utilize fat, severe lipemia may be present, even up to 20 per cent or more. This is usually associated with severe lipoid histiocytosis, involving particularly the spleen and liver, but often the entire reticulo-endothelial system.

Children of Diabetic Mothers.—Until the advent of insulin therapy, pregnancy was almost unknown in diabetic patients. With the aid of insulin it has been possible for diabetic patients to conceive and produce live babies. Owing to the metabolic vicissitudes of diabetes the percentage of mortality is considerably higher than in the normal and there are disturbances in the sex hormone balances which unless compensated for may lead to abortion. There is a distinct tendency of infants of diabetic mothers to be well above average in size and weight. A high proportion of such infants who died soon after birth have shown hypertrophic islands of Langerhans.

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Chapter 31

THE BLOOD AND BONE MARROW

MAURICE N. RICHTER

THE BLOOD

The composition of the blood depends on the state of the body as a whole, as well as upon the functioning of its various organs. During the passage of blood through the tissues there is an exchange of chemical constituents, the removal of cells from the blood stream by physiologic processes, and their replacement by the activities of the blood-forming organs. The bone marrow, spleen, lymph nodes, and reticulo-endothelial system play an active part in the formation and destruction of blood cells, and together are referred to as the hematopoietic (or, more accurately, the hemolytopoietic [Krumbhaar]) system. These organs and the circulating blood should be studied together. Their separate consideration in the discussions which follow is for convenience only.

The Blood Cells

Blood cells are conveniently divided into two groups, those which contain hemoglobin (the erythrocytes) and those which do not (the leukocytes). The leukocytes are further classified according to the type of nucleus or of cytoplasmic granules. A third element, the platelet, is a fragment of cytoplasm of the megakaryocytes. All these cells arise in the blood-forming organs, and pass through developmental stages before entering the blood stream.

The Erythrocytes.—The erythrocytes are biconcave discs, about 7.5 microns in diameter. They have no nucleus. They contain hemoglobin, which, during their passage through the alveolar capillaries of the lung, forms an unstable compound (oxyhemoglobin) with the oxygen of the alveolar air. In this combined form the oxygen is carried to the tissues, where it is liberated.

The detailed structure of the erythrocyte is not completely understood. It may undergo changes in shape during passage through the smallest capillaries, with subsequent return to the biconcave form. This plasticity suggests an external membrane of special structure. It is not known whether this membrane contains much or all of the hemoglobin, or whether the latter is dissolved in the internal substance of the cell.

Abnormal erythrocytes are of two general types: those which are abnormal for the adult circulating blood because they are immature, and those which present morphologic abnormalities not found in health in erythrocytes or their precursers at any age. The former are discussed under the heading of development of the erythrocytes. The latter type of abnormality comprises changes in size, especially decreased size (microcytes), changes in shape, with the formation of fragmented or deformed cells (schizocytes), or of spherical, sickle-shaped, or oval cells, all the latter being described under hemolytic anemias. Abnormalities in staining reaction are due mainly to deficient hemoglobin content or to immaturity.

The Leukocytes.—In most of the leukocytes of the circulating blood the nuclei are convoluted or segmented, the segments being connected by delicate strands. This characteristic gives to them the name *polymorphonuclear leukocytes.* In addition, their cytoplasm contains granules of one of three types, which may be distinguished by their staining reactions to acid, basic, and neutral dyes.

A small proportion of the leukocytes (about 5 per cent) contain granules stainable with acid dyes, of which eosin is the one most commonly used. They are therefore known as *acidophilic* or *eosinophilic leukocytes.*

A few leukocytes (less than 1 per cent) have granules stainable by basic dyes (*basophilic leukocytes*), of which methylene blue and its derivatives are those represented in the common blood stains. The granules are metachromatic and are stained purple rather than blue. They are soluble in water, and therefore may not be found in tissue sections unless the tissues are suitably fixed. It is of further interest that, although hematoxylin is a basic dye, it stains these granules poorly or not at all. The basophilic granules contain heparin.

The majority (about 65 per cent) of the leukocytes contain granules stainable with neutral mixtures of acid and basic dyes, and are hence called *neutrophilic leukocytes.* Neutral dyes of this type are formed in mixtures of eosin with methylene blue and its derivatives, but not in mixtures of eosin with hematoxylin. The latter combination, commonly used routinely in the staining of tissue sections, is therefore unsuitable for the demonstration of neutrophilic granules.

In all of these granular leukocytes the nucleus contains coarse particles of chromatin. No nucleoli are present. The several parts of the nucleus are formed by convolutions and segmentation of the round nucleus of the myelocyte.

From two to five segments are usually present, each connected with others by delicate chromatin strands. In a few cells, convolution without segmentation results in irregular, twisted, bandlike nuclear structures. These cells are phagocytic, and play an important part in inflammation, q.v.

Lymphocytes are mononuclear cells, formed in various lymphoid structures. The cells vary in size and appearance, but all have basophilic cytoplasm, and a single round, oval, or slightly indented nucleus that is deeply stained. In many of the cells the nucleus is small and dense, and the cytoplasm may be represented by only a thin, basophilic rim around the nucleus. In other cells the cytoplasm is more abundant and less basophilic. Most of the lymphocytes are nongranular. In a few a special type of granulation stained by azure-eosin mixtures is present. These granules are comparatively coarse, vary in size, and are red in the usual blood smear preparations. Only a few are present in a single cell. These granules have not been demonstrated in tissue sections, even by the same staining method that demonstrates them in smears. Lymphocytes are concerned with the formation of antibodies, and are found in various inflammatory reactions (see inflammation, page 35).

Monocytes are also mononuclear cells, and are larger than lymphocytes. Their nuclei are sometimes round or oval, but are often of irregular shape due to indentations and incisures, with convolution of the parts. Usually, but not always, the cytoplasm contains minute granules, often numerous and uniformly distributed. These granules are also stained by azure-eosin mixtures, but differ from those in lymphocytes in that they are smaller, more numerous, and contain oxidase and peroxidase ferments. In sections the granules can be demonstrated only by methods for the demonstration of such ferments. Formerly, these cells, because of the atypical convolutions of the nucleus, were erroneously believed to be transitional stages between lymphocytes or other mononuclear cells, and polymorphonuclear leukocytes.

Monocytes are phagocytic. They are also ameboid, and migrate toward sites of injury where their phagocytic function aids in the disposal of cell fragments and bacteria (see section on Inflammation and Repair) and in the development of specific cellular reactions, such as in tuberculosis.

The Platelets.—The blood platelets are small, nonnucleated structures composed of slightly basophilic cytoplasm containing a few minute azurophilic granules. The diameter of the platelets is about 2 to 3 microns, and under normal conditions they are usually uniform in size and appearance. The platelets contain a thromboplastic substance necessary for coagulation of the blood; hence, they play an important part in clotting and are to be found in large numbers in thrombi.

Development of the Blood Cells

All the blood cells pass through developmental stages, during which they undergo changes in appearance. The earliest recognizable blood cells in postnatal life are large mononuclear cells with single large nuclei which, in sections, have but little chromatin. In smears the chromatin is arranged in a delicate, uniform reticulum. One or more prominent nucleoli are

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Plate X.—This plate illustrates differences in the appearance of immature blood cells as seen in tissue sections and in smears. It is important to appreciate the differences in appearance brought out by the two methods of preparation. For illustrations of all cell types as seen in smears, consult standard atlases and textbooks of hematology. *a*, *b*, and *c* show various forms of developing red cells. *d*, *e*, and *f* show different stages in the development of granular leukocytes.

a, Section of spleen, showing blood formation in the pulp. Erythroblasts are seen within a sinus, and a few myelocytes in the surrounding pulp. There is a tendency for the erythroblasts to be grouped with others of approximately the same stage of development, rather than to be mingled indiscriminately. The cells in the lower part of the sinus are in early stages of development, those in the upper part are in later stages. The distinction between normoblasts and megaloblasts cannot be made in sections.

b, Smear of bone marrow in case of hemolytic anemia. There are numerous normoblasts in various stages of development. The early stages have the more basophilic cytoplasm. Compare the nuclear structure of the normoblasts with that of the megaloblasts in *c*.

c, Smear of bone marrow in pernicious anemia. The nucleated cells are all megaloblasts. The large ones with basophilic cytoplasm are in early stages, those with acidophilic cytoplasm are in late stages of development. In the early stages the nuclear structure distinguishes the megaloblasts from normoblasts (see *b*). In late stages the cell body is usually large in comparison to the size of the nucleus. The nonnucleated red corpuscles vary in size, the large ones being megalocytes. One has a small remnant of nuclear material (Howell-Jolly body). See also Fig. 792.

d, Blood smear in acute myeloid leukemia. Six immature cells without granules are illustrated (myeloblasts or hemocytoblasts). The two cells of similar appearance but with azurophilic granules are promyelocytes. Note that more detail in nuclear structure may be seen in the smear than is visible in sections (*e*). See also Fig. 784.

e, Section of bone marrow, chronic myeloid leukemia. Stained with eosin-azure B-methylene blue. The numerous cells with small violet granules are neutrophilic myelocytes. There are fewer eosinophilic myelocytes with larger red granules. There are also a few immature cells with basophilic cytoplasm without granules. These are myeloblasts or hemocytoblasts. Note that all of these cells are smaller, and their characteristics less readily recognized than the corresponding cells in *d* and *f*. If the section were stained with hematoxylin and eosin, none of the neutrophilic myelocytes would have granules. Two megakaryocytes are shown, and in the lower left corner is a group of nucleated red cells. See also Fig. 774.

f, Blood smear, chronic myeloid leukemia. Immature white cells in various stages of development and with different types of granules are shown. In the center are three promyelocytes with azurophilic granules. An eosinophile leukocyte is shown in the upper right corner. There are two eosinophile myelocytes. A basophile myelocyte is seen in the lower right corner. There are also three neutrophile metamyelocytes. See also Fig. 773.

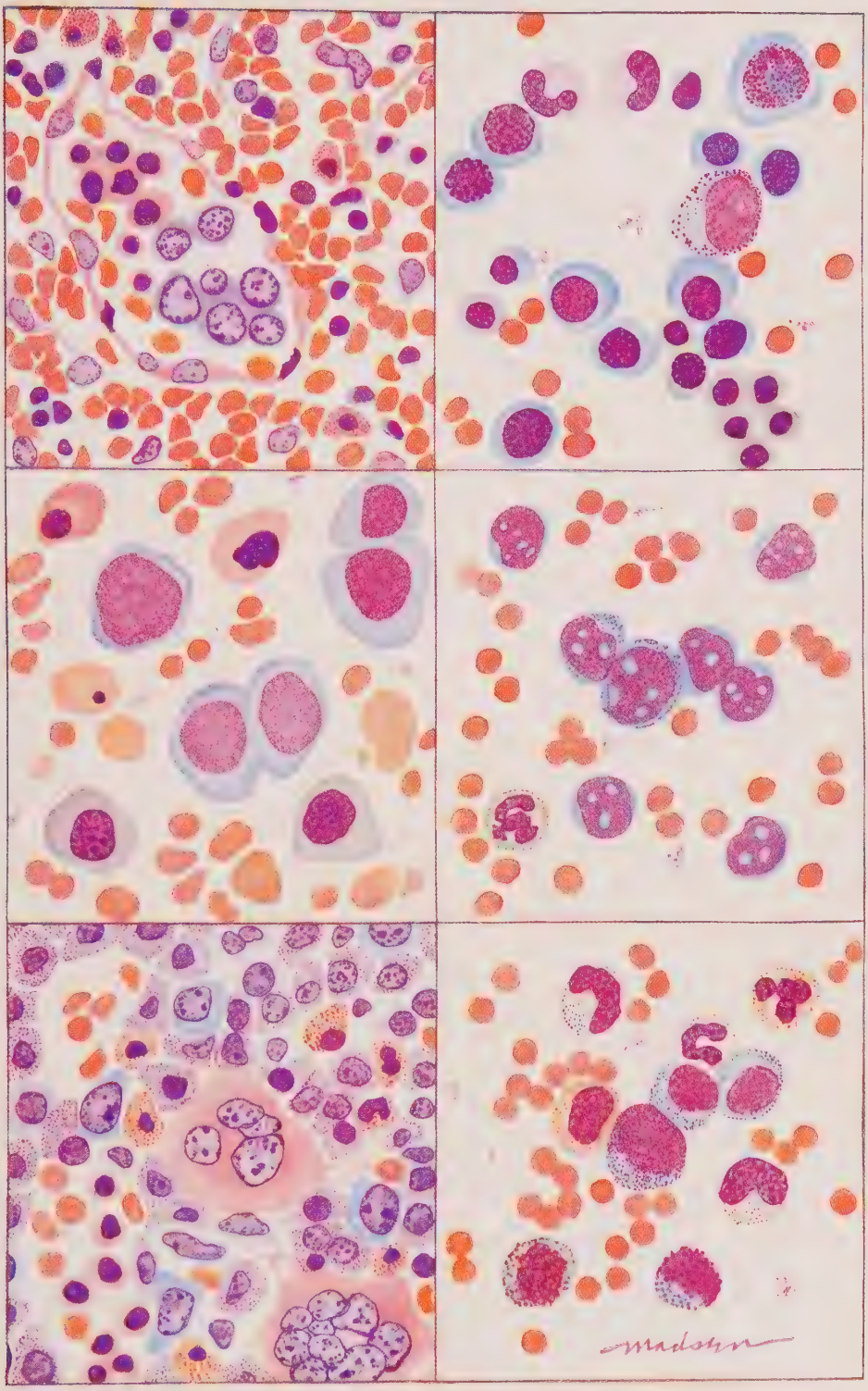


PLATE X. *(For legend see opposite page.)*

usually present. The cytoplasm is basophilic, and contains neither hemoglobin nor granules.

Opinions differ as to whether the cells which later become erythrocytes, granular leukocytes, lymphocytes, monocytes, or megakaryocytes are identical, and their subsequent differentiation dependent upon environmental conditions (monophyletic theory), or whether they are actually specific cells, unalterably oriented from the beginning in a certain direction of differentiation, too subtle for detection by our present methods (polyphyletic theory).

According to the monophyletic theory, the primitive cell from which all types of blood cells are derived is termed the "hemocytoblast" or "stem-cell." In the polyphyletic theory, a separate cell of origin for each type is necessary, which is termed, respectively, "erythroblast" (megaloblast or normoblast), "myeloblast," and "lymphoblast." The origin of the monocyte is still unsettled, but a "monoblast" is described which may be derived from the myeloblast, or directly from reticulo-endothelial or mesenchymal cells. "Megakaryoblasts" are similarly described as arising from myeloblasts. The details of the various theories of cell origin are too numerous for this discussion. It may be pointed out, however, that if there are morphologic differences among the primitive cells, they are so slight that for fifty years all debates regarding their existence have produced only inconclusive evidence.

Development of the Erythrocytes.—In the normal adult, red cells are formed only in the bone marrow. The marrow is not a homogeneous organ, however, and the red and white cells have different sites of formation, although this is not always evident. One of the conditions necessary for the formation of erythrocytes is an intravascular position of the primitive cells, while the white cells develop outside of the vessels. Unless the marrow is depleted, the great mass of developing cells obscures details, and it is impossible to tell whether cells are within or outside of the vessels. The intravascular position of the erythroblasts is more readily detected when extramedullary formation of blood cells occurs in the spleen, as in the case of some anemias. (Plate X, *a*.)

The formation of hemoglobin requires an adequate amount of iron, and probably traces of other minerals, especially copper. Vitamins and hormones also play some part in the development of the cells. The effects of endocrine glands on blood formation are not fully known.

Of the necessary vitamins, the most important is vitamin B_{12}. This is present in the food, and is absorbed during digestion, deposited in the liver, and mobilized as needed. (See pernicious anemia, page 881.)

Little is known about the method of destruction of red cells. Although red cells undergo phagocytosis by various cells in the body, this mechanism is hardly enough to account for the enormous number of cells destroyed each day, estimated at 2 to 3 per cent of the total number of cells in the body, or about one billion cells per minute. It is more likely that red cell destruction occurs in the general circulation, the products then being removed by the phagocytic action of the reticulo-endothelial system.

One of the least understood mechanisms is that which controls the delivery of cells to the circulation after they are completely developed. It has been suggested that the cells develop within sinusoids that are at first collapsed. Only after the cells become mature does the distended sinus open into the circulation, and the cells are swept into the blood stream.

The cells from which erythrocytes develop are nucleated. Morphologically the earliest stages cannot be distinguished from the other primitive cells already described. During the course of their development these immature erythrocytes acquire hemoglobin and undergo changes that identify them specifically as developing red blood corpuscles. Several names have been applied to these immature cells. For convenience we will refer to them as *erythroblasts*.

Two types of erythroblasts have been described, "megaloblasts" and "normoblasts." A great deal of misunderstanding has arisen from the fact that these terms have not always been used in the same sense. The main differences center around the questions of whether the two types are distinct and independent, or whether the normoblast is a later stage in the development of the megaloblast; and whether the megaloblast, as seen in pernicious anemia, for example, is identical with the primitive cell of the same name found in the embryo.

The latter question is mainly of academic interest; the former has practical applications in diagnosis as well as theoretical implications in the interpretation of disease.

The most widely accepted view at present is that the megaloblast and the normoblast are early and late stages, respectively, in the development of the red cell; and that the substance effective in pernicious anemia is necessary for the completion of this development. It has been shown, however, that this view is open to question. There are many who believe that the two types of nucleated red cells are separate and distinct, without transition from one to the other, and possess cytologic characteristics by which they may be distinguished. If these criteria are rigidly adhered to, "megaloblasts" are found only in pernicious anemia and related anemias in which the "hematopoietic principle" or "antipernicious anemia" factor is absent. At the present time it is preferable to make this distinction, and the term "megaloblast," as used here, refers to the particular type of cell to be described (Plate X, *c*).

Normoblasts.—Normoblasts pass through a series of developmental stages, with accompanying changes in size and staining reactions. In the earlier stages the cells are larger, and have little or no hemoglobin. The chromatin network in the nucleus is less delicate than in the megaloblast. The cytoplasm is basophilic at first, but undergoes a gradual change in staining reaction as the amount of hemoglobin increases.

The intermediate stages of development are therefore accompanied by various degrees of *polychromasia*, as indicated by the staining of cytoplasm with both acid and basic dyes. When methylene blue and eosin are used as the basic stains, various degrees of purplish cytoplasmic stain result. The older cells have their full amount of hemoglobin and have lost all the basophilic substance in the cytoplasm. They are there-

fore *orthochromatic,* and their cytoplasm is stained by eosin alone. Basophilic material often remains for a period after loss of the nucleus.

Study of the nucleated red cells during the course of their development also discloses a filamentous cytoplasmic material stainable only while the cells are unfixed by so-called vital dyes (e.g., brilliant cresyl blue, neutral red). This reticulum is present for a short time after loss of the nucleus, and thus serves to identify such cells as relatively young ones.

In some cells the basophilic material in the cytoplasm is seen in the form of punctate bodies to which the terms *punctate basophilia* or *basophilic stippling* have been applied. The term *basophilic degeneration* has also been used, but the designation is hardly correct, since the bodies are present in normal young cells (in embryos, for example) as well as in pathologic states.

The relation between polychromasia, basophilic stippling, and reticulation of erythrocytes is not fully established. It seems, however, that all represent the same basophilic substance in the cytoplasm of young red cells, and that the differences in their appearances are due to the methods of demonstration. In preparations vitally stained by brilliant cresyl blue, the substance appears as reticulum; in smears fixed in alcoholic staining solutions, it appears either as diffuse or punctate basophilia.

During the development of the erythroblast important changes also occur in the nucleus. This structure becomes smaller and more compact, the chromatin network is denser and coarser, resulting, in the late stages, in a small pyknotic nucleus without discernible inner structures. In intermediate stages, rather coarse chromatin particles are sometimes disposed in a radial fashion. This nucleus finally disappears, sometimes by solution (karyolysis), sometimes by fragmentation (karyorrhexis) and extrusion. A minute particle of chromatin material sometimes remains in the cell after the rest of the nucleus is lost. This particle is known as a *Howell-Jolly body.* For reasons that are not understood, splenectomy results in the appearance of these bodies in some of the circulating erythrocytes.

A ring- or figure-of-eight-shaped body, with staining characteristics similar to that of nuclear material, is occasionally encountered in the circulating erythrocyte of severe anemic states. It has aways been thought that this structure, known as *Cabot's ring,* represented the nuclear membrane after solution of the nuclear substance. Recently, however, it has been shown that the ring structures can be produced in nonnucleated cells experimentally, especially by hemolytic agents which cause changes in the lipoproteins in the surface layer of the erythrocyte.

MEGALOBLASTS.—Megaloblasts are usually larger than normoblasts, but size alone is not the main criterion for recognition. The most important feature is the structure of the nucleus in which the chromatin particles are of minute size, and are arranged to give the impression of uniform stippling or fine reticulation. Coarser clumps of chromatin, as seen in normoblasts, are not present. In later stages, the nucleus becomes denser and may be pyknotic. As the cytoplasm acquires hemoglobin, it becomes acidophilic, showing the same phenomena of polychromasia as do the normoblasts.

Loss of nucleus of the megaloblast leaves a nonnucleated cell of larger size than the normal erythrocyte, usually with full hemoglobin content. This is called a megalocyte. It is a mature cell, the end result of the development of the megaloblast, and is to be distinguished from the macrocyte, which is a young erythrocyte, developed from a normoblast, but slightly oversize because of immaturity.

Development of the Leukocytes.—In the normal adult, polymorphonuclear leukocytes are formed only in the bone marrow. They develop from less mature cells, the "hemocytoblasts," "stem-cells," or "myeloblasts" already mentioned. These primitive cells are relatively large, with large, rounded nuclei containing comparatively little chromatin. Because of this feature the nucleus in sections is vesicular, and in smears has a fairly uniform distribution of delicate chromatin strands or granules, forming a fine reticulum. There are usually several nucleoli. The cytoplasm is basophilic, and without granules. (Plate X, *d.*)

By the acquisition of cytoplasmic granules, these myeloblasts become *myelocytes.* The first granules formed are of a deep purple color when stained in smears by azure-eosin dyes, and are known as azurophilic granules. Some of these granules are minute, others are large and of irregular shape. The presence of these azurophilic granules represents one stage of development, for the granules later disappear and their place is taken by one of the types of granules seen in the adult polymorphonuclear cells. The cells in this early and temporary stage are known as *promyelocytes.* At this stage the nucleus still has its delicate chromatin reticulum, and several nucleoli. The cytoplasm is basophilic.

The myelocytes which then develop are of three types, identified by the neutrophilic, acidophilic, or basophilic granules as in the adult granular leukocytes. In the myelocyte stage the nucleus is round or oval, but has lost its nucleoli. As the cell develops, the structure of the nucleus becomes coarser, and indentations appear in its outline. Myelocytes with indented nuclei, representing the first stage in polymorphism, are termed *metamyelocytes.* In the early myelocyte stages the basophilic character of the cytoplasm may obscure the granules; in the late stages this basophilia becomes less pronounced, and finally disappears.

Lymphocytes are formed in the lymph nodes, in the spleen, and in the lymphatic tissue of the intestinal tract and other sites. As noted above, the primitive cells from which they are derived (lymphoblasts) are so similar in appearance to the myeloblasts that they are often thought to be identical. The stages through which these cells pass in the course of their differentation are not marked by such conspicuous features as nuclear segmentation or granule formation, and are therefore less easily recognized. There is, however, a gradual thickening of the nuclear strands, with deeper staining of the nucleus as a whole. Nucleoli disappear, and the whole cell, including the nucleus, becomes smaller. The cytoplasm be-

comes less basophilic, and a few azure granules that appear in some of the cells are probably part of the aging process.

Monocytes are of disputed origin. One opinion is that they are derived from myeloblasts; another is that they come from the reticulo-endothelial system; and still another view is that they are altered lymphocytes. Monocytes are also derived from cells morphologically identical with myeloblasts. The nucleus becomes indented or irregularly lobulated, the nucleoli disappear, and the chromatin is slightly coarser. Fine azurophilic granules appear in the cytoplasm, at first only a few, but later the cells become filled with them. The site of origin of these cells is variously believed to be the bone marrow, the spleen, and the lymph nodes. There is a belief also that the reticulo-endothelial cells in various places may differentiate into monocytes.

The *blood platelets* are fragments of the cytoplasm of megakaryocytes, which are also derived from primitive cells of the type described above, and acquire their special characteristics by subsequent differentiation. The nucleus becomes polymorphous, and sometimes multipolar mitoses result in multiple nuclei. Granule formation in the cytoplasm is at first diffuse; later these granules form small groups which, at the periphery of the cell become separated and, with a small amount of cytoplasm, form platelets. Cells in the early stages in this process of differentiation are called *megakaryoblasts*, those in the later stages are called *premegakaryocytes*.

Techniques for Study of the Morphology of the Hemopoietic System

The blood is usually studied in smear preparations stained by one of the so-called blood stains (Wright, Giemsa, etc.) based on combinations of eosin with methylene blue and some of its decomposition products. The details of preparation and staining of the blood smears will be found in textbooks on clinical pathology. On the other hand, the blood-forming organs are ordinarily studied by means of sections, although smears or imprints may also be made.

It is important to know the differences in appearance between blood cells studied in sections and those studied in smears (see Plate X). In sections the cells maintain their shape and size, except for minor changes resulting from shrinkage in preparation; in smears the cells are spread out on the slide and are therefore larger. In smears the whole cell is seen, but in sections only a portion of the cell may be present, especially if the section is thin. In sections, cells and structures may be studied in relation to each other, but in smears these special relationships are lost. There are also important differences in staining. The smear method permits demonstration of finer nuclear detail than is seen in sections, as well as the azurophilic granules of lymphocytes and monocytes which are never stained by ordinary methods in sections. The granules of monocytes may be stained in sections by the oxidase or the peroxidase methods. Neutrophilic granules are readily stained in smears, but with some difficulty in sections, and not at all if hematoxylin and eosin only are used. Basophilic granules are stained poorly or not at all by hematoxylin, but may be demonstrated in sections as well as smears if stains containing methylene blue are used. These granules are water-soluble, however, and are often dissolved in preparation. Sections prepared by the freezing method, stained with thionin, etc., are best.

The smear technique is therefore the more useful one for identification of individual cells; sections are necessary for recognition of topographical relationships.

The usual method of fixing tissues in formalin and staining sections in hematoxylin and eosin is suitable only when a diagnosis can be made on the basis of general topographical features, and the study of cell detail is not required. For the latter study, fixation in Helly's solution and staining of sections with eosin and one of the basic blue aniline dyes, such as methylene blue or azure (Giemsa's stain is one such solution), has long been the method of choice. Special techniques such as the oxidase or peroxidase reactions, stains for reticulum, and the other methods of general histology may occasionally be required.

CONDITIONS AFFECTING PRINCIPALLY THE ERYTHROCYTES

Under normal conditions the number of erythrocytes in the circulating blood varies but slightly. The accepted number for adult males is 5,000,000 per cubic millimeter, and for females 4,500,000. This number is influenced by such factors as age, sex, barometric pressure, degree of activity, and psychic factors. The influence of age is the most conspicuous factor. Compilations of data from several sources show that at birth the erythrocyte count is a little over 5,000,000, that it drops to below 4,500,000 during the first year, and increases gradually during childhood. During puberty the figure for males becomes slightly greater than that for females, the adult count being reached at about 20 years of age.

Low barometric pressure, resulting in low oxygen tension of alveolar air, is usually associated with an increase in the erythrocyte count. When the change in pressure is sudden, the additional cells are probably derived from available stores in the spleen and splanchnic vessels. When the pressure continues low, stimulation of the bone marrow may occur as a result of the low oxygen tension.

During the first few months of life erythrocytes are slightly larger than in adults, and during childhood slightly smaller. The concentration of hemoglobin in the cytoplasm, however, does not change.

Anemia

Anemia is a condition in which the amount of blood in the body is decreased. From a practical standpoint the term means a reduction in the number of erythrocytes and the amount of hemoglobin per unit volume of blood. The rarely used terms *oligemia* and *oligocythemia* refer, respectively, to a reduction in the amount of blood and the number of erythrocytes in the body as a whole.

The process of formation of red cells and their delivery to the circulation is a continuous one. Since the number of cells in the blood remains within narrow limits, it follows that the rate of cell destruction is equal to that of cell formation. It is evident, therefore, that anemia results either from an increase in the rate at which cells are destroyed or lost, or from a decrease in the rate at which they are formed. On this basis anemias may be classified as follows:

I. Anemia due to increased rate of cell destruction or loss.
  A. Loss of blood from the body: external hemorrhage, acute and chronic.
  B. Destruction of blood within the body.
    1. Internal hemorrhage.
    2. Hemolytic anemias.
      a. Due to hereditary factors.
        aa. Congenital spherocytic anemia (hemolytic jaundice).
        bb. Sickle cell anemia.
        cc. Erythroblastosis fetalis.
        dd. "Mediterranean" anemia (thalassemia).
      b. Due to nonhereditary factors (acquired hemolytic anemia).
        aa. Chemical, bacterial, or parasitic causes.
        bb. Due to circulating antibodies.
        cc. Due to undetermined causes.
      c. Hemoglobinurias.

II. Anemia due to decreased rate of cell production.
  A. Nutritional deficiencies.
    1. Deficiency in iron.
    2. Deficiency in vitamins.
      a. Deficiency in vitamin B_{12}.
    3. Deficiency in endocrine secretions.
  B. Inhibition of marrow activity: aplastic anemia.
    1. Due to physical or chemical agents.
    2. Due to undetermined causes.
  C. Mechanical interference with blood formation.
    1. Neoplastic or leukemic infiltration of bone marrow.

It is evident that difficulty will be encountered in fitting all cases into special categories. For example, anemias due to external hemorrhage, if severe, become anemias due to iron deficiency. Anemias associated with malignant neoplasms may be due to mechanical interference with blood formation because of marrow metastases, toxic absorption, loss of blood, and probably other causes.

ANEMIAS DUE TO INCREASED RATE OF CELL DESTRUCTION OR LOSS

Loss of Blood From the Body.—The simplest form of anemia of this type is that due to acute loss of blood from the body (external hemorrhage). Following such loss, regeneration of blood occurs, and in an otherwise normal individual the blood values are brought to normal within a short period of time, depending upon the amount of blood lost.

Examination of the peripheral blood immediately after the hemorrhage shows no numerical or morphologic changes in the cells, since the loss of all elements is proportional. Shortly thereafter, there appears an increase in the number of platelets, with a resultant decrease in coagulation time. An increase in leukocytes occurs during the next few hours. The increase is in adult neutrophiles, with occasional immature forms in severe cases. This increase is probably due to a redistribution of cells from such reservoirs as the spleen or splanchnic vessels, and not to regeneration of cells in the bone marrow.

Only after two or three days is evidence of marrow hyperplasia usually encountered. This is manifested first by an increase in the number of reticulocyte. Ordinarily, nucleated red cells (normoblasts) appear only after severe hemorrhage.

There is an initial decrease in the number of red cells, due to an influx of tissue fluids which restores the blood volume. This is followed by a gradual increase over a period of several weeks, as the number of cells is augmented by increased production of cells in the bone marrow.

The bone marrow undergoes hyperplasia, with an increase in the number of all elements, especially nucleated red cells. As in all cases of marrow hyperplasia, the increase in volume of erythropoietic tissue is at the expense of the marrow fat. At the border between red and yellow marrow, especially in the long bones, a slight increase in vascularity occurs, with the appearance of developing blood cells. In the red marrow itself,

there is a reduction in the number of fat cells. The iron needed for the formation of hemoglobin is derived from the various storage depots of the body.

Chronic Blood Loss.—When a second loss of blood occurs before regeneration is complete, the bone marrow is no longer normal, and there may be a deficiency of iron. The anemia is then not only due to blood loss, but is further complicated by inadequate blood formation. This form of anemia is seen commonly in such conditions as gastric or duodenal ulcer, bleeding hemorrhoids, ulcerating neoplasms, especially of the alimentary tract, and less commonly in certain blood disorders in which repeated hemorrhages occur (purpura, aplastic anemia, leukemia). Because of depletion of the iron stores, formation of hemoglobin lags behind the development of red cells, with resultant hypochromia.

Destruction of Blood Within the Body.—In contrast to the conditions noted following external loss of blood, internal hemorrhage or destruction of blood within the body does not result in iron loss. Instead, about 85 per cent of the iron derived from the liberated hemoglobin is available for storage and use in the formation of new cells. The presence in the blood and tissues of pigments derived from hemoglobin is therefore one of the conspicuous features of most hemolytic anemias. The bilirubin content of the blood is increased, often with resultant jaundice. In such cases this condition must be distinguished from jaundice due to obstruction of the bile passages (see page 85).

Hemosiderosis is likewise a common accompaniment of hemolytic processes. Iron-containing pigments are found especially in the spleen, liver, and bone marrow.

The bone marrow becomes markedly hyperplastic, with abundant nucleated red cells of normoblastic type. The marrow hyperplasia is naturally more marked when hemolysis is active. The most marked hyperplasias are probably those encountered in chronic hemolytic conditions such as spherocytic anemia (hemolytic jaundice).

The Hemolytic Anemias

The term hemolytic anemias includes a variety of anemias in which excess hemolysis is an important accompaniment, and in some instances the probable cause of the anemia.

Hemolytic Anemias Due to Hereditary Factors

In some cases the hemolysis is due to the presence of defective red cells, which are subject to abnormally rapid destruction; in other cases the hemolysis is due to the action of extracorpuscular substances, not all of which have been identified. One of the methods used to determine which mechanism is responsible is that of cross transfusions, with determination of the life span of the transfused cells. Under normal conditions the average life span of the red cell is about 120 days, and the cells disappear from the circulation at a uniform rate. If normal cells disappear at a normal rate when transfused into a patient with hemolytic anemia, and the patient's cells are destroyed at an accelerated rate in a normal individual, the assumption is that an intracorpuscular defect is present. If, however, transfused normal cells disappear at an accelerated rate in the patient, an extracorpuscular hemolytic mechanism is present.

Congenital Hemolytic Icterus (Spherocytic Anemia).—This condition is characterized by the presence in the blood of spherical erythrocytes which, in addition to their abnormal shape, are smaller than normal and are less resistant to the action of hemolytic agents and to mechanical trauma than are normal erythrocytes (spherical microcytes with "increased fragility").

The disease is hereditary, and is transmitted as a Mendelian dominant character. It occurs in, and is transmitted by, either sex. It may be congenital and recognized during infancy or childhood, or it may be detected only later in life, in which case it is usually considered to be acquired.

The anemia is variable in degree, with periods of exacerbation during which there is evidence of increased hemolysis ("hemolytic crisis"), and often long periods of relative quiescence, with moderate anemia and slight but variable icterus. The spleen is enlarged, and the erythroblastic elements of the bone marrow undergo hyperplasia.

The blood picture is one of anemia with spherical microcytes and an increase in the number of reticulocytes (Fig. 765). The latter may reach considerable, proportions, especially during hemolytic crises. The microcytosis can best be demonstrated by the "Price-Jones curve," which requires micrometric measurement of the individual cells, or more simply by the diffractometer or hematocrit, which

measure, respectively, the mean cell diameter, and the cell volume. There are no significant changes in the white cells or in the platelets.

The accompanying jaundice is of the hemolytic type, that is, it is "acholuric." However, the large amount of pigment excreted in the bile may lead to the formation of pigment calculi with resultant biliary obstruction. The degree of jaundice fluctuates, being most marked during periods of increased hemolysis. The spleen is enlarged, and shows characteristic changes (see page 924). The marrow is hyperplastic (see page 904).

however, that spherical microcytes may persist, and cell fragility may still be increased.

The presence of erythrocytes of abnormal size and shape and with increased fragility has led to the belief that the excessive destruction of cells is due to their structural abnormalities. This belief is furthered by the occasional presence of other congenital anomalies. Hemolytic anemias with similar corpuscular changes may, however, be associated with and are presumably the result of hemolytic substances in the blood plasma. These cases are described under the heading of Acquired Hemolytic Anemia.

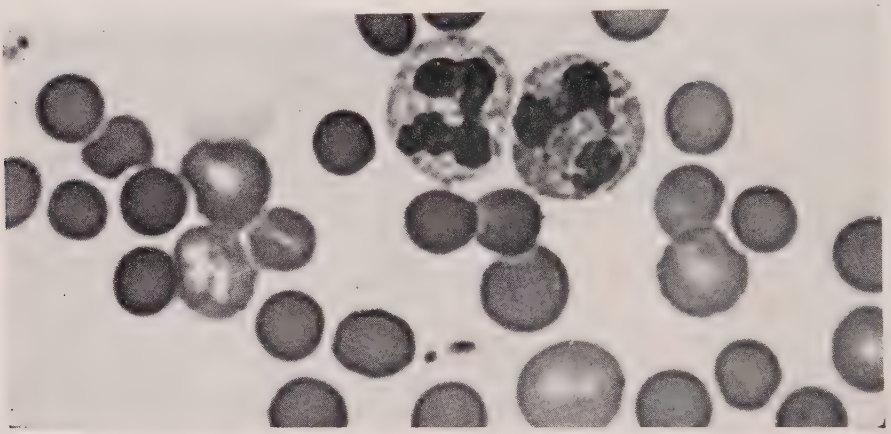


Fig. 765.—Blood smear, spherocytic anemia (hemolytic jaundice). The small deeply stained erythrocytes are the spherical microcytes characteristic of the disease.

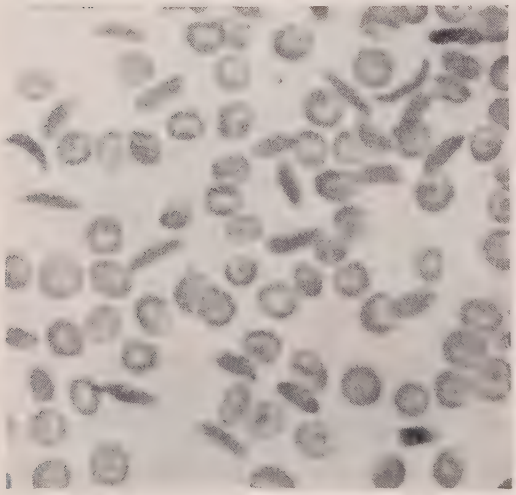


Fig. 766.—Smear of peripheral blood, in case of sickle cell disease. There are many elongated "sickle" cells, as well as "target" cells.

A striking change in the blood picture and in the patient's general condition usually follows splenectomy. The red cells and hemoglobin increase, the reticulocytosis decreases, and evidence of hemolysis (jaundice, increased fecal urobilinogen, etc.) disappears. It is noteworthy,

Sickle Cell Disease.—This is an hereditary disease characterized by abnormally shaped erythrocytes, and usually accompanied by periods of anemia of hemolytic type. Pain in the joints or abdomen, and ulcers of the legs are of frequent occurrence.

The disease appears to be transmitted as a Mendelian dominant character. It occurs almost exclusively in the Negro race, there being only an occasional case report in which the possibility of Negro ancestors apparently has been excluded. Among North American Negroes, the disease occurs in from 7 to 8 per cent of individuals. Of those affected, about 1 in 40 have an accompanying anemia. A distinction is thus made between the *sickle cell trait*, or *sicklemia*, in which the red cells are normal in number but are abnormally shaped or can be made to assume the characteristic abnormality by methods to be described, and *sickle cell anemia*, in which the anemia is also present.

Neel[69] suggests that the disease is due to a gene which, when present in only one parent (heterozygous condition), causes the sickle cell trait, but when present in both (homozygous condition) results in sickle cell anemia.

Occasionally, elongated red cells with narrow bodies and pointed extremities are found in stained blood smears. These cells are often curved, suggesting a "sickle" shape. The number of such sickle cells is usually small, and they may be absent. In sealed wet film preparations, however, nearly all the cells undergo changes in shape.

Elongated and curved cells with attenuated or filamentous extremities are common, as are other bizarre shapes (Fig. 767). The change takes place as the erythrocytes utilize the oxygen in the preparation, and the effect reaches its maximum after a few hours. The same changes occur when blood is placed in a test tube and oxygen is driven off by passing nitrogen, hydrogen, or carbon dioxide through the mixture. When oxygen is readmitted, the cells resume their normal shape. Pauling and associates[70] demonstrated that in sickle cell disease a hemoglobin is present which differs electrophoretically from normal hemoglobin, moving as a positive rather than as a negative ion. This abnormal hemoglobin, in its reduced state, is much less soluble than reduced normal hemoglobin, and its crystallization within the erythrocytes probably causes them to assume the "sickle" shapes. Singer and co-workers[75, 76] have shown that an additional abnormal hemoglobin of fetal type is present in the cells of sickle cell anemia, but not in those of the "trait."

In sections of fixed tissues, the presence of sickled cells is variable. Fixation in formaldehyde solutions often preserves the sickled shape, whereas Zenker's solution does not.

The degree of anemia in sickle cell disease varies considerably from case to case, and from time to time in the same case. During periods of exacerbation it may be severe, the red cell count falling to a level of 1,000,000, with a proportional reduction in hemoglobin. In addition to the sickle cells mentioned, there may be found in smear preparations round cells with central and peripheral dark areas, separated by a pale zone. These "target" cells are not infrequent in this disease, but they are, however, found also in other diseases. Nucleated red cells (normoblasts) are common when anemia is present, and reticulocytes are increased. Polychromatophilic cells and basophilic stippling may also be encountered. The fragility of the erythrocytes to hypotonic saline is moderately decreased.

Neutrophilic leukocytosis is common in this disease. When associated with pains in the bones, abdomen, or other organs, mistaken diagnoses have led to unnecessary operations.

Associated with this form of anemia is jaundice of the hemolytic type.

Stasis of red cells may be observed in the capillaries of various organs, attributed to the greater difficulty encountered by sickled cells in passing through the capillaries. The formation of capillary thrombi may be observed, with infarction of the spleen and lung. The vascular changes are probably responsible for many of the acute but temporary pains that occur. The cause of the leg ulcers is not known, but the histologic changes are those of ordinary chronic inflammation with ulceration.

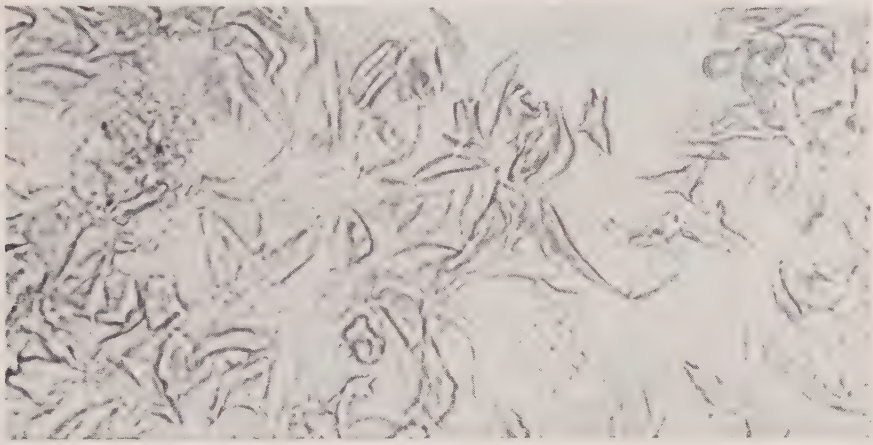


Fig. 767.—Blood film, wet preparation, in sickle cell anemia. Note the distorted erythrocytes, some of which are elongated and have filamentous processes at their extremities.

Fig. 768.—Wet preparation of blood in case of sickle cell disease. Several erythrocytes have assumed the "sickle" shape. Long, tenuous processes on some of the cells are clearly seen. Phase-contrast microscope.

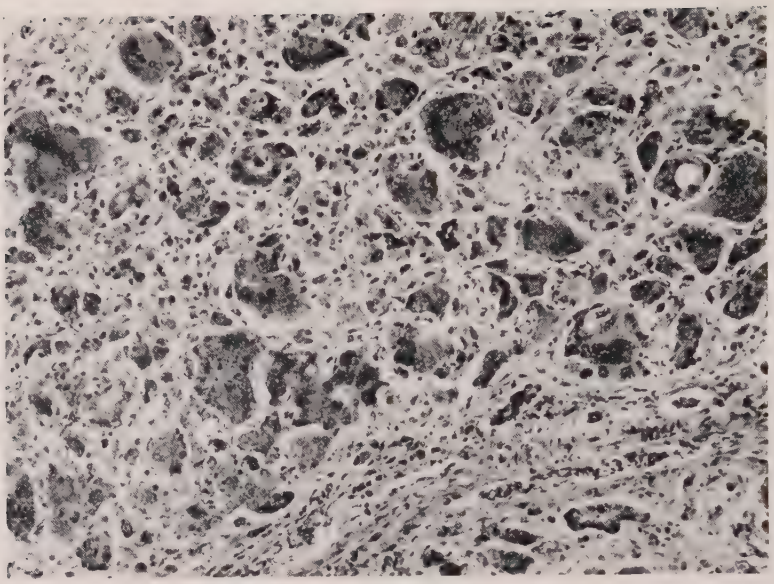


Fig. 769.—Liver, erythroblastosis fetalis. There is severe alteration of the hepatic architecture, with distortion of the lobular pattern, and intralobular and perilobular fibrosis. A small focus of erythropoiesis is seen in the center of the photograph. (×234.)

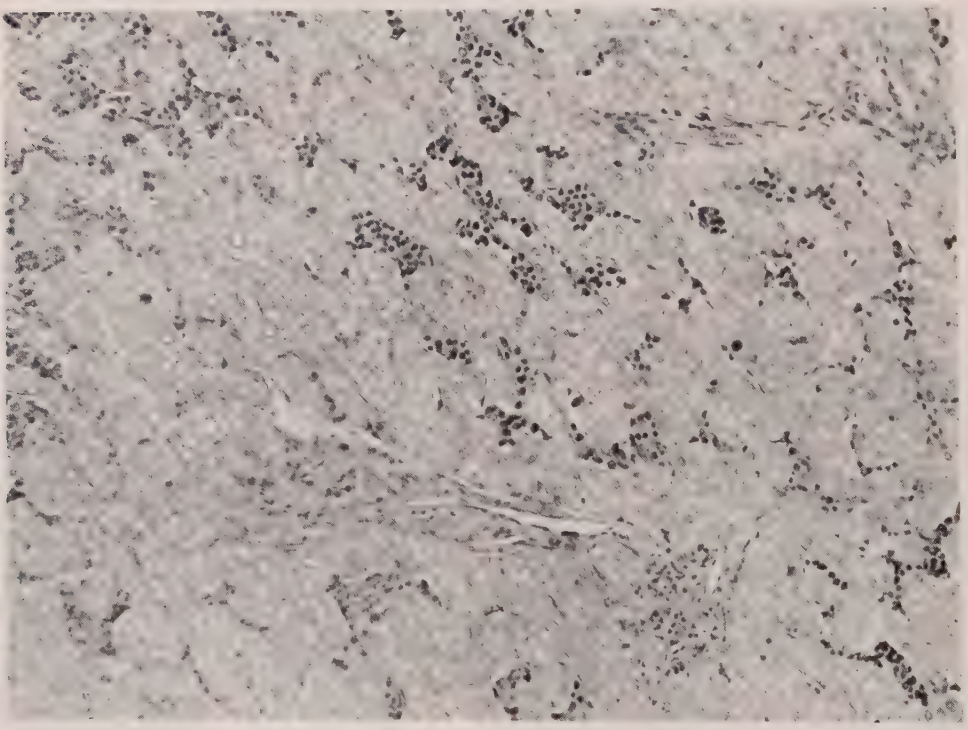


Fig. 770.—Liver, Mediterranean anemia. There are collections of nucleated red cells in the sinusoids. (×234.)

The spleen is commonly enlarged in young individuals, but because of scarring becomes small in older patients. For details of the splenic changes, see page 926.

The condition of the bone marrow depends on the severity of the condition at the time of examination. In the presence of severe anemia, the marrow is hyperplastic, with reduction in fat. The hyperplasia affects both granulocytic and erythroblastic elements. The nucleated red cells are of normoblastic type, and some are of sickle shape. Capillary congestion is often present, and there may be areas of fibrosis, sometimes with calcification, presumably as a result of hemorrhage into the marrow. Few changes in the bones have been noted. With hyperplasia of the marrow, mild osteoporotic changes have been observed, as in other anemias with increased marrow cellularity. In addition, sclerotic changes have been described which, in their most marked form, lead to replacement of hemopoietic tissue by connective tissue, osteoid tissue, and new bone. The changes are nonspecific.

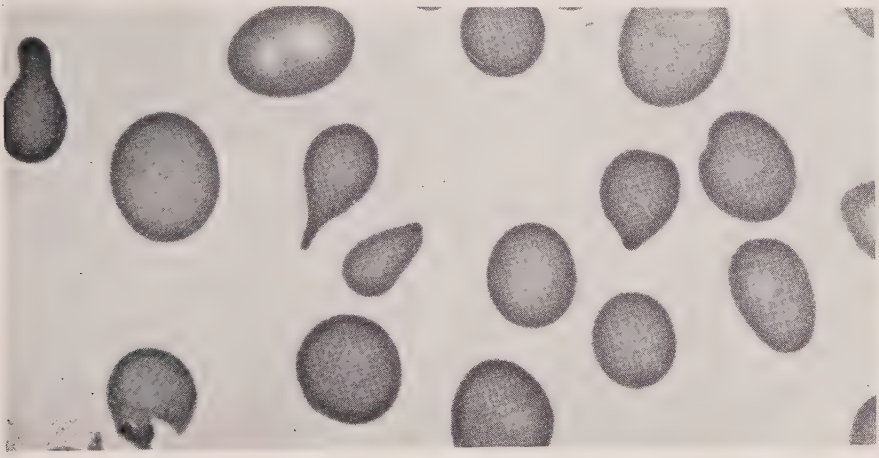


Fig. 771—Blood smear, pernicious anemia. Note the variations in size and shape of the erythrocytes. The largest cells in the field are megalocytes, the small distorted ones are poikilocytes.

Erythroblastosis Fetalis (Congenital Hydrops; Icterus Gravis; Anemia of the Newborn).—This form of anemia is congenital and familial. An hereditary factor is involved, the mechanism of which has only recently been described. The anemia is caused by an interaction of maternal and fetal blood factors, with resultant destruction of fetal blood. In the majority of cases the mechanism is as follows:

The red blood cells of about 85 per cent of individuals contain a factor known as the Rh factor (Landsteiner and Wiener), which is inherited as a Mendelian dominant character. If, therefore, either parent transmits the factor (Rh positive), the fetus will be Rh positive. If the mother's blood is Rh negative, the Rh factor acts as an antigen, and the mother will be immunized, with the production in her blood of anti-Rh agglutinins. These antibodies pass to the fetus, and their interaction with the Rh factor of the fetus results in blood destruction. Similarly, immunity may be produced by transfusion of Rh-negative individuals with Rh-positive blood. The immunity thus produced will affect subsequent fetuses in the same way, hence the familial incidence.

The Rh factor is not the only one capable of producing the disease, although it is the most common. Immunization by the A and B factors has also been reported in rare instances.

The disease occurs in one of three forms: *congenital hydrops,* in which effusions occur in the serous cavities, with severe edema of the organs, including the placenta; *icterus gravis,* in which jaundice, occurring within the first day or two, dominates the clinical picture; and *anemia of the newborn,* in which there is severe anemia with erythroblastosis.

In addition to the edema and serous effusions, the main lesions are extramedullary hematopoiesis and damage to the liver. The former includes blood formation in various organs, of which the liver and spleen are the most important. The cells formed are mainly of the erythroblastic series, but myelocytes, and, sometimes, megakaryocytes are also present. In the liver there are often numerous foci of developing blood cells associated with degenerative changes in the liver cells, and diffuse fibrosis. In individuals who survive beyond infancy, blood formation is less marked, but the fibrotic and degenerative changes are more pronounced, producing a diffuse cirrhosis. The edema is probably due in part to liver damage. Similarly, liver damage may superimpose obstructive jaundice on that caused by hemolysis.

Yellow discoloration of the basal nuclei (kernicterus) is sometimes evident on gross examination of the brain, and cellular degeneration may be noted microscopically.

Mediterranean Anemia (Thalassemia).—This form of anemia occurs principally but not exclusively in individuals of Italian and Greek descent. In its most severe form, it appears as a disease of children characterized by anemia, enlargement of the spleen, yellowish discoloration (but not jaundice) of the skin, and skeletal changes, particularly in the skull, that result in a "mongoloid" appearance. The early literature contains von Jaksch's description of such cases under the term "pseudoleukemia infantum." Cooley and Lee limited this group more accurately, and the disease is often referred to as Cooley's anemia.

THE BLOOD PICTURE.—The anemia is severe. The most frequent red cell counts are between 2,000,000 and 3,000,000. The cells are smaller than normal, with reduced hemoglobin content. In the blood smear there is considerable variation in size, with many larger and many smaller than the mean. It is characteristic of the large cells to be extremely pale, with most of the hemoglobin concentrated at the periphery, and sometimes an additional mass of hemoglobin in the center, giving the cell a "target" appearance. The resistence to hypotonic saline is increased.

Nucleated red cells are commonly found in the circulation. They are of normoblastic type, but vary in maturity. Their number is extremely variable, even reaching figures over 100,000 per cubic millimeter. It is of interest that sudden and sustained marked increases in normoblasts may follow splenectomy. Other evidences of cell immaturity are polychromasia, basophilic stippling, Howell-Jolly bodies, and increased numbers of reticulocytes. An increase in leukocytes, with the presence of immature forms, is of frequent occurrence, and was partly responsible for the name "pseudoleukemia infantum" given by von Jaksch.

The severe forms of this disorder are usually fatal within a few months, so that affected individuals seldom reach adolescence. It has been noted, however, that the parents, siblings, or other relatives of the patients may have certain of the features found in the patient, but in comparatively mild degree and without symptoms. These features may be "target" cells, or cells of ovoid shape, or increased resistance, associated with comparatively mild anemia.

Studies of the patients with various degrees of anemia indicate that the condition is hereditary, and is transmitted as a Mendelian dominant character. The mild grades of anemia are found in adults as well as in children, and are probably found in individuals one of whose parents had the disease. The more severe cases are probably those in which the condition is present in both parents. In this respect the mechanism of inheritance is similar to that in sickle cell disease.

The nature of the inherited defect is not entirely clear, but it has been shown that an abnormal hemoglobin, resembling that in the fetus, is present.[75] The morphologic expression of this abnormality is the presence of the thin, hypochromic cells, including "target" and ovoid cells, mentioned above.

HEMOLYTIC ANEMIAS DUE TO NONHEREDITARY FACTORS

Acquired Hemolytic Anemia.—Several types of hemolytic anemia result from the destruction of erythrocytes by extracellular, nonhereditary mechanisms, of which physical and chemical agents, parasites, and antibodies are the best known.

An important form of anemia is similar in many respects to congenital hemolytic icterus (page 875) but is acquired in later life, and is associated with the presence of erythrocytes that have been sensitized by an adsorbed antibody. This is a gamma globulin, and is most readily detected by the use of a rabbit antihuman globulin serum (Coombs' test; antiglobulin test).

Spherocytosis may or may not be present. It has been shown, however, that spherocytosis is not necessarily a congenital malformation, for erythrocytes placed in lytic solutions pass through a series of shape changes and finally become spherical before hemolysis occurs. The spherical state is, therefore, a "critical" stage, in which hemolysis may occur without further changes in size or shape. The importance of hemolytic agents is emphasized when hemolytic anemia with spherocytosis is produced experimentally in guinea pigs by injecting them with hemolytic serum obtained by immunizing rabbits against guinea pig erythrocytes. Furthermore, cases of hemolytic anemia have been described in which immune hemolysins were demonstrated in the blood but disappeared after splenectomy. Dameshek, who has been responsible for most of the recent work indicating the action of hemolytic substances, believes that some cases of spherocytic anemia are due to the action of hemolysins; that spherocytosis is the result of the action of lytic substances; and that spherical cells so produced are more readily hemolyzed than are normal cells because of their "critical" state. The spleen is an important site of destruction, aided, perhaps, by stasis within its sinusoids. Although some of these cases are improved by splenectomy, the results of the operation and the changes described in the spleen are less constant than in the "typical" cases.

ANEMIAS DUE TO DECREASED RATE OF CELL PRODUCTION

As already noted, some of the anemias associated with hemolysis may be due to defective blood formation. Until more is known about the causes of these conditions, proper classification is not possible.

ANEMIA DUE TO LACK OF IRON

Iron is necessary for the formation of hemoglobin. If the amount of iron available is insufficient, hemoglobin will not be formed in adequate amounts, and many of the red cells will be deficient in hemoglobin content. Pallor of the red cells in stained smear, low color index, and low

mean corpuscular hemoglobin concentration are found on examination of the blood.

There are various reasons for iron deficiency. As noted above, chronic loss of blood is one of the causes. Inadequate intake of iron through faulty diet is a less common cause. Interference with assimilation of iron through gastrointestinal disturbances is also encountered.

Among the clinical syndromes associated with this form of anemia is *chlorosis,* an anemia occurring almost exclusively in adolescent girls and young women. In this country this disease has been especially common among immigrants of the poorer classes, and it has been known in Europe since the sixteenth century. The name chlorosis was used because of the "greenish" pallor of the skin. About the beginning of the twentieth century there was a sudden and marked decline in the incidence of this type of anemia, so that only occasional cases are now encountered.

Another form of this anemia occurs almost exclusively in women, and is associated with low hemoglobin content and small size of the red cells. This is termed *simple hyperchromic microcytic anemia,* and is often associated with achlorhydria, and less frequently with dysphagia (Plummer-Vinson syndrome).

Pernicious Anemia (Addison's Anemia; Biermer's Anemia)

Pernicious anemia is a chronic anemia characterized by an abnormal type of blood formation, associated with achylia gastrica and disorders of the gastrointestinal tract and nervous system.

The details of the mechanism by which this disease is produced are not fully understood. Castle[100, 101] has shown that normal gastric juices contain a substance ("intrinsic factor") that is not present in the gastric juice of individuals with pernicious anemia. It is now believed that this "intrinsic factor" influences the absorption of vitamin B_{12} (Castle's "extrinsic factor"), resulting in deposition of the vitamin in the liver, and thus making it available for use in cell development. Administration of B_{12} in minute doses leads to remissions, with beneficial effects on the anemia and other symptoms. It is thus thought to be the substance formerly referred to as the "hemopoietic principle" or "erythrocyte maturing factor."

Amelioration of the anemia also follows administration of "folic acid" (pteroylglutamic acid), one of the substances in the vitamin B complex. The remissions produced by folic acid are incomplete, however, and the substance does not alleviate nor prevent degenerative changes in the central nervous system. The mechanism of its action is still under investigation. There may also be other deficiencies, for example, lack of a neurotrophic factor as yet unidentified, with resultant changes in the central nervous system.

It is widely believed that megaloblasts are the precursors of normoblasts, and that in pernicious anemia the maturation of some of the cells is arrested at the megaloblast stage. Jones[116] has pointed out that some of the observations on which this view is based are inadequate, and suggests an alternative interpretation. Briefly, Jones believes that megaloblasts do not develop into normoblasts, but only into megalocytes; and that their disappearance after therapy is due to such maturation. The controversy is not closed, however, for Lathja[117] reports the ripening of megaloblasts into normoblasts in vitro under the influence of folic acid or citrovorum factor, and the conversion of normoblasts to megaloblasts in vitro on addition of pernicious anemia serum, suggesting an "inhibitory factor" in the latter. Thompson[125] also finds a factor inhibiting erythropoiesis, and suggests that the mechanism of pernicious anemia is more complex than a simple deficiency. Further investigation is needed.

The occurrence of pernicious anemia is influenced by several factors, both environmental and genetic. It is predominantly a disease of middle life, being observed rarely in persons under 30 years of age. It is prevalent in the temperate zones, especially in the Scandinavian countries, Canada, and the British Isles. Males are affected more frequently than females in the English-speaking countries, but the ratio is different elsewhere.

The relative importance of heredity as an etiological factor has not been determined. That it does play a role is apparent from the racial distribution, the familial incidence, and the occurrence of achlorhydria with or without associated hypochromic anemia in relatives of patients with pernicious anemia. Askey points out that the heredity factor can explain the racial, geographic, and climatic distribution of the disease. Hereditary deficiencies of gastric secretion may, if Castle's intrinsic factor is diminished, result in the development of pernicious anemia. With loss of gastric acidity but retention of the intrinsic factor, hypochromic anemia may result.

The disease is chronic, the onset insidious, and the anemia is ordinarily severe when the condition is first recognized.

The most common symptoms are referable to changes in the vascular system, the digestive system, and the nervous system. In the first group are weakness and fatigue, pallor, and shortness of breath; in the second group are glossitis and gastrointestinal disturbances.

Nervous system involvement leads to numbness and tingling sensations in the extremities, loss of vibratory sensation, lack of coordination, and other symptoms.

Changes in the Blood.—There are often periods of remission and relapse, because of which the degree of anemia varies considerably. During relapse, the red cells may be greatly reduced in number. Counts of 1,000,000 or less per cubic millimeter are not rare. The hemoglobin is not reduced in proportion to the reduction in erythrocytes, hence the amount of hemoglobin per cell is greater than normal (high color index; high mean corpuscular hemoglobin). In the stained smear, this is manifested by deep staining of the cells, which do not have the usual central pale area. This is not due to an increased concentration of hemoglobin per unit volume of cell, but to an increase in size of the cell itself. Macrocytosis is thus one of the characteristic features of the disease. Not only are the cells of greater than average size, but occasional ones are of giant size. There is, however, considerable variability in size and shape, especially when the anemia is severe. Microcytes as well as larger cells are present. Many of the red cells show, in addition, various abnormal shapes (poikilocytosis). (Fig. 771.)

lar significance because their presence indicates a lack of the so-called antipernicious anemia principle, whether due to insufficient "intrinsic factor" in the gastric juice as in pernicious anemia, or to failure of absorption or storage of the antipernicious anemia principle, as in sprue and similar gastrointestinal disturbances.

Contrary to common impression, megaloblasts are not always as numerous as normoblasts, nor are they invariably found. It is the presence of megaloblasts rather than their number that is the important finding.

The number of leukocytes is reduced, usually to 3,000 or 4,000 per cubic millimeter, occasionally lower. The reduction is in the neutrophilic leukocytes, the lymphocytes remaining in normal absolute numbers, though in relatively higher proportions. An occasional myelocyte is sometimes found. A characteristic feature is the presence of neutrophilic leukocytes which are larger than normal, and have hypersegmented nuclei. They have been called "giant neutrophiles," "macropolycytes," and "pernicious anemia neutrophiles," and by some are considered as characteristic of the disease as are the changes in the red cells. Their presence has been attributed to a pathologic alteration in the process of white cell formation.

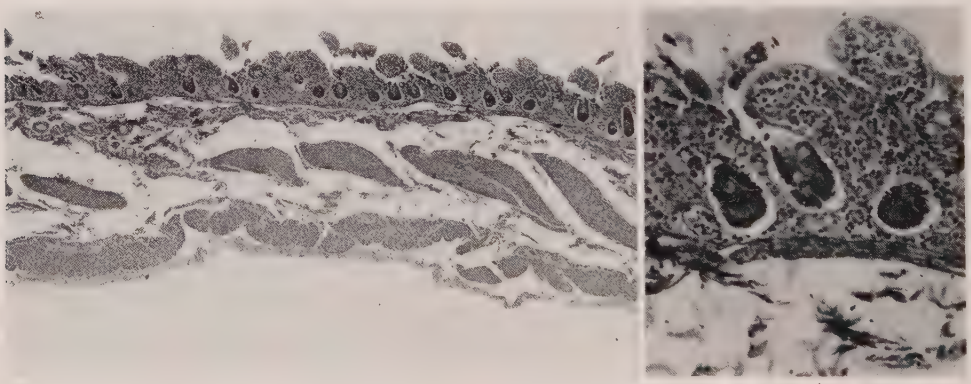


Fig. 772.—Stomach in pernicious anemia. The photograph on the left (×43) shows the whole thickness of the stomach wall. There is atrophy of all coats. The glands of the mucosa resemble those found in the small intestine, rather than gastric glands. Details of the glands are shown in the photograph on the right (×170).

The variations in size can be demonstrated by plotting a frequency curve of the diameters as measured in stained smears (Price-Jones curve). The variability in size (anisocytosis) is recognized in the curve by broadening of the base, as there are more cells of both small and large diameters present than in normal blood. It is also seen that the mean diameter is greater than normal.

Immature red cells are commonly found in the blood. These include cells with polychromatophilic or basophilic cytoplasm, or with basophilic stippling, or sometimes with nuclear remnants such as Howell-Jolly bodies or Cabot's rings. Nucleated red cells may be present, and include both normoblasts and megaloblasts. Normoblasts may be found in any type of anemia. Megaloblasts, however, are of particu-

The blood platelets are also reduced in number, due apparently to alterations in the megakaryocytes.

The Bone Marrow in Pernicious Anemia.—The changes during relapse are: *hyperplasia* of the marrow, with reduction in the amount of fat in the long bones, and its replacement with red cellular marrow; increased erythropoietic activity, with the presence of megaloblasts and megalocytes (Plate X, *c*); the presence of pathologic neutrophiles; a reduction in the number of megakaryocytes; and deposition of hemosiderin in phagocytic cells.

These changes are naturally affected by antipernicious anemia therapy. In relapse, whether due to therapy or occurring spontaneously, the marrow approaches the normal, and in intermediate stages the changes vary accordingly.

Alimentary Tract Changes.—The tongue is reddened, its mucosa atrophied, and often deep fissures are noted. Atrophy of the gastric mucosa occurs, sometimes associated with chronic inflammation. The atrophy is most marked in the fundus, which is the region in which the intrinsic factor is formed. There may also be found glands with cells of the intestinal type of epithelium, including Paneth cells.

The argentaffine cells normally present in the mucosa of the stomach and intestine are decreased in number. These cells contain yellowish fluorescent chromaffine granules, and purines similar to those present in liver extracts that are therapeutically effective. Jacobson has shown that the reduction in number of the argentaffine cells also occurs in sprue, but not in macrocytic anemias that do not respond to liver therapy. The possibility that a secretory product of these cells is related to the formation or absorption of substances necessary for the development of blood cells has not been investigated.

The Nervous System.—The principal changes in pernicious anemia are degeneration of the posterior and lateral tracts of the spinal cord, with loss of nerve fibers and degeneration of the myelin sheaths. Degeneration of the ganglia of the dorsal roots and of the peripheral nerves may also be observed. The changes in the cord are identical with those of posterior-lateral sclerosis (subacute combined degeneration, see page 1320).

Changes in Other Organs in Pernicious Anemia.—There is no wasting, and the patients appear to be in good nutrition. The skin is pale, and has a slightly yellowish color. If the patient died during a relapse, or without having received liver therapy, iron deposition is found in the liver, spleen, bone marrow, and kidneys. Foci of blood formation in the liver and spleen may be present but are of inconstant occurrence.

The heart is dilated. The muscle is flabby, often with fatty changes, and the formation of typical "tigering" striations. Fatty changes in the liver and kidneys are also found. The subcutaneous fat is lemon-yellow, and the muscles deep red.

The degree of change in the organs depends in part on the treatment received. In patients who have received adequate treatment for pernicious anemia, but who die of intercurrent infections, the organs may show none of these changes except in the case of the stomach and central nervous system.

Other Macrocytic Anemias

In addition to pernicious anemia, there are several other forms in which macrocytosis is a prominent feature. Deficiency of vitamin B or other hemopoietic substances may occur not only as a result of lack of a gastric factor, as in pernicious anemia, but also because of inadequate diet, or through deficient absorption resulting from intestinal disturbances (as in sprue), or because of liver disease (especially cirrhosis) which may prevent proper storage. Macrocytic anemia is not uncommon in pregnancy, and may be due to increased requirements, with a drain on the usual stores of the hemopoietic factor. Many cases may show combinations of these factors.

Not all macrocytic anemias are due to lack of substances effective in pernicious anemia, or to their improper storage or utilization. In certain nutritional macrocytic anemias, for example, Wills has suggested deficiency of a different, so far unidentified factor. Lack of the "Wills factor" may lead to development of an anemia morphologically like pernicious anemia, with which it may be confused.

Macrocytosis is also observed in Mediterranean anemia, and in some cases of marrow hyperplasia with entrance of young (larger) cells into the blood stream.

Aplastic Anemia

This term was originally used to indicate a form of anemia in which there was little or no evidence of regenerative activity on the part of the bone marrow. "Aplasia" of the marrow was therefore considered to be the underlying mechanism (Fig. 790). Support for this view was found in cases of anemia due to chemical poisons, especially benzol, in which severe depression of marrow activity may occur. Other chemicals especially associated with the occurrence of anemia are organic arsenic compounds (especially the arsphenamines), colloidal gold and silver, and hair dyes. It should be noted, however, that the clinical and hematologic picture of aplastic anemia may occur without hypoplasia of the marrow, and that especially in the early cases reported, examination of the marrow was incomplete.

Irradiation by radium or x-rays may result in aplastic anemia, although the effect on the production of leukocytes is usually more marked than the effect on the red cells. The more carefully histories are taken, the more frequently exposure to toxic substances is found to be a factor. The impression is readily gained that unrecognized exposure to toxic substances is the cause of many cases that are apparently spontaneous in origin.

The chief symptoms of aplastic anemia are referable to reduction of the red cells, white cells, or platelets, and vary in intensity according to the degree to which these three elements are affected. When the reduction in red cells is extreme, the anemia and its resulting weakness and fatigue may be the presenting symptoms; when leukopenia is pronounced, there may be severe infection, often of a gangrenous type. This is sometimes associated with ulcerations, especially in the oral cavity but sometimes affecting the nasopharynx, the intestinal tract, or the anal region. Reduction in platelets is associated with a tendency to bleed, which may manifest itself in the form of purpuric spots, hematomas, or severe hemorrhages from the nose or mouth or into the intestines.

The onset is usually insidious, and may be indicated by any of the above symptoms. Not infrequently the first symptoms are recognized long after exposure to toxic substances has ceased. The disease is almost invariably fatal, and is seldom of long duration.

Changes in the Blood.—The reduction in the number of red cells is usually severe, or becomes so during the course of the disease. The

reduction in hemoglobin is proportional to that of the cells. The mean cell diameter and mean corpuscular volume of the red cells are usually normal. The red cells, as they appear in stained smears, show no conspicuous changes. Only occasionally are evidences of immaturity observed, and then in slight degree, such as the presence of a few polychromatophilic cells, or stippling, or even an occasional normoblast. The reticulocyte count is seldom elevated, and is often lower than normal.

The leukocytes are also reduced in number, the effect being seen mainly in the granular cells. The lymphocytes, however, are also reduced, so that white counts lower than the total number of lymphocytes normally found are encountered. Leukocyte counts of 1,000 are not rare, and lower counts have been reported. Myelocytes and even myeloblasts are occasionally noted, but are not of common occurrence.

The blood platelets are also diminished, with prolongation of the bleeding time and poor clot retraction.

As a rule, the changes in the blood are permanent and progressive. The gradual lowering of values eventually involves all types of cells. This feature, a "progressive hypocythemia," is one of the most constant findings, and more nearly describes the condition than does the more commonly used term "aplastic anemia."

Changes in the Bone Marrow.—The histology of the bone marrow in aplastic anemia varies considerably, even among cases with similar clinical and hematologic features. Fatty marrow, with hemorrhages or areas of gelatinous degeneration without areas of blood formation, may be the principal finding (Fig. 790). However, cases showing all degrees of cellularity of the marrow have been observed. Not infrequently, developing blood cells are present to such an extent that the condition cannot be regarded as due to marrow aplasia. In some instances, in fact, there has been extreme hyperplasia. This discrepancy between the blood picture and the condition of the bone marrow is difficult to explain. It has been suggested that the mechanism regulating the delivery of cells to the blood stream may be at fault, rather than the development of the cells.

It should be noted that cellular marrow is not, in itself, evidence of hemopoietic activity. In many of the cases classified as aplastic anemia, cursory examination of the marrow may be misleading, as numerous lymphoid cells, including plasma cells, may replace hemopoietic tissue. Furthermore, the state of the marrow is not necessarily the same in all bones.

It has been suggested that the term "pseudoaplastic anemia" be used to designate a discrepancy in the blood and marrow pictures. It seems, however, that the various changes observed may be merely different phases of the same process. This is well shown in some cases of benzol poisoning in which hyperplastic marrow presents a very different picture from that of the usual aplasia.

Changes in Other Organs.—Ulceration of the oral mucosa and that of other sites has already been mentioned in connection with aplastic anemia. These ulcers are often associated with extensive inflammatory reaction in the surrounding tissues, often of gangrenous character. The inflammatory reactions may show but few granular leukocytes, although other features of inflammation may be present, such as edema, fibrin deposits, and hyperemia.

Hemosiderosis of the organs, as seen in hemolytic anemias, does not occur in aplastic anemia, unless repeated transfusions have been given, nor are extramedullary foci of blood formation observed.

Polycythemia

Polycythemia refers to a numerical increase in erythrocytes per unit volume of blood. The polycythemia is said to be relative when the change is due to reduction in plasma volume with corresponding concentration of the red cells. Absolute polycythemia is an actual increase in the total number of circulating erythrocytes.

Relative Polycythemia

Dehydration, such as occurs in severe diarrhea, vomiting, or sweating, or passage of plasma from the blood into the tissues as in shock or loss of electrolytes, results in concentration of the erythrocytes. A transient increase may also occur after contraction of the spleen by adrenalin, which forces stored blood into the circulation. These alterations all disappear when the conditions causing them are no longer operative.

Erythrocytosis

Erythrocytosis is a form of polycythemia in which there is an absolute increase in the number of circulating erythrocytes due to recognizable causes. An important factor in many forms of erythrocytosis is anoxemia. This may result from reduced oxygen intake, such as occurs at high altitudes. Those living under such conditions may have red cell counts of 7,000,000 to 8,000,000 per cubic millimeter, and similar changes occur in experimental animals when subjected to reduced barometic pressure. The degree of response varies among individuals, but in general the increase in count is greater at the higher altitudes. The increase in the number of cells is accompanied by a corresponding increase in the amount of hemoglobin, and in the volume of packed cells.

Similarly, the low oxygen tension occurring in some forms of heart disease results in erythrocytosis. The highest erythrocyte and hemoglobin values are found in those forms of congenital heart disease in which cyanosis is also present. This occurs when a direct communication between right and left sides of the heart or between the pulmonary artery and the arterial circulation acts as a shunt, and permits unoxygenated blood to enter the peripheral arterial system. Red cell counts over 10,000,000 per cubic millimeter have been reported.

In acquired heart disease the changes are less marked. Mitral stenosis causes the greatest

alteration in the count, as a result of the vascular congestion within the lung, and the fibrotic changes in the tissues that interfere with oxygen exchange.

Pulmonary disease may also lead to anoxemia, and thus to erythrocytosis. Emphysema, and less frequently fibrosis, silicosis, Ayerza's disease, and other conditions interfering with the circulation are some of the causes.

Anoxemia may also result from the presence of abnormal respiratory pigments such as methemoglobin or sulfhemoglobin, which reduce the oxygen-combining power of the blood.

Of chemical substances that may cause erythrocytosis, cobalt is one of the most important. The mode of action of cobalt is not known, but it is apparent that erythrocytosis may result from its prolonged administration. It is possible that cobalt, and perhaps other metals, may be necessary for the formation of hemoglobin, but the minimal requirements are so low that evidence from deprivation experiments is inconclusive.

Polycythemia Vera (Osler-Vaquez Disease; Erythremia)

Polycythemia vera is a disease of unknown etiology, characterized by an increase in the total volume of blood and of the number of erythrocytes. Clinically the disease is insidious in onset, chronic in course, and is associated with splenomegaly and symptoms due to vascular alterations.

The disease usually begins in middle life, affects both sexes, and is occasionally familial. It develops slowly, usually with a peculiar cyanosis as the first symptom. Other symptoms are usually such as may be caused by vascular changes. These include headache, tinnitus, and ecchymosis in skin or mucosae. More severe vascular changes with venous thrombosis are common, and cerebral vascular accidents are sometimes the cause of death. Hypertension does not ordinarily occur, but its occurrence in a group of cases not associated with splenomegaly was noted by Gaisböck, and this syndrome is known by his name.

Thrombosis of small vessels may result in ulceration of skin or mucosal surfaces. Duodenal ulcer, for example, is four times as frequent among patients with erythremia as among those without, and is due to occlusion of the mucosal and submucosal arterioles by thrombi.

Pathologic Changes.—The blood volume is increased. The blood is dark and viscous, and the erythrocyte content per unit volume is increased. Erythrocyte counts of 8,000,000 to 10,000,000 are not uncommon, and some in excess of this number have been reported. In cases with unusually high figures, the mean volume of the erythrocyte is usually less than normal. The hemoglobin content of the blood depends on the erythrocyte content, but the increase is not always as great as the increase in cell number. Morphologic changes in the red cells are not common unless hemorrhages have occurred. However, occasional nucleated red cells may be found in the circulation, even in the absence of anemia.

The viscosity of the blood and the specific gravity are increased and the sedimentation rate is decreased. The extent of these changes depends on the degree of increase in number of the red cells.

An increase in the number of circulating leukocytes is not unusual. This increase is ordinarily moderate in degree, but not infrequently is sufficiently great to suggest leukemia. The leukocytosis may be associated with the presence of myelocytes, and involves not only the neutrophiles, but often the eosinophiles and basophiles as well.

It is of particular interest that occasionally the development of leukocytosis with immature cells, associated with the presence of infiltrations of these cells in various organs, has supervened in cases that began with the hematologic features of polycythemia. Some of these cases have had the general features of myeloid leukemia, usually of of the chronic type, but occasionally of the acute form. This association suggests an etiological relationship between erythremia and leukemia, but the available information does not permit further conclusions to be drawn.

A marked increase in blood platelets may occur, and gives further evidence that the marrow hyperplasia is not limited to the development of but one cell type.

In long-standing cases, anemia has been known to develop. This is usually of the so-called "secondary" type, but occasionally has resembled pernicious anemia.

Changes in other organs are mainly those related to the increased blood volume and to vascular complications. At necropsy, the veins are dilated and tortuous, and the viscera greatly congested. The spleen is enlarged, and engorged with blood. The bone marrow is hyperplastic, all of the cell types being increased in relatively normal proportions. The changes in both of these organs are described under the respective organ headings.

Etiology.—The cause of erythremia is unknown. The hyperplasia of the bone marrow has been likened to the proliferation of white corpuscles in leu-

kemia, but without convincing proof that the two conditions are related. It has also been suggested that anoxia, which is known to cause marrow hyperplasia and polycythemia, may be the underlying factor in erythremia. It has been suggested that fibrous thickening of the marrow capillaries may lead to anoxia, or that the same result may follow plugging of the pulmonary capillaries by megakaryocytes.

Other explanations include the presence of an excess amount of the "intrinsic factor" involved in pernicious anemia; the presence of endocrine disturbances; failure of the spleen to destroy red corpuscles at a normal rate; and the presence of constitutional or hereditary factors. None of these suggestions is convincing.

CONDITIONS AFFECTING PRINCIPALLY THE LEUKOCYTES

The conditions affecting the development and maturation of the white cells are not well known. In the normal adult, granular leukocytes are formed only in the bone marrow. Lymphocytes are formed in the lymphoid tissues, which include not only the lymph nodes and the spleen, but also lymphoid tissue in the form of small foci, scattered in the interstitial tissues of various organs. The mucosa of the intestinal tract contains large numbers of lymphocytes, and in some areas there are well-developed lymph follicles. Monocyte formation has been noted in bone marrow, spleen, lymph nodes, and probably in other tissues with reticulo-endothelium.

In the maturation of the granular leukocytes, two morphologic changes occur by which the stage of development can be accurately determined, namely, segmentation of the nucleus, and the appearance of the specific granules in the cytoplasm. The stages in maturation of the lymphocytes are less easily recognized. The cell becomes smaller, the nucleus more deeply stained, the cytoplasm less abundant and often less basophilic. The nucleus remains more or less round, however, and the few "azure" granules which appear in the cytoplasm are of inconstant occurrence, and cannot be demonstrated in sections of tissues. Moreover, the question of whether some of these changes are reversible is a disputed point. Monocytes undergo changes that are distinguishable to some degree, for convolution of the nucleus, and acquisition of "azurophilic" granules may be observed. The latter are not demonstrable in sections.

Although something is known about the site of formation of the leukocytes, and the stages through which they pass, practically nothing is known about the factors that influence their maturation or their delivery to the blood stream. It has been noted that substances affecting the delivery of cells to the circulation, for example, typhoid toxins, do not necessarily induce maturation of new cells, which would indicate the presence of two independently controlled processes.

Normal Values

Despite our lack of knowledge concerning factors that control the number of cells in the circulation, the existence of such controls is evident from the fact that under normal circumstances the number of cells remains within narrow limits. The total number of leukocytes, for example, is ordinarily between 5,000 and 10,000 per cubic millimeter of blood. Moreover, the proportions of the various types are also controlled. The following table indicates the variations of the different types ordinarily found in healthy adults:

	Per Cent
Polymorphonuclear neutrophiles	60-70
Polymorphonuclear eosinophiles	1-5
Polymorphonuclear basophiles	0-1
Lymphocytes	20-30
Monocytes	5-10

Rapid fluctuations in the number of leukocytes in the circulation are reported by Sabin and associates, who found that increases and decreases in the total number of white cells and of individual types occurred at rhythmic intervals. The increments in granular leukocytes occurred at about hourly intervals, and, therefore, these cells form the greater proportion of all the white cells. The total number of leukocytes varied accordingly. The lymphocytes varied with a half-hourly interval, indicating the presence of a mechanism independent of that for the granular cells. Although the rhythmic nature and the significance of these fluctuations are still under discussion, the occurrence of fluctuations within short intervals offers an explanation for some of the apparent discrepancies in white cell counts observed in various disease states.

Leukocytosis

An increase in the number of circulating leukocytes above the upper limit of

normal is referred to as leukocytosis. The most common form of leukocytosis is that in which the increment is in the neutrophilic leukocytes, and is therefore known as *neutrophilic leukocytosis,* or more simply, as neutrophilia. Similarly, an increase in the eosinophilic or basophilic leukocytes is called eosinophilia or basophilia. It should be noted, however, that because of the comparatively small proportions of these cells normally present in the circulation, the numbers may be increased considerably before the increase is reflected in the total count.

Lymphocytosis refers to an increase in the lymphocytes in the circulation, and *monocytosis* to an increase in the number of monocytes.

An increase of short duration may occur as the result of circulatory changes by which cells in relatively stagnant portions of the circulation, such as the spleen or the splanchnic vessels, are brought into the general circulation. It may also result from the presence of chemotactic substances, which have the property of withdrawing cells from the bone marrow.

Menkin has found a substance in inflammatory exudates that is capable of producing a leukocytosis in experimental animals. This substance, which he refers to as the leukocytosis-promoting factor, appears to be related to one of the globulin fractions. Following its injection into dogs, a leukocytosis develops in which the relatively immature leukocytes are increased to a greater extent than are those which are fully formed. This suggests that the factor acts on the marrow, with liberation of the younger cells. This substance is not the same as leukotaxine, which, according to Menkin, is the substance in exudates that influences migration of leukocytes from the vessels by its chemotactic property. Experiments indicating hormonal regulation of leukocytosis through action of the diencephalon have also been reported.[157]

A leukocytosis that is sustained for any considerable time must be dependent on an increased production of the cells involved, and to that extent reflects the condition of the blood-forming organs.

Neutrophilic Leukocytosis.—This most common form of leukocytosis occurs in a great many pathologic conditions, and a few that may be considered physiologic (in newborn infants, after muscular exertion, during labor). The most common causes are acute infections and intoxications. It is also found in certain types of aseptic necrosis (e.g., myocardial infarction), occasionally in the presence of malignant tumors, and regularly after severe hemorrhage, especially into the serous cavities.

Not all these conditions, however, are invariably accompanied by leukocytosis. Among the bacterial infections, for example, those caused by pathogenic cocci are more likely to induce leukocytosis than are others. In some infections no leukocytosis occurs; there may even be a reduction in the number of leukocytes (see leukopenia). The degree to which the white count is elevated depends on the nature of the etiological agent, the resistance of the individual, and the state of the blood-forming organs.

Since the increase is in neutrophilic leukocytes, these cells are increased not only in absolute numbers, but also in their proportion to the total number of white cells. In the more severe infections morphologic changes take place also in the leukocytes, some of which are immature (myelocytes, metamyelocytes) and some of which show pyknotic nuclei, vacuolated cytoplasm, or abnormally large or basophilic granules. These are often referred to as "toxic" changes.

Rarely, bacteria may be found within leukocytes, especially in cases of sepsis.

Eosinophilic Leukocytosis.—Eosinophilic leukocytosis is commonly found in certain parasitic diseases, especially hookworm infection and trichinosis; in diseases of the skin; in allergic disorders; in chronic myeloid leukemia; in Hodgkin's disease; in certain infections, such as scarlet fever; and inconstantly in a few miscellaneous conditions.

The increase in eosinophiles may be extreme, these cells forming 85 to 90 per cent of the total number of leukocytes, a tremendous increase in the presence of an elevated leukocyte count. Calculation of the absolute numbers of the various types of cells gives a better idea of their numerical changes than is obtained from percentages alone.

Except in leukemia, the eosinophiles are adult cells. Few if any eosinophilic myelocytes appear in the circulation.

Basophilic Leukocytosis.—Basophilic leukocytes are often increased in number when there is an increase in eosinophiles. This increase is usually slight, and unless the cell count is calculated on the basis of absolute numbers rather than percentages, the increase may be overlooked. Only in myeloid leukemia are large numbers of basophiles found.

Lymphocytosis.—Lymphocytosis occurs especially in those conditions associated with pathologic changes in lymphoid tissue. The highest counts are found in lymphatic leukemia. Some chronic infections are commonly accompanied by lymphocytosis, especially tuberculosis, and secondary syphilis. Among acute infections, infectious mononucleosis and pertussis are often the causes of high lymphocyte values. Lymphocytes are also increased in number during the period of recovery following various acute infections in which neutrophilic leukocytosis occurs.

Not infrequently, a decrease in the number of neutrophiles causes a proportional increase in lymphocytes without an increase in their absolute number. This is called a "relative lymphocytosis," and does not indicate pathologic changes in lymphoid tissue.

Morphologic changes in the lymphocytes include the presence of pathologic forms such as are seen in infectious mononucleosis, Türk's "irritation" forms and plasma cells. The latter are occasionally seen in small numbers in vari-

ous infections. In the exanthemas, especially rubella, they are found in appreciable numbers.

The separation of lymphocytes into large and small varieties in the differential count is of little, if any, importance.

Infectious Mononucleosis

Infectious mononucleosis is an infectious disease of unknown etiology, occurring principally in children and young adults, and characterized by fever, enlargement of lymph nodes and spleen, elevation of the white cell count, the presence of abnormal mononuclear cells in the blood and of heterophile antibodies in the blood stream.

The disease is contagious, and in several instances has occurred in epidemic proportions in children's institutions. In addition to lymph node and splenic enlargement, the symptoms include fever, general malaise, and other symptoms of an acute general infection. The name "glandular fever," by which the disease was first known, illustrates the early recognition of two of its important features. Recently, symptoms referable to mild alterations in other organs (for example, the liver, kidneys, and nervous system) indicate that the infectious agent is more widely distributed in the body than was formerly believed.

Blood Changes.—The elevation in the white count, and the presence of abnormal white corpuscles, associated with lymph node enlargement, suggests leukemia. The distinction must be carefully made, for leukemia is invariably fatal, while death from infectious mononucleosis has been rare.

In the majority of cases the total leukocyte count is between 10,000 and 20,000 per cubic millimeter, but counts as high as 60,000 have been reported. Leukopenia is sometimes noted, particularly during the first few days.

These changes are accompanied by the presence of abnormal white cells, the nature of which has been the subject of numerous discussions. They are abnormal lymphocytes. The best descriptions of them are given by Downey, who recognized three types. They include cells with moderately basophilic and sometimes vacuolated cytoplasm and marked lobulation of the nucleus; cells with more abundant cytoplasm, and nuclei resembling those of plasma cells; and cells with more diffusely scattered chromatin particles, giving the nucleus a superficial resemblance to the immature cells seen in leukemia. Careful morphologic studies indicate that the cells are not primitive in type, nor are they related to monocytes. Their lymphocytic nature is evident both in blood smears and in the tissue sections of involved lymph nodes.

A serologic test of considerable diagnostic importance (heterophile antibody test of Paul and Bunnell[175]) is based on the fact that blood serum of affected individuals agglutinates and hemolyzes sheep erythrocytes in greater dilutions than is the case with normal serum. The antibodies responsible for this reaction are called "heterophile antibodies." They are not absorbed by guinea-pig kidney (differential test), which distinguishes the condition from serum disease, in which agglutinins are also observed.

Pathologic Anatomy.—The changes in the lymph nodes, spleen, and marrow are described in the appropriate sections. Changes in other organs have seldom been studied. In the few cases that were studied at necropsy, infiltrations of lymphoid cells, including the types described in the lymph nodes, were seen in the interstitial tissues of many organs. Some of the infiltrations were extensive enough to resemble those in leukemia. The diverse symptoms presented by the patient are thus explained by variations in the extent and distribution of lesions and in the organs involved. (See also pages 922 and 938.)

Acute Infectious Lymphocytosis

Acute infectious lymphocytosis is a specific form of lymphocytosis due to an unidentified agent. The disease is infectious and contagious and is observed in children and young adults. It usually begins with an infection of the upper respiratory tract, but the symptoms may be so mild as to escape attention.

The blood picture is one of marked leukocytosis, with total white counts that may reach 100,000 per cubic millimeter. The lymphocytes are greatly increased in both absolute and relative numbers. In contrast to infectious mononucleosis the lymphocytes are of normal morphology and small size. The disease also differs from infectious mononucleosis in being of short course, and in having no heterophile antibodies in the blood. Recovery occurs without complications.

Monocytosis

There are few bacterial infections in which monocytosis occurs. In tuberculosis, monocytes may be increased in the peripheral blood, in addition to playing an important part in the formation of the tubercle. The monocyte-lymphocyte ratio has received considerable attention in the clinical study of tuberculosis, and, when elevated, is considered an unfavorable prognostic sign. In subacute bacterial endocarditis there may be a moderate increase in monocytes, occasionally with the presence of phagocytic cells in the circulation.

During the period of recovery from acute infections, the number of monocytes may be increased. In pneumonia, for example, there is an increase during the stage of resolution, and it is probable that these cells play some part in the development of this process.

Protozoan parasites and Hodgkin's disease sometimes cause monocytosis.

Morphologic changes in monocytes are not rare. Vacuoles in the cytoplasm probably indicate phagocytosis, and occasionally contain particles of cells, malarial pigment, and, rarely, bacteria. Immature monocytes (monoblasts) are found mainly in monocytic and myeloid leukemia, but not in all cases; and less frequently in pernicious anemia. Abnormally formed cells are not uncommon in the leukemias.

Because of the small proportions of monocytes usually present, their numerical changes may not be appreciated unless calculated in absolute numbers.

Leukopenia

When the number of circulating leukocytes is below the lower limit of normal, the condition is referred to as leukopenia. All cell types may be involved, but ordinarily the neutrophilic leukocytes show the most marked and sometimes the only reduction.

Leukopenia usually results from failure of the bone marrow to produce white cells in sufficient quantities. This occurs in certain infections such as typhoid fever or paratyphoid fever; brucellosis; in some cases of tuberculosis, especially the miliary forms. It is common in several virus diseases, such as influenza, measles, and after infestation by certain parasites, especially in malaria. The occurrence of leukopenia in diseases that ordinarily are characterized by leukocytosis indicates marrow failure, and, therefore, lowered resistance or overwhelming infection.

Leukopenia is also found in association with pernicious anemia, Banti's syndrome, and Gaucher's disease. In its most severe form it occurs in agranulocytosis, aplastic anemia, and the leukopenic forms of leukemia.

A number of chemicals may cause leukopenia, among them several in common use as therapeutic agents: amidopyrine compounds, sulfonamides, thiouracil, barbiturates, colloidal gold, and arsenic. Benzol, mentioned in connection with aplastic anemia, is not used as much now as formerly. Physical agents, such as radioactive substances, are also capable of causing leukopenia.

In anaphylactic reactions leukopenia is common, but not as the result of marrow insufficiency. It is caused by vascular changes resulting in accumulation of the white cells in such vascular areas as the spleen or the pulmonary vessels.

Dougherty and White[12, 33] demonstrated a reciprocal relationship between the adrenal cortex and the lymphoid system, evidenced by lysis of lymphocytes following use of adrenal cortical or pituitary extracts.

Almost complete disappearance of eosinophiles from the circulating blood also occurs after administration of cortisone, or of adrenocorticotropic hormone in the presence of normal adrenal glands. The latter substance may therefore be used to test for the functional adequacy of the adrenals (Thorn test[161]).

Agranulocytosis

Agranulocytosis is a form of leukopenia characterized by associated necrotizing inflammatory lesions, especially in the throat, fever, and a blood picture in which extreme reduction in white cells may occur without changes in erythrocytes or platelets. The majority of patients are women of middle age. The course is usually acute.

Within recent years the importance of drugs and drug allergy in the development of leukopenia has been recognized, and many cases of agranulocytosis are now known to be caused by drug administration. The drug most commonly involved is amidopyrine, but cases have also followed administration of sulfonamides, thiouracil, dinitrophenol, barbiturates, and other drugs. The use of drugs, however, is not the only etiological factor. Agranulocytosis also occurs without known drug administration, and the disease occurs only in a small proportion of individuals who use the drugs mentioned. The part played by individual susceptibility, allergy, and other factors, has not been accurately determined.

The change in the blood is primarily that of extreme reduction in the number of leukocytes. This affects especially the granular cells, which may disappear completely. The cells present are nearly all lymphocytes, and in a few cases, moderate numbers of monocytes. Immature or abnormal cells are rarely encountered, except during recovery when myelocytes may appear. No changes in the red cells or platelets are noted.

The necrotizing lesions are most often encountered in the oral and pharyngeal mucous membranes, but may occur in other parts of the alimentary system, or in the skin. These lesions, associated with fever, and often terminating with pneumonia, are obviously the result of bacterial infection. However, they are probably the result, rather than the cause, of the agranulocytosis. Although large numbers of bacteria may be present, and the lesions may be accompanied by other evidences of inflammation (congestion, edema), leukocytes are absent or rare. It may be difficult or impossible to find adult leukocytes in any of the organs in patients who have died. The absence of leukocytes permits invasion of the tissues by bacteria.

Leukemia

Leukemia is a disease characterized by a greatly increased production of white blood cells, the failure of many of the cells to reach maturity, and by the accumulation of such cells not only at the normal sites of their formation, but also in the interstices or organs in which they are not ordinarily found. In most cases the cells appear in large numbers in the circulating blood.

Varieties of Leukemia.—The increase in cell production may involve any one of the varieties of white corpuscles. The types commonly recognized are: myeloid (or myelogenous) leukemia, in which the granular leukocytes or their precursors are increased; lymphatic leukemia, in which the increase is in lymphocytes or their precursors; and monocytic leukemia, in which monocytes and their developmental forms are involved. Rare forms in which a specific cell type is involved are known by the name of the cells involved, for example: eosinophilic, plasma cell, and megakaryocytic leukemias. It is not certain that these should be regarded as separate entities.

Clinical Features.—All forms of leukemia are fatal. Any of the varieties may occur in acute, subacute, or chronic forms. The acute forms ordinarily begin with symptoms of acute infection, and are often associated with acute inflammatory, and sometimes gangrenous lesions of the oral mucosa. A hemorrhagic tendency is common and symptoms of severe anemia are present. Enlargement of the spleen or of superficial lymph nodes may be noted, but are not of constant occurrence. In the acute forms the duration may be as short as a few days but is ordinarily several weeks or months.

The onset of chronic leukemia is insidious. The first symptom noticed is usually enlargement of lymph nodes or of the spleen, often with weakness and other symptoms of the accompanying anemia.

Both sexes are affected, but the disease is usually more common in males. The disease may occur at any age, but most of the acute cases occur in children and in young adults, while most of the chronic cases occur in middle or older age groups. It is also noted that among the acute leukemias, the myeloid form may occur at any age, while the lymphatic type occurs predominantly in the first three decades.

Etiology.—The etiology of leukemia is unknown. The clinical resemblance of acute leukemia to acute infection has suggested that the latter may be an etiological agent. No single infectious agent has been consistently found, however, and those isolated from leukemic tissues have been incapable of reproducing the disease, and were probably secondary invaders.

In comparing the tissue changes in myeloid leukemia with those in lymphatic leukemia, it is noted that in the former condition excessive development of the myeloid cells is accompanied by atrophy and encroachment upon the lymphoid tissue, while the reverse is true in lymphatic leukemia. This led to the suggestion that the myeloid and lymphoid systems were mutually antagonistic. This view has recently been amplified and modified by Miller and associates, who have extracted substances from the urine of leukemic patients that give specific tissue reactions when injected into guinea pigs. The substance in the urine of patients with myeloid leukemia produces marrow hyperplasia and infiltrations of myeloid cells in other organs, similar to that seen in human myeloid leukemia. The substance obtained from urine in lymphatic leukemia produces lymphoid infiltrations. In monocytic leukemia and in Hodgkin's disease the urine appears to contain both of these substances in approximately equal proportions.

The substance producing lymphoid infiltration was identified as hydroxy acids (lymphokentric acid) and that causing myeloid infiltration as noncarbinol acids (myelokentric acid). It is suggested that the myeloid substance stimulates the proliferation of myeloid cells without maturation, and the lymphoid substance similarly stimulates proliferation but not maturation of lymphocytes. Each substance inhibits the proliferation of the opposite type of cells, permitting the cells to mature. Miller and Turner thus explain the findings in chronic myeloid leukemia as the result of an excess of myeloid substance with a normal amount of lymphoid substance. In chronic lymphatic leukemia these conditions are reversed. In acute leukemia one or the other substance is absent, permitting proliferation without maturation.

The best available evidence at the present time indicates that leukemias are neoplasms. The overproduction of cells, their immaturity and occasional abnormalities, the infiltrative growth and colonization in distant organs, and the invariably fatal outcome are all counterparts of characters shown by other neoplastic conditions.

Moreover, the occurrence of cases with some features of tumors (for example, lymphosarcoma) and some features of leukemia, or the occurrence of the leukemic blood picture in tumorlike conditions in which blood changes had previously been absent, suggest a close relationship between such conditions (see chronic lymphatic leukemia, page 892). It should also be noted that the incidence of leukemia in radiologists is several times as high as in the general population, suggesting that X-radiation is leukemogenic as well as carcinogenic.

There is, in addition, supporting evidence from comparative and experimental studies. For example, leukemia may be transmitted from one fowl to another by a filtrable agent. In this respect it is similar to certain neoplasms of the fowl (e.g., Rous sarcoma). In mice, leukemia may be transmitted under certain conditions by means of transplants of leukemic cells, thus resembling the transplantation of mammalian tumors (e.g., breast carcinoma in mice). The conditions necessary for transfer of leukemia are similar to those for other tumors; that is, the cells must be viable, and the inoculation must be made in animals of suitable genetic constitution. In both tumors and leukemia the disease developing after inoculation results from the growth and development of the cells introduced, and not from stimulated growth of the host cells. Further similarities between leukemia and other neoplasms are noted in hereditary factors, the presence of a factor in the mother's milk that influences the incidence, the possibility of immunizing animals against inoculation of transmitted cells, the production of leukemia by carcinogenic agents, and numerous other features.

It should be noted that recognition of the neoplastic nature of leukemia does not preclude the presence of an infectious agent, for neoplasms may themselves depend on such agents. Recent studies implicating viral agents in neoplasms generally, and in leukemia in particular, require confirmation.

Chronic Myeloid Leukemia

In chronic myeloid leukemia a great increase in the number of circulating white cells occurs in the majority of cases, the count often being between 100,000 and 500,000. Counts over 1,000,000 have been recorded, but those within the normal range are rare. The proportions of the cell types vary, but the number of immature cells is always large (Fig. 773, Plate X, *f*). Ordinarily, all stages in the development of granulocytes may be found, including neutrophilic, eosinophilic, and basophilic forms. Myelo-

cytes in the intermediate and late stages of development are usually the most numerous, but less mature forms (myeloblasts) are also present. Mitoses in circulating cells are occasionally encountered. The general picture, with its variety of cells and stages of development, is not unlike the picture seen in smears of bone marrow. Although cells with nuclear abnormalities are occasionally encountered, the great majority are cells of normal morphology, like those in comparable stages of development which occur in normal bone marrow. Not infrequently, nucleated red cells appear in the circulation. Megakarocytes may also be encountered and are often accompanied by increased numbers of platelets.

In this disease there are certain well-recognized variations in the blood picture. For example, cases in which the leukocyte count is normal or decreased and in which no immature

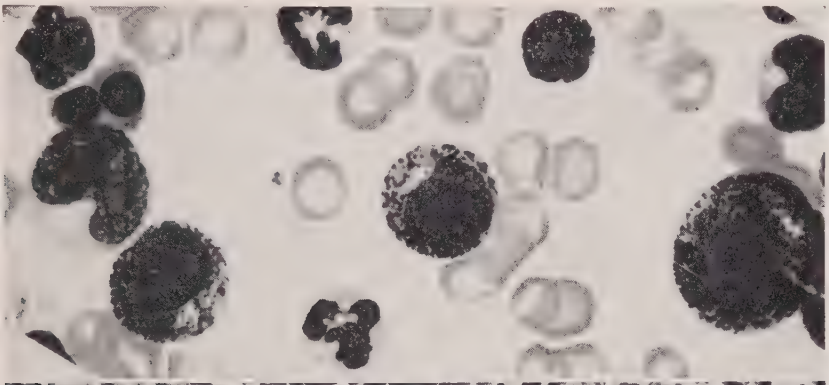


Fig. 773.

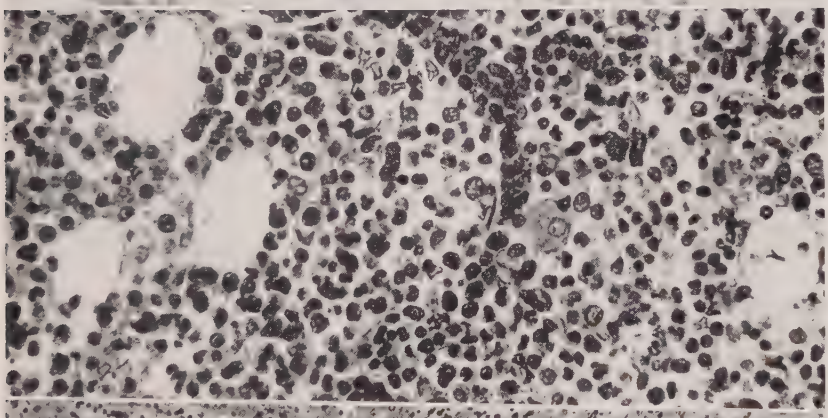


Fig. 774.

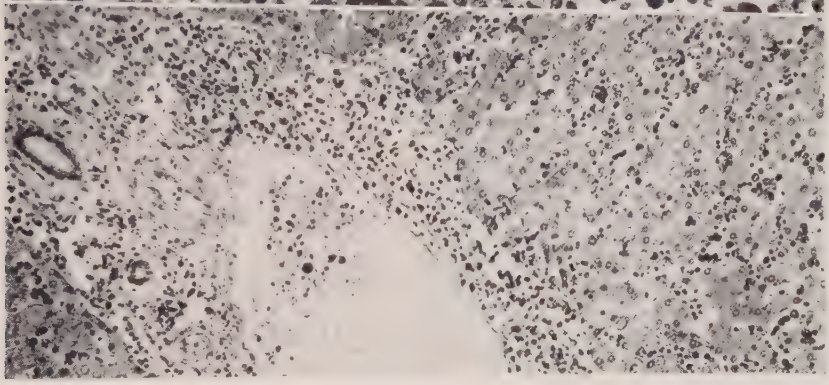


Fig. 775.

Fig. 773.—Blood smear, chronic myeloid leukemia.

Fig. 774.—Section of bone marrow, chronic myeloid leukemia. Although many cells cannot be identified in the photomicrograph, comparison with Fig. 779 shows a greater variation in cell types than is found in chronic lymphatic leukemia.

Fig. 775.—Section of liver in chronic myeloid leukemia. There is infiltration of the portal connective tissue, as well as accumulation of cells in the sinusoids. Individual cells cannot be identified in the photomicrograph.

forms appear in the circulation ("aleukemic" leukemia) are rare. Increased proportions of the primitive forms (myeloblasts) occur, especially in the terminal phase. In rare cases the eosinophilic or basophilic myelocytes and leukocytes dominate the blood picture.

Pathologic Changes in Chronic Myeloid Leukemia.—The fundamental change in the tissues is overproduction of leukocytes and their developmental forms. These cells are presumably produced first in the bone marrow, enter the circulation in large numbers, and colonize in various organs where their presence is referred to as "myeloid metaplasia." The cells

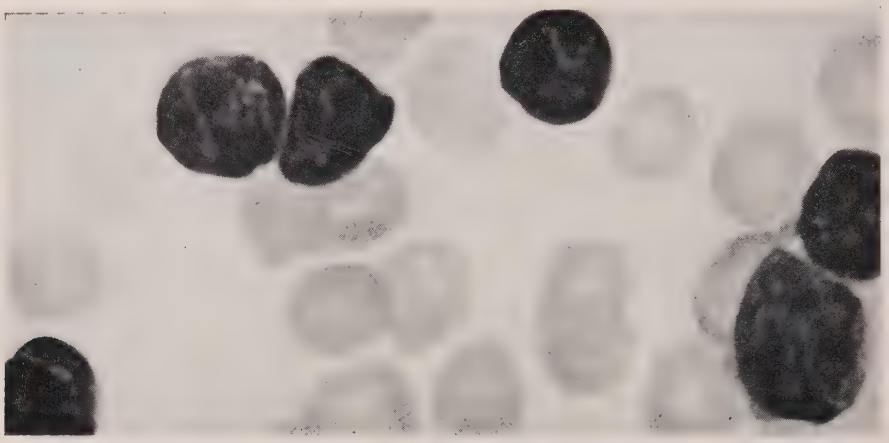


Fig. 776.—Blood smear, chronic lymphatic leukemia.

Fig. 777.—Enlarged lymph nodes along the lower part of the aorta and the iliac arteries in chronic lymphatic leukemia.

continue to divide in their new environment, and many of those in the circulation arise in such metaplastic deposits. (Figs. 773, 774 and 775.)

The hyperplasia in the bone marrow is extreme. The details are described on page 905. The accumulation of cells in the spleen leads to great enlargement of that organ, with cellular changes described in the section on Spleen (page 927).

Similar infiltrations occur in the lymph nodes, especially in the interstitial tissue of the medullary and perifollicular regions. When this change is extensive, there is nearly complete replacement of the lymphoid tissue by myeloid cells of various types. When the change is slight, only occasional myelocytes, and rarely megakaryocytes may be found among the lymphocytes.

Chronic Lymphatic Leukemia

In this condition the increase in the number of leukocytes is less than in the myeloid form. In most cases the white count is between 50,000 and 200,000; wide variations occur at short intervals, without corresponding changes in the patient's condition.

The great majority of the white cells are lymphocytes (Fig. 776). Ordinarily the propor-

tion is above 85 per cent, occasionally 99 per cent. The cells are usually of small size, and rather closely approach the normal small lymphocyte in appearance. Often, however, they are somewhat larger, and may show varying but slight degrees of immaturity (prolymphocytes). Very early stages of development are uncommon in the chronic cases, and appear only in the terminal phase.

Myelocytes and normoblasts occur occasionally, particularly when there has been infiltration of the bone marrow, with resultant anemia.

The blood platelets are reduced in number.

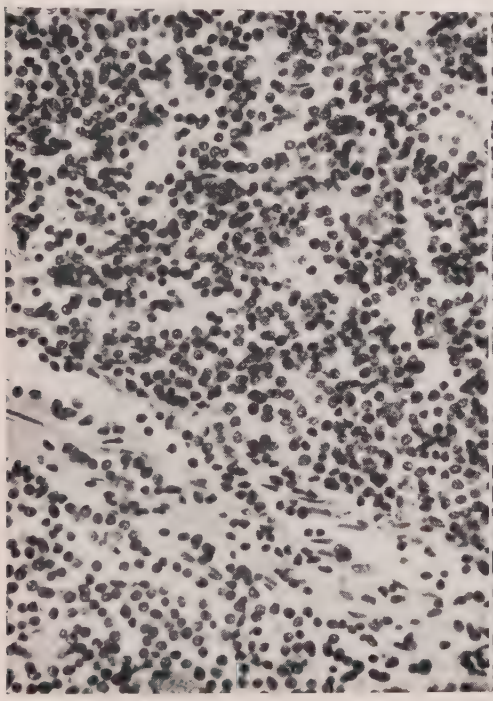


Fig. 778.

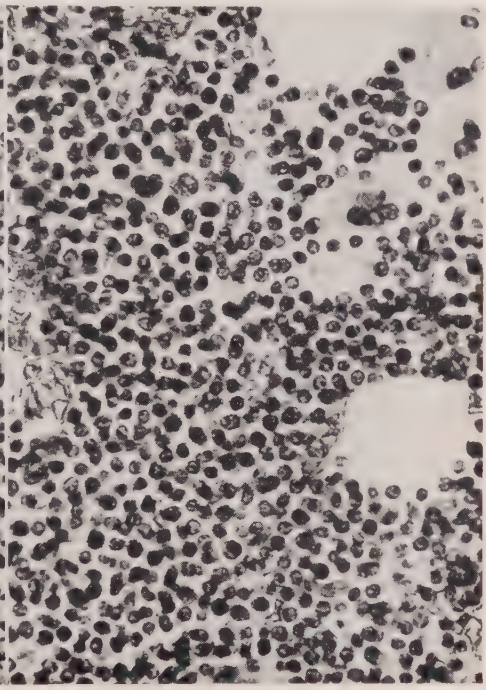


Fig. 779.

Fig. 778.—Section of lymph node, chronic lymphatic leukemia. The histologic picture is uniform over the entire node, with replacement of follicular and medullary areas by diffuse lymphoid accumulations. Note invasion of capsule in left lower corner.

Fig. 779.—Section of bone marrow, chronic lymphatic leukemia. The marrow is infiltrated by lymphoid cells. The megakaryocytes in the upper right corner are the only remaining marrow cells that can be recognized in this photomicrograph.

Variations in the number of circulating leukocytes are not rare. Occasionally, normal or subnormal counts are found (pseudoleukemia) usually accompanied by a relative increase in lymphocytes. In some instances, low values may be found throughout the course of the disease; in other cases, increased numbers of lymphocytes appear in a later stage, so that the typical "leukemic" blood picture is developed. The presence or absence of a "typical" blood picture does not, therefore, indicate a special disease entity, but merely different phases of the same disease. In fact, lymphatic leukemia and the less widely disseminated lymphomas (especially lymphosarcoma, reticulum cell sarcoma, giant follicle lymphoblastoma, and Hodgkin's disease) are closely related, and may be of essentially the same nature. It has long been known that transitions from one to another of these conditions may occur, and Custer and Bernhard[205] have recently shown these changes to be more frequent than formerly suspected.

Pathologic Changes in Chronic Lymphatic Leukemia.—The overproduction of lymphoid cells results in enlargement of lymph nodes and spleen and, often, of the lymphoid aggregates in such organs as the lung and alimentary tract. The lymph node enlargement may be widespread, involving both deep and superficial groups, with such enlargement of the most minute nodes that the impression of newly formed structures is readily obtained. The enlargement is usually most conspicuous in the cervical region, but there is nearly always associated enlargement of the axillary and inguinal nodes and those of the mediastinum, the mesentery, and the retroperitoneal groups. The enlarged nodes are discrete and soft, and

the cut surface is grayish and velvety. (Fig. 777.)

Microscopically, the lymph nodes are overrun with lymphoid cells (Fig. 778). The abundance of cells results in obliteration of the normal architectural markings of the lymph nodes, with loss of distinction between cortical and medullary areas, loss of germinal centers, and of the outlines of sinuses. Cells in division are seen in various parts of the node. The capsule is often infiltrated, and the cells may infiltrate the surrounding tissues. In chronic cases most of the cells approach in appearance that of the small lymphocyte, but there are usually some larger and younger cells among them. Isolated phagocytes with ingested nuclear debris, such as are normally seen in the germinal centers, are often distributed more or less uniformly throughout the lymph node.

Fig. 780.

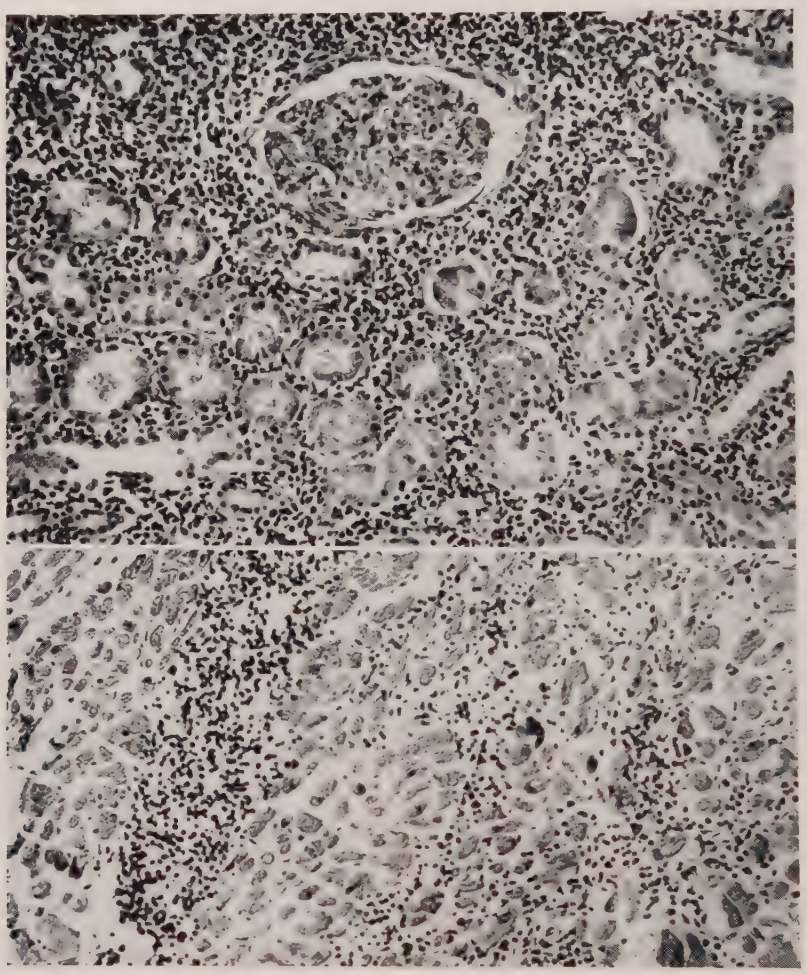


Fig. 781.

Fig. 780.—Section of kidney, chronic lymphatic leukemia. The leukemic cells infiltrate the tissue spaces around glomeruli and between tubules. (See also Fig. 467.)

Fig. 781.—Infiltration of myocardium in chronic lymphatic leukemia.

The changes in other organs are mainly those of infiltration of leukemic cells. In the spleen, this results in great enlargement, with lymphoid collections described in more detail on page 928. In the liver the infiltrations are especially noted in the portal areas, where large collections

of lymphocytes may be present. In addition, the large number of cells in the circulation is reflected in the accumulation of lymphocytes singly and in small groups within the sinusoids. Infiltrations in other organs take the form of interstitial collections of lymphocytes that insinuate themselves between parenchymal structures, usually without causing apparent degenerative changes in the latter. (Figs. 779, 780, 781, 782, and 783.)

mental forms (myeloblasts), their number often constituting more than 90 per cent of the total white cell count (Fig. 784, Plate X, *d*). The finding of small numbers of myelocytes is often an indication that differentiation is in the granuloblastic line. In occasional cases, however, evidence of differentiation is lacking, and it may be impossible to determine whether the leukemia is of myeloid or lymphoid type.

Occasionally, abnormal granules appear in the cytoplasm. Rod-shaped structures staining red in Romanowsky type stains are known as Auer bodies, and probably occur only in acute myeloid leukemia. Granules and particles with similar staining characteristics are sometimes found in segregation vacuoles.

Fig. 782.

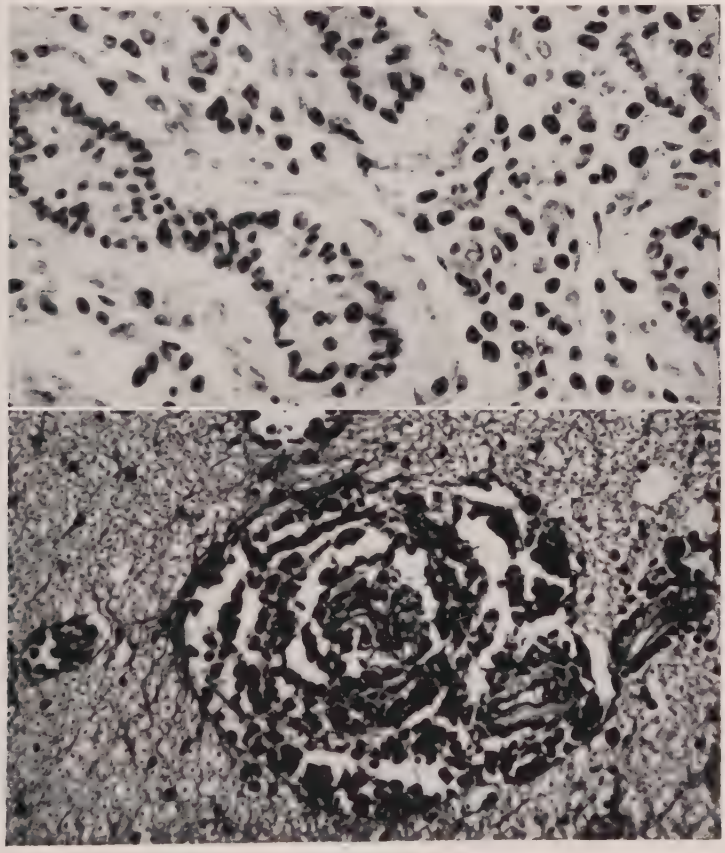


Fig. 783.

Fig. 782.—Infiltration of testis in chronic lymphatic leukemia.
Fig. 783.—Perivascular infiltration of cerebrum in chronic lymphatic leukemia.

Acute Myeloid Leukemia

In most cases of this type of leukemia the total white count is between 15,000 and 50,000. Usually the count is low at first, even much below normal. Primitive cells are usually present in high proportions even when the total white count is low, with increase later. In contrast to chronic myeloid leukemia, the acute cases show preponderance of the early develop-

Not infrequently, atypical myeloblasts and promyelocytes are encountered. For example, some myeloblasts are usually small, with scanty cytoplasm, and are difficult to distinguish from lymphocytes. Atypical nuclear structures, especially with lobulation, may cause cells to resemble monocytes.

The degree of differentiation of the cells is variable, and usually bears some relation to the course of the disease. Cases in which the most primitive cells are observed usually run an acute course, while those in which a considerable number of cells are partially differentiated (promyelocytes or myelocytes) are likely to be less acute. The term *subacute leukemia* is sometimes applied to such cases.

Reduction in the number of erythrocytes and the amount of hemoglobin is often severe. In many cases, also, there is a reduction in the number of blood platelets, often associated with bleeding.

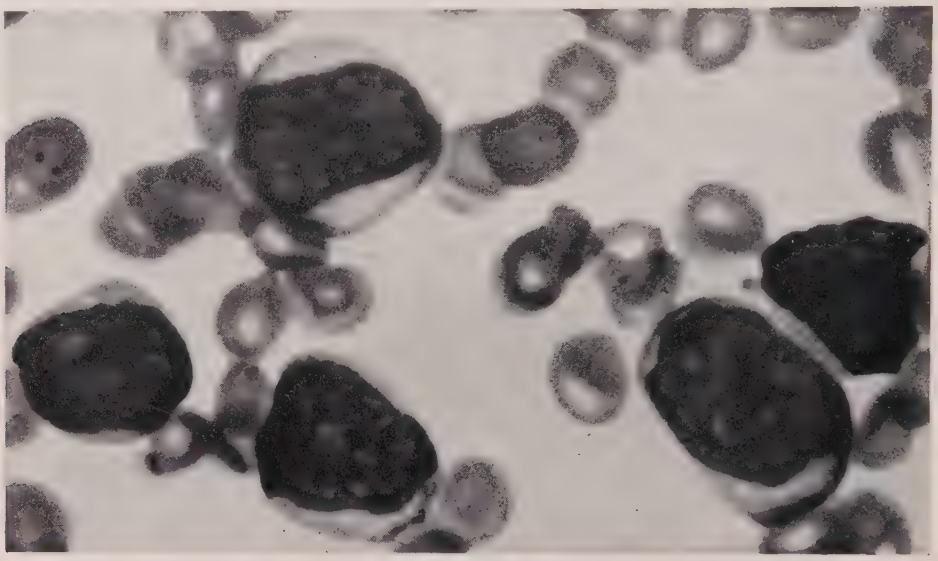


Fig. 784.—Blood smear, acute myeloid leukemia. Note the similarity of the immature white cells (myeloblasts or hemocytoblasts) to large lymphocytes.

Fig. 785.—Mesenteric lymph nodes, acute myeloid leukemia.

Acute Lymphatic Leukemia

In cases of this type the cell changes are similar to those in acute myeloid leukemia in

that there occurs an increase in the number of white cells, associated with high proportions of primitive cells. Early stages in which the total count is low, but in which primitive cells are present in the blood are occasionally seen.

In most cases, it may be observed that forms intermediate between primitive cells (lymphoblasts-hemocytoblasts) and lymphocytes are present, indicating that differentiation proceeds along the lymphatic line. When the primitive cells only are present, it may be impossible to differentiate between lymphatic and myeloid leukemias.

Severe anemia and reduction of platelets are of common occurrence, with bleeding as in the myeloid form (Figs. 787 and 788).

Fig. 786.—Cut surface of liver in acute lymphatic leukemia. The pale areas around the portal canals represent leukemic infiltrations.

Pathologic Changes in Acute Leukemia.—In acute leukemia, cell collections are found in various tissues, as in the chronic form, but usually with certain differences. In the first place, the cells involved are relatively immature. As the primitive cells are all much alike, this causes considerable difficulty in distinguishing between the myeloid, lymphoid, and monocytic forms, as noted under description of the blood picture. In the second place, the infiltrations are sometimes less extensive than in chronic leukemia, especially in the myeloid form. For example, the enlargement of the spleen is not great. The element of time appears to play an important role in the accumulation of cells in this organ. The bone marrow is infiltrated in all forms, and the preponderance of primitive cells is an important diagnostic point. In the lymph nodes, involvement is usually greater in the lymphatic form than in others.

Monocytic Leukemia

Several types of leukemia have been described under this heading. In one form ("Schilling type"), the leukemic cells are morphologically similar to monocytes. In another form ("Naegeli type") the cells are less mature, and there are varied proportions of myeloblasts, monoblasts, and monocytes. In still another form, the cells are atypical myelocytes which, because of their abnormal features, resemble monocytes.

The controversies over the origin of monocytes under normal circumstances are carried over to the origin of cells in monocytic leukemia. In some cases the origin of the cells from the reticulo-endothelial system has been described, and the cases are referred to as "leukemic reticulo-endotheliosis." In most cases, however, participation of the reticulo-endothelial system is not clearly demonstrated. The presence in the blood of myeloblasts, and of intermediate stages in their development into monocytes, strongly suggests that such cases are in reality cases of myeloid leukemia in which monocytes or cells resembling them are produced in unusual numbers. In many instances

the presence of immature cells indicates the presence of leukemia even if the monocytes are disregarded. A further difficulty in interpretation is encountered in certain cases in which granules can be demonstrated by Giemsa and similar staining methods, in the cytoplasm of the leukemic cells in tissue sections. Such granules are presumably neutrophilic in nature, for the specific granules of normal monocytes are not demonstrated by this technique. One is thus confronted with a situation in which monocytes are found in the blood, but the cells in the tissues are apparently myelocytes or promyelocytes. Further study of the group of monocytic leukemias is needed to establish criteria for the identification of these subtypes.

Fig. 787.

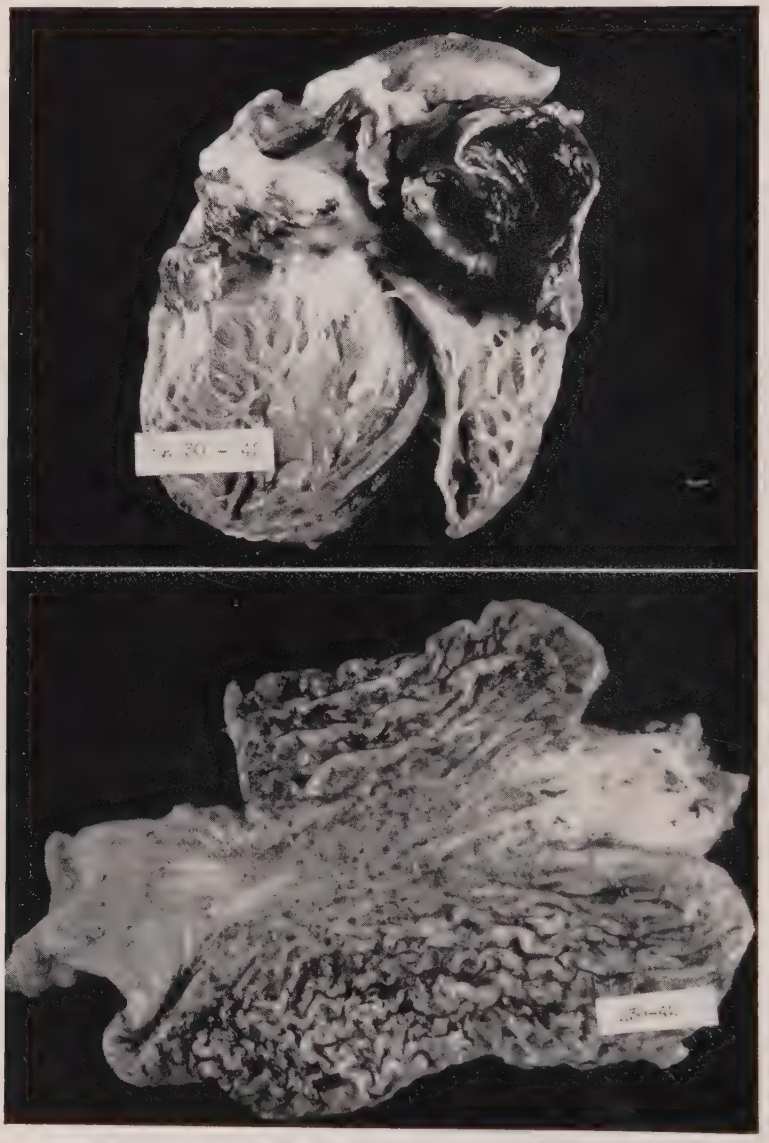


Fig. 788.

Fig. 787.—Hemorrhage into myocardium in case of acute lymphatic leukemia.
Fig. 788.—Petechial hemorrhages in gastric mucosa, in case of acute lymphatic leukemia. Same case as Fig. 787.

The site of infiltrations in monocytic leukemia is similar to that of other acute leukemias, especially the myeloid form.

The bone marrow, spleen, and lymph nodes are usually involved, and infiltrations may also be found in other organs. (Fig. 789.) In some instances infiltration of the gingivae has been a prominent feature.

Unusual Forms of Leukemia

Leukopenic and Aleukemic Leukemia.—Not all cases of leukemia have increased white cell counts, nor do they all have immature cells in the circulation. The blood picture is but one feature. It varies from case to case, and may change both qualitatively and quantitatively during the course of the disease. When the white count is subnormal, the term *leukopenic leukemia* is used. When the white count is within normal limits, and no immature cells are found in the circulation, the term *aleukemic leukemia* is applied.

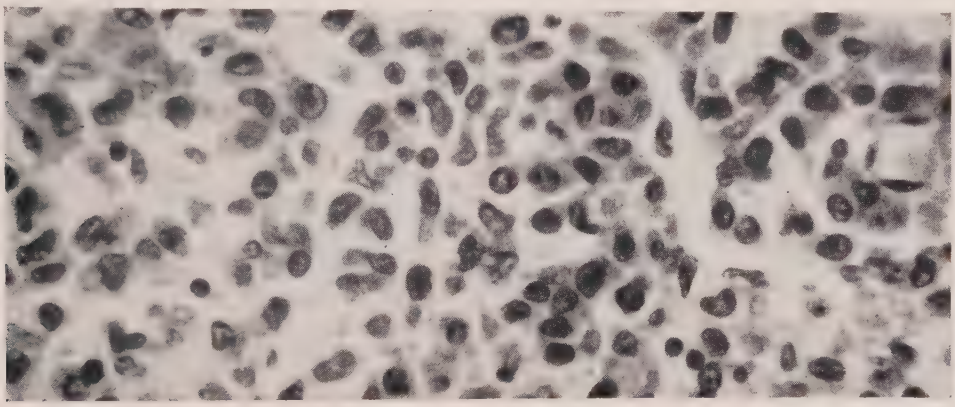


Fig. 789.—Section of lymph node, monocytic leukemia. In tissue sections, monocytes have no cytological characters by which they may be identified accurately, and the nature and origin of the leukemic cells in this case are not satisfactorily demonstrated.

Leukopenia is a phase that is seen not infrequently in the early stages of acute myeloid leukemia, and less commonly in other forms. Ordinarily, this phase is temporary, but in occasional cases low counts have persisted throughout the course.

Aleukemic leukemia is less common, particularly in the myeloid form. This was formerly called "pseudoleukemia," a term that, fortunately, is becoming obsolete.

Leukosarcomatosis and lymphosarcomatosis refer to conditions in which more or less localized lymph node enlargement is associated with a leukemic blood picture (usually lymphatic) and leukemic infiltrations. In leukosarcomatosis the local growth resembling a tumor is often in the mediastinum. At first there is little or no change in the blood picture, but later the cells enter the blood stream in large numbers. This change may appear suddenly, as if the tumor had ruptured into a blood vessel. Attempts to demonstrate morphologic differences between the cells of these cases and those of the usual lymphatic leukemia have not been convincing. A study of many intermediate forms, and the results of experimental studies of leukemia in mice indicate that lymphatic leukemia, lymphosarcoma, and related conditions are different manifestations of the same condition. The different manifestations probably depend on the relation between the neoplastic cell and the rest of the body, by which the spread of the cells is rendered easy in some cases and difficult in others.

Chloroma is a form of leukemia associated with tumorlike growths of a greenish color. The leukemia is usually of the acute myeloid type. The greenish color often involves the infiltrated viscera as well as the nodular tumors. In some cases the blood serum is greenish, and in one case the writer noted a greenish tint in the fundus oculi.

The color is due to an unidentified substance (protoporphyrin? choleglobin derivatives?). It fades on exposure to air, but the color may be restored in tissues by oxidizing agents. Similar greenish infiltrations have been noted in myeloid leukemia in rats.

Eosinophilic leukemia has been described. It differs from the ordinary myeloid leukemia in that most of the eosinophiles are mature cells. Because of this, its inclusion in the leukemias has been doubted.

Basophilic leukemia is a form of myeloid leukemia in which basophilic leukocytes and myelocytes are unusually prominent. It should be noted that in addition to the basophiles, immature cells of other types, including myeloblasts, are usually present in sufficient numbers to warrant a diagnosis of leukemia even without taking into consideration the cells with basophilic granules.

It is of interest that in these cases the basophilic granules are more readily soluble than are those of normal tissue mast cells. In a case studied by the writer, from 20 to 40 per cent of the circulating white cells had basophilic granules, but in paraffin sections of fixed blood during life and in the organs at necropsy, no basophiles could be demonstrated. In such cases,

the use of smears, or of frozen sections stained with basic metachromatic dyes is essential.

Megakaryocytic leukemia is also a form of myeloid leukemia, in which megakaryocytes are unusually prominent in the tissues, and a few may appear in the blood. The presence of megakaryocytes has already been noted in chronic myeloid leukemia, and also in osteosclerosis with myeloid metaplasia. It may be difficult or impossible to distinguish between these two conditions. It seems undesirable to add to this confusion by using a special name for this type of leukemia.

Plasma cell leukemia is rare, and is related to plasma cell myeloma in much the same way as lymphatic leukemia is related to lymphosarcoma. The total white count and the proportion of plasma cells have varied considerably in the reported cases.

HEMORRHAGIC DISEASES

The Mechanism of Coagulation

Clotting or coagulation of blood is due to the action of a substance in the plasma, known as thrombin, which is absent in normal blood, but develops during coagulation and changes fibrinogen into fibrin. Various theories have been advanced regarding the origin of thrombin, the conditions under which it is formed and under which it performs its function. The contact of platelets with a foreign substance causes their rupture, with liberation of a substance which reacts with thromboplastinogen to form thromboplastin. The latter may also be formed from tissues, by trauma. Thromboplastin, in turn, reacts with prothrombin, which is probably composed of two or more components. For this reaction at least three other substances are necessary: calcium, calcium cofactor, and a substance known as "factor 5" or "labile factor." The result of this action is the formation of thrombin, which converts fibrinogen to fibrin. There are probably also several anticoagulants present, the action of which keeps the blood in a fluid state.

Thus, the rate at which coagulation occurs, the degree of contraction of the clot and retraction of the walls of severed vessels, the presence or absence of defective endothelial lining, all influence the occurrence of abnormal bleeding.

A great variety of "hemorrhagic diseases" have been described, with hemorrhages into the tissues or from mucosal surfaces. The diagnostic methods available for the study of these cases are limited. Two important tests are the length of time bleeding continues following a small puncture in the skin (bleeding time), and the length of time required for coagulation under standardized conditions (coagulation time). The following classification (modified from that of Quick) is based primarily on the results of these tests:

Outline of Hemorrhagic Diseases

I. Bleeding and coagulation time normal.
   - A. Traumatic bleeding (cuts, erosion of vessels, etc.).
   - B. Capillary defects.
     - a. Dietary deficiencies (avitaminoses).
     - b. Hereditary (hereditary telangiectasia).

II. Bleeding time prolonged; coagulation time normal.
   - A. Thrombocytopenic purpura hemorrhagica.
   - B. Thrombotic thrombocytopenic purpura.
   - C. Hereditary pseudohemophilia.

III. Coagulation time delayed; bleeding time normal.
   - A. Diminished prothrombin.
     - a. Lack or poor utilization of vitamin K.
   - B. Diminished thromboplastin.
     - a. Increased resistance of platelets.
       - 1. Hemophilia.
   - C. Diminished fibrinogen.
   - D. Anticoagulants in the blood.
     - a. Liberation of heparin into the body (anaphylactic shock).

Of the many conditions included in the above summary, two are of particular interest: thrombocytopenic purpura hemorrhagica, because of the changes in the blood, the effect of splenectomy, and the presence of splenic changes which, although not constant, suggest the presence of this condition when seen in surgically removed spleens; and hemophilia, because of its special clinical features and the necessity of distinguishing it from purpura.

Table XI (after Quick[291]) shows the essential clinical and laboratory findings in the two diseases.

TABLE XI

	THROMBOCYTOPENIA	HEMOPHILIA
Heredity		Sex-linked, recessive
Sex	Males and females	Males
Transmitted by	Males and females	Females
Bleeding	Immediate, petechial and ecchymotic, mucosal	Delayed, ecchymotic
Hemarthrosis	Absent	Common
Coagulation time	Normal	Prolonged
Bleeding time	Prolonged	Normal
Platelet count	Decreased	Normal
Tourniquet test	Positive	Negative
Clot retraction	Absent	Normal

Hemophilia

Hemophilia is an hereditary tendency in males to bleed.

The disease is transmitted as a Mendelian recessive character, the responsible gene being situated in the X chromosome. It is thus a sex-linked character, appearing in males, but transmitted by conductor females. Although, theoretically, the mating of a conductor female with a hemophilic male may result in hemophilic daughters, the occurrence of hemophilia in the female is extremely rare.[283] It is not known whether this is due to the infrequency of such matings, or to the possible lethal effect of such gene combinations, resulting in death of the embryo. (See also page 1345.)

In hemophilia bleeding occurs following only slight trauma. The tendency to bleed is evident in early childhood, and persists throughout life.

The principal characteristic noted in the blood is prolonged coagulation time, the cause of which is not clear. One explanation involves the blood platelets which, although normal in number, fail to agglutinate and disintegrate normally. Others believe that there is a deficiency of a precursor of thromboplastin, and still others that there is an excess of an anticoagulant factor.

Pathologic Changes.—The morphologic changes observed in the tissues are meager, except for the presence of hemorrhages. The bone marrow shows a diffuse hyperplasia during the periods of bleeding, following which the cellularity of the marrow returns to normal. Increased numbers of platelets and mature megakaryocytes in the marrow have been described.

Thrombocytopenic Purpura Hemorrhagica (Werlhof's Disease)

In this condition the bleeding is in the form of petechial spots and ecchymoses in the skin, from mucous membranes, and sometimes in other tissues. Children and young adults are more frequently affected, and the disease is slightly more common in females than in males.

The number of platelets in the circulating blood is reduced, usually below 50,000 per cubic millimeter. This number often seems to be a "critical point" below which bleeding may be expected, although it does not always occur even with lower platelet counts. Reduction in the number of platelets is often accompanied by an abnormal increase or decrease in their size. There are no important changes in the leukocytes, and anemia occurs only as the result of hemorrhage. Other characteristic features are prolongation of the bleeding time, and failure of the blood clot in vitro to retract. The clotting time is normal.

Pathogenesis.—Inasmuch as blood platelets are known to play an important part in coagulation and in retraction of the clot, it is natural that the reduction in the number of circulating platelets should be considered important for the development of the hemorrhagic phenomena. However, the relation between the number of platelets and the other phenomena mentioned is not entirely consistent.

Furthermore, the reason for the reduced number of platelets is disputed. According to one view, destruction of platelets occurs more rapidly than normal in the spleen. In many cases rapid improvement after splenectomy certainly indicates that the spleen has an important function related to the number of platelets, but the mechanism of its action is not clear. The pathologic changes found in the spleen are minor in comparison with the pronounced effect of splenectomy. Platelets are difficult to recognize in sections, but have been seen within phagocytic cells when studied by supravital methods. An extractable substance has been found in the spleen in cases of purpura, the injection of which caused thrombocytopenia in rabbits. It has not been shown that the action of this substance is specific, however.

A second view postulates defective formation of platelets in the bone marrow. This appears to be due to influence of the spleen (hypersplenism), and is usually corrected by splenectomy.

Defects in capillary endothelium have also been considered of etiological importance, although such defects have not been demonstrated morphologically. The occurrence of hemorrhages after application of a tourniquet (as in the tourniquet test) may be related to dilatation rather than injury of capillaries. On this basis it has been suggested that in purpura there is a continuous overproduction of histamine resulting in capillary dilatation. Platelets remove histamine and are themselves changed in the process, becoming more readily destroyed.

Pseudohemophilia

The bleeding tendency in this disease is similar to that in hemophilia. The condition is hereditary, but unlike hemophilia is transmitted by either males or females, and appears in both sexes.

The bleeding time is prolonged, the coagulation time is normal, and the number of platelets is normal or slightly increased. The nature of the defect in clotting has not been demonstrated. By means of the capillary microscope irregular and distorted vessels have been observed in the nail bed. After injury, they do not disappear or retract as do normal vessels.

Thrombotic Thrombocytopenic Purpura

This is an acute, febrile, usually fatal disease. The important clinical findings are: thrombocytopenic purpura, hemolytic anemia, and transitory neurological signs of a focal nature.

The main pathologic change is the occlusion of arterioles and capillaries in many organs by multiple thrombi. It is widely believed that these thrombi are composed principally of platelets, and that their formation results in removal of platelets from the circulation. Meacham and associates[288] have demonstrated a degenerative lesion of the vessels, with aneurysm formation. This, they believe, is the primary lesion, and is followed by the formation of thrombi composed not of platelets, but of a hyaline material.

THE BONE MARROW

Normal Structure and Function

The bone marrow is the soft, cellular, vascular, and fatty material that occupies the spaces between the trabeculae and in the Haversian canals of the bones. It varies in amount and cellular content in different bones or parts of bones, and at different ages.

In infants and young children the marrow consists of developing blood cells. In older children and in adults blood development is abundant in the vertebrae, the sternum, the ribs, and the skull, but in the long bones blood formation is confined to the epiphyseal regions, becoming replaced by fat in the shaft. This change begins about the sixth year, and is complete by about the eighteenth. In the other bones, fat appears but does not result in localization of hematopoiesis to focal areas.

The hematopoietic tissues of the marrow comprise developing red and white blood cells, and sinusoidal capillaries so closely mingled that the relationship of the cells to the vessels or to one another cannot ordinarily be determined. In lower animals (fish, reptiles, birds) erythropoiesis is exclusively intravascular and granulopoiesis extravascular. A study of regenerating marrow following hypoplasia in man, and experimentally produced hypoplasia in small mammals has suggested that the same conditions obtain in mammals. The early stages of erythropoiesis occur in sinusoidal capillaries which are collapsed, and through which blood is not circulating. Only after the contained cells are mature does the communication with the circulation open. For this reason, developing erythroblasts are often found in groups, while the granulocytes appear to be diffusely scattered throughout the marrow.

The cell types found in red bone marrow represent the various stages in the formation of erythrocytes, granulocytes, and blood platelets. The erythrocytes arise from nucleated erythroblasts (normoblasts) which pass through various developmental stages (described in the section on Blood) before losing their nuclei. Megaloblasts are not present in normal marrow. The granulocytes likewise undergo maturation, beginning as nongranular mononuclear cells (myeloblasts or hemocytoblasts). The acquisition of granules leads to the formation of mononuclear granular cells (myelocytes or granuloblasts), which by subsequent nuclear convolutions become polymorphonuclear leukocytes (granulocytes). The most numerous of these are those with neutrophilic granules.

The megakaryocytes of the marrow are probably the source of blood platelets. These cells also develop from a primitive mononuclear cell (myeloblast or hemocytoblast), pass through stages of hypertrophy and nuclear convolution (megakaryoblasts), and finally develop in their cytoplasm minute azurophilic granules of a specific type. Fragmentation of small portions of this granulated cytoplasm results in the formation of blood platelets.

Other cell types are present in small numbers. Scattered lymphocytes are common, and there may be actual follicles with germinal centers. Plasma cells are also represented. Phagocytic cells derived from the reticulo-endothelium are present but not conspicuous. The fatty marrow of the diaphyses of the long bones contains only fat cells, a few capillaries, and a small amount of supporting stroma.

The relative proportions of red and fatty marrow vary with age and in various diseases. The decrease in the amount of red marrow and the variations in red marrow content of the different bones are important in the interpretation of marrow pictures. For normal values see Custer.[299, 300]

The *function* of the bone marrow is the production of erythrocytes and granular leukocytes. Under normal circumstances this is accomplished in such a manner that the cells are produced and enter the circulation at a rate equal to that at which they are destroyed, thus maintaining a level of cells in the circulation within narrow limits. Alterations in the rate of cell production are usually reflected in the peripheral blood picture, so that examination of the blood indicates with reasonable accuracy the state of the marrow. There are instances, however, in which the morphology of the marrow and that of the blood are not in accord. This occurs mainly in cases in which the number of cells in the blood is reduced (anemia, leukopenia), but developing cells are found in abundance in the marrow. This may be the result of incomplete development ("maturation arrest") and is sometimes indicated by increased proportions of young cells, with few adult forms.

Examination of the bone marrow during life is comparatively easy, and is being utilized with increasing frequency.

From the practical standpoint, examination of the marrow is of value in determining the type of anemia when this is not apparent from the blood picture; in differentiation of leukemia (especially aleukemic forms) from conditions that may resemble it (agranulocytosis, purpura hemorrhagica, Banti syndrome, anemias, etc.); in the detection of specific cell types in certain diseases (Gaucher's disease, Niemann-Pick's disease, disseminated lupus erythematosus) or of tumors or parasites (malaria, Leishmania); in the study of hypersplenic states and in studying the progress of a disease and the effect of treatment.

Bone Marrow Changes in Disease

Atrophy and Hypoplasia.—These terms refer only to changes in the red marrow, that is, the hematopoietic tissue. Gross examination reveals a decrease in the amount of red marrow in the long bones, and its replacement by fat. The fat tissue (yellow marrow) expands and encroaches on the space occupied by the red marrow, except in cases of acute atrophy in which the space may be occupied temporarily by edema fluid, or gelatinous degeneration. In conditions accompanied by a tendency to bleed, hemorrhage in the marrow may be a prominent feature, especially following trauma incident to biopsy examination.

Histologically, reduction may be noted in the number of all cellular elements, or only in some. In *aplastic anemia,* for example, the reduction in amount of blood-forming tissue may result in

large areas of fat replacement, with few or no hematopoietic elements (Fig. 790). Not infrequently this reduction in erythroblasts and myelocytes is accompanied by an increase in lymphocytes and plasma cells, which, under low magnification, may give a false impression of the degree of hematopoietic activity. There is, however, considerable variation in the bone marrow in this condition. Although the marrow in such locations as the sternum and the vertebrae may be replaced by fat, it may, on the other hand, be deep red and contain abundant developing blood elements. This is true not only in those cases in which no etiological factor is evident, but also in cases in which there is clear evidence of the action of chemical or physical agents. When the marrow is hypoplastic, cell development may be limited to focal areas of small size, scattered in fatty, hemorrhagic, or gelatinous marrow. The hypoplasia usually involves both erythroblastic and myelocytic elements, and the number of megakaryocytes is reduced also. Primitive cells are present in increased numbers in practically all cases. In more cellular marrows there is an increase in the later stages, especially among the myelocytes and megakarocytes. In benzol poisoning, Mallory and associates[347] found abnormal giant cells indistinguishable from those found in Hodgkin's disease. They also noted a progressive fibrosis of the marrow, the fibrous tissue replacing the fat cells rather than the hematopoietic elements.

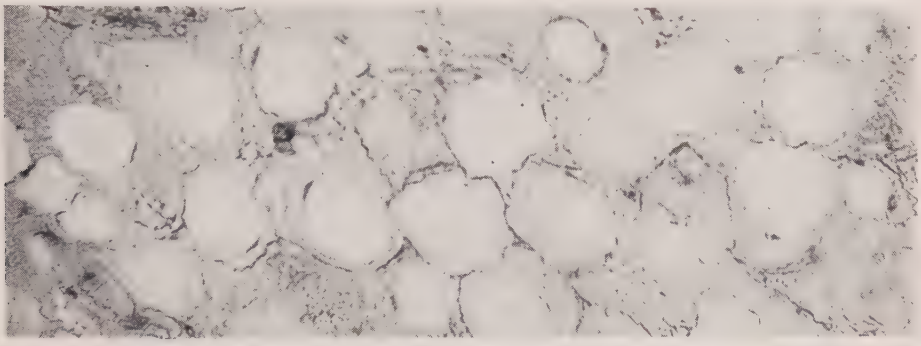


Fig. 790.—Aplasia of bone marrow. No blood-forming cells are present. The spaces between the fat cells contain gelatinous and fibrinous material. This is the "classical" finding in aplastic anemia, but all gradations in cellularity of the bone marrow may be encountered.

Aplasia of the leukoblastic elements alone is found in *agranulocytosis.* The reduction may be so severe that no adult leukocytes are found. Darling, Parker, and Jackson[344] have shown that the marrow picture depends on the stage at which it is examined. In cases in which death occurred during the first four days, examination showed hyperplasia of the primitive cells, with arrest of maturation at that stage. In cases of longer duration, adult granulocytes were lacking, myelocytes were greatly reduced, and increased but variable numbers of plasma cells were found, which, in the more prolonged cases, were present in enormous numbers. Recovery is followed by a return to the normal condition, but often there is a stage of leukoblastic hyperplasia in which myelocytes are abundant.

Not infrequently, there are present in the marrow small lymphoid cells which have a tendency to form accumulations simulating follicles (Fig. 791). This resemblance is due in part to the fact that in the central portions the cells are separated by edema, resulting in a clearer area resembling a germinal center. The resemblance is superficial, however, for the large primitive cells of germinal centers are lacking, and there are no mitoses. The erythroblastic elements and the megakaryocytes are unchanged.

Aplasia and Hypoplasia of the Megakaryocyte-Platelet Elements.—Hypoplasia of these elements does not occur without similar changes in other cells. Reduction in mega

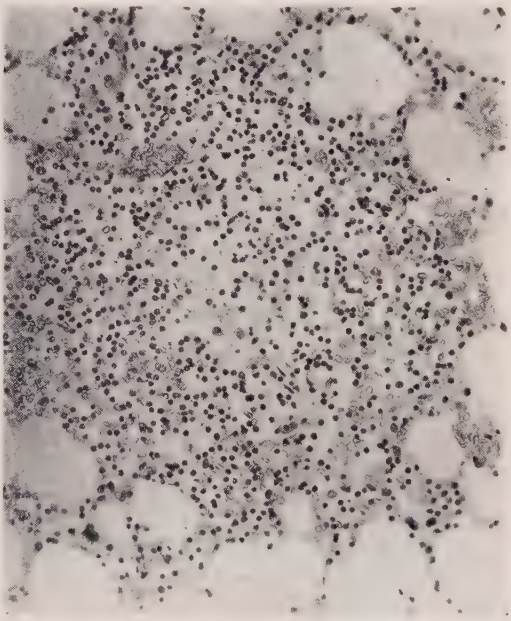


Fig. 791.—Section of bone marrow in agranulocytosis. No mature leukocytes are present. The cells with small dark nuclei are probably lymphocytes. The photomicrograph shows a focal collection of such cells with a relatively clear central area, superficially resembling a lymph follicle.

karyocytes has already been mentioned in connection with aplastic anemia. It also occurs in conditions with marrow replacement (fibrosis, sclerosis, tumors, or leukemia). A moderate decrease in megakaryocytes is also noted in pernicious anemia. In *idiopathic thrombocytopenic purpura hemorrhagica* the number of megakaryocytes may be normal or increased, but the production of platelets from them may be inhibited.

Hyperplasia of Bone Marrow.—Hyperplasia is of common occurrence. In most instances it is a reactive change and, as such, is not specific for any particular condition.

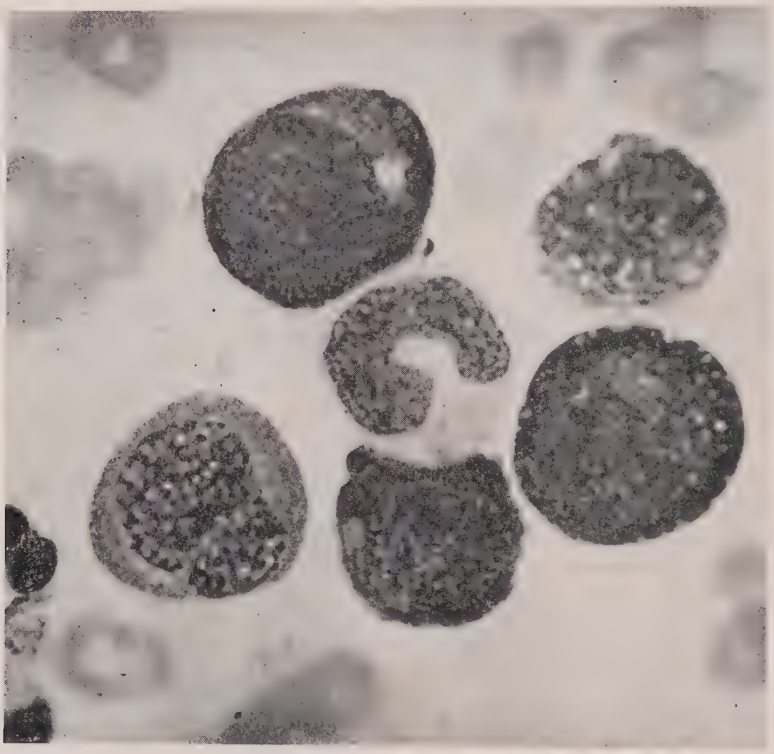


Fig. 792.—Smear of bone marrow in pernicious anemia. Of the six nucleated cells in the center of the field, five are megaloblasts. The central cell is a metamyelocyte.

Erythroblastic hyperplasia occurs in most forms of anemia. The increase in the number of cells is mainly in the erythroblasts, which, except for the "pernicious" and related forms of anemia, are of normoblastic type. In moderate degrees of anemia the increase is in the late and intermediate stages. The hyperplasia takes place at the expense of the fat. There may be an associated increase in the number of myelocytes, especially if the disease is accompanied by leukocytosis. In hemolytic anemias (e.g., spherocytic anemia) the erythroblastic hyperplasia is especially marked, and early forms (proerythroblasts) are often numerous (Plate X, *b*).

Erythroblastic hyperplasia is also found in various forms of *erythrocytosis* and erythremia (polycythemia vera), in which it is associated with increased leukopoiesis and large numbers of megakaryocytes. Thickening of the walls of the small arteries in the marrow has been described.

In *pernicious anemia* and other forms of anemia associated with deficient formation, absorption, or utilization of the "hematopoietic principle," the hyperplasia is said to be of the megaloblastic type, because megaloblasts are present in variable numbers (Plate X, *c*, Fig. 792). As in the peripheral blood, both megaloblasts and normoblasts are present, and their distinguishing features are observed best in smear preparations. The most important point to note is not the number of megaloblasts, but the fact that any can be found. The marrow changes depend on the stage of the disease. During relapse, hyperplasia occurs at the expense of the fat, so that only occasional fat cells may be seen in such sites as the sternum and vertebrae, and the yellow marrow of the long bones is encroached upon or even replaced by red.

The nucleated red cells tend to occur in groups, and there is often similarity among the stages of development within the group. Because of the high cellular content of the marrow, it is usually impossible to determine whether the cells are within or outside of the sinusoids.

In addition to hyperplasia of erythroblastic elements, an increase occurs also in the number of myelocytes, especially the neutrophiles. These cells proliferate in the tissue spaces around the

groups of nucleated red cells, and often appear within the groups, intermingled with the erythroblasts. This proliferation is in contrast to the decrease in the number of leukocytes in the peripheral blood. Megakaryocytes are usually reduced in number.

The bone marrow shares in the general deposit of blood pigment, and hemosiderin is commonly found in phagocytic reticulum cells.

The changes described occur in pernicious anemia during periods of relapse, and are modified by specific therapy. The most obvious changes are in the erythroblastic cells. The proportion of megaloblasts is reduced, and that of normoblasts increased. In a full remission, megaloblasts may be difficult to find. The increased number of normoblasts results in large numbers of macrocytes and reticulocytes, and this is reflected in the peripheral blood picture. In a remission that has been maintained for some time, the degree of hyperplasia decreases, and the cell content of the marrow approaches the normal.

Changes among the myelocytes are less marked than among the erythroblasts. In the early stages of remission large numbers of cells are still present, with a gradual decrease later. Not infrequently the number of eosinophile myelocytes is increased, with a concomitant increase in the adult eosinophiles in the blood. Megakaryocytes are again seen in normal numbers.

In *sickle cell disease* the presence of sickled cells can be demonstrated especially in sections of formalin-fixed tissue. When anemia is present, the marrow is hyperplastic, and nucleated red cells are numerous, some of them showing the same abnormal sickle shapes as are seen in the adult cells. Myelocytes including eosinophiles are also increased in number. Hemosiderin is often found in small amounts in phagocytic cells.

In addition to the hyperplasia, congestion of the capillary vessels is noted. Most of these are filled with sickled erythrocytes. After repeated attacks of anemia, fibrosis of the marrow may occur.

Leukoblastic Hyperplasia.—The most common form is that associated with *leukocytosis* in the peripheral blood. Although leukocytosis may occur as a temporary phenomenon due to changes in the distribution of cells in the circulation, a sustained leukocytosis such as is found in common infectious diseases depends on the presence of hyperplasia in the bone marrow. The hyperplasia involves mainly the leukoblastic elements, with the formation of large numbers of myelocytes and adult leukocytes (Fig. 793). In most instances these are neutrophilic cells associated with peripheral neutrophilia. In conditions characterized by eosinophilia, a great increase occurs in the marrow eosinophiles. Increased numbers of megakaryocytes are common, but changes in the erythroblasts are not striking. When anemia results from an infectious process, there may be erythroblastic hyperplasia, usually of moderate degree, and overshadowed by the greater increase in granular cells. The early stages of myelopoiesis (myeloblasts) are seldom found in appreciable numbers, the increase being in the later developmental stages (myelocytes and metamyelocytes).

In *leukemia* the leukoblastic activity of the marrow reaches its greatest extent. In chronic *myeloid leukemia,* so many developing white cells may be present as to give the marrow a grayish tint. In exceptional cases this condition has been referred to as "pyoid" marrow. Ordinarily, however, the marrow is abundant, soft, and light red in color.

Microscopically, there is seen a great numerical increase in all stages of granulopoiesis. The greatest increase is usually in the neutrophilic cells, but eosinophiles are also found in abundance. Basophiles are usually increased, but the solubility of the granules makes it difficult to demonstrate them except in smears. All stages in the development of the cells are seen, including the nongranular "myeloblast." Megakaryocytes often share in the numerical increase, and form a conspicuous part of the picture. Erythropoiesis is ordinarily reduced but occasionally may be very active in spite of the presence of anemia.

In *acute myeloid leukemia,* also, the numerical increase in cells is observed, but often is less marked. In contrast to the varied cell types seen in the chronic cases, the great majority of cells are of the primitive type, and hence exhibit less morphologic variation. Myeloblasts (hemocytoblasts) are abundant, and the more mature granular myelocytes may be present in only small numbers. Red cell formation is often greatly reduced, and megakaryocytes are infrequent. Because of the morphologic similarity of myeloblasts and lymphocytes in sections, cell types are more readily identified from smear preparations (see blood picture of acute leukemia). When Auer bodies are present in the peripheral blood, they may also be found in the marrow smears, and in sections stained by azure-eosin or similar method.

In *chronic lymphatic leukemia* the marrow is nearly always involved. The infiltrations of lymphoid cells are secondary, however, and probably occur at relatively different stages in different cases. When involvement is extensive, the marrow is overrun with lymphoid cells that correspond morphologically with those in the peripheral blood and the other organs. Most of them are in intermediate or relatively late stages of development. In some cases, especially the "aleukemic" cases, the involvement of the marrow may not be uniform. Instead, poorly defined nodular accumulations of lymphoid cells may be observed.

In *acute lymphmatic leukemia* the condition of the marrow is similar to that in the acute myeloid form. The difference lies in the cell types; in the myeloid form the cells show some degree of differentiation into leukoblastic cells. Differentiation is often difficult, and may even be impossible in the acute cases with only "stem cells" (hemocytoblasts).

In *monocytic leukemia* the marrow contains numerous monocytes, monoblasts or monocyte-like cells. As noted under the description of the blood in this condition, the cell types are somewhat variable, particularly as to the degree of differentiation of the cells. In some cases the marrow is overrun with cells which, morphologically, are monocytes. Usually some earlier forms (monoblasts) are seen in association with them. In other cases the number of adult monocytes is less, and the monoblasts play a more conspicuous role. Primitive cells (hemocytoblasts) are also present in appreciable quantities. Be-

cause of the increased number of primitive cells and myelocytes, often the impression is obtained that a diagnosis of leukemia (myeloid) would be justified even if the monocytes were not present.

In infectious mononucleosis, most authors agree that no specific changes occur in the marrow. Cells similar to those in the peripheral blood may be found in smears of aspirated marrow, but their presence is usually attributed to admixture of blood. Schleicher,[355] however, found hypertrophy of the reticulum, with in situ development of ab-

and may be either focal or generalized in character. Both occur in association with a wide variety of conditions, including the leukemias, certain forms of anemia, bone diseases, bone metastases, poisoning, and irradiation, and have been produced experimentally by various procedures. (For summary and classification, see Herbut and Erf.[389]) The relation of myelofibrosis to myelosclerosis is obscure.

The variety of greatest interest is the generalized form occurring in the absence of any known causative factor (idiopathic primary generalized

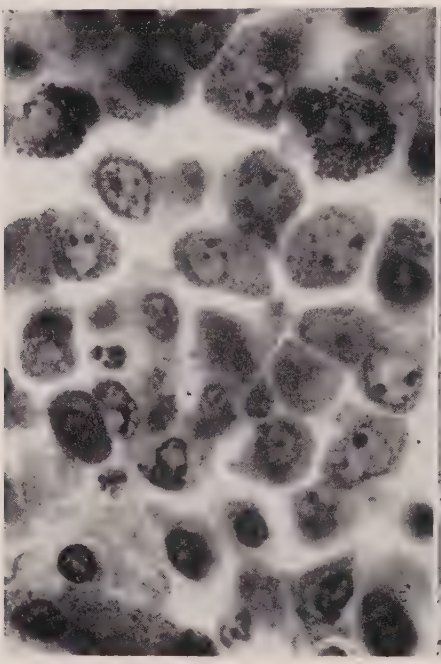


Fig. 793.

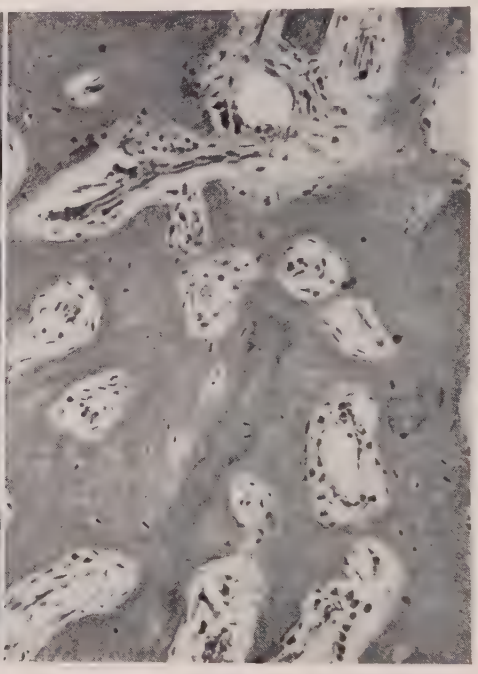


Fig. 794.

Fig. 793.—Myelocytic hyperplasia of bone marrow. Nearly all the cells shown are myelocytes. Those with large distinct granules are eosinophiles. The majority of the cells contain neutrophilic granules which, because of their small size, are relatively indistinct. Section stained with eosin-azure B-methylene blue.

Fig. 794.—Osteosclerosis of bone marrow. The encroachment on the marrow and replacement of its cells by trabeculae of bone result in severe anemia, usually with extramedullary blood formation.

normal lymphocytes, and the formation of reticuloendothelioid granulomas.

In acute disseminated lupus erythematosus, smears of the bone marrow may show mature neutrophilic leukocytes with ingested nuclear material ("LE" cells) (Fig. 795). These are more numerous if the marrow has been centrifuged and allowed to stand before the preparation of smears. Similar cells can be produced from bone marrow or blood cells of normal persons by contact with plasma from patients with lupus erythematosus. The ingested material is probably the same as the "hematoxylin-staining" bodies found in other tissues in this disease, and their production is apparently due to the activity of a substance in the gamma globulin fraction of plasma.

Fibrosis and Sclerosis of the Bone Marrow.—These conditions may occur singly or together,

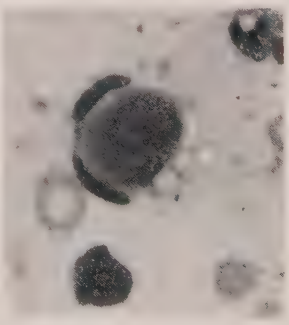
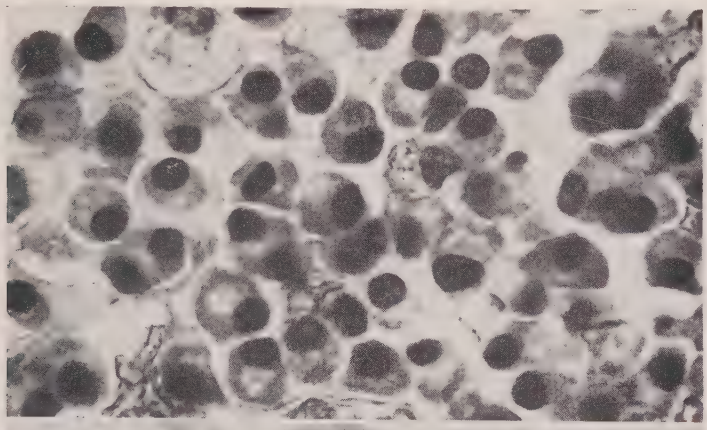


Fig. 795.—"LE" cell produced by incubating "normal" bone marrow in the plasma of a patient with lupus erythematosus. (×936.)

myelofibrosis or myelosclerosis). The marrow is replaced by fibrous connective tissue, or is encroached upon by thickening of the trabeculae of bone (Fig. 794). The reduction in the amount of functioning marrow results in low values of erythrocytes, leukocytes, and platelets in the blood, usually associated with the presence of occasional immature forms. In a few cases, the proportions of myelocytes and myeloblasts may be great enough to suggest a diagnosis of leukemia. The similarity to leukemia is emphasized by the frequent occurrence of extramedullary hematopoiesis. This is a compensatory phenomenon, and its extent apparently depends on the degree of encroachment on the functioning marrow. The most extensive extramedullary blood formation occurs in the spleen, which may be greatly enlarged and converted into an active blood-forming organ (see myeloid metaplasia of the spleen, page 929). In some cases myeloid metaplasia is so extensive that it is impossible to determine with certainty whether we are dealing with leukemia associated with osteosclerosis or myelofibrosis, or with marrow replacement with its resultant myeloid metaplasia. The terms "agnogenic myeloid metaplasia," "nonleukemic myelosis," "leukoerythroblastic anemia," while not always synonymous, apply to certain instances of these conditions.

In *Hodgkin's disease* bone marrow involvement is usually of the same type as that found in other affected organs. Accumulations of large mononuclear cells are present, probably derived from reticulum cells, associated with multinucleated and polymorphonuclear giant cells, eosinophiles, etc. Areas of necrosis are commonly found, and, in late stages, fibrosis. Such lesions are not often diffuse, but are irregularly dispersed in the marrow. The lesions in this disease are described under Lymph Nodes, in Chapter 32.

Fig. 796.



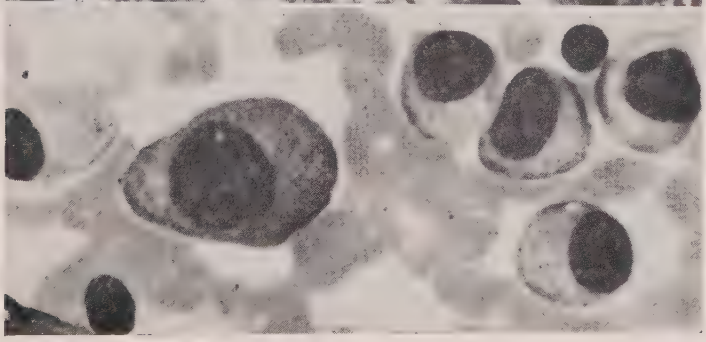


Fig. 797.

Fig. 796.—Plasma cell myeloma. Section of bone marrow.
Fig. 797.—Plasma cell myeloma. Smear of bone marrow.

Granulomatous inflammation of the bone marrow may occur in those conditions in which similar lesions occur elsewhere, such as miliary tuberculosis, Boeck's sarcoid, brucellosis. The lesions are of the same morphology as in other organs.

Tumors of the Bone Marrow

Primary Tumors.—*Leukemia* is properly regarded as a neoplasm, and the involvement of the marrow in this disease is the most frequent form of primary tumor. It

is discussed above. Tumors of bone (including Ewing's tumor) are described under the osseous system.

Multiple myeloma is a tumor arising in the bone marrow, especially in sites where red marrow is ordinarily found (vertebrae, ribs, skull, ends of the long bones). The nodules are usually multiple and their growth is usually accompanied by local absorption of bone, producing an x-ray picture that is easily recognized. Because of the bone absorption, spontaneous fractures are of common occurrence. (See also discussion on page 1241.)

ing reaction with basic dyes that is usually seen with plasma cells in inflammatory exudates. These cells are readily recognized in biopsies or aspirated marrow (Figs. 796 and 797). The older literature contains reference to "round cell" and lymphocytic myelomas, most of which were probably of the "plasma cell" type. Myelocytic myelomas have been described occasionally, and in a few instances the tumors seen are composed of many of the cell types seen in marrow. It is doubtful whether these should be included in the same category. Erythro-

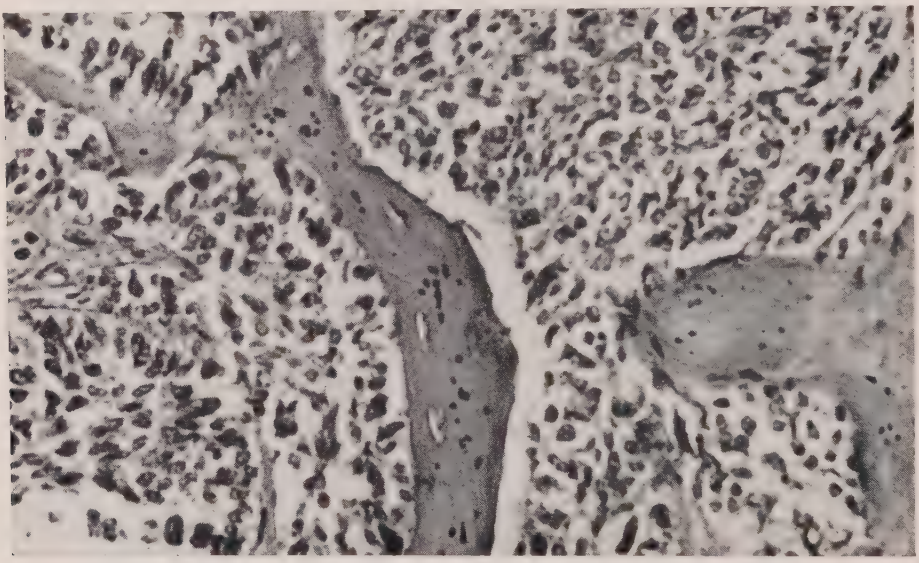


Fig. 798.—Secondary carcinoma of bone marrow, following carcinoma of cervix uteri. In the field shown, the blood-forming cells are completely replaced by tumor.

The nodules are usually soft, red, vascular masses, sometimes protruding through the cortex of bone. In occasional cases the growth of the tumor is diffuse rather than nodular (diffuse myelomatosis) and its nature may not be evident either on x-ray or gross anatomical examination.

Microscopically, practically all types of myeloma have cells that resemble plasma cells in that they have small, dark, eccentric nuclei with more or less radial arrangement or peripheral clumps of chromatin. Often a paranuclear clear zone is present. Occasional cells have two or more nuclei, but mitoses are extremely rare. The cytoplasm is moderately basophilic, but does not give the intense stain-

blastic myeloma has been described but rarely. Recently, cases have been reported in which the myeloma cells of the plasma cell type are associated with polymorphonuclear giant cells somewhat resembling megakaryocytes.

The histogenesis of the common plasma cell myeloma is not clear. Although plasma cells are commonly found in the bone marrow, the cells of myeloma do not exhibit all the tinctorial characteristics of inflammatory plasma cells, and may not be derived from them. It has been suggested that the myeloma cells develop from reticulum or reticulo-endothelial cells. If this is the case, the occurrence of the variants mentioned could be explained, as the reticulum cells are supposedly potential sources of cells of various types. Moreover, plasma cells pass through developmental stages during which the typical features of the adult cells are not present. Tumors composed of

cells in these developmental stages (plasmablasts and young plasma cells) show corresponding variations that are probably responsible for the diverse descriptions in the literature.

Two chemical findings associated with this tumor are of interest. In the majority of cases there is found in the urine at some time a globulin-like substance known as Bence-Jones protein. This substance coagulates at low temperature (40° to 60° C.), the coagulum dissolving when the solution is boiled, and reappearing when cooled to 60° C. The material is not present in normal bone marrow or urine. Kidneys excreting the material often contain tubular casts around which epithelial giant cells have formed (see Fig. 474, page 589). The second chemical characteristic is a change in the proportion of protein fractions in the blood. The globulin fraction (especially beta globulin) is greatly increased, and this change is of considerable diagnostic value because of the relatively few conditions in which it occurs. These abnormal proteins are probably formed in the plasma cells of the tumor. Snapper has shown that the administration of Stilbamidine to patients with plasma cell myeloma results in the appearance of basophilic granular aggregates in the cytoplasm of the cells. These granules contain ribose nucleic acid, presumably from the dissociation of protamine ribonucleate. This phenomenon has not been observed after similar therapy in other conditions.

Multiple myeloma is occasionally accompanied by the presence of myeloma cells in the peripheral blood, and accumulations of these cells in various organs. When such infiltrations are extensive, the picture is suggestive of leukemia. It is possible to arrange cases in series according to the extent of such infiltrations, beginning with cases showing localized multiple nodules without extramedullary tumor cells, and ending with those in which there is more or less diffuse infiltration, and tumor cells are present in the blood, resembling "plasma cell" leukemias. The series is not unlike that seen in the lymphosarcoma-lymphatic leukemic group.

Secondary Tumors of the Bone Marrow.—The most common secondary tumors are metastases from carcinomas, especially of the prostate, the breast, and the thyroid gland, hypernephroid carcinomas of the kidney, and neuroblastomas (sympathicoblastoma) of the adrenal glands. The deposits may be of microscopic size, but not infrequently they form nodules of tumor tissue (Fig. 798) that destroy the bony trabeculae and erode the cortex, and often result in fracture from comparatively slight trauma. Metastases occur in the red marrow, especially at sites where the nutrient vessels enter. The secondary deposits are hematogenous. The bones most frequently involved are vertebrae, ribs, pelvic bones, and femur.

Disturbances in blood formation with changes in the peripheral blood picture often accompany marrow metastases, although, with the exception of the leukemias and myelomas, the presence of tumor cells in the blood is exceedingly rare. The interference with blood formation may take the form of severe anemia which fails to respond to any form of therapy; there may be immature white cells in the blood in sufficient numbers to suggest leukemia; or a reduction in platelet formation may lead to hemorrhagic tendencies simulating thrombocytopenic purpura hemorrhagica.

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The Bone Marrow

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Anemia

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Pernicious and Related Anemias

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Aplasia and Hypoplasia

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346. Jaffe, R. H.: Arch. Path. **16**: 611, 1933 (agranulocytosis).
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Polycythemia

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Also see references 62 to 73 in Chapter 32.

Chapter 32

THE SPLEEN, LYMPH NODES, AND RETICULO-ENDOTHELIAL SYSTEM

MAURICE N. RICHTER

THE SPLEEN

Normal Structure and Function

The spleen is generally regarded as a lymphoid organ, and, as such, comprises the largest single collection of lymphocytes and reticulo-endothelial cells in the body. It is situated in the blood vascular, rather than the lymphatic system. Its vascular structure is peculiar in that it permits an unusual degree of dilatation (and thus of swelling of the organ) and a close association of circulating cells with the cells of the pulp.

The capsule of the spleen is a thin membrane composed of connective tissue with elastic fibers, the outer surface of which is peritoneum. From the capsule, trabeculae traverse the organ and form a framework within which is the splenic pulp. The trabeculae are composed of connective tissue with elastic fibers and occasional smooth muscle cells.

The pulp of the spleen is composed of two portions. The "white pulp" consists of lymphatic tissue so disposed as to form a sheathlike covering around the arteries. The "red pulp" is the tissue surrounding the venous sinuses (sinusoids) and is often referred to merely as the "pulp."

The arterial branches pass along the trabeculae until they reach a diameter of about 0.2 mm., when they pass into the pulp and become surrounded by the lymphatic sheath. This lymphatic tissue forms aggregates (lymph follicles, often called Malpighian corpuscles) with central areas composed of developing lymphocytes ("germinal centers") or of reticulum cells and cellular debris ("reaction centers"), as in lymph nodes. Along the smaller branches, the arteries have a sheath of compact reticulum cells ("sheathed arteries" of Schweigger-Seidel), which are not prominent in the human spleen, and then form short straight vessels (penicilli) which do not anastomose. These smaller vessels have only a thin layer of lymphoid cells surrounding them.

The manner of communication between the smallest arterial branches and the veins is unknown. The venous system begins with an extensive network of wide, distensible sinuses separating the red pulp which surrounds them. The sinus endothelium differs from that of ordinary veins because its cells are phagocytic, they are part of the reticulo-endothelial system, and their cytoplasmic processes are connected with those of the reticulum cells of the surrounding pulp. The lining cells are arranged longitudinally. Outside these cells, reticulum fibers are circularly arranged, forming latticelike bands which are best demonstrated by silver staining methods.

A disputed question is whether the spaces between the lining cells and fibers are closed by a cytoplasmic membrane or whether spaces remain through which cells can enter the pulp. This problem has been studied by several methods, including various staining techniques, perfusion, injection of foreign substances and alien blood cells, and by direct observation. Of the various methods used to study this problem, the most interesting is that of Knisely,[6] who transilluminated the spleen in living small mammals and described closed connections between the terminal arteries and the venous sinuses. MacKenzie and co-workers,[10] using the same method, were unable to confirm these findings, and found the capillaries communicating directly with the pulp spaces. The circulation through the pulp spaces is intermittent, and variable both in the amount of blood contained and in the relative amount of cells and plasma. With distention of the pulp spaces, the concentration of cells becomes greater. It is in the pulp spaces, therefore, that the blood cells come into intimate contact with tissue phagocytes, and there destruction of the blood cells and elaboration of the products derived therefrom take place.

The pulp spaces contain, also, various other cells, including fixed and motile macrophages and lymphocytes, as well as the leukocytes, plasma cells, and other forms that are normally present in small numbers, but are increased in inflammatory and other reactive conditions.

Lymphatic vessels are found in the capsule and along some of the trabeculae. They do not appear in the pulp.

The functions of the spleen are related principally to its content of lymphocytes and of reticulo-endothelial cells, and to its distensible sinuses and pulp spaces, which act as temporary storage sites for blood. With the exception of storage the functions of the spleen are therefore similar to those of the lymph nodes and the reticulo-endothelial system. It is of interest, however, that following removal of the spleen its functions are taken over by other organs, with no lasting ill effects. The results of splenectomy are most evident in those cases in which one of the pathologic activities of the spleen (usually that related to blood destruction) has been excessive.

The formation of lymphocytes is an important function. It varies with the same conditions that cause variations in lymphocyte formation in the nodes, and is probably related to the production of antibodies.

The phagocytic activity of the *reticulo-endothelial* system in the spleen is evidenced by the presence of various substances in phagocytic cells. Hemosiderin and malarial pigments, ingested erythrocytes, bacteria, parasites, and lipid material are examples.

Phagocytosis may not be the only mechanism by which destruction of blood elements is accomplished, even though the spleen is the principal site at which it occurs; nor is it entirely clear that an increase in the circulating blood elements following splenectomy necessarily indicates that splenic destruction of blood cells was excessive. Nevertheless, cases have been described in which, following splenectomy, all the cellular elements of the blood (erythrocytes, leukocytes, and platelets) have been increased and the patient's condition correspondingly improved, whatever part the spleen may have played in the reduction of the cells. The supposed excessive splenic activity in these cases is referred to as "hypersplenism," q.v.

The reticulo-endothelial cells also play a part in the elaboration of certain metabolic products (kerasin, sphingomyelin) which, under normal conditions, are transported to other parts of the body without accumulating in the reticulum cells. In certain diseases, however (Gaucher's and Niemann-Pick's diseases) failure of mobilization results in the accumulation of these substances in cells of the spleen, as in other parts of the reticulo-endothelial system.

The probability of a depressing action of the spleen on marrow functions is still under discussion, as is the occurrence of hemolytic substances in the blood serum.

Congenital Anomalies

Congenital absence of the spleen has been reported in rare instances. It is possible that some of these were cases of extreme atrophy of the spleen such as might occur in sickle cell disease, rather than congenital absence. Of greater significance is the presence of accessory spleens which have the same structure and function as that of the main spleen, and may enlarge when the latter is removed. When splenectomy is performed for the purpose of eliminating the spleen as a functioning organ (in contrast to its removal for traumatic rupture), the objective is not attained unless accessory spleens are removed at the same time. Pathologic alterations in the spleen resulting from systemic conditions are generally found also in accessory spleens.

Regressive Changes

Hyaline degeneration in the walls of the central arterioles is a common finding. The change is especially prevalent in the older age group, and in cases of hypertension.

Amyloid is deposited in the spleen under the same conditions as in other organs, and is therefore found mainly when these deposits occur in other sites. In systemic diseases the spleen is the organ most frequently involved.

The spleen is often enlarged, but the increase in size is variable, depending on the degree of involvement. In cases with only slight amyloid deposits, the size of the organ may be within normal limits. Two types of involvement are generally recognized, one in which amyloid is deposited in the follicles, the other in which involvement of the spleen is more diffuse. In the former type the involved follicles are prominent on the cut surface, their waxy and translucent appearance suggesting sago grains; hence, the term "sago spleen" has been applied to this form. With more diffuse involvement, the spleen is firm and the edges rounded. In this type of case the spleen is ordinarily larger, weights up to 400 or 500 grams often being encountered. The cut surface is uniform, without recognizable follicles, and has a characteristic translucent, waxy appearance.

Microscopically, the amyloid has the same appearance as in other organs and is demonstrated by the same staining methods (methyl violet, iodine green, iodine, etc.). When the amount of amyloid is small, its location just beneath the endothelium of the arterioles and sinusoids is readily demonstrated. In advanced cases, however, the deposits are large, often nodular, and the disruption of splenic structure makes it difficult to detect this relationship. As mentioned above, the amyloid may be limited to the follicles, or diffusely deposited in the pulp, or it may involve both structures. Not infrequently, lipid deposits are associated with the amyloid, and can be demonstrated by the usual stains for fats.

Focal necroses are often the result of systemic infections. They are of microscopic size, and usually consist of areas of necrosis associated with collections of polymorphonuclear neutrophiles. As a rule, these are found in the pulp, but necrosis of the follicles is sometimes seen in systemic infections.

Multiple necroses of larger size also occur, giving to the cut surface the characteristic picture of numerous yellowish and whitish areas of necrosis of varied sizes and irregular shapes (Fig. 799). These occur under a variety of circumstances, with and without vascular occlusion. The latter type was first described as a terminal event in uremia by Feitis,[17] who introduced the term "Fleckmilz." Since that time, "Fleckmilz" has been indiscriminately, and perhaps erroneously, applied to cases of multiple splenic necrosis of any etiology.

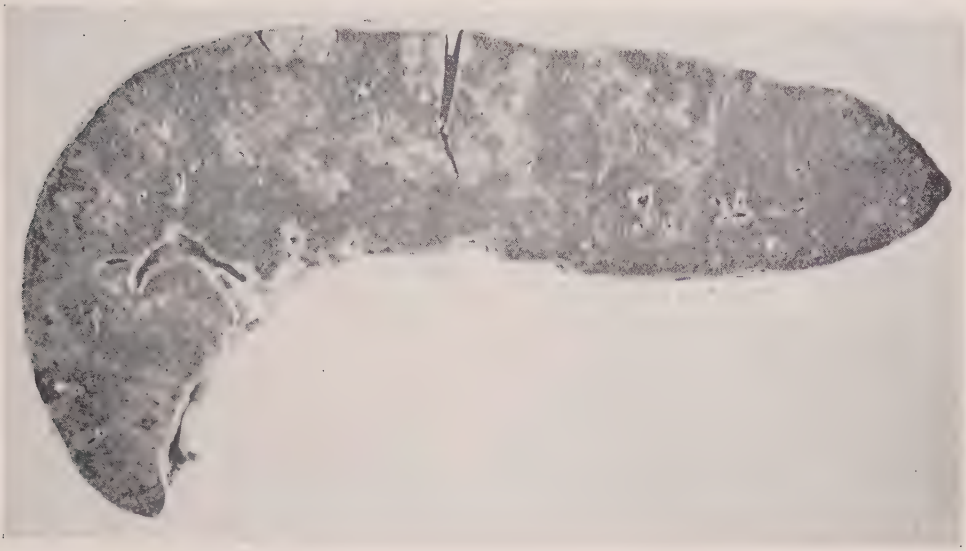


Fig. 799.—Multiple necroses of the spleen. ("Fleckmilz" of Feitis.)

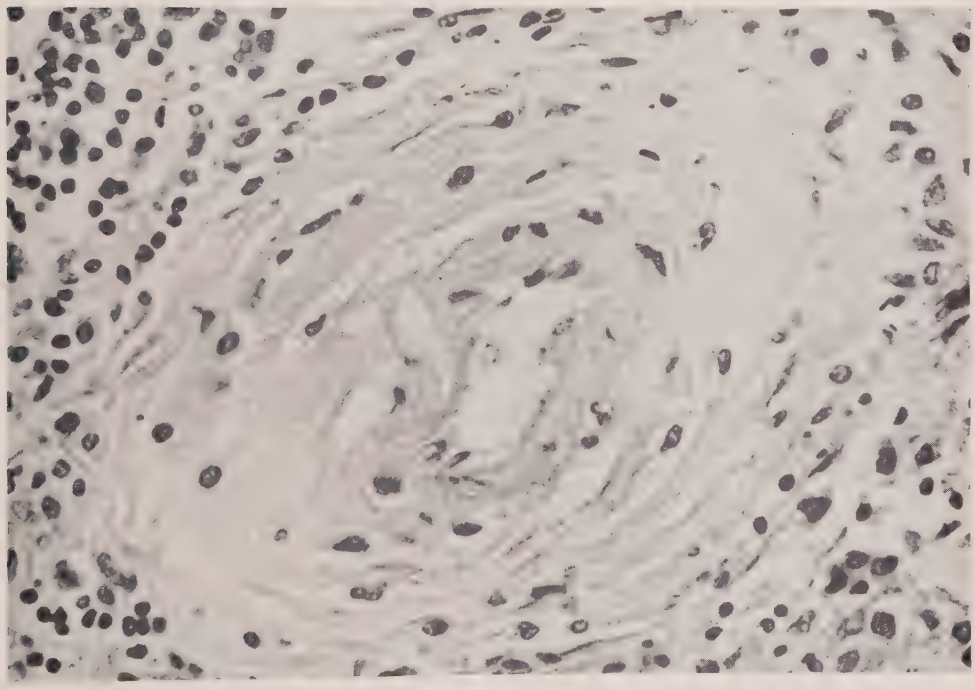


Fig. 800.—Periarterial fibrosis of the spleen in lupus erythematosus. The collagen fibers form concentric strands around the central arteriole of the follicle.

Atrophy of the spleen occurs in the aged, in wasting diseases, and as the result of scarring following the hemorrhages of sickle cell disease.

The alteration in the collagenous connective tissue that occurs in lupus erythematosus is a diffuse change and sometimes results in changes in the spleen. There is fibrosis around the central arteries of the lymph follicles, with the formation of more or less concentric layers of collagen fibers around the vessels (Fig. 800). The fibrosis is presumably the result of previous alterative changes of a degenerative or inflammatory nature.

Pigmentation

The most common pigment in the spleen is hemosiderin. It can be found in minute amounts in nearly all spleens, and is increased in the presence of hemolytic processes. In hemochromatosis, pernicious anemia, sickle cell disease, and other anemias the amount of pigment may be considerable. It is ordinarily found in phagocytic cells in the pulp, but occasionally impregnates reticulum fibers or the "Gitterfasern" of the sinusoids. In hemochromatosis it may be accompanied by hemofuscin. Hematoidin may occasionally be found in areas of hemorrhage or infarction.

Malarial pigment is also found in phagocytic pulp cells.

Anthracotic pigment is of occasional occurrence.

Rupture

Rupture of the spleen occurs as the result of trauma, although in some instances the trauma is so slight that the rupture is considered "spontaneous." In such cases there is an underlying pathologic condition (malaria, typhoid fever, leukemia, cysts, etc.), usually accompanied by enlargement of the spleen. An interesting but rare sequel to rupture is autoplastic implantation of splenic tissue in the peritoneum, with subsequent development of numerous small peritoneal implants of splenic tissue.

The Spleen in Circulatory Disturbances

Disturbances of the Systemic Circulation

Active hyperemia is of common occurrence in acute infections, and is a part of the associated "acute splenitis" ("acute splenic tumor").

Passive hyperemia is caused by interference with the venous return through the portal circulation. This may be due to a general increase in systemic venous pressure such as occurs in cardiac decompensation, or to changes in the portal circulation alone. In the latter case the increased pressure within the spleen causes dilatation of the collateral vessels. The result is the type of splenomegaly seen in Banti's syndrome, and is described under that heading.

In passive hyperemia accompanying cardiac disease, there is slight or moderate enlargement of the spleen, which is resilient or of a "rubbery" consistency. The cut surface is dark red, and traversed by thickened trabeculae. The sinuses are engorged with blood. In long-standing cases there is an increase in connective tissue of the pulp and trabeculae, with atrophy of the lymphoid tissue. In spite of the large amount of blood in the organ, hemosiderin deposition is not ordinarily increased, except in those cases in which there is active inflammatory disease of the valves.

Hemorrhages into the splenic substance are sometimes found in acute infections. They are more commonly seen in splenomegaly associated with portal hypertension (Banti's syndrome), where they appear as small, brown spots ("tobacco nodules") on the cut surface of the spleen.

Infarction is due to occlusion of the splenic artery or its branches by thrombosis or embolism. Arterial thrombi follow the extension of inflammatory processes to the walls of the splenic vessels, and occur also in leukemia. Emboli are most commonly the result of heart disease, either with mural thrombi in the cavities or vegetations on the valves of the left side of the heart. The infarcts are conical in shape, as they correspond to the distribution of the occluded vessel. They are grayish or whitish areas with hemorrhagic peripheral portions. In the central portions the tissue is necrotic, with absence of nuclear staining. In later stages the necrotic tissue is removed and replaced by fibrous connective tissue. If the embolus contains bacteria, the infarct may undergo rapid softening and suppuration ("septic infarct").

Disturbances of the Portal Circulation

Splenomegaly Due to Portal Congestion.—When congestion occurs as a result of disturbances in the portal circulation, the enlargement of the spleen is often accompanied by changes that were first recognized by Banti, and have since

been considered part of the syndrome that bears his name. These changes are: splenomegaly, anemia, and ascites, and often leukopenia and hemorrhage from esophageal veins.

As originally described by Banti, this syndrome begins with enlargement of the spleen and anemia (the term "splenic anemia" was formerly applied to this stage), followed by cirrhosis of the liver and ascites. This sequence was explained by Banti as being the result of an infectious process in the spleen and splenic vein, with subsequent involvement of the liver.

Later work has shown that a variety of pathologic changes may be associated with the clinical features described by Banti. These include: cirrhosis of the liver, thrombosis of the splenic vein, schistosomiasis, cavernomatous transformation of the portal vein, aneurysm of the splenic artery. Rousselot and Thompson[52] produced the condition in dogs by injecting minute particles of silicon dioxide into the splenic vein. Cirrhosis of the liver developed, and, when this reached a sufficiently advanced stage, there was increased splenic vein pressure, and splenomegaly. These conditions are probably to be considered causative factors, rather than results of the splenic lesions. Thus, although Banti described cases in which cirrhosis was the terminal event, it is probable that when cirrhosis and splenomegaly are associated, the cirrhosis is the antecedent condition, though often unrecognized. The single feature common to all is the interference with the venous return through the portal circulation, with consequent increase in splenic vein pressure. That increased pressure does occur has been demonstrated by actual measurement. The resultant increase in venous pressure within the spleen and, probably, a reversal of blood flow in the splenic vein cause dilatation of the collateral venous channels in the gastrosplenic ligament, the diaphragm, the esophagus, and the stomach. Hemorrhages from the dilated esophageal varices are common, recurring often, and are frequently the cause of death. It is apparently the difference in pressure between the two venous circulations that accounts for the differences between the splenic and vascular changes in portal congestion and those in cardiac congestion.

The explanation is not entirely satisfactory for all cases, however. Although an "obstructive factor" is seen in many cases, there are a considerable number in which an anatomical obstruction cannot be demonstrated. The difficulty of interpreting all cases on the basis of splenic vein hypertension is evident from Ravenna's[49] review, although it is not clear that in all cases the splenomegaly is primary, as he suggests.

Splenectomy has not been uniformly beneficial in this condition. It cannot be relied on to give permanent relief of symptoms or to prevent the occurrence or decrease the frequency of bleeding from esophageal varices.

Recent studies indicate that the occurrence of esophageal varices and the results of splenectomy depend in part on the site of obstruction in relation to the point at which the coronary vein enters the portal or splenic vein. If the obstruction is distal to this point of entry, esophageal varices will not result, and splenomegaly may be beneficial. If the site of entry is distal to the obstruction, esophageal varices may result, and would not be influenced by removal of the spleen. In such cases anastomosis of the portal vein to the vena cava, or the splenic to the renal vein, provides a way for the blood to by-pass the obstruction, and may relieve the back pressure.

Gross Changes.—The degree of splenic enlargement in portal congestion is variable. Enormous spleens are occasionally found, although weights of over 6,000 grams are uncommon. More often the weight is between 500 and 1,000 grams. The organ is firm, and the cut surface does not ordinarily bulge above the capsule. The color of the cut surface varies from deep red to salmon color, and the expression "meaty" is often applied to its appearance. The Malpighian corpuscles are less distinct than usual but the trabeculae are prominent. It is common to find small, punctate, brown spots on the cut surface, the so-called "tobacco nodules" or "Gamna-Gandy nodules" (Fig. 801). They represent deposits of iron salts in areas of hemorrhage, and are described under the microscopic features. The splenic vein is dilated and tortuous, and there may be sclerotic changes in its wall.

The splenic capsule is irregularly thickened, and frequently adhesions to the diaphragm and neighboring structures are seen.

Microscopic Changes.—Microscopically, the malpighian corpuscles are atrophic, and often without "germinal centers." The sinuses of the pulp are prominent, apparently increased in number ("sinus hyperplasia"), and a few are dilated (Fig. 802). An occasional megakaryocyte may be found in their lumina. An increase of reticulum fibers, especially in the pulp, results in "fibrosis," more prominent in long-standing cases.

Fig. 801.—Cut surface of the spleen in portal congestion (Banti's syndrome). The trabeculae are more prominent than usual. The dark spot near the capsule in the upper part of the photograph is a siderotic nodule (so-called "Gamna-Gandy body").

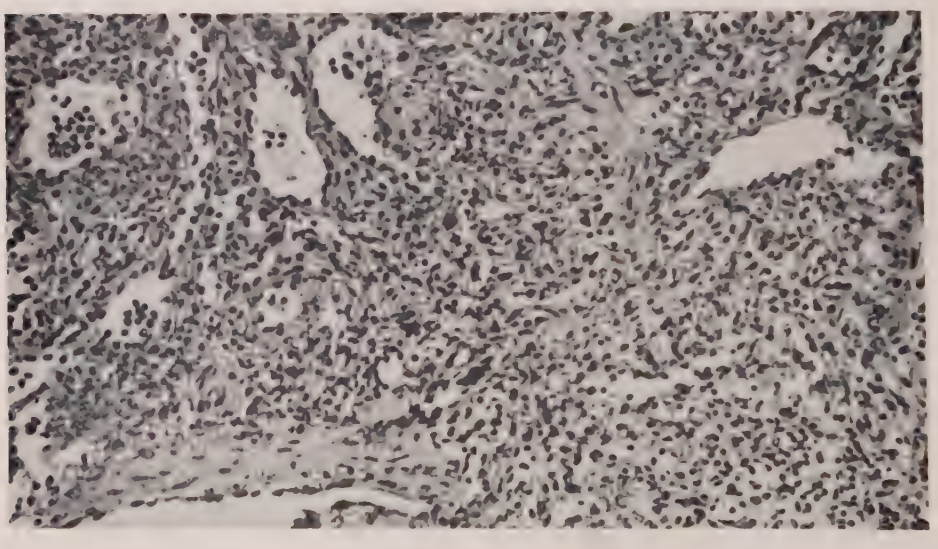
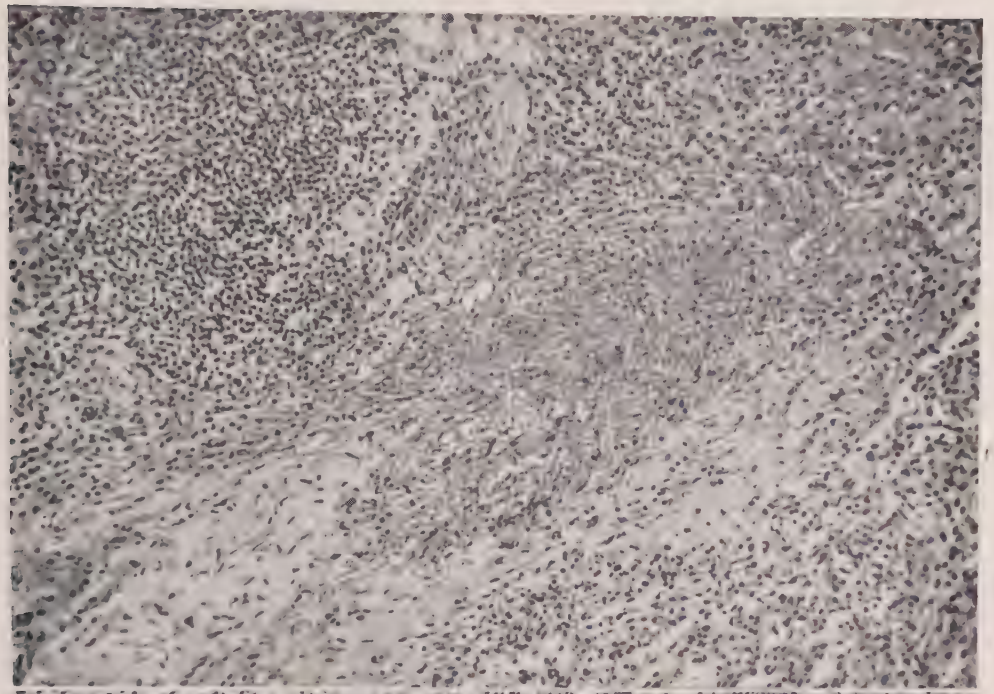


Fig. 802.—Section of spleen in portal congestion (Banti's syndrome). There is fibrosis of the pulp with enlarged and irregularly shaped sinusoids.

Fig. 803.



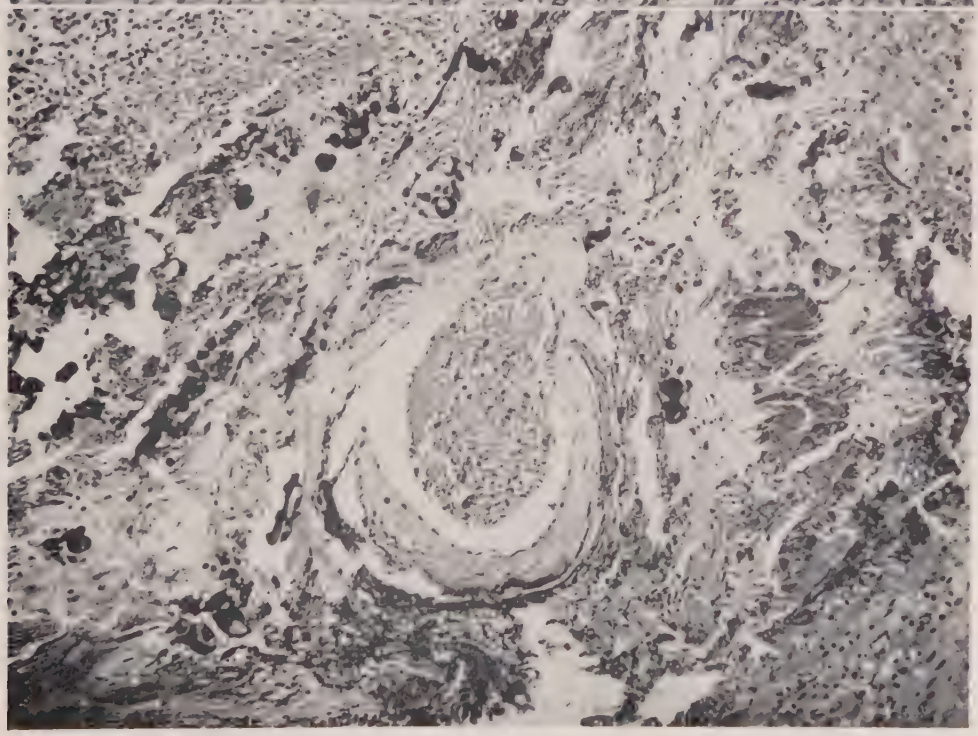


Fig. 804.

Fig. 803.—Section of spleen in portal congestion (Banti's syndrome). Note the hemorrhage in the center of the photomicrograph, at the peripheral portion of a follicle. This is the first stage in the formation of a siderotic nodule.

Fig. 804.—Section of spleen in portal congestion (Banti's syndrome). A siderotic nodule (Gamna-Gandy body) with deposits of iron and calcium on the collagen fibers.

Hemorrhage occurs in and around the follicles, and along the trabeculae (Fig. 803). The subsequent organization of these hemorrhages is accompanied by the deposition of iron and calcium salts, which become encrusted on connective tissue and elastic fibers. The result is the "Gamna-Gandy nodule" described above. The encrusted fibers are swollen, highly refractile, light green, and bear a superficial resemblance to mycelia, for which they have been mistaken. (Fig. 804.)

The features described may be modified in degree, especially by the duration of the portal stasis. They are apparently not modified to any appreciable extent by the cause of the stasis.

The Spleen in Systemic Infections

Enlargement of the spleen is a common occurrence in acute systemic infections. The nature of the circulation in the spleen is such that blood passing through it is brought into intimate contact with the pulp cells. Many of the latter are phagocytic, and capable of ingesting bacteria as well as necrotic cells and tissues. The reaction of the spleen to bacterial and toxic substances in the blood is similar to that of the lymph nodes to similar substances brought to them by the lymph. Bacteria and their products are not the only substances that may cause splenic swelling of this type. Rich[32] has shown that in experimental animals, injection of foreign protein may give rise to an acute swelling of the spleen with formation of cells of the types found in acute splenic tumors of bacterial origin. The reaction of the spleen includes dilatation and engorgement of the sinuses, increase in number and variations in type of the pulp cells, and necrosis of cells in follicles and pulp. The degree of these changes is varied.

Ordinarily, in reaction to generalized acute infections (septicemia, pneumonia, etc.) the spleen is moderately enlarged and soft ("acute splenic tumor"; "acute splenitis"; "acute splenic hyperplasia"; "septic spleen"). The cut surface appears as soft red or grayish-red pulp in which structural characteristics may be obscured. The consistency is sometimes so changed as to be "mushy" or diffluent, and the pulp bulges over the cut surface of the capsule. This change is more common in septicemia than in other infections.

Microscopically, the congestion is accompanied by an increase of cells in the pulp. Many of these are neutrophilic leukocytes, some of which undergo necrosis. The resulting liberation of ferments is probably responsible in part for the softening of the organ. Accumulations of leukocytes may be seen in the pulp, as well as increased numbers in the sinuses. Neutrophilic myelocytes are often present, but only in small numbers. Leukocytes, however, are not the only important cells present; in some cases they may be inconspicuous. Rich[33] has described mononuclear cells of lymphoid type, identified and differentiated from other pulp cells by a characteristic mode of locomotion in tissue cultures. Phagocytic mononuclear cells containing ingested erythrocytes, bacteria, or necrotic leukocytes are often found. Plasma cells are of common occurrence. As a rule, the follicles are atrophic, and their borders indistinct, but in some cases, especially in sepsis, they may have necrotic centers ("reaction centers"). The number and types of cells vary in different cases, so that different histologic pictures may be present in cases with the same gross features.

In *typhoid fever* the enlargement of the spleen is considerable, and the weight may reach 500 grams. The organ is soft but not diffluent, and is usually red because of congestion. Leukocytosis in the spleen is not generally an accompaniment of typhoid fever, and the grayish appearance caused by leukocytes is therefore less marked than in sepsis from other causes. Mononuclear cells are numerous, however. Focal areas of necrosis are commonly seen in the pulp, sometimes surrounding groups of bacteria.

In *streptococcus septicemia* the softness and flabbiness of the spleen is extreme, and the pulp is easily scraped from the bulging surface. Some of the subacute forms of bacterial infection (subacute bacterial endocarditis, for example) are commonly accompanied by marked splenic enlargement. In such cases the pulp of the spleen is cellular, but the cell types include more lymphoid cells than polymorphonuclear leukocytes, with plasma cells and other mononuclear forms in predominating numbers. In subacute bacterial endocarditis, infarction of the spleen is common, and the infarcts are likely to be infected.

Infectious Mononucleosis

Changes in the spleen have been described in only a few instances. Smith and Custer[35] have described the alterations in seven cases in which rupture occurred. The spleens were enlarged to three or four times the normal size. The rupture occurred during the third or fourth week of the disease. They found it possible to recognize the presence of the disease by the following changes: large numbers of atypical lymphocytes, similar to the cells seen in lymph nodes, are distributed diffusely throughout the pulp and are clumped in sinusoids; follicles are reduced in number and in size, and are usually without germinal centers; lymphoid cells infiltrate the capsule, the trabeculae, the adventitia of arteries, and the subintimal zones of various sinuses and veins. Infiltration and edema of the capsule and trabeculae result in spreading of the fibers and structural weakening of the organ, and explain the occurrence of rupture after trivial injuries. The cellular infiltration around the small arteries separates them from the surrounding trabecular connective tissue.

Chronic Granulomatous Inflammation of the Spleen

The spleen may be the site of chronic granulomatous processes similar to those commonly found in other organs, in the presence of tuberculosis or syphilis, or other less well-known inflammatory diseases the nature of which is obscure.

Tuberculosis.—In acute miliary tuberculosis the spleen is commonly involved. Enlargement of the organ may be only slight. Ordinarily, miliary tubercles can be seen through the capsule, and sometimes on the serosal surface. On the cut surface the tubercles are numerous and approximately the same size as the follicles, so that it may be difficult to differentiate between them. Ordinarily the tubercles are more sharply outlined and of a grayer color. In subacute forms the tubercles are larger, and of conglomerate type. The enlargement of the spleen is greater, and caseation of the tubercles may be evident grossly.

In chronic nonmiliary tuberculosis, involvement of the spleen is less frequent, and the number of tubercles may be small. Sometimes only single tubercles of large size ("tuberculomas") are present; at other times small, firm, fibrous or calcified nodules, representing healed tubercles are seen. Sometimes the spleen is greatly enlarged, the splenomegaly being the principal clinical symptom of the tuberculous process.

Fig. 805.

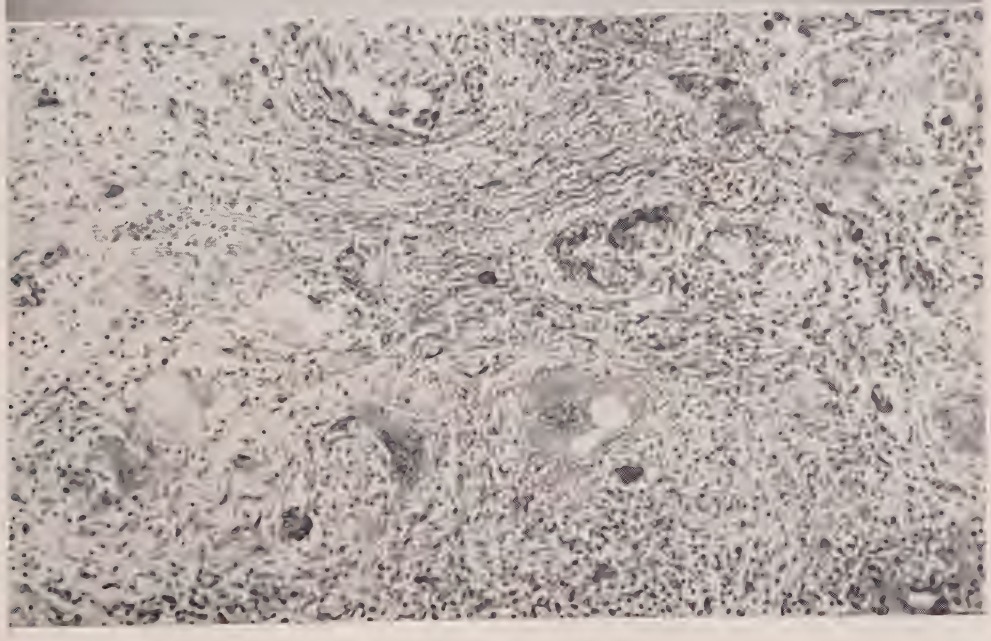


Fig. 806.

Fig. 805.—Chronic granulomatous inflammation of the spleen, probably Boeck's sarcoid. The histologic appearance in shown in Fig. 806.

Fig. 806.—Histologic structure of the granulomatous nodules in the spleen shown in Fig. 805. Note the tubercle-like arrangement, with giant cells and fibrosis.

The microscopic picture corresponds to the stage of development of the tubercles, and is similar to that seen in tuberculous inflammation in other organs. In the miliary forms the tubercles are found scattered throughout the spleen, mostly in the pulp, but occasionally also in the follicles. Larger tubercles are found in the pulp only.

The spleen is often involved in generalized sarcoidosis of Boeck and its enlargement may be the most conspicuous clinical feature, even to the point of suggesting splenomegaly due to portal hypertension. There are nodules of various size having the general appearance of tubercles, but without caseation. Histologically, the lesions are usually the same as those in other organs.

In rare instances, however, there are large nodules in which the histologic picture is altered by extensive fibrosis. Kay[28] reported 4 such cases, one of which (Figs. 805 and 806) was included in the first edition of this work under the heading "chronic granulomatous inflammation of the spleen of undetermined cause." This patient died 5 years after splenectomy, with lesions of sarcoidosis in the lungs, lymph nodes, and kidneys. In some cases the duration is much longer. (See also page 670.)

Syphilis.—The spleen is involved in both congenital and acquired forms of the disease. In congenital syphilis, splenic enlargement is due to cellular hyperplasia, with numerous macrophages containing ingested red cells and hemosiderin in the sinuses. Plasma cells may be numerous, and leukocytes may be increased in number. There may also be congestion and increase in fibrous tissue as a result of liver involvement. Spirochetes are numerous and usually may be easily demonstrated. Gummas are rarely observed.

In acquired syphilis, splenic enlargement in the secondary stage has been little studied. It is probably in the nature of a chronic cellular hyperplasia. In tertiary syphilis, enlargement is not common but in certain cases there may be a considerable degree of enlargement. Some of these splenomegalies are due rather to an accompanying syphilitic involvement of the liver than to syphilitic processes in the spleen itself, and therefore present some of the features of Banti's syndrome. The presence of gummas is rare, though occasionally solitary gummas of considerable size are found.

Brucellosis.—Moderate enlargement of the spleen is common in this condition. Histologically the lesions resemble those of the lymph nodes and are found in various parts of the pulp. If the lesions occur near the follicles, the latter are involved in the granulomatous process. In some instances the wall of the splenic vein, or of its tributaries within the spleen, is involved, with the formation of intimal granulomas.

The Spleen in Parasitic Diseases

In the acute stages of *malaria* the attacks of fever are accompanied by enlargement of the spleen, due mainly to congestion, and to accumulations of parasites in the pulp. In chronic cases there is a progressive increase in fibrous connective tissue. In acute malaria the spleen is soft and the degree of enlargement comparatively slight, while in chronic malaria the organ may be enormously enlarged (weights of over 6,000 grams have been recorded) and firm. This is the so-called "ague cake" common in tropical countries. Because of the deposition of malarial pigment, the cut surface has a distinctive color usually described as slate-gray. (See also page 374.)

Malarial parasites and the pigment formed by them (hematin) are found in the red cells, in the sinus endothelium, and in phagocytic pulp cells. The amount of pigment increases with the duration of the infection. Ash and Spitz[23] note that its first appearance is in the form of single grains, which later form amorphous masses in macrophages and occur free in the pulp. Dilatation of the sinuses may be a conspicuous feature.

The malarial spleen is peculiarly susceptible to rupture, from even comparatively slight trauma.

Leishmaniasis (kala-azar) is caused by *Leishmania donovani,* which are found in large numbers in reticulo-endothelial cells. The splenic enlargement in this disease is progressive, and in cases of long standing may be very great. An increase in connective tissue also occurs in chronic cases. The capsule is thickened, large numbers of phagocytic cells are present, especially in the pulp and sinuses, and within these are the parasites, sometimes closely packed in the cytoplasm. Areas of necrosis are common. (See also page 368.)

In *schistosomiasis,* parasites are only rarely found in the spleen, but the organ is usually enlarged due to cirrhotic changes in the liver caused by the parasites. The clinical features and splenic changes may therefore be similar to those in other forms of splenomegaly due to portal hypertension (Banti's syndrome).

Certain *mycotic infections* may involve the spleen. When they are of systemic distribution, the organisms and the lesions caused by them have the same appearance in the spleen as in other organs. These infections are described in detail in Chapter 15.

The Spleen in Diseases of the Blood

The relation of the spleen to the formation and destruction of blood cells has been discussed. Splenic changes have been described in diseases involving all the cellular elements of the blood, the red cells, white cells, and platelets.

Conditions Affecting Principally the Erythrocytes

Splenomegaly is not uncommon in certain types of *anemia.* It is one of the characteristic features of **spherocytic anemia** (hemolytic jaundice, see page 875). In the congenital type, weights of 500 to 1,000 grams are not uncommon. The size of the organ, however, is likely to change during the course of the dis-

ease, becoming larger during exacerbations and decreasing during periods of improvement.

On gross examination, the most conspicuous feature is the deep red, almost purple color of the organ, especially of the cut surface. This color is due to the large amount of contained blood. The capsule is ordinarily smooth, and is seldom thickened or adherent to surrounding structures. *Microscopically,* the condition is usually readily recognized (Fig. 807). The most prominent features are: increased amount of blood in the pulp and sinuses, increased prominence of the sinus walls, normal size of the follicles, and absence or a relatively small amount of blood pigment deposition. The increased amount of blood results in filling of the pulp spaces and consequent separation of the sinuses by large numbers of erythrocytes. The amount of blood within the sinuses may vary in a surgically removed spleen, according to the method of removal. The walls of the sinuses are usually prominent because of swelling of their lining cells, which, together with dilatation of the sinuses, sometimes gives a false impression, under low magnification, of epithelium-lined, glandlike spaces. The follicles, although of normal size, are widely separated because of the large amount of blood in the pulp. Small hemorrhages in the pulp are occasionally seen.

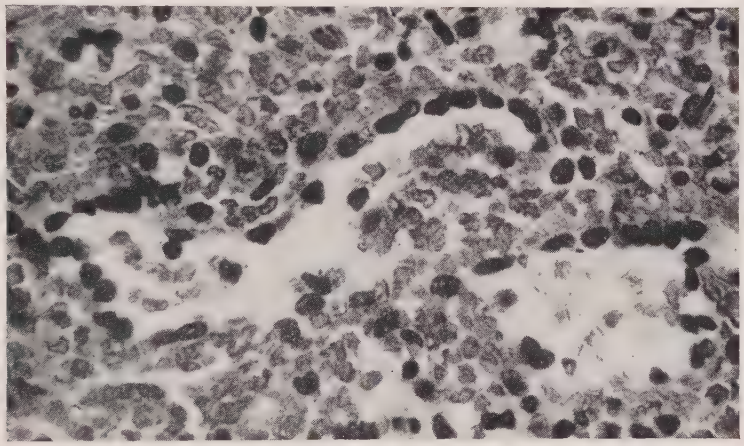


Fig. 807.—Section of spleen in spherocytic anemia (hemolytic jaundice). Note the prominent nuclei in the endothelial cells lining the sinusoids, and the many erythrocytes in the pulp spaces between the sinusoids.

The importance of the spleen in the development of spherocytic anemia is evident, from the constancy with which splenomegaly occurs, the variations in size of the spleen with changes in the degree of anemia, and the usually prompt improvement in the patient's condition after splenectomy. As noted under Diseases of the Blood, spherocytic anemia is of the "hemolytic type," that is, it is associated with an increased rate of destruction of red cells within the body. Whether this is due to an increase in the physiologic activity of the spleen (hypersplenism) in removing abnormal (spherical) cells from the circulation and initiating the breakdown of the hemoglobin by destruction of the cells, or to the action of a hemolytic agent on normal cells, is not known. In either case, however, it is of interest to note that deposition of iron-containing pigments in the spleen is not a constant feature, as is the case in many other hemolytic syndromes, but may occur only during exacerbations of the hemolytic process. Ordinarily, little or no iron-containing pigment is demonstrated by the Prussian blue or Turnbull blue reactions on tissue sections, with the exception of focal collections that occur in organizing hemorrhages. Of interest also is the fact that extramedullary blood formation is not commonly found in the splenic pulp.

If accessory spleens are present their histologic features are the same as those of the main spleen. Frequently, after splenectomy, these accessory spleens enlarge and take over the functions of the spleen to such an extent that the therapeutic value of splenectomy is lost. In several instances, failure of splenectomy to relieve the anemia has been associated with the presence of accessory spleens, and in a few cases a second operation for the removal of the accessory spleens has been necessary.

In acquired hemolytic anemia (see page 880), the changes in the spleen are varied. The organ is enlarged and the pulp engorged as in the congenital type, but prominence of the sinuses and swelling of sinus endothelium may not be present. In some cases iron deposition is a

marked feature, and extramedullary blood formation may be noted in the splenic pulp.

In **sickle cell disease** the changes in the spleen are also characteristic, although a relationship between the splenic changes and the degree of anemia has not been demonstrated. There is, however, a difference in appearance between the spleens of young individuals during acute attacks, and those of older patients showing end results of many attacks of anemia. In the former group the spleen is usually slightly or moderately enlarged and of a deep red color. In older individuals the spleen is the seat of scarring, and is therefore small and contracted. A prominent feature is the occurrence of hemorrhages, especially in the vicinity of follicles. Not infrequently, the follicles are surrounded by hemorrhage so that they appear to be in the center of pools of unchanged blood (Fig. 808). Associated with the hemorrhages are groups of dilated and engorged sinuses. The subsequent history of the hemorrhages is that of organization with fibrosis and deposition of blood pigment in large amounts. These changes result in irregular scarring which, when extreme, causes marked reduction in the size of the organ. Atrophy from this cause has resulted in extremely small spleens. For example, in Steinberg's[61] case, the weight was 2.4 grams.

Sickle-shaped erythrocytes may be demonstrated in the spleen and other organs if appropriate methods are used. It has been our experience that solutions of formaldehyde, or fixatives containing formaldehyde (Bouin, Helly), preserve the sickle shape of the erythrocytes, while after fixation in Zenker's stock solution the cells are of normal shape.

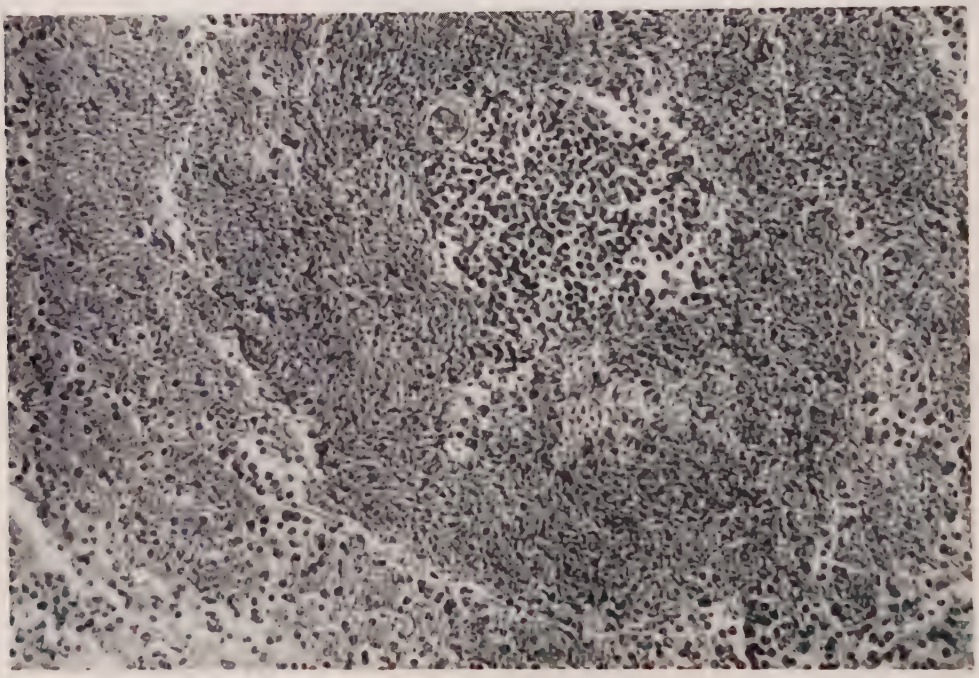


Fig. 808.—Section of spleen in sickle cell anemia. Hemorrhage has occurred in the peripheral portion of a lymphoid follicle, replacing the lymphocytes in that area. The erythrocytes are elongated.

The changes in the size of the sinuses and the occurrence of hemorrhages have been attributed by Rich[59] to developmental anomalies in the ampullary portions of the sinuses. Diggs,[58] however, believes that the abnormally shaped erythrocytes pass through the small vessels less easily than do normal cells, resulting in interference with the circulation which, though often temporary, is the cause of the changes observed in many organs.

As is the case in spherocytic anemia, extramedullary blood formation does not ordinarily occur in sickle cell disease. In the latter, however, hemosiderosis is often seen in phagocytic pulp cells, as well as in the scarring caused by organization of hemorrhages.

In untreated **pernicious anemia** the enlargement of the spleen is slight or moderate, and its gross appearance is not greatly changed. Hemosiderosis is common, the pigment being found mainly in the phagocytic cells of the pulp. Ingested red cells may also be found in the pulp macrophages. Other changes are inconstant, and are sometimes related to the patient's age (fibrosis of pulp or perifollicular areas; hyaline changes in the central arteries). The occurrence of nucleated red cells in the splenic sinuses has been reported, but their numbers are usually small, and the appearance is often that of cells caught in their passage through the organ rather than of foci of cells developing there. Piney and others refer to these cells as "megaloblasts," but as noted in this volume in the section on the Blood, the identity of megaloblasts is uncertain when the section method is used. Myelocytes are found infrequently. In cases adequately treated (as by liver preparations) the changes described may not be found.

Other forms of anemia produce no characteristic changes in the spleen. In aplastic anemia, the anemias secondary to various toxic or infectious conditions, or in chronic blood loss, changes are not ordinarily noted in the spleen unless secondary involvement of the marrow is accompanied by extramedullary hematopoiesis, or, unless, more infrequently, secondary tumor deposits are seen in the spleen itself. In myelofibrosis or osteosclerotic anemia, blood formation in the spleen may be extensive, and the organ may be greatly enlarged. These conditions are discussed under Myeloid Metaplasia.

In **polycythemia vera,** the spleen is often greatly enlarged and contains much blood, yet upon microscopic examination the changes encountered are found to be of inconstant occurrence. Hyperemia of the pulp is usually described as a conspicuous feature in this disease. Blood formation is not part of the picture, and phagocytosis of red cells and deposition of iron pigments are either absent or negligible. Thrombosis of the splenic vein may occur, as in blood vessels in other organs. Infarcts may be noted, also, as the result of thrombi. In a number of cases, splenic tuberculosis has been described.

Conditions Affecting Principally the Leukocytes

Of all the diseases involving the white blood cells, *leukemia* produces the most significant splenic changes.

In **chronic myeloid leukemia** the spleen may reach a greater degree of enlargement than that caused by any other disease. The average weight in Krumbhaar's cases was 1,872.2 grams, but weights of 10,000 grams are recorded. The organ is firm, the capsule thickened, and the cut surface red or pink and smooth. Follicles cannot usually be identified on gross examination. Infarction is common. So-called "myeloid metaplasia" reaches its greatest extent in this disease. The splenic pulp is the seat of large numbers of myelocytes, often accompanied by smaller numbers of nucleated red cells and megakaryocytes. There are thus present in the spleen (as well as in other sites) all the blood cells ordinarily found in bone marrow. The literature is replete with attempts to explain their presence in situations where such cells do not normally appear. These explanations fall into three main groups. According to one theory, the cells are derived from multipotent cells normally present in the splenic pulp (reticulo-endothelial or related cells) which, in common with similar cells in other parts of the body, are the source of the extramedullary myelocytes and other myeloid cells. This implies a more or less diffuse "systemic" proliferation and differentiation of the reticulo-endothelium. A second theory, and the one that has probably received the most support, is that the cells in the spleen and other organs have been deposited there from the blood, as metastases from the hyperplastic (neoplastic) bone marrow. This is in accord with the neoplastic theory of leukemia. The third view, originally advanced by Ziegler, and revived by Wiseman and associates,[16a] considers the myeloid and lymphoid tissues to be mutually antagonistic, with atrophy of the lymphoid tissue permitting hyperplasia of the myeloid system. Miller and associates have modified this view (see Leukemia, page 890) and described the presence of a substance (myelokentric acid) that may be responsible for the myeloid metaplasia.

We are not able, at present, to give a decisive opinion as to the origin of the cells. Their varieties, as noted above, include all those normally found in bone marrow. They may, however, be present in different proportions. Neutrophilic myelocytes are usually the most numerous and are found at all stages of development. The number of eosinophilic myelocytes varies con-

siderably, but they are usually present in conspicuous numbers and in proportions greater than in normal marrow. Basophilic myelocytes may also be found in considerable numbers if studied in smears or frozen sections, but the granules are usually dissolved in preparation of sections. The earlier nongranular stages (myeloblasts, hemocytoblasts) are found in small proportions.

Nucleated red cells are of normoblastic type, and their appearance in the spleen is probably due to marrow involvement, in much the same way as when the marrow is the seat of metastases from other organs with tumor involvement. Megakaryocytes vary greatly in number, being rare in some cases, and conspicuous by their large numbers in other cases.

Diffuse fibrosis throughout the pulp is a common finding. The follicles do not participate in the myeloid change. They are small, their borders are indistinct and are encroached upon by the surrounding cells in the pulp. Germinal centers are absent or inactive.

Not infrequently, Charcot-Leyden crystals are seen, usually free in the splenic pulp.

In **acute myeloid leukemia** enlargement of the spleen is only slight, and in cases of short duration the organ may be of normal size. Myeloid cells are found in the splenic pulp, but they include fewer varieties and fewer stages of cell development than are found in chronic leukemia. Instead, there are seen numerous cells in early stages of development (myeloblasts, hemocytoblasts) and comparatively few of the late granular forms. The relative proportions of early and late forms vary, as they do in the circulating blood. However, there may be a discrepancy between the blood and tissue findings; in some cases, more of the partially developed cells (myelocytes) may be found in the tissues than in the circulation. This is more noticeable in the case of eosinophiles because of their conspicuous granules. Usually a small number of granular myelocytes are present, mostly neutrophilic. As their granules require special staining methods for demonstration, and as megakaryocytes are either absent or present in very small numbers, the general picture is one of comparatively uniform types of cell accumulations.

Auer bodies, when present in the circulating myeloblasts, may be found in smears or in sections stained by azure and eosin stains, or by peroxidase or oxidase methods. Charcot-Leyden crystals and other unidentified acidophilic crystalline and amorphous particles may occasionally be found in phagocytic cells.

Rupture of the spleen is a rare complication in acute myeloid leukemia.

Chronic lymphatic leukemia is also accompanied by splenomegaly, but the degree of enlargement is not as great as in the myeloid form. In most cases the weight is between 800 and 2,000 grams. The spleen is firm, the cut surface in some cases light red, with a homogeneous, "meaty" appearance. The appearance of the follicles varies. In most cases they cannot be distinguished, but sometimes they are of normal size, or even enlarged. Infarcts are less common than in chronic myeloid leukemia.

The principal microscopic feature is the large number of lymphoid cells that appear to overrun and obliterate most of the architectural markings. The follicles have indistinct outlines, and their germinal centers are replaced by closely packed lymphocytes. For the same reason the sinuses are often indistinguishable. Mitoses among the lymphocytes are not limited to the follicles but are observed in all parts of the tissue. Ordinarily, myelocytes, erythroblasts, and megakaryocytes are not found. Occasionally, they are present in small numbers, due probably to marrow involvement.

In **acute lymphatic leukemia** the enlargement of the spleen is less marked than in the chronic form. The changes are similar to those in the chronic form but the cells are less mature. This immaturity may be expressed in greater average cell size, and clearer nuclei, but the differences between young and old lymphocytes are not striking.

Monocytic leukemia is usually acute, and changes in the spleen consist of infiltration with cells corresponding to those in the circulation. As noted elsewhere, it is often difficult to distinguish between monocytes and monoblasts on the one hand, and atypical myeloblasts and promyelocytes on the other. It is of interest that in some cases the spleen and other organs contain various myeloid cells (e.g., eosinophiles) in numbers greater than would be expected from the blood picture.

In **agranulocytosis** no specific changes in the spleen have been described. As is the case in other organs, it may be impossible to demonstrate leukocytes in the tissues.

Wiseman and Doan[75] have reported a series of cases in which neutropenia occurs as a result of excessive destruction of leukocytes by phagocytes in the splenic pulp. The condition occurs in acute, subacute, and chronic forms. Its essential features are leukopenia (neutropenia) associated with splenomegaly and hyperplasia of the bone marrow. There may be varying degrees of anemia (always of hemolytic type), and of purpura due to

thrombocytopenia. The condition is thus related to both hemolytic jaundice, in which there is excessive destruction of red cells, and to thrombocytopenic purpura hemorrhagica, in which the platelets are reduced. Splenectomy is apparently curative. Detailed studies of the spleen are meager, but the work of Wiseman and Doan indicates that numerous phagocytic cells present in the pulp have ingested granular leukocytes.

The term "**primary splenic neutropenia**" has been suggested for cases in which the action of the spleen is directed mainly toward the granular leukocytes, and the term "**splenic panhematopenia**" for cases in which the red cells, white cells, and platelets are markedly reduced in number. The latter form has been described by Doan and Wright[74] and occurs both as an apparent "primary" and as a secondary condition. (See also Hypersplenism.)

Conditions Affecting Principally the Platelets

In **thrombocytopenic purpura hemorrhagica,** the spleen is of normal size or only slightly enlarged. On gross examination it presents no significant features. The changes found on microscopic examination are comparatively slight but relatively constant. The follicles are usually of normal size, but often have enlarged germinal centers containing numerous immature lymphocytes, frequently in mitosis. Adult neutrophilic and eosinophilic leukocytes are found in increased numbers in sinuses and pulp. Megakaryocytes are found in the splenic sinuses, a point stressed particularly by Nickerson and Sunderland.[77] They are usually present in small numbers only, and careful search may be necessary for their demonstration. Alrutz, Nortell, and Piette[76] have described minute particles, which they considered degenerated platelets, in the endothelial cells lining the sinuses. Platelets, however, are difficult to recognize in sections, and have been little studied. The bodies resemble more closely those observed by Pappenheimer in hemolytic jaundice. These comparatively slight changes are hardly sufficient to explain the usually prompt and striking amelioration of the condition following splenectomy.

Hypersplenism

Except for the formation of cells and storage of blood, the functions of the spleen are not readily observed by direct observation. Presumptive evidence of other functions, especially influence on the development or destruction of blood elements, is seen in the results of splenectomy in certain diseases. This is particularly true when anemia, leukopenia, or thrombocytopenia is improved by splenectomy.

It is assumed that in such cases there is hyperactivity of those functions of the spleen which have to do with the destruction of cells (Doan) or to inhibition of their formation in the bone marrow (Dameshek), and accordingly, the term "hypersplenism" has been applied. Hypersplenism is therefore a clinical concept, indicating a condition in which there is peripheral cytopenia (anemia, leukopenia, or thrombocytopenia, or any combination thereof) that is improved by splenectomy. It may occur in the course of recognized diseases, such as Gaucher's disease, Boeck's sarcoid, Banti's syndrome, hemolytic anemia, and other conditions (secondary hypersplenism), or as an apparent primary condition (primary hypersplenism). Splenic neutropenia and splenic panhemocytopenia probably belong in this group, and the possible relationship to congenital hemolytic icterus and idiopathic thrombocytopenic purpura has been suggested.

The morphologic changes that are found with hypersplenism are thus varied. Those changes that may be attributed specifically to splenic hyperactivity are not sufficiently well recognized to establish the condition as a pathologic entity.

Myeloid Metaplasia

The presence in other organs of cells ordinarily found only in the bone marrow (myelocytes, nucleated red cells, or megakaryocytes) is referred to as *myeloid metaplasia,* or *extramedullary hematopoiesis.* It occurs in varying forms and degree in many disease conditions and is, therefore, not diagnostic of any one. It is more common in the spleen than in any other organ. In its minor forms, as seen, for example, in acute splenic tumor, it consists merely of occasional myelocytes in the splenic pulp.

Nucleated red cells are often found in the spleen in anemic states. The most common antecedent condition is the presence in the bone

marrow of secondary tumor deposits. In such cases, erythroblasts appear in groups of varying sizes within the splenic sinuses. This intravascular position is characteristic for erythroblasts, in contrast to the extravascular development of myelocytes. The erythroblasts may be in the early stage of development, but there is a tendency for the cells in each group to be of approximately the same stage. The erythropoiesis is sometimes accompanied by myelocyte formation, and occasionally by megakaryocytes.

The most extreme degree of blood formation in the spleen is found, of course, in leukemia, where the whole pulp may be overrun with myeloid cells. Comparable pictures, however, may be seen in severe cases of marrow replacement, such as occurs in *osteosclerosis* or *osteofibrosis*. The associated "myelophthisic anemia" is accompanied by intensive extramedullary blood formation in which various tissues participate, so that difficulty may be encountered in deciding whether the case is one of leukemia with osteosclerosis or of osteosclerotic anemia with extramedullary hematopoiesis.

The disease is slowly progressive. Immature cells of both red and white forms are present in the peripheral blood, but their percentages are ordinarily small, although the total leukocyte count may be increased. Clinically, the condition resembles myeloid leukemia (or, more rarely, hemolytic jaundice), from which it may be distinguished by the failure to develop characteristic blood and bone marrow pictures. Splenic puncture alone does not provide enough material on which to base a diagnosis. Inasmuch as irradiation, which is usually employed in the treatment of leukemia, and splenectomy, as employed in hemolytic jaundice, usually prove fatal, the importance of careful diagnostic study is obvious.

The Spleen in Lipidoses

The reticulo-endothelial cells of the spleen constitute an important site for the storage of various substances, whether formed within the cells, or ingested by them.

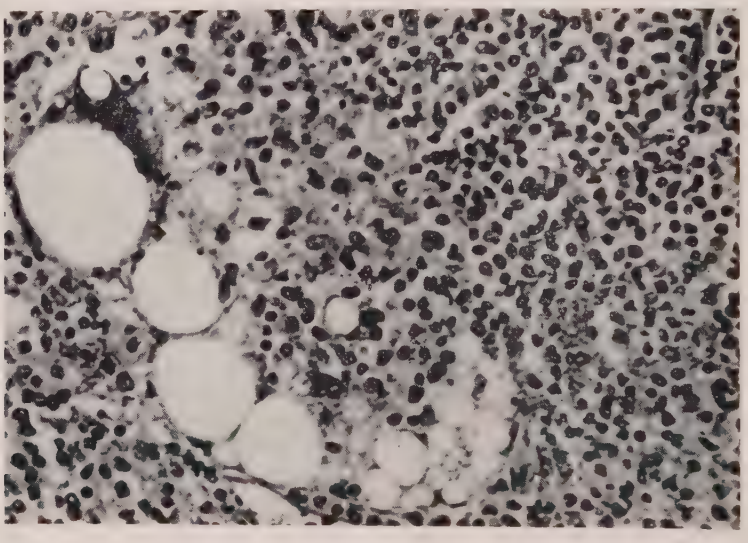


Fig. 809.—Lipid granuloma of spleen, probably due to ingestion of mineral oil. The vacuolated cells are in the peripheral portion of a lymph follicle.

Under such conditions the enlargement of the spleen may be extreme, and its appearance indistinguishable from that in myeloid leukemia. The changes in the spleen presumably occur as compensation for the failure of the bone marrow; hence, splenectomy and irradiation are contraindicated.

Extensive blood formation is occasionally encountered without recognizable associated conditions to which it may be attributed. In such cases the degree of splenic enlargement and of myeloid "metaplasia" may be considerable. Hickling[66] described such cases under the term "chronic nonleukemic myelosis." Jackson, Parker, and Lemon[67] have suggested the term *"agnogenic myeloid metaplasia of the spleen"* to indicate our lack of knowledge of the underlying causes.

Lipids in excessive amounts are found in the spleen in various disease conditions, but especially in disturbances of lipid metabolism. The feeding of lipids and oils may result in their deposit in the spleen as in the experimental work of Anitschkow (1914) with cholesterol, or of Stryker[101] with mineral oil. Vacuolated cells in or near the follicles, apparently identical with those described by Stryker, are not uncommon in human spleens, and presumably are often the result of mineral oil ingestion (Fig. 809). The mode of transport to the spleen is not known.

Lipemia associated with diabetes may also result in lipid deposits in the spleen.

The most important lipid deposits in the spleen are of three types: cholesterol (Hand-Schüller-Christian's disease), kerasin (Gaucher's

disease), and sphingomyelin (Niemann-Pick's disease).

The general features of these conditions are discussed under The Reticulo-endothelial System (page 950). The following account refers only to the splenic changes.

In **Hand-Schüller-Christian's disease** the lipid within the reticulo-endothelial cells is cholesterol. The involved cells form aggregates of varying size and appearance. Ordinarily, splenic involvement is not a conspicuous part of the picture, but vacuolated cells ("foam cells," "xanthoma cells") may be seen in the spleen. According to Jaffe and Lichtenstein,[89] the condition is related to Letterer-Siwe's disease in which similar aggregates of lipid-containing cells are seen in various organs, including the spleen, forming nodules up to 1 or 2 mm. in diameter.

Gaucher's disease is a disturbance of lipid metabolism in which kerasin is found within the cells of the spleen, the liver, the bone marrow, and sometimes in the lymph nodes. The nature and origin of the deposits are discussed on page 951.

The spleen is often tremendously enlarged, and may weigh 8,000 grams. These spleens are among the largest encountered in any condition. The enlargement is not always so great, however, and may not be noted clinically. The capsule is usually without adhesions, but through it may be seen grayish, yellowish, or reddish areas, and necroses (Fig. 810). The cut surface has similar areas, the larger ones being more or less nodular and the very small ones scarcely discernible. The necroses are sometimes in the form of infarcts but may be of irregular shapes, and occluded vessels are not always found. (Fig. 811.)

Fig. 810.

Fig. 811.

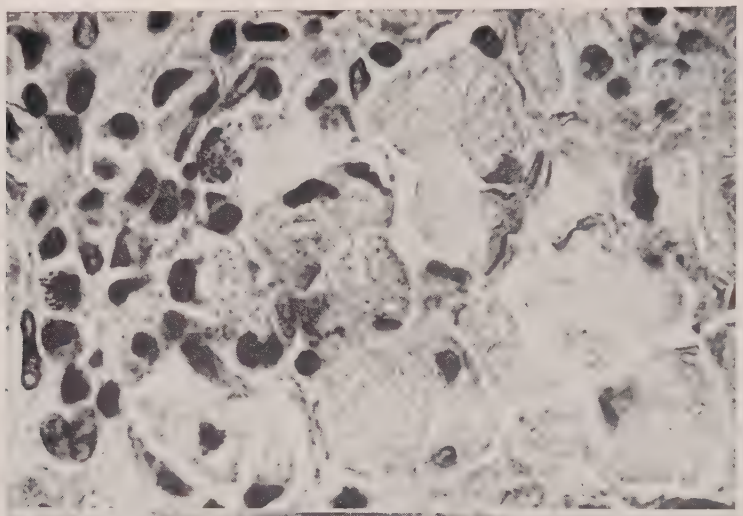
Fig. 810.—Gaucher's disease. Enlarged spleen, with areas of necrosis seen through the capsule. The cut surface is shown in the next figure.

Fig. 811.—Gaucher's disease. Cut surface of the spleen shown in Fig. 810.

The microscopic picture is characterized by the presence of so-called "Gaucher cells." These are the cells of the reticulo-endothelial system that are enlarged because of their content of kerasin. In appearance they are strikingly uniform, being of large size (20 to 80 microns), with a comparatively small nucleus and large cell body. Occasionally, cells with two nuclei are seen, but cell division is not observed. The cytoplasm is relatively clear, but contains granules or striations, the latter forming fascicle-like structures that are found in no other condition. (Figs. 812, 813.)

The "Gaucher cells" have been considered by various authors to arise from endothelium, reticulum, or hematopoietic cells. In the current literature, they are usually referred to as of reticulo-endothelial origin, a view that expresses the close relation of reticulum and endothelial cells in the spleen. It is often difficult to determine whether the cells are within the splenic sinuses or outside. Many sinuses are dilated, however, and lined by Gaucher cells. Hematopoiesis is not usual, but may occasionally be seen in the dilated sinuses. Large numbers of Gaucher cells are also seen

Fig. 812.



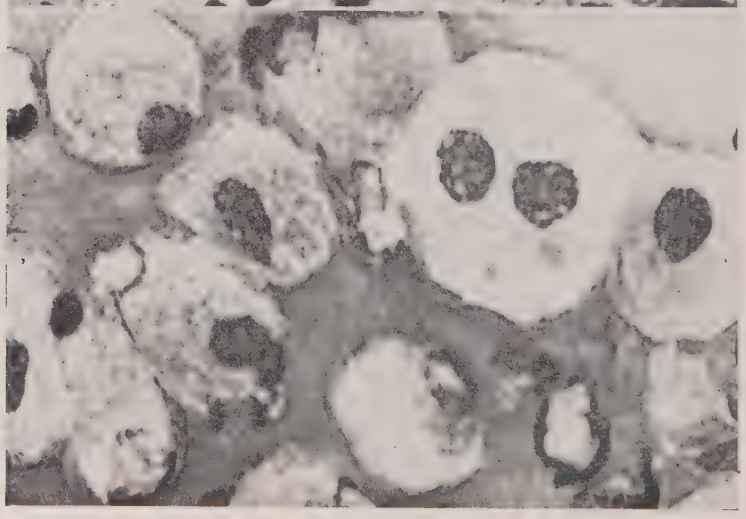


Fig. 813.

Fig. 812.—Gaucher's disease. Section of spleen showing the characteristic cells with striated cytoplasm.

Fig. 813.—Gaucher's disease. Smear from the cut surface of the spleen, showing numerous Gaucher cells.

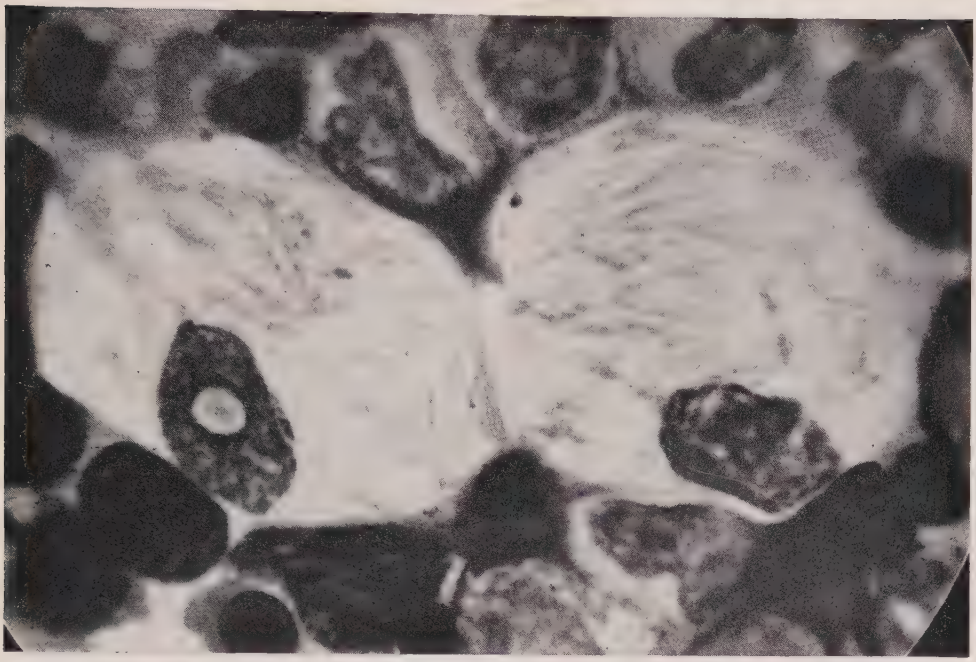


Fig. 814.—Gaucher cells in smear of bone marrow. The typical striations are clearly shown.

around, and presumably between, the sinuses. They are not ordinarily encountered in the Malpighian corpuscles, although the latter are often reduced in size by encroachment of Gaucher cells at the periphery.

The nodules seen grossly are large areas with accumulations of the characteristic cells. Hemorrhage and necrosis produce the variations in color and general appearance.

The presence of kerasin cannot be demonstrated histologically by the ordinary stains for lipids (in contrast to Niemann-Pick's disease). Chemical analysis of the spleen, however, shows large amounts of kerasin. The presence of iron may often be demonstrated by the usual histochemical reactions.

Puncture of the spleen (or more often, the bone marrow) for diagnostic purposes yields large numbers of the characteristic cells, which are readily recognized in either smears or sections (Figs. 813 and 814).

Niemann-Pick's Disease.—In this condition the spleen contains large quantities of sphingomyelin (see page 952). The organ is enlarged, and although the condition occurs only within the first two years of life, the weight has reached 480 grams. The capsule is smooth, the cut surface often has many minute, yellowish, glistening deposits.

Microscopically, the pulp of the spleen contains numerous vacuolated mononuclear cells, apparently arising from the reticulo-endothelial cells. They vary from 20 to 50 microns in diameter, and are mononuclear, with clear cytoplasm containing many small vacuoles. Mitoses are not observed. As in Gaucher's disease, the cells are situated in the pulp, be-

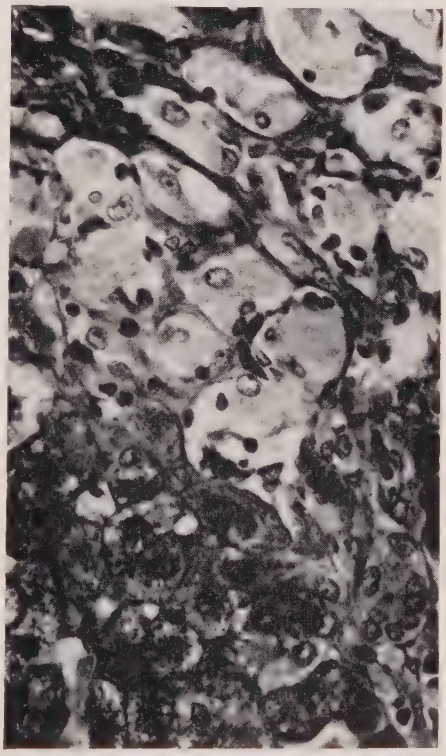


Fig. 815.—Gaucher's disease. Section of liver, showing typical cells in the sinusoids.

tween the sinuses, and encroaching on the follicles (Fig. 816). They differ from those of Gaucher's disease, however, in having vacuoles rather than striations or granules, and in containing lipids that may be demonstrated histologically by fat-soluble dyes.

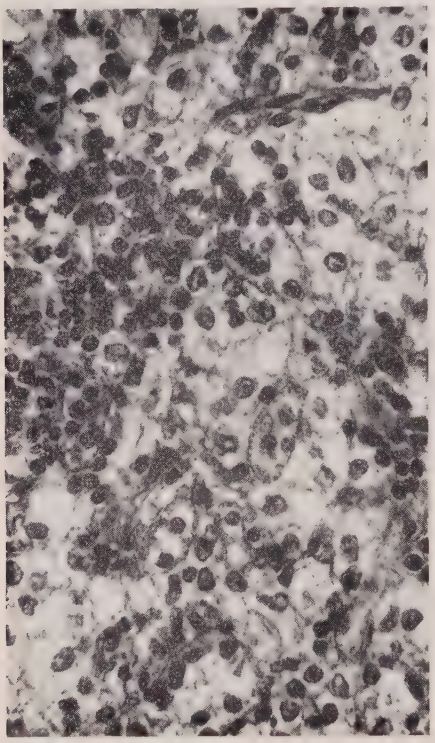


Fig. 816.—Niemann-Pick's disease. Section of spleen, showing large mononuclear vacuolated cells in the pulp.

Tumors of the Spleen

Primary Tumors of the Spleen.—Primary splenic tumors are rare. The most common benign tumor is *hemangioma,* which occurs either in the form of small nodules which are discovered only at autopsy, or as large cavernous hemangiomata that may cause a considerable degree of splenic enlargement. The smaller tumors are often poorly demarcated from the surrounding splenic tissue, and insinuate themselves into the pulp in such a way that it is not always certain whether they represent local dilatation of sinuses with thickening of their walls, or a new growth, or malformations. Some of them have been described under the term "hamartoma." Some are multiple, and may be associated with hemangiomas in other organs. Large cavernous hemangiomas may grow to great size, and involve most of the organ. *Lymphangioma* is a less common benign tumor. Other benign tumors (fibroma, chondroma, osteoma) are rare.

It is probable that the leukemias and certain other forms of "malignant lymphoma" should be regarded as neoplasms, and as such they constitute the most common of the malignant tumors of the spleen. However, they are not necessarily to be regarded as primary tumors. In myeloid leukemia, the problem to be solved is the origin of "myeloid metaplasia." In lymphatic leukemia the question is whether the spleen participates in a general involvement of the lymphatic system, or whether it is the site of secondary deposits, or whether both conditions prevail. By the time the disease reaches a stage at which the spleen can be examined, the changes have progressed beyond the point at which their origin can be determined.

An exception is the lesion formerly described as "giant follicle hyperplasia" of the spleen and lymph nodes, in which the early changes consist mainly in an increase in the number and size of the lymphoid follicles. This lesion is now recognized as an early stage in the development of a malignant lymphoid tumor (see tumors of lymph nodes, page 940). The literature contains a number of references to primary round cell sarcomas of the spleen, sometimes with small cells, sometimes with large. These probably fall into the same groups of *lymphosarcoma* seen in lymph nodes; namely, lymphosarcomas in which the appearance of the cells approaches that of small lymphocytes; those in which the cells are larger, and resemble more primitive cells (lymphoblasts); and those in which the tumor cells are apparently of reticulo-endothelial origin. In the last-named group are to be included the reticulum cell sarcomas arising during the course of Hodgkin's disease.

Secondary Tumors of the Spleen.—Secondary involvement of the spleen usually results from direct extension of tumors in neighboring structures, extension or metastases by way of the lymphatics, or metastases by the blood stream.

Direct extension usually involves only the surface of the organ. In most instances, the capsule separates the tumor from the splenic substance. Occasionally, however, the tumor penetrates the capsule and extends directly into the spleen.

The lymphatics of the spleen are situated in the capsule, the trabeculae, and along the larger vessels. It is in these sites, therefore, that lymphatic deposits are seen. An interesting form of involvement is that in which multiple secondary deposits are seen within the follicles, presumably as a result of extension through the lymphatics in the sheaths of the central arteries. Blood-borne metastases reach the splenic pulp. They are usually associated with similar metastatic growths in other organs.

Secondary tumors of the spleen usually occur in the form of tumor nodules, sometimes single, sometimes multiple, and usually of small size. Less commonly, minute, more or less diffuse, hematogenous metastases may cause moderate enlargement of the spleen, but without the formation of tumor nodules recognizable to the naked eye.

The frequency with which the spleen is involved secondarily by tumor formation is slight when we consider its high degree of vascularity. Willis[112] gives the average frequency of involvement as 4 per cent of all fatal malignant tumors. The reason for this infrequent involve-

ment is not understood. Carcinomas metastasize largely by way of the lymphatics, and the spleen has comparatively few lymphatic channels, which probably accounts for the absence of deposits in many instances. Whether tumor cells reaching the spleen are destroyed more readily than those in other organs is a question that has never been settled.

The Spleen in Hodgkin's Disease

Involvement of the spleen in Hodgkin's disease is the rule, but the degree of involvement is variable. It is extremely rare for the spleen to be the only organ involved. In most instances the splenic lesions are similar in appearance to those in the lymphoid structures. When the lesions in the spleen are few and small, the organ may not be enlarged. Moderate degrees of splenomegaly are not uncommon, however, and the spleen may reach a weight of 2,000 grams. The lesions are of the same types as those in the nodes, and therefore vary in size, consistency, and histologic structure according to the types of cells present, the amount of fibrosis, and the presence or absence of necroses. Nodular involvement, with irregular areas of necrosis, gives to the cut surface a mottled appearance that has been compared to porphyry.

Histologically, the lesions appear both in the follicles and in the pulp. Involvement of the walls of the veins is not uncommon, and the cell collections may elevate the intima of the vessels. The cell types are described in the section on Lymph Nodes (page 944).

Cysts of the Spleen

Cysts of the spleen are rare. They include parasitic cysts, of which those due to *Taenia echinococcus* are of the most frequent occurrence, and neoplastic cysts, which are usually cystic lymphangiomas (Fig. 817), hemangiomas, or dermoids. "Pseudocysts" result from cystic degeneration of infarcts or hematomas. In all forms, the cysts may be single or multiple.

Fig. 817.—Multiple cysts of spleen. The cysts are lined by endothelium, and contain coagulated protein. This lesion is usually termed cystic lymphangioma. The patient was a male, aged 16 years, who suffered rupture of the spleen in an automobile accident. (Courtesy Dr. Saul Kay.)

Splenomegaly

To the clinician, the occurrence of splenomegaly, especially in its chronic form, is of special interest because it presents difficult problems in differential diagnosis. Except in leukemia, hemolytic jaundice and malaria, in which the blood examination and history render the diagnosis comparatively easy, the case is likely to be consigned to one of the vague groups formerly referred to as "splenic anemia," "pseudoleukemia,"

or similar terms that have no sound pathologic or physiologic basis. From the standpoint of the pathologist, many of these conditions are unrelated, so that a classification serves merely as a list of groups, convenient mainly for purposes of discussion. The following classification is a modification of one advocated by Klemperer.[91]

Classification of Splenomegaly

A. Inflammatory Splenomegaly
   1. Bacterial and parasitic infections

B. Infiltrative Splenomegaly
   1. Deposition within cells
      a. Cholesterol lipidosis (Hand-Schüller-Christian)
      b. Cerebroside lipidosis (Gaucher)
      c. Phosphatid lipidosis (Niemann-Pick)
   2. Deposition within reticulum
      a. Amyloidosis

C. Splenomegaly Associated With Cell Formation
   1. Leukemia
   2. Agnogenic myeloid metaplasia
   3. Osteosclerosis and osteofibrosis
   4. Erythroblastic anemias
   5. Hodgkin's disease
   6. Reticulosis

D. Splenomegaly Associated With Cytopenia
   1. Anemia
      a. Splenic neutropenia
         dice), congenital
      b. Acquired hemolytic anemias
      c. Sickle cell anemia
      d. Mediterranean anemia
   2. Leukopenia
      a. Splenic neutropenia
   3. Thrombocytopenia
      a. Thrombocytopenic purpura hemorrhagica
   4. Pancytopenia
      a. Splenic panhemocytopenia

E. Neoplasms

F. Cysts

G. Chronic Disturbances of Blood Circulation
   1. Peripheral venous hypertension
      a. Chronic passive congestion
   2. Portal hypertension (congestive splenomegaly)
      a. Banti's syndrome
   3. Polycythemia vera

THE LYMPH NODES

Normal Structure and Function

The lymph nodes are encapsulated nodules of lymphatic tissue situated along the course of the lymphatic vessels. They are composed of a network of reticulum cells and fibers, within the meshes of which are lymphocytes. Connective tissue trabeculae continuous with the capsule, pass through the node, incompletely separating it into several parts. In the peripheral (cortical) portions of the node are nodules of densely packed lymphocytes in which are often seen lightly stained spherical areas ("germinal centers") in which the reticulum fibers are scanty, the lymphocytes less closely arranged and in general larger than in other parts of the node. Large reticulum cells also contribute to the clarity of the picture. Mitotic divisions are often found among the large cells in germinal centers.

In the central ("medullary") portions of the node the lymphocytes are generally smaller and more closely packed, and are arranged in cord-like masses between lymph vessels. Plasma cells are normally found in small numbers among the lymphocytes.

Lymph enters the node through afferent vessels in the capsule and leaves by efferent lymphatics at the hilus. A prominent lymph sinus is seen at the periphery of the node, just beneath the capsule, and smaller sinuses run along the trabeculae toward the efferent vessels.

The cells lining the lymph sinuses are strikingly like the neighboring reticular cells, with which they are connected physically by cytoplasmic processes and associated physiologically by reason of their phagocytic properties. Desquamation of the endothelial cells of the sinus with accompanying formation of phagocytic cells (macrophages) in the sinuses is of common occurrence.

An important function of the lymph nodes is the removal of various substances from the lymph as it filters through them. Particulate matter (e.g., coal dust, hemosiderin, tattoo pigments), cells (e.g., tumor cells) and bacteria are the most readily observed, but invisible toxic substances of various types also pass through the nodes, and may effect morphologic changes. According to some, the clear areas described are the sites in which toxins are destroyed, and should therefore be called "reaction centers." Viruses, according to Drinker and Yoffey[118] are not filtered out efficiently.

A knowledge of the course of lymphatic drainage from the various organs is of practical importance in the clinical interpretation of local lymph-node enlargement.

Inflammatory Conditions of Lymph Nodes

Nonspecific Inflammatory Conditions

Acute Lymphadenitis.—In the transportation of bacteria and toxic substances to regional lymph nodes from foci of infection, subsequent changes in the nodes depend on the nature of the infecting organism, the patient's resistance, and other factors that determine the morphology of the inflammatory reaction.

In comparatively mild reactions, polymorphonuclear leukocytes and large

mononuclear leukocytes (monocytes) appear in the lymph sinuses and to a lesser extent among the lymphocytes, the former being transported by the blood stream, the latter derived presumably from the lining cells of the sinuses. Both types of cells exhibit various degrees of phagocytic activity. Bacteria, dead cells, and tissue fragments, often unrecognizable, may be seen in their cytoplasm. Erythrocytes may also appear in the sinuses, and many are engulfed by the phagocytes.

When the inflammation is due to one of the common pyogenic organisms, the development of the inflammatory reaction proceeds in much the same fashion as in other tissues (see Chapter 3) and may lead to suppuration and abscess formation. The inflammatory reaction often involves the neighboring lymph vessels.

Enlargement of lymph nodes from draining foci of infection is common. The nodes are usually tender and there may be reddening of the skin and infiltration of the surrounding tissue. If suppuration occurs, the node may be soft and sinuses may open on the surface.

Chronic Lymphadenitis.—As in chronic inflammatory processes in other sites a greater number of mononuclear cells and fewer polymorphonuclear leukocytes are usually observed. The sinuses may be filled with phagocytes; and various mononuclear cells, plasma cells, and other types commonly found in chronic inflammatory states appear among the lymphocytes (Fig. 818). Some of these cells undergo mitosis. The reticulum cells also proliferate and are presumably the source of some of the mononuclear types.

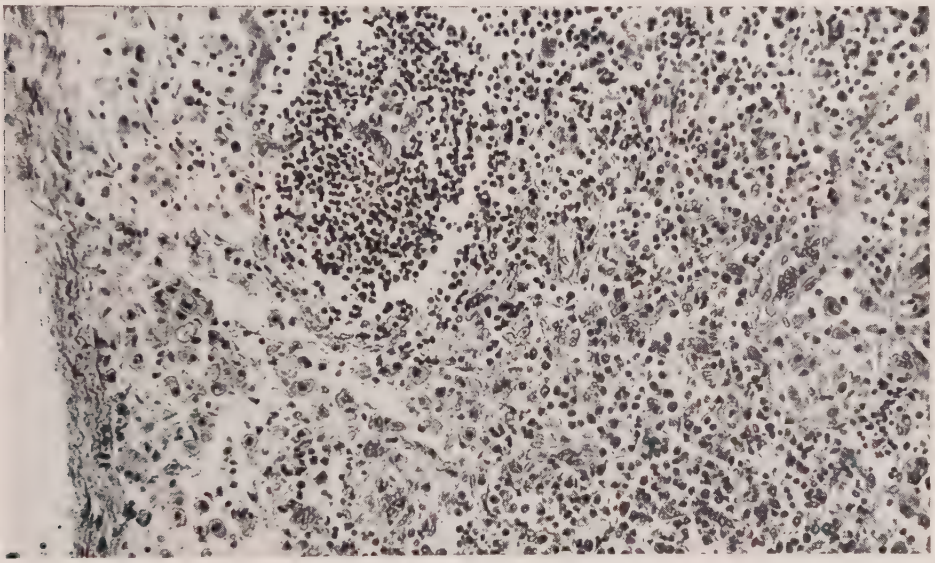


Fig. 818.—Chronic lymphadenitis. Many large mononuclear cells are seen in the dilated peripheral lymph sinus.

The lymph nodes become enlarged and tender and the surrounding tissue is edematous. Frequently in drainage from superficial infections such as in the extremities, involvement of the afferent lymphatic vessels is indicated by red lines going toward the node. On gross examination the nodes appear soft and elevated, and the contents bulge above the cut surface. They are hyperemic, and small hemorrhages or areas of necrosis may be present.

Various degrees of fibrosis may result, and for this reason it is usually undesirable to select for biopsy nodes ordinarily subject to long-standing mild inflammatory changes (e.g., inguinal lymph nodes).

The histologic picture varies considerably. In some cases enlargement of "germinal centers" and an increase in the number of lymphocytes may be the most conspicuous evidences of reaction. The "germinal center" ("secondary nodule") enlargement may suggest the giant

follicle type of malignant lymphoma. (See page 941.) In other cases, filling of the sinuses with mononuclear cells, apparently derived from the lining cells, is a prominent feature. Proliferation of reticulum cells in the intersinusoidal medullary stroma is less common, but is seen in some forms, for example, dermatopathic lymphadenitis.

In chronic lymphadenitis the enlarged nodes are not ordinarily accompanied by the same degree of edema and tenderness as in acute inflammations. The enlarged nodes are firm, depending on the amount of fibrosis that has occurred.

Specific Inflammatory Conditions

The two conditions just described come under the heading of "nonspecific" inflammations, in which the etiological agent is not apparent from the morphology of the reaction alone. If bacteria are the causative agents, their presence may often be detected by bacteriologic methods or by staining techniques. In some instances, however, the causative agent evokes a reaction which can be related with more or less certainty to the inciting cause, because of the predominance of certain cell types, or their arrangement in recognizable and specific aggregates.

Tuberculosis.—Tuberculous involvement of lymph nodes is commonly found due to drainage from a focus of tuberculosis. Tuberculosis of the bronchial lymph nodes almost always arises from a primary infection in the lung parenchyma, while mesenteric nodes are usually affected in cases of tuberculous enteritis. Single nodes or node groups may be affected, or there may be widespread involvement of lymph nodes as part of a disseminated tuberculosis.

Boeck's Sarcoid.—The involvement of lymph nodes in sarcoidosis of the Boeck type is common and is ordinarily associated with lesions in other organs (see page 670).

Dermatopathic Lymphadenitis (Lipomelanotic Reticulosis).—This inflammatory change is not the result of the action of a specific agent. Its association with lesions of the skin (dermatitis, eczema, etc.) and the fact that the lesions are easily recognized warrant separate discussion of the condition.

It is not uncommon to observe generalized enlargement of superficial lymph nodes in cases of extensive dermatitis of various types. Clinically, these cases may resemble malignant lymphoma (leukemia, lymphosarcoma, etc.) with skin manifestations, and in exceptional cases may be accompanied by leukemoid blood reactions.

Microscopically there is proliferation of the reticulum cells of the lymph node, sometimes forming poorly defined accumulations in the pulp, between the sinuses or follicles. These accumulations may be found in any part of the node. When they are extensive, they replace much of the lymphoid tissue but do not appear in the tissue around the lymph node. The reticulum cells are not arranged in any specific order, but appear as diffuse sheets of cells. Mitoses may be present but are not common.

Not infrequently some of the cells contain melanin and hemosiderin pigment (Fig. 819). Eosinophiles are of occasional occurrence.

Syphilis.—Enlargement of lymph nodes may occur in any stage of congenital or acquired syphilis. Regional nodes draining the primary lesion become enlarged, and generalized node enlargement may accompany the secondary stage (see page 273).

Infectious Mononucleosis.—The changes in the peripheral blood and other clinical features are described on page 888.

The enlargement of superficial lymph nodes is so common as to have suggested the pseudonym, "glandular fever." There are few accurate descriptions of the histologic and cytologic changes, for the benign nature of the disease has limited study mainly to biopsy material, usually lymph nodes. In one case Ziegler described changes in many organs (liver, spleen, kidney, etc.) besides the lymph nodes, thus emphasizing the fact that the disease is a generalized infection not limited to lymphoid tissue. His findings offer a morphologic basis for the protean manifestations which are often encountered.

The lymph node lesions described in the literature vary considerably in type and extent. Downey and Stasney[133] have shown that this variation is due in part to the severity of the disease and the stage of its development. (Other factors also influenced the morphology of the lesions, for individual nodes varied in different areas.) This variation in histologic structure is an important diagnostic feature, as is does not occur in lymphatic leukemia.

The most important pathologic alterations seem to be the presence of small groups of large cells with clear nuclei and lightly basophilic cytoplasm which appear in various parts of the lymph nodes, and scattered large and small atypical lymphoid cells with very basophilic cytoplasm and coarse nuclear structures (Fig. 820). Downey and Stasney[133] have shown that the former are rounded reticulum cells, from which normal as well as atypical lymphocytes are developed. Gall and Stout[135] have emphasized the diagnostic importance of atypical lymphoid cells, and the need for special staining such as methylene-blue-phloxine or similar methods, for demonstrating them in sections. Downey and Stasney stress the importance of imprints of the nodes, by which they show conclusively that the atypical cells of the nodes and of the circulating blood are the same, and that they are formed in the lymphoid tissues. Supravital staining confirms the absence of monocytes as it does in the

blood. Several authors have mistakenly called the atypical lymphoid cells "lymphoblasts."

The hyperplasia of reticulum cells sometimes simulates that found in Hodgkin's disease, but may be distinguished by the fact that in infectious mononucleosis the hypertrophied reticulum cells are more likely to occur in small, rounded groups, and are accompanied by the atypical lymphoid cells described above, while eosinophiles, necrosis, fibrosis, and capsular invasion are absent.

Lymph Nodes in Other Specific Infections

In addition to the specific infectious diseases mentioned, there are others in which the lymph node changes have features that are sufficiently characteristic to be of diagnostic value. Many of these changes are discussed in the sections dealing with specific infections. Briefly, we may mention the extensive necrosis of lymphoid tissues with numerous mononuclear phagocytes

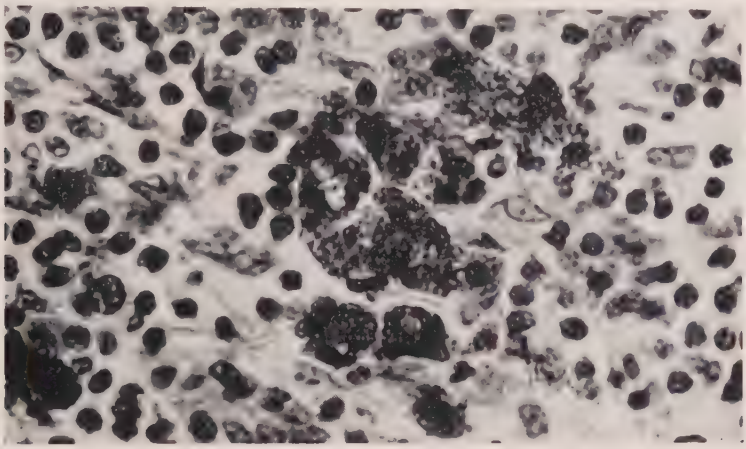


Fig. 819.—"Dermatopathic" lymphadenitis. The dark granular pigment in the large phagocytic cells is melanin.

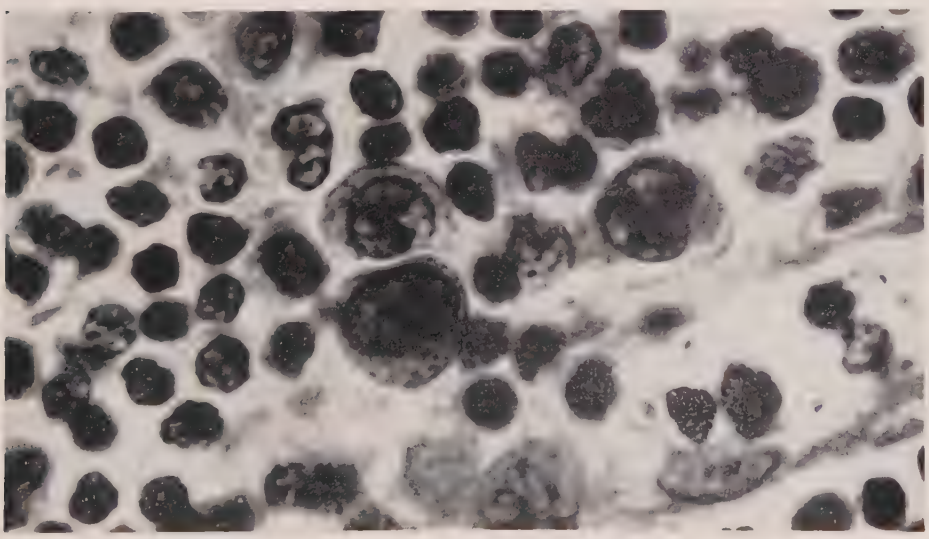


Fig. 820.—Lymph node in infectious mononucleosis. The three large cells in the center are the so-called "infectious mononucleosis cells" characteristic of the disease. Section stained with eosin-azure B-methylene blue.

In spite of these differences, errors may occur if attempts are made to interpret the changes in individual nodes without reference to the clinical and hematologic features of the case.

containing bacilli in typhoid fever; the hemorrhagic inflammations, necrosis, and suppuration of bubonic plague; the necrosis often associated with peripheral leukocytes and macrophages in tularemia; the specific granulomas of

leprosy; peculiar giant cells of the Warthin-Finkeldey type, in the prodromal stages of measles; and infections with such organisms as filaria, histoplasma, leishmania, coccidioidomycosis, blastomycosis, or actinomycosis.

Two such infections should be mentioned especially because of their association in the recent literature with Hodgkin's disease. Infection with *Brucella* may result in lesions accompanied by necrosis, fibrosis, mononuclear and giant cell formation so that a superficial resemblance to the lesions of Hodgkin's disease is produced. Torula infection (*Cryptococcus hominis*) is also accompanied by mononuclear and giant cell accumulations, and on several occasions has been found in association with Hodgkin's disease (see also page 344).

Brucellosis.—The histologic changes in lymph nodes in brucellosis are worthy of special mention because of the similarity of the reaction to that in certain cases of Hodgkin's disease. An important feature is the presence of large mononuclear cells of reticulo-endothelial origin, which increase in number and undergo changes in form similar to changes in cells of the same origin in Hodgkin's disease. There are produced not only large mononuclear forms, but also multinuclear and polymorphonuclear giant cells with lobulated nuclei. Many of the mononuclear cells are phagocytic, and appear within the lymph sinuses, as well as in the interfollicular and medullary portions. In advanced cases, much of the nodal structure is replaced by such cells, accompanied at times by small numbers of plasma cells and eosinophiles, and by areas of necrosis. Fibrosis also occurs in the later stages. Sometimes the focal accumulations of cells with necrosis may suggest tuberculosis, but the resemblance to true tubercles is usually superficial. The resemblance to Hodgkin's disease may also be only superficial, but with the possibility of wide variation in the histologic reaction in each disease, and the occurrence in each of the same general types of cells, the difficulty of differentiating between them must be borne in mind. The lesions described are seen only in those cases with a prolonged course.

The lymph node lesions in *lymphopathia venereum* are also of interest. They consist mainly in swelling of the node and the presence of minute abscesses filled with yellowish purulent exudate. The abscesses differ from those ordinarily caused by pyogenic organisms, in that the wall of the abscess and the surrounding tissue contains many mononuclear cells, rather than polymorphonuclear leukocytes. Other features of the disease are described elsewhere (see page 291).

Tumors of Lymph Nodes

Primary Tumors (Malignant Lymphomas)

All primary tumors of lymph nodes are malignant. They almost invariably arise either from lymphoid cells or from reticulo-endothelial cells, or their derivatives. In this connection it should be recalled that lymphocytes probably arise from reticulum cells, either directly or indirectly through the more primitive "lymphoblast" stage.

The tumor may arise from these cells at any stage in their development. For example, it may be composed mainly of small, adult lymphocytes, or of larger primitive lymphoid cells ("lymphoblasts"), or of any intermediate stage in the lymphoid series. It may consist largely of reticulum cells, with or without the formation of reticulin fibers, and occasionally with the development of bizarre giant multinuclear or polymorphonuclear forms similar to those seen in Hodgkin's disease.

The close genetic relationship of the cells involved has provided a basis for several classifications, all of which have been influenced by their author's viewpoints on cell genealogy, and none of which has been generally accepted. A further difficulty is the occurrence of intermediate forms and transitions, discussed under interrelationships.

When individual nodes are examined in the absence of complete information about the case, or without knowledge of changes elsewhere in the body, it may be impossible to designate correctly the subgroup to which each belongs. An example of this is seen in tumors composed principally of lymphocytes. Without further information it cannot be determined whether or not the tumor cells entered the blood in large numbers and, therefore, whether the condition should be called "leukemia" or "lymphosarcoma." The convenient term "malignant lymphoma" may be used to include the several varieties. Although it is desirable for purposes of study to classify the tumors as accurately as possible, it is not clear to what extent minute subdivisions are of clinical importance.

The several proposed classifications in which divisions are based on cell size, morphology, or relationships, all depend on the identification of cells by the common section technique. The disagreement of various authors as to identification and interpretation shows the need for supplementing these studies with other technical methods.

While admitting the difficulties of classification and the occurrence of intermediate forms, it is convenient to consider primary tumors of lymph nodes under the following types:

1. Tumors composed of lymphocytes or lymphoblasts
   a. With diffuse proliferation of lymphoid cells (lymphosarcoma)
   b. With increase in size and number of secondary nodules (giant follicle lymphoblastoma)
   c. With presence of tumor cells in the circulation (lymphatic leukemia)
2. Tumors composed of reticulum cells (reticulum cell sarcoma)
   a. Tumors composed of uniform cells larger than lymphocytes, with clearer nuclei, and often with small cytoplasmic processes suggesting origin from reticulum cells
   b. Tumors composed of large polymorphous cells with cytoplasmic processes, often with the formation of giant cells with polymorphous or multiple nuclei, and sometimes with an increase in reticulin fibers

Lymphosarcoma.—In tumors of this type the neoplastic cells are lymphocytes in some stage of development. Detailed study reveals cells in various stages, and it is likely that in each case cells in stages from the most primitive to the mature lymphocyte are present. Nevertheless, the great majority of cells are of approximately the same degree of maturity, resulting in strikingly uniform appearance.

In the form with diffuse proliferation of lymphoid cells, normal structures of the lymph node are obscured or destroyed by an overgrowth of lymphoid cells. Secondary nodules (germinal centers) disappear, the sinuses become filled with cells, the capsule and trabecula may be infiltrated. Mitoses are observed in all parts of the node, and pathologic mitotic figures are often present. Occasionally, isolated phagocytes containing cellular debris are scattered throughout the tissue. In the majority of cases the morphology of the cells approaches that of normal small lymphocytes (Fig. 822). Indeed, if sections alone are studied, the resemblance may be close. Cytologic studies, particularly of smears or imprints, usually disclose differences which suggest that maturity has not quite been reached.

Such cases may conveniently be referred to as the "lymphocytic" type. If, however, the predominant cell is comparatively undifferentiated, approaching in appearance that of the primitive "stem cell" mentioned elsewhere, the term "lymphoblastic" lymphosarcoma is often used.

Giant Follicle Lymphoma.—It is convenient to discuss at this point that form of malignant tumor in which the formation of numerous large follicles or germinal centers is the most significant feature. The condition was originally considered benign, and was described as "giant follicle hyperplasia" affecting lymph nodes and spleen. It is now known that the condition ultimately becomes malignant, although long periods may elapse before the clinical signs of malignancy are apparent. The essential histologic feature is the development of greatly enlarged follicles not only in the peripheral portions of the nodes where follicles are ordinarily found, but also in the central portions (Fig. 821). The enlargement of the follicles causes compression of the interfollicular tissue, and distortion of the reticular fibers. Coalescence of adjacent follicles is occasionally noted. Large follicles may be seen not only in the lymph nodes but also in the spleen.

The enlarged follicles which often occur in chronic lymphadenitis may simulate giant follicle lymphoma. In the latter condition, however, there is an increase in absolute number of follicles as well as in their size, a tendency for the "germinal centers" to coalesce, and a tendency for the follicles to become separated from the surrounding tissue when sectioned. Although the latter change is probably an artefact, Gall and Mallory[161] have called attention to its frequency in this disease, and its usefulness in diagnosis. When, in the later stages, the condition becomes malignant, the follicular structure of the nodes is lost, and the tissue assumes the characteristics of one or another of the malignant node tumors, such as lymphosarcoma or reticulum cell sarcoma, or, less frequently, of lymphatic leukemia, or Hodgkin's disease. Sometimes, the preservation of a few giant follicles in an otherwise diffuse lymphosarcoma may

suggest that the disease began as giant follicle type lymphoma.

The course of this type of tumor is of longer duration than that of other forms of lymph node tumors and the response to radiation therapy is more satisfactory. In the late stages, a change in structure may occur and the features of other forms of lymphosarcoma, lymphatic leukemia, or of Hodgkin's disease may be present.

Reticulum Cell Sarcoma.—Because reticulum cells have various capacities for development, it is not surprising that several types of tumor have been described under this name.

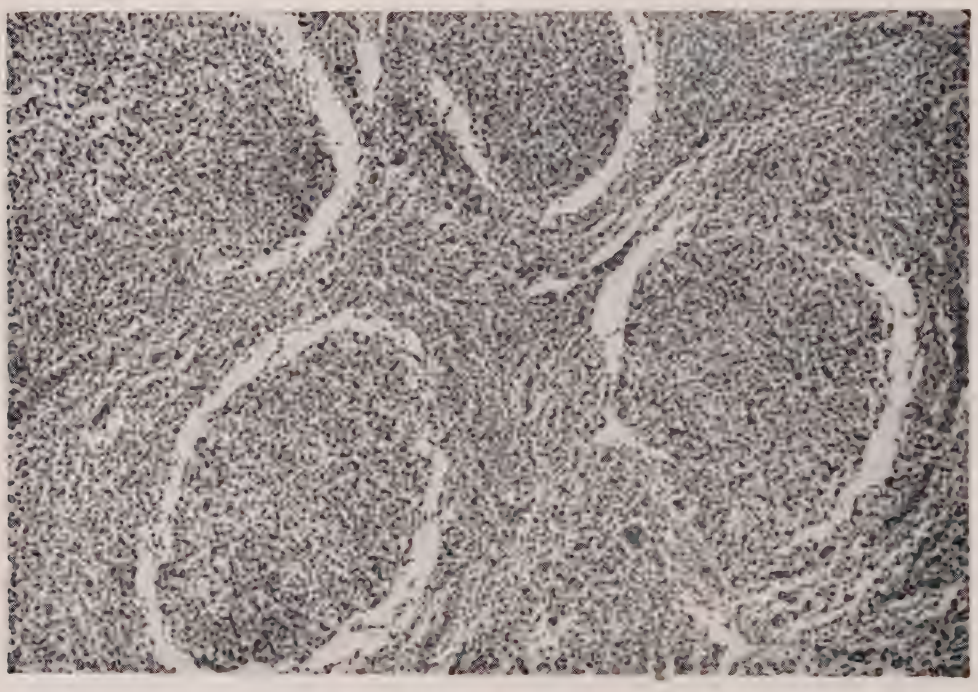


Fig. 821.—Malignant lymphoma, giant follicle type. The spaces around the follicles are artifacts due to shrinkage, and are more frequently found in the central portion of the nodes, to which the fixative penetrates less readily.

In one type, the cells are uniformly larger than lymphocytes, and have cytoplasmic processes that suggest the reticulum as their origin (Figs. 823 and 824). Reticulum fibers may be increased but this is not a constant feature. Indentations of nuclei may suggest a relation to monocytes. Gall and Mallory state that such tumors are composed not of reticulum cells, but of clasmatocytes.

Tumors in this group may simulate anaplastic carcinoma or unpigmented melanoma, from which they must be distinguished.

In another type of reticulum cell sarcoma, the most conspicuous feature is the presence of giant cells, usually polymorphonuclear or multinuclear, and often of bizarre type. Cytoplasmic processes are common, and there are intermediate stages in the development of these cells from hypertrophied reticulum cells (Figs. 825 and 826). There may or may not be an increase in reticulin fibers.

The cells of this tumor are often morphologically identical with the giant cells (Reed-Sternberg) of Hodgkin's disease. This is not surprising, as in both cases the cells are derived from the reticulum. The term "Hodgkin's sarcoma" is sometimes applied to this form but is better reserved for those cases in which there is evidence of the existence of other changes characteristic of Hodgkin's disease.

Gross Anatomical Features.—The distribution of lesions in tumors of the "malignant lymphoma" group varies from case to case. In some instances the

local growth is followed by enlargement of the regional lymph nodes, or by distant metastases. In other cases widespread enlargement of lymph nodes and of the spleen may simulate leukemia. This relationship is further emphasized if the tumor cells enter the blood stream in sufficient numbers to present a "leukemic" blood picture. The terms "lymphosarcomatosis" and "leukosarcomatosis" are applied to some of the variants, and are discussed under leukemia.

Lymphoid tumors that remain localized create the impression that they are benign lesions. In certain situations (the lower portion of the colon and rectum), "benign lymphomas" may occur, but elsewhere similar tumors nearly always show

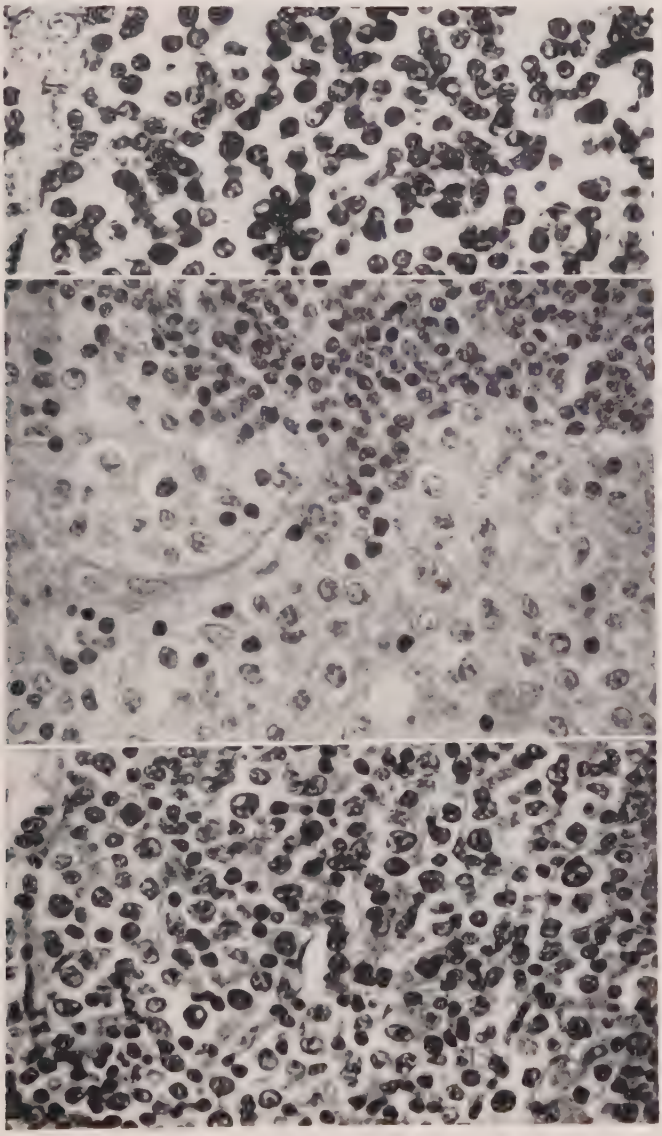


Fig. 822.

Fig. 823.

Fig. 824.

Fig. 822.—Malignant lymphoma, lymphocytic type (lymphosarcoma). Note the similarity in cell type to that in chronic lymphatic leukemia (Fig. 775).

Fig. 823.—Malignant lymphoma, reticulum cell type (reticulum cell sarcoma). The tumor cells are larger than the small lymphocytes, their nuclei are less dense, and their cytoplasm less deeply stained.

Fig. 824.—Malignant lymphoma. This is probably of reticulum cell type, as indicated by the variations in size and appearance of the cells.

evidence of malignancy, although sometimes only after long intervals.

Lymphatic Leukemia.—Although related to the other tumors of lymph nodes, the lesions in leukemia are described under Leukemia (page 893).

Secondary Tumors of Lymph Nodes

Malignant tumors very frequently metastasize to lymph nodes. Carcinomas especially spread by way of the lymphatics, and their deposits are seen in the regional lymph nodes, and later in those more distant. The metastases may be seen grossly as nodular, firm areas replacing the lymphoid tissue, or they may be of microscopic size. The smaller metastases are usually found in the peripheral lymph sinuses, but the larger ones occur in any part of the node. Complete replacement of the lymphoid tissue by the tumor is not uncommon.

Metastases in lymph nodes ordinarily have the same morphologic characters as the primary tumor and are subject to secondary changes such as necrosis and fibrosis.

Hodgkin's Disease

Hodgkin's disease is a progressive and fatal condition involving principally the lymph nodes and other lymphoid tissues of the body. Clinically, its dominant manifestation is enlargement of lymph nodes and, often, of the spleen. The disease is from two to three times as common in men as in women. It may occur

Fig. 825.

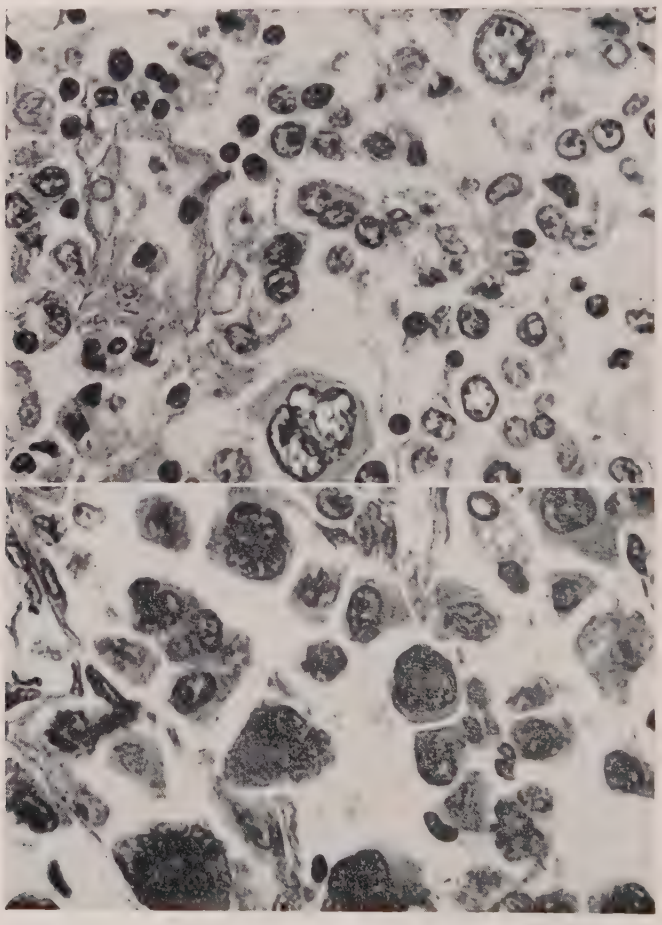
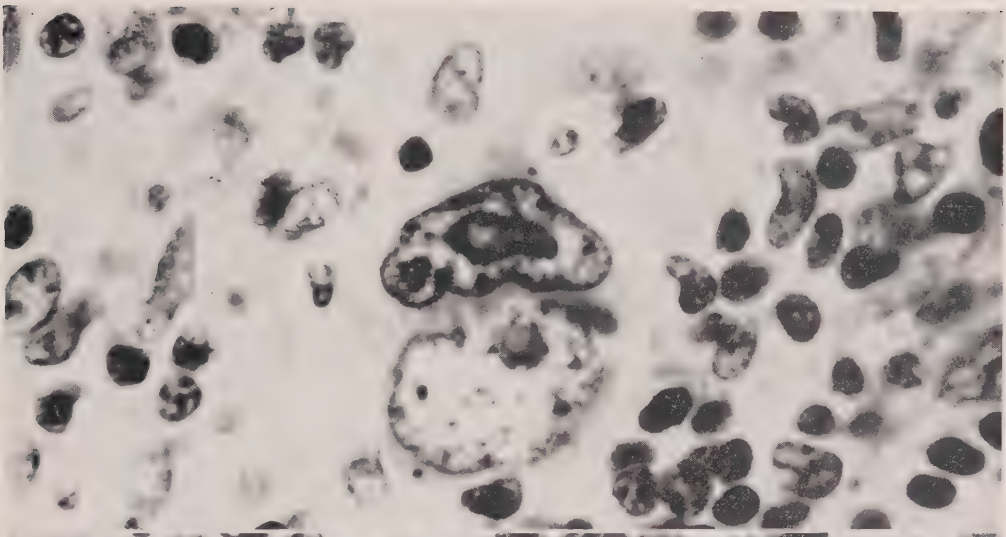


Fig. 826.

Fig. 825.—Malignant lymphoma, reticulum cell type (reticulum cell sarcoma) with occasional polymorphous giant cells.

Fig. 826.—Malignant lymphoma, reticulum cell type (reticulum cell sarcoma) with many polymorphous giant cells.

Fig. 827.



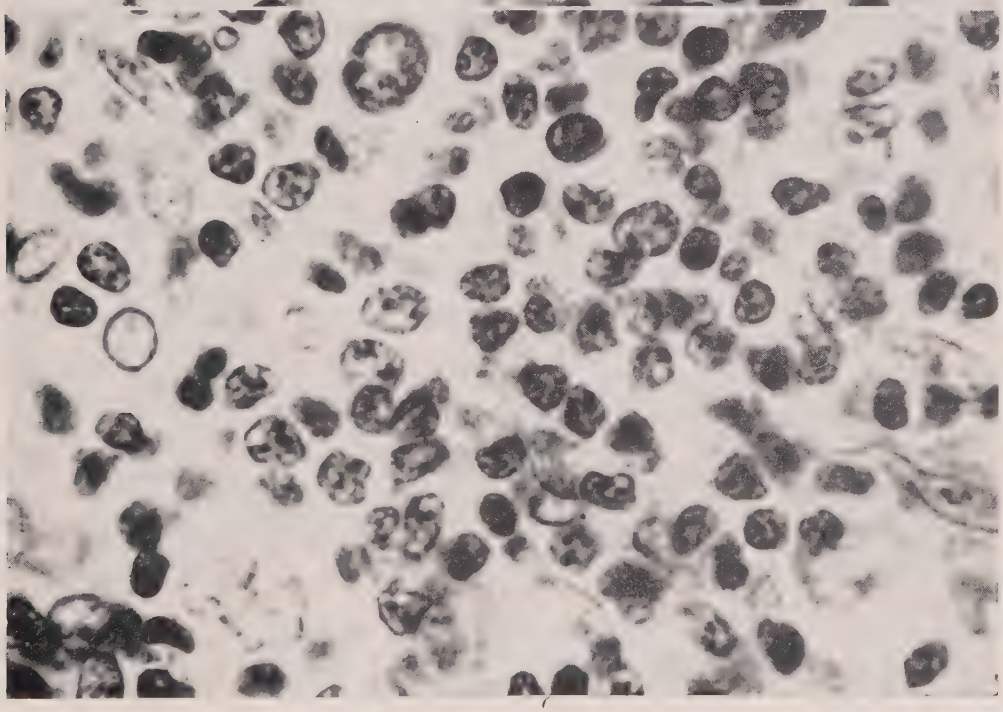


Fig. 828.

Fig. 827.—Lymph node, Hodgkin's disease. A giant cell with bilobed nucleus is seen in the center of the field.

Fig. 828.—Lymph node, Hodgkin's disease. In addition to the enlarged reticulum cells and giant cells, there is a group of cells with eosinophile granules in the center of the field.

at any age, but is most common between the ages of 20 and 40 years, perhaps because the number of individuals of this age is greatest.

Any lymph node group may be enlarged, the most common site of involvement being the cervical region. The degree of enlargement and the consistency of the nodes vary, as the alterations within the nodes change during the course of the disease.

Histologically, the changes occurring in Hodgkin's disease vary considerably from case to case, and in different situations in the same case. These variations have resulted in various interpretations regarding the nature of the disease and its relation to other conditions (neoplasms, bacterial infections, viruses).

The earliest recognizable evidences of Hodgkin's disease are enlargement and proliferation of the reticulo-endothelial cells of the lymphoid tissues, especially those of the interfollicular and intersinusoidal areas (Fig. 827). The cells are at first closely associated with other reticulum cells, but these connections are soon lost, and free cells enlarge and undergo further morphologic changes. Their nuclei become indented, then polymorphous, to form giant cells resembling megakaryocytes. Some of the giant cells have nuclei with separate lobes, and resemble Langhan's giant cells. The large mononuclear and giant cells are often referred to as "Dorothy Reed" cells or "Sternberg's giant cells" because their wide recognition as characteristic elements in Hodgkin's disease dates from the descriptions of these authors. It is not generally known that Greenfield described the cells as early as 1878. They have been erroneously referred to as megakaryocytes, but are different in origin and structure.

After the cell formation just described, other cells appear in varying numbers and proportions. Among them are eosinophilic leukocytes, plasma and other lymphoid cells, neutrophilic leukocytes, and fibroblasts. Of these, the eosinophiles are often the most conspicuous, but are not always present. Areas of necrosis are often found, sometimes involving large areas, at other times only individual cells. There is no characteristic arrangement of cells around the necrotic areas as, for example, in tuberculosis.

In the later stages there is progressive fibrosis, with reduction in the number of cells (Figs. 829, 830, 831, and 832). The fibrosis is sometimes extreme and may result in the formation of areas of fibrous connective tissue with comparatively few cells, so that a diagnosis may be difficult.

The *etiology* of Hodgkin's disease is unknown. Various organisms have been found in the tissues, either by culture or by animal inoculation, but none has been proved to be the cause of the disease. Sternberg first suggested the tubercle bacillus as the etiological agent. L'Esperance found avian tubercle bacilli in some cases and believed them to be of importance in certain forms of the disease. These views have not gained much support. It is not rare to find Hodgkin's disease and concomitant tuberculous infection in the same tissues, but the two lesions are usually distinguished readily.

Recently, Forbus[139] and his associates have found *Brucella melitensis* with suggestive frequency. This finding is of interest because some of the changes commonly found in Hodgkin's disease (reticulum cell proliferation, fibroblastic proliferation, necrosis, eosinophilia, plasma cell infiltration) are known to occur in some of the lesions caused by *Br. melitensis.* In their most recent reports, however, Forbus and his associates are still unwilling to claim an etiological relationship.

In a few instances *Cryptococcus hominis* has been found in the tissues, but there is nothing to suggest that this is more than an accidental association.

Other organisms (diphtheroids, amoebae, viruses) have been investigated with similar negative results. An ultramicroscopic substance was isolated by Gordon,[140] and found to cause characteristic paralyses in rabbits and guinea pigs on intracerebral inoculation. It appears, however, that this substance is related to the eosinophile cells, and not to the causative agent of the disease.

Many pathologists consider Hodgkin's disease a neoplasm. It is difficult to conceive of a neoplasm in which the tumor cells are of so many different types, yet one which does not belong in the category of "mixed" tumors. It would be necessary to consider the reticulum cell (Reed-Sternberg cell) as the neoplastic element, and the other cells as part of the response to its development.

In some cases of Hodgkin's disease the proliferation of the reticulum cells over-

shadows all other elements, and there is formed a tumor with the morphologic characteristics of a reticulum cell sarcoma, and with metastatic phenomena (Fig. 833). The similarity is furthered by the occurrence in some cases of reticulum cell sarcoma of giant cells indistinguishable from those of the Reed-Sternberg type. Although the criteria of distinction are not rigidly set, it seems preferable to reserve the term "Hodgkin's sarcoma" for those cases in which there is some evidence of the pre-existence (or co-existence) of the more pleomorphic form (Hodgkin's lymphoma; Hodgkin's granuloma), in the course of which a reticulum cell sarcoma has developed (compare Figs. 828 and 833). The term "reticulum cell sarcoma" is applied when such evidence is lacking. The development of a tumor in the course of some cases is not conclusive evidence that all cases are primarily neoplastic.

Grand[141, 142] has made interesting observations on the growth of lymph node tissue from cases of Hodgkin's disease in tissue cultures. He found that after from 48 to 72 hours multinuclear giant cells identified as "Reed-Sternberg" cells grew out of the cultures. These cells, as well as fibrocytes, macrophages, and lymphocytes, contained cytoplasmic inclusions within vacuoles, the inclusion being clumps of fine granules (elementary bodies?) stainable vitally by brilliant cresyl blue. Similar inclusions were not found in control cultures, but were present

Fig. 829.

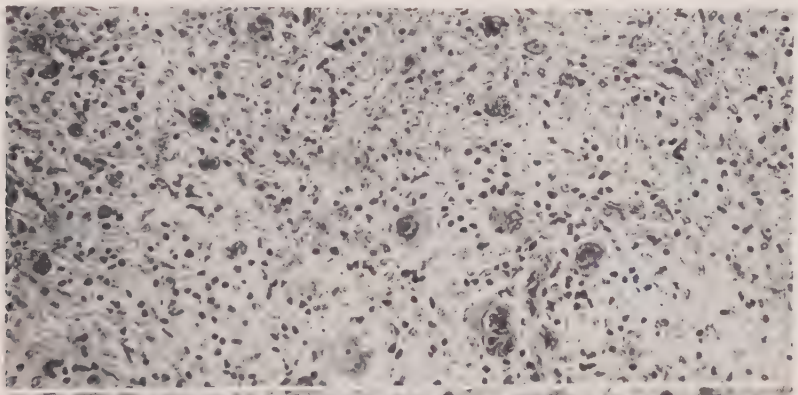


Fig. 830.

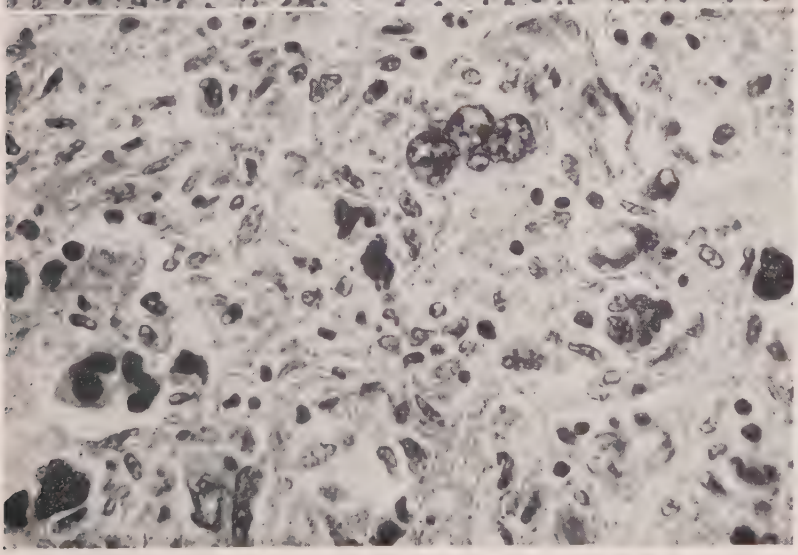


Fig. 829.—Lymph node, Hodgkin's disease. The most prominent features are the numerous giant cells and the increase in amount of fibrous connective tissue.
Fig. 830.—Lymph node, Hodgkin's disease. The giant cells are of diverse types.

when normal lymph nodes were grown in a culture medium containing a noncellular extract of nodes of Hodgkin's disease. Furthermore, the supernatant extract from cultures of Hodgkin's disease tissue, when injected on the chorio-allantoic membranes of incubated eggs, produced vesicles which when grown in tissue culture contained the same type of inclusions.

The possibility that these inclusions may indicate the presence of a virus cannot be overlooked, but further evidence is needed before such conclusions can be drawn.

The tissue culture method may, however, offer information of practical importance in diagnosis, for the giant cells growing out of the cultures were a constant finding in Hodgkin's disease and were not found in other conditions.

Interrelationships of the Malignant Lymphomas

It has long been known that cases of malignant lymphoma sometimes present features of more than one subvariety, or exhibit changes in type during their course. This not only causes practical difficulties in diagnosis, but also suggests that the different types are related to each other. Thus lymphosarcoma has been

Fig. 831.

Fig. 832.

Fig. 833.

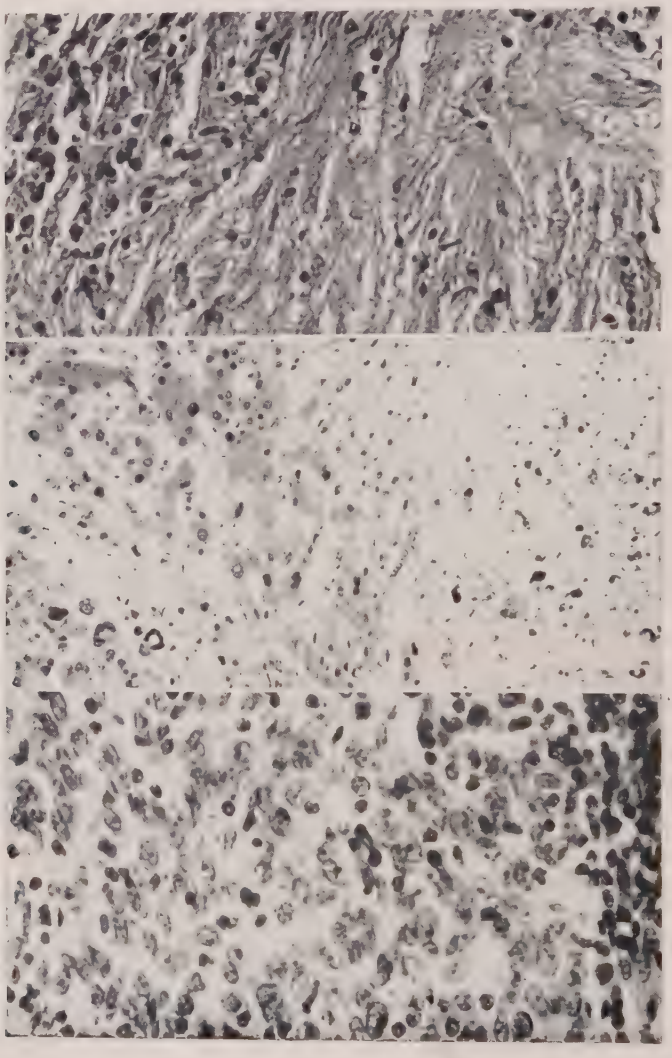


Fig. 831.—Lymph node, Hodgkin's disease. Advanced fibrosis, with depletion of cells.

Fig. 832.—Liver in Hodgkin's disease. There is extensive replacement of liver substance, especially in the portal areas. The cell types are the same as in lymph nodes.

Fig. 833.—"Hodgkin's sarcoma." This is really a reticulum cell sarcoma arising during the course of Hodgkin's disease. In the area depicted, the lymphoid tissue is replaced by a tumor composed almost entirely of reticulum cells. However, other lymph nodes and other areas of the same lymph node show different histologic pictures. Compare with Fig. 828, which is from the same case.

observed to terminate with a leukemic blood picture; Hodgkin's disease has been associated with leukemia, lymphosarcoma, or reticulum cell sarcoma; the different forms of Hodgkin's disease have occurred concurrently or in sequence; giant follicle lymphoma has terminated in any one of these "lymphoma" types. Mycosis fungoides and Spiegler-Fendt sarcoid (q.v.) are also related conditions. Custer and Bernhard have substantiated these observations by study of a large series of cases. (See Leukemia.)

Experimental evidence of the relation of leukemia and lymphosarcoma is obtained from study of such conditions in mice, in which all intermediate forms occur. Transplantation of leukemic cells may lead to the development of lymphosarcoma, or vice versa (Richter and MacDowell). The results may be influenced by the site of inoculation (Furth) or by the character of the host as well as by the inoculated cells themselves. (See references under Comparative and Experimental Studies on Leukemia.)

Lesions resembling Hodgkin's disease have been observed only rarely in animals, and it is not certain that the lesions are the same as the disease in human beings.

THE RETICULO-ENDOTHELIAL SYSTEM

Normal Structure and Function

The reticulo-endothelial system comprises certain cells known as reticulo-endothelial cells, which, although situated in many different parts of the body, bear certain similarities in morphology and in function. Their best-known function, and the one by which they are most readily identified, is *phagocytosis*. By the injection of vital dyes these cells may be demonstrated in various parts of the connective tissues, the endothelial cells of the lymph nodes, in the spleen, the liver, and the bone marrow. Recent observations have shown that certain cells formerly believed to belong to more highly specialized portions of other organs also have phagocytic properties, and their relationship to the reticulo-endothelial system is under discussion. These include cells of the supporting structures of the brain (oligodendroglia), the adrenal glands, and the heart (myocytes).

Phagocytosis is not the only property common to most cells of the reticulo-endothelial system. The ability to become cells of the circulating blood after a process of differentiation is possessed by many of them, although the varieties of cells that may be so formed, the types and sites of the cells from which they may be formed, and the conditions under which the process occurs, are still matters of controversy. The formation of antibodies is also a function of the reticulo-endothelial cells. Morphologic or functional changes in the reticulo-endothelial system may thus occur in a wide variety of diseases, and a complete discussion of the pathology of the "system" would include aspects of its participation in many conditions discussed in other chapters.

In this discussion the use of the term "reticuloendothelial system" will be restricted to include only those cells of the lymph nodes, the spleen, the liver, and the bone marrow which have phagocytic and storage properties and also the ability to differentiate into cells of the circulating blood. Specifically, these are the lining cells of the lymph nodes and the neighboring cells of the reticulum; the similar lining cells of the sinuses of the bone marrow, and the reticular and phagocytic cells between the sinuses; the Kuppfer cells of the liver; and certain cells of the diffuse connective tissues, the pulp of the spleen, and the interstices of the marrow and lymph nodes. The use of many different names for these cells is confusing, and it is therefore necessary to understand how these terms are used by various authors in order to be able to interpret their views regarding cell relationships.

The Reticulo-endothelial System in Infectious Diseases

The phagocytic property of reticulo-endothelial cells is in part responsible for the failure of certain bacteria and other organisms to attain unlimited growth after entering the body. This is evidenced by the "natural resistance" shown by certain animal species to specific infections. In some cases this resistance may be lowered if the reticulo-endothelial cells become filled with phagocytosed particles (carbon, dyes, etc.), thus reducing their capacity for phagocytosis of organisms. On the other hand, phagocytic activity is increased by immunization.

The part played by the reticulo-endothelial system in local inflammatory reactions consists mainly in phagocytosis of organisms, and in the production of the motile and fixed phagocytes which participate in the inflammation (see chapter on Inflammation).

Phagocytosis of bacteria is, in general, preliminary to their destruction. In most cases, ingestion of bacteria is followed by changes in their morphology and staining reactions, and finally by their disintegration. Certain organisms, however, resist the digestive activity of the phagocytes, at least for long periods of time. Lepra bacilli, for example, remain within the cells for a long time and disappear only gradually. Similarly, tubercle bacilli show comparatively slight changes after phagocytosis, and their disappearance is also an extended process. In Leishmaniasis the parasites remain unchanged within the cells. In all these conditions in which ingested organisms are destroyed slowly or not at all, the relative ineffectiveness of therapeutic procedures suggests that the cells of the host protect the invaders.

The reticulo-endothelial cells possess still another capacity in addition to phagocytosis. In the course of many infectious diseases there occur swelling and proliferation of these cells, especially in the lymph nodes and spleen, sometimes locally, sometimes as a widespread reaction. Local proliferation is common in the sinuses of lymph nodes, as a part of the reaction of the cells in chronic lymphadenitis. Proliferation in nodes, spleen, liver, and marrow are noted, for example, in typhoid fever.

Systemic hypertrophy and hyperplasia of reticulo-endothelial cells of unknown etiology

occur in several forms. In some of these the nature of the condition is obscure, and the diseases are poorly delineated. For example, diffuse hyperplasia occurs in a form described as "aleukemic reticulosis" or "reticulo-endotheliosis," in which the widespread hyperplasia is not unlike that seen in some leukemias. Furthermore, somewhat similar cases have been described in which leukemic cells (usually monocytoid) were found in the blood stream. The term "leukemic reticulo-endotheliosis" is often applied to such forms, and the condition is often considered synonymous with monocytic leukemia. From these observations it is evident that the distinctions between inflammatory hyperplasia and neoplasia of the reticulo-endothelial system are not clear.

Reticulo-endothelial System in Diseases of the Blood

Relation to Blood Cell Formation

The part played by the reticulo-endothelial system in the formation of blood cells has already been discussed. Briefly, it is believed that free reticulo-endothelial cells may undergo differentiation into blood cells of various types. Those cells that lie within sinusoidal vessels may become erythroblasts; those that remain extravascular may become white cells of different types, according to their environment.

Relation to Blood Cell Destruction

The role of the reticulo-endothelial system in blood destruction is better known. Visible evidence of such action is seen in the presence of erythrocytes, hemosiderin, and cell fragments within the cells.

The function of the reticulo-endothelial system in the destruction of blood elements is apparently directed to erythrocytes, leukocytes, and platelets. It is assumed that the beneficial effect of splenectomy in certain diseases associated with excessive cell destruction is due to the elimination of the body's largest single collection of reticulo-endothelial cells. (See Hypersplenism.)

Excessive destruction of erythrocytes is noted especially in most of the hemolytic anemias. Pernicious and sickle cell anemias, for example, are accompanied by hemosiderin deposits in the cells. However, it must be remembered that the presence of such intracellular deposits is not conclusive evidence of excessive phagocytic activity. Hemolysis may occur by other mechanisms (as in hemolytic anemia), and phagocytosis, when present, may represent only the metabolism and storage phases of the destroyed cells.

Excessive destruction of leukocytes has been noted in the condition of splenic granulocytopenia, in which enlargement of the spleen is associated with leukopenia. Ingestion of leukocytes by the splenic pulp cells has been described. It has also been suggested that in certain other conditions associated with leukopenia, there is a similar destructive action of the reticulo-endothelial cells, directed toward the leukocytes.

In thrombocytopenic purpura, the role of the reticuloendothelial system is not understood. Although phagocytosis of platelets has been observed in the spleen, there are other possible explanations for the thrombocytopenia. (See thrombocytopenic purpura and hypersplenism.)

The Reticulo-endothelial System in Disturbances of Lipid Metabolism

The presence of excessive amounts of lipids in cells of the reticulo-endothelial system is noted especially in three conditions, in each of which a different type of lipid predominates. These are *Hand-Schüller-Christian's disease* in which the lipids are cholesterol compounds, *Gaucher's disease* in which the substance in the cells is the cerebroside kerasin or a compound thereof, and *Niemann-Pick's disease* in which the phosphatid sphingomyelin is found.

Hand-Schüller-Christian's Disease.—This is a form of visceral xanthomatosis in which cholesterol esters are found in enlarged phagocytic cells, especially in the skull, but also in other bones, and to a less extent, in other organs. The accumulations of lipid-containing cells are often found in association with eosinophiles, giant cells, and other forms, and destruction of bone, with a resemblance to a granulomatous process. The studies of Jaffe and Lichtenstein,[89] Farber,[87] and others indicate that the condition previously described as "solitary granuloma" or "eosinophilic granuloma" of bone is a localized form of this disease. (See also discussion on page 1215.)

Small, often microscopic, foci are found in some of the organs, sometimes forming miliary-sized collections. In this form, the picture merges into that of the more widely disseminated deposits of Letterer-Siwe's disease. In fact, it has been suggested that "eosinophilic" or "solitary granuloma" of bone, Hand-Schüller-Christian's disease, and Letterer-Siwe's disease (nonlipid histiocytosis) are different expressions of the same basic disorder. Eosinophilic granuloma is the mildest form, as the lesions are often solitary, are limited to the bones, and have a tendency to heal spontaneously. Letterer-Siwe's disease represents the most serious expression of the disorder, as the lesions are widespread, occurring in various other organs besides the skeleton, and usually cause death after several months (Figs. 834 and 835). In Hand-Schüller-Christian's disease the bone lesions are most prominent in the skull, and, as a result of bone destruction and xanthomatous deposits, diabetes insipidus and exophthalmos are associated with the disease.

Gaucher's Disease.—In this condition, cells of the reticulo-endothelial system contain large amounts of kerasin. The cells in the spleen are

filled to such an extent that the resulting splenic enlargement is often greater than in any other condition. The bone marrow is also involved, and the liver and lymph nodes may also contain the characteristic cells. (Figs. 810-815.)

Kerasin is a cerebroside. It was formerly thought that its presence in the splenic and other reticulo-endothelial cells was evidence of their storage capacity for abnormal substances circulating in the blood. More recently, however, it has been suggested that the kerasin is formed in the cells where it is found, and that its presence in large amounts is due to faulty transport to other sites. This view is based on the fact that kerasin is normally formed from lignoceric sphingosine in reticulo-endothelial cells. Kerasin may not, however, occur as a pure substance. Thus Uzman[102a] suggests that kerasin is present in the form of a lipoprotein, and that the disease may result from a genetic defect by which a protein is formed which has an abnormal affinity for kerasin.

Gaucher's disease is common in children, and may often be recognized early. Except for weight and pressure symptoms due to the spleen, there may be comparatively few symptoms, so that when the condition is found in adults the duration cannot be determined. In a few instances the disease has been discovered only incidentally at necropsy, even in advanced age. The disease is familial, occurring frequently among siblings, but not in successive generations. In some instances it has been accompanied by minor congenital anomalies. Anemia of mild degree is common, but the blood shows no characteristic changes. Only rarely have Gaucher cells in the circulating blood been described. The lesions in the spleen, marrow, and lymph nodes have been described in the appropriate sections.

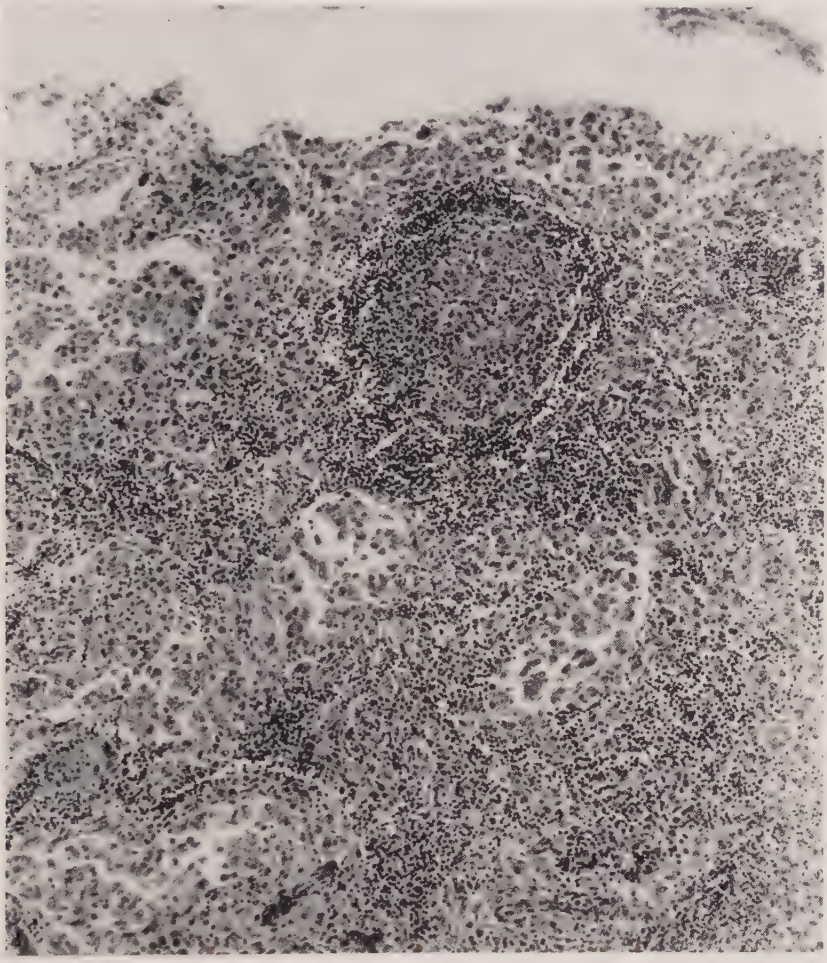


Fig. 834.—Lymph node, nonlipoid reticulo-endotheliosis (Letterer-Siwe's disease). Several nodular collections of large mononuclear cells are seen, as well as more diffuse infiltrations. (×116.)

Niemann-Pick's Disease.—This is a metabolic disease in which the cells of the reticulo-endothelial system, and also many free histiocytes of other organs, contain large amounts of sphingomyelin. This substance, like kerasin, is formed from lignoceric sphingosine, which combines with choline and phosphoric acid.

The disease occurs only in infants. It may be congenital, and no patient has lived more than two years. It is evident that constitutional factors are involved from the facts that the disease occurs more often in females than in males, is more common in the Hebrew race than in others, and often occurs as a familial condition. Involvement of the brain may lead to amaurotic idiocy, with lesions similar to those found in Tay-Sachs syndrome (see page 1313).

The group is heterogeneous. Some of the cases are examples of monocytic leukemia, which is sometimes referred to as "leukemic reticulo-endotheliosis." This is based on the assumption that the leukemic cells are derived from reticulo-endothelium, the evidence for which is not conclusive.

Another variety is known as **"nonlipoid reticulo-endotheliosis" or "Letterer-Siwe's disease."** The basic change is proliferation of reticulo-endothelial cells in various organs, but particularly in the lymph nodes, spleen, and bone marrow. Some of the lesions are in the form of small focal collections of mononuclear cells, superficially resembling miliary tubercles or Boeck's sarcoid. There is no necrosis. Some of the cells are phagocytic, and may contain ingested red cells or hemosiderin but lipoids are not demonstrated histologically. Multinucleated giant cells are often found, but are not usually numerous. Other lesions appear as diffuse proliferations of cells without nodule formation. The disease occurs in both adults and children, but with somewhat different clinical features. In adults, there is often generalized lymphadenopathy, or there may be prolonged fever, simulating typhoid fever. It is usually fatal after several months or a year. In children the disease is more acute, with fever, enlarged spleen, liver, and lymph nodes. There are commonly petechial or purpuric manifestations, or a skin lesion resembling infected eczema. Death usually occurs in about six weeks.

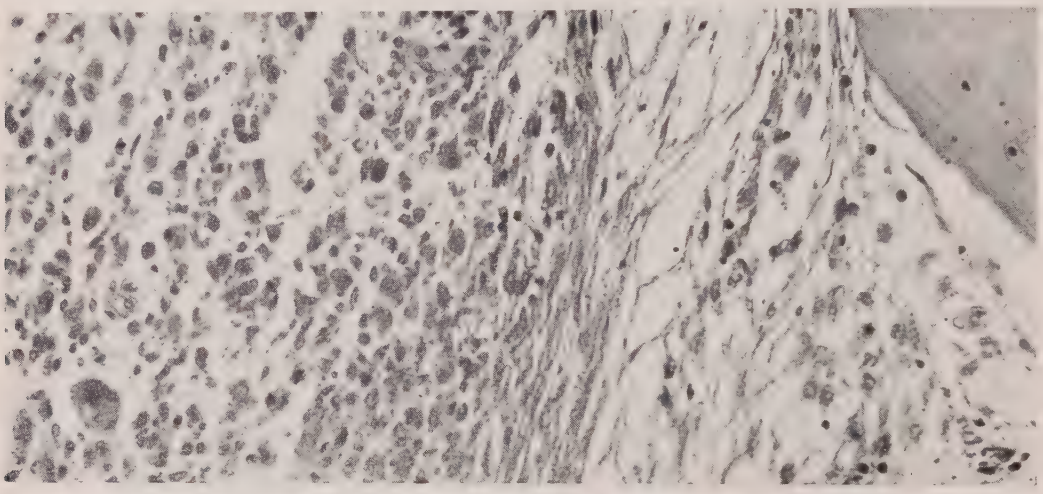


Fig. 835.—Bone marrow in Letterer-Siwe's disease. Nodules and diffuse proliferations of mononuclear cells, with a few giant cells, replace areas of the bone marrow.

The typical cells in the various organs contain numerous minute vacuoles, which gives them the appearance of "foam cells" (Fig. 816). Their appearance in the spleen is described in the section dealing with that organ. They are, however, much more widely distributed in the body than are the special cells in Gaucher's disease, and have been found in the circulating blood. Their presence in the bone marrow is of diagnostic importance, but lesions of the bony structures are not common. Involvement of the lungs, with numerous minute foci of foamy cells in the pulmonary alveoli, is frequently present.

Although chemical examination of the involved organs shows a great increase in the amount of sphingomyelin, the quantity of total phosphatids in the blood serum is low.

Diffuse Reticulum Cell Proliferation: Reticulo-endotheliosis

This term has been applied to a poorly defined group of diseases in which widespread proliferation of reticulo-endothelial cells occurs, apparently with systemic distribution.

The disease in children is thought to be related to Hand-Schüller-Christian's disease and eosinophilic granuloma of bone, as mentioned above.

Tumors of the Reticulo-endothelial System

The tumors of the reticulo-endothelial system are the same as the reticulum cell sarcomas described in the section on lymph nodes.

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Chapter 33

THE THYMUS

W. A. D. Anderson

Structure and Function

The thymus is an epithelial and lymphoid structure prominent during childhood. Its relative size is greatest at time of birth, when it weighs 10 to 14 grams, and its absolute size is greatest at puberty, when the average weight is about 35 grams. In adult life it undergoes atrophy and replacement by fatty tissue. Little factual information is available about functional activity of the thymus. By some it has been considered to have an endocrine secretion, and to have functional interrelationships with other endocrine glands. Others have considered its function to be similar to that of lymphoid organs and tissues elsewhere. It may produce lymphocytes and myelocytes. There is evidence that some cases of leukemia may be primary in the thymus.[21] Rowntree and his associates[4] have found that administration of thymic extracts to successive generations of rats results in precocity of growth and development. Shay and his collaborators[3] have found that destruction of the thymus by radiation in young male rats arrests testicular development and produces pituitary changes typical of castration, but the changes are not permanent. Definite knowledge regarding its functional importance awaits future discovery.

The weight of the normal thymus has been the subject of much investigation and controversy. It has been maintained that the thymic tissue is very labile, and undergoes rapid and marked involutionary changes during illness. Hence, normal values are found, according to this concept, only in cases of sudden or accidental death. The size of the thymus is dependent on the general nutritional state of the body, and in dehydration and undernourishment the size and weight may be less than half of normal. Approximate average weights of the thymus at various ages are as follows:

Birth	12 grams
2 weeks	16 grams
6 months	18 grams
2 years	22 grams
5 years	24 grams
10 years	26 grams
12 years	30 grams
15 years	35 grams

The epithelial elements of the thymus develop from the third, and perhaps also from the fourth, branchial pouch, in close association with the parathyroid glands. The lymphoid structures develop somewhat later in fetal life than the epithelial component. The epithelial cells form concentric collections known as Hassall's corpuscles. Like other lymphoid structures the thymus is highly sensitive to radiation. Important pathologic changes in the thymus are not common, and are mainly hyperplasia and tumor formation.

Atrophy

In addition to the physiologic atrophy which occurs after puberty, an atrophy occurs in most serious illnesses or infections of childhood. *Dubois' abscess* is a cyst of the thymus due to persistence of the embryonic duct which gives rise to the epithelial structures. It may be associated with congenital syphilis. Thymic cysts of a sufficient size to produce symptoms are very rare, particularly in adults.[20]

Hyperplasia

Hyperplasia of the thymus occurs in hyperthyroidism (Graves' disease), acromegaly, some cases of Addison's disease, and in eunuchs. In infants or young children an enlarged thymus may occasionally cause respiratory compression, and produce symptoms of dyspnea, cyanosis, stridor, etc. Characteristic giant cells may be prominent in the thymus in measles.[17]

Status Thymicolymphaticus.—The concept of status thymicolymphaticus is that of a constitutional abnormality in certain persons characterized by enlarged thymus, generalized lymphoid hyperplasia, hypoplasia of the aorta, atrophy of the adrenals, and underdevelopment of testes or ovaries. Such individuals are supposedly subject to sudden death as a result of relatively trivial stimuli, e.g., mild trauma, anesthesia, etc. It is probable that the thymus plays no role in the condition other than being part of the generalized lymphoid hyperplasia. That such a condition actually exists is often doubted.

Tumors

Tumors of the thymus (thymomas) are rare. Malignant tumors of the thymus arise either from the lymphoid elements of mesenchymal origin (lymphosarcoma) or from the epithelial structures of branchial cleft origin (carcinoma). The thymic lymphosarcomas are similar to malignant lymphoid tumors elsewhere but may be differentiated from other lymphosarcomas by the presence of some reticular epithelium. The rare thymic carcinomas may show some

concentric arrangement of the cells suggesting Hassall's corpuscles, or simply solid sheets or strands of epithelial cells, often with admixture of lymphoid cells. Mixed thymomas are composed of both reticular epithelium and lymphoid cells. The histologic appearance of this variety may suggest Hodgkin's disease. They may be differentiated from Hodgkin's disease by the larger multinucleated giant cells which are two to four times the size of the Reed-Sternberg cells of Hodgkin's disease, by the tendency to a concentric type of fibrosis with abortive Hassall's corpuscles, and by the appearance of the reticulo-epithelial cells which have a more clearly demarcated outline, coarser nuclear chromatin, and larger nucleoli. The mixed tumors are locally infiltrative. Some thymomas are well encapsulated and essentially benign. Leukosarcomas of the thymus have been described in acute leukemias.

Fifteen to 25 per cent of cases of myasthenia gravis are associated with a benign tumor of the thymus (thymoma). *Myasthenia gravis* is a condition of weakness or abnormal fatigability of muscles. It is believed due to some interference with the transmission of impulses across the myoneural junction, a condition temporarily overcome by administration of prostigmine and simulated by curare poisoning. Lymphocytic infiltrations (lymphorrhages) are found in affected muscles. The nature of the association of the condition with the thymus is uncertain. The thymic tumors sometimes have been characterized by epithelial metaplasia. In many, but not all, cases of myasthenia gravis in which thymic tumor is absent, a thymic hyperplasia of lymphocytic cells has been found, without a generalized lymphoid hyperplasia. Surgical removal of the thymus has been reported to have improved some cases but usually removal of the thymic tumor has no effect on the course of the myasthenia. Other conditions in which similar hypertrophy of the thymus, muscular weakness, and creatinuria occur, are hyperthyroidism, adrenal cortical deficiency, and castration.

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Chapter 34

THE PITUITARY GLAND (HYPOPHYSIS)

John E. Kraus

STRUCTURE AND FUNCTION

Embryology

The pituitary is a small endocrine organ situated in the sella turcica. Its main division is into anterior and posterior lobes. The anterior lobe arises from Rathke's pouch (craniopharyngeal duct) an evagination of the roof of the posterior nasopharynx. From there the cells migrate upward to reach their final position in the sella turcica. Small portions of pituitary tissue may be left along this course and give rise to epithelial tumors or simply remain as small remnants of pituitary tissue. Such ectopic nests of pituitary tissue are most often found in the pharyngeal mucosa (pharyngeal pituitary gland) or in the body of the sphenoid bone. The posterior lobe develops as a downgrowth from the floor of the third ventricle, and hence is of nervous origin. The posterior lobe becomes enveloped anteriorly by the anterior lobe.

Anatomy

The hypophysis is an approximately bean-shaped body having an average weight in the adult of about 0.63 gram[1] (0.6 gram in males and 0.7 gram in females[2]). The maximum weight is usually found in the fourth decade, after which there is a gradual decrease until the eighth decade. The size of the hypophysis has a positive correlation with stature, just as does the brain. It is about 15 per cent larger in women, and also is larger in Negroes than in white people.

The hypophysis lies imbedded in an osseous saddle of the cranial base, called the sella turcica, and is connected with the floor of the third ventricle by a stalk about 1 cm. or more in length. The hypophysis on the upper surface, facing the brain, is covered by dura mater with an opening in the middle for the stalk (diaphragm of the sella).

Two distinct parts are evident on a horizontal section through the hypophysis. The larger, which corresponds to the anterior lobe, is kidney-shaped and consists of a grayish-white or light grayish-red parenchyma with fibrous tissue at the paired hilus. The other smaller part of the hypophysis represents the posterior lobe, being rounded in shape, grayish or grayish-brown in color and fitting in the excavation of the kidney-shaped anterior lobe. Between both lobes there is a small, brownish zone, not always grossly discernible, and containing small colloid-filled follicles. This part of the hypophysis is frequently called the middle lobe or pars intermedia.

The hypophysial stalk, which connects the hypophysis with the interbrain, is covered by a thin coat of anterior lobe parenchyma extending from the anterior lobe as far as the infundibulum. This part of the hypophysis is called pars tuberalis.

It is convenient to consider the hypophysis as two parts, the adenohypophysis, consisting of the anterior lobe, pars tuberalis, and pars intermedia, and the neurohypophysis, consisting of the posterior lobe and hypophysial stalk. While convenient to use the term pars intermedia for the colloid-containing posterior portion of the anterior lobe, this does not correspond to the true pars intermedia as found in lower animals.

The hypophysis receives its blood supply through branches of the internal carotids.

There is a nervous connection between the hypophysis and the nuclei of the hypothalamus. The supraoptic and possibly the paraventricular nuclei are the sources of the tractus supraoptico-hypophyseus, which converges in the tuber cinereum toward the infundibulum through which it enters the enlarged division of the neural lobe. A few nerve fibers pass from the neural lobe through the intermediate region and reach slightly into the anterior lobe.

Histology

Anterior Lobe.—The parenchyma of the anterior lobe is arranged in solid strands of epithelial cells.

Besides cells which appear strongly stained, and therefore are called chromophiles, there are cells, the cytoplasm of which is sparse and poorly stained. These cells are called chromophobes. Among the chromophiles there are cells stained red with eosin (eosinophiles) and others, which are stained blue with hematoxylin (basophiles). The eosinophilic cells are smaller than the basophilic cells, and the stainable cytoplasmic granules are much finer and more compact. The more numerous third type is represented by the chief cells (chromophobes), which, in contrast to the chromophiles, are small and have a scanty nongranular, poorly-outlined cytoplasm.

All three cell types contain isotropic lipoid droplets in the form of small round bodies, either solid or ring-shaped, which increase in size and number with the age of the individual.

The morphogenetic relationship among the various cell types in the anterior lobe has been a matter of dispute, but evidence indicates that the eosinophiles and basophiles arise from the chromophobe cells as two independent cell types, which never pass into one another. The eosinophiles develop under normal conditions directly from the reserve of chromophobe cells, whereas

the basophiles spring either directly from the reserve cells or through the intermediation of a nongranular transitional cell.[1]

The normal numerical proportions of the three cell types of the anterior lobe are of importance, as these change radically in various physiologic and pathologic conditions. The most careful analyses are those of Rasmussen[3] and show that the eosinophiles vary from 23 to 60 per cent, the basophiles from 4 to 27 per cent, and the chromophobes from 34 to 66 per cent in different individuals. The same author studied the histology of the anterior lobe in children with regard to the changes in the proportion of cell types.[4] While the numerical proportions of the three cell types are subject to great individual differences, the location appears more or less constant, the eosinophiles occupying especially the lateral parts of the anterior lobe, the basophiles the anterior and middle part, whereas the chromophobes appear scattered through the anterior lobe and are chiefly dispersed among the basophiles. According to Plaut,[5] the anterior lobe of the newborn almost always contains small calcium concentrations.

Pars Intermedia.—The portion of the hypophysis called pars intermedia is, in human beings and anthropoid apes, a part of the anterior lobe and has nothing to do with the middle lobe or pars intermedia in animals lower than the anthropoid apes. It is characterized by follicles and small cysts filled with colloid, but the cells are not different in nature from those in the remaining anterior lobe. The parenchyma of the pars intermedia constitutes about 1.1 per cent of the glandular portion.

Pars Tuberalis.—In adults, the pars tuberalis consists of a coat of cell strands surrounding the hypophysial stalk from all sides as a continuation of the anterior lobe. The cells of the pars tuberalis belong to all three cell types, the basophilic cell being predominant, while the eosinophiles are the least in number. There are many thin-walled blood vessels, veins, sinusoids, and few arteries.

In about 32 per cent of individuals, the pars tuberalis contains groups of squamous epithelial cells without keratinization which represent rudimentary structures, remnants of the involuted craniopharyngeal canal. They are important as the matrix from which the craniopharyngiomas originate.

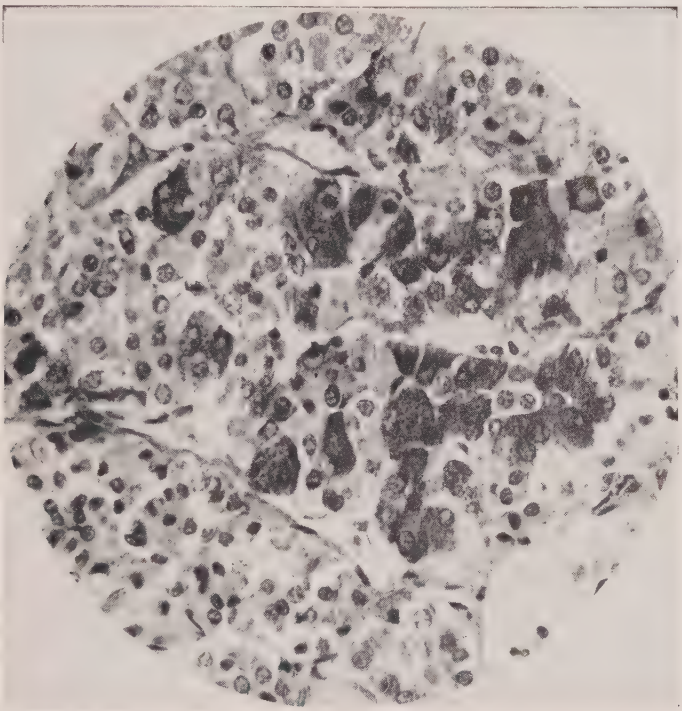

Fig. 836.—Pituitary gland. Normal anterior lobe showing all three cell types. The large dark cells are the basophiles, the smaller cells lightly stained are the eosinophiles, the small cells with scanty cytoplasm are the chromophobes.

Posterior Lobe and Hypophysial Stalk.—The posterior lobe is made up chiefly of neuroglia, which, however, differs from the glia found elsewhere. It forms a protoplasmatic network in which the round or oval nuclei are imbedded. Griffiths[8] called these glial cells "pituicytes," ascribing to them endocrine function.

Pigmented cells are almost constantly found in the posterior lobe of adults. The pigment is deposited in the thickened parts of oblong and sometimes cylindric glial cells or in multipolar giant glial cells. The nature of the pigment

is unknown. It is not present at birth, but increases in amount with age and renders the posterior lobe of aged people brown.

The posterior lobe contains, at all ages, basophilic cells in varying number.[9] This so-called basophilic invasion is a process intensified by age. The basophiles are arranged in small groups or in large areas, and begin the invasion from the adjacent parts of the anterior lobe. The basophiles in the posterior lobe degenerate and apparently give origin to brownish pigmented bodies of about the same size. Another substance found in the posterior lobe is colloid in the form of round homogeneous drops (Herring's hyaline bodies), which may also be a product of the basophilic invasion, although Gersh and Tarr[10] have regarded them as artifacts due to the fixation.

The hypophysial stalk is chiefly made up of glia, nerve fibers, and blood vessels, if one disregards the very thin epithelial layer covering especially the anterior surface, known as pars tuberalis. Nonmyelinated nerve fibers (the hypothalamic-hypophysial tract) serve as a functional connection between the hypophysis and the vegetative centers of the interbrain. The peculiar blood vessel system found in the stalk represents a link between diencephalon and the posterior lobe. A system of lymphatic channels in the hypophysis has not as yet been demonstrated.

In all parts of the neurohypophysis, but especially in the posterior lobe, large round cells frequently are found, the cytoplasm of which appears pale and extremely finely granulated. These cells occur in the small groups or tumorlike nodules. Their histogenesis is not clear. They have been considered as degenerated basophiles, or as low-differentiated neurogenic elements, or as "onkocytes" such as are found in other glandular organs (salivary glands, parathyroid, thyroid, etc.).

The Hypophysis in Pregnancy.—In pregnancy, the anterior lobe enlarges because of a marked proliferation and hypertrophy of the chromophobes. The weight of the hypophysis increases with successive pregnancies, and it averages 1.06 grams in multiparas compared with 0.83 gram in primiparas. Because of the marked cell proliferation, the hypophysis assumes a more rounded shape, so that the upper surface bulges out from the sella turcica. At the peak of their development, these proliferated cells, called pregnancy cells, are arranged in wide strands and show, when compared with the chromophobic cells from which they have arisen, a more abundant cytoplasm containing extremely fine eosinophilic granules.

After birth, the pregnancy cells undergo gradual recession, changing again into chromophobes. The number of chromophobes increases with each pregnancy, so that the hypophysis of a multiparous woman is characterized by a greater number of chief cells as compared with the hypophysis of a nulliparous woman.

The Pharyngeal Hypophysis.—In the midline of the roof of the nasopharynx, the pharyngeal hypophysis occurs in adults as an oblong organ, 5 to 6 mm. in length and 0.5 to 1 mm. in width. It is imbedded in the fibrous tissue between the pharyngeal mucosa and the cranial base and consists of alveoli with a lumen which, in aged people, contains colloid. The cells forming these alveoli are the same as in the anterior lobe.

The Physiologic Significance of the Hypophysial Cells and Their Products

Many functions of the hypophysis are known, but their relationship to the various cell types is only partially clarified. The eosinophilic cells are certainly the producers of the growth hormone, yet they also play a part in sugar metabolism, since they are probably the elements that produce the diabetogenic factor. The gonadotropic hormones seem to be produced in the basophilic cells, but these cells also appear related to fat and cholesterol metabolism and blood pressure. The same cells also seem to produce the adrenocorticotropic hormone, the so-called ACTH, which plays such an important part in the treatment of collagen diseases, certain inflammatory lesions of the skin, eye, bowel, in congenital hypoglycemia, etc. The task of the chromophobe cells is to produce chromophiles as well as pregnancy cells. The function of the latter is not known with certainty, but it may be assumed that they are important for growth of the fetus and play a role in the initiation of the lactation.

The lipoid granules in the epithelium of the anterior lobe do not represent products of a specific secretory activity, but rather breakdown substances of cellular metabolism. The colloid of the hypophysis usually is not considered an active endocrine product, though it contains gonadotropic hormone. Colloid globules found in the neurohypophysis may not represent a vehicle for the hormones passing through the hypophysial stalk to the interbrain, but it has been ascertained that the gonadotropic hormone takes this route.[18] It is unlikely that the pigment of the posterior lobe has any endocrine action; rather, it might represent a wear-and-tear product, as are many other pigments of the human body.

DEVELOPMENTAL DISORDERS OF THE HYPOPHYSIS

Heterotopy

The complicated embryonic processes in the hypophysial region create conditions favorable for heterotopy of various sorts of tissue, some of which may originate tumor growth. Most important is the displacement of squamous epithelium, found in adults in more than 50 per cent of the cases in the pars tuberalis, the upper and anterior surface of the anterior lobe, sometimes in the upper portion of the pars

intermedia, and also in the pharyngeal hypophysis. These squamous cells never show cornification but sometimes central liquefaction resulting in tiny cysts. Representing derivatives of the craniopharyngeal canal, they constitute the matrix for the craniopharyngioma, one of the most important pituitary tumors.

In contradistinction to the craniopharyngioma, another epithelial tumor, the cholesteatoma, sometimes found in the neighborhood of the hypophysis, is derived from displaced particles of the epidermis. The existence of keratohyaline granules in these tumors supports this opinion.

Salivary Glands, Ciliated Epithelial Cysts, Ependymal Cysts, in the Hypophysis

Small accumulations of tubular glands morphologically similar to salivary glands are found in the posterior lobe, usually very close to the colloid cysts of the pars intermedia. They are believed to be derived from the buccal cavity. By retention of secretion, they may become dilated and hard to distinguish from colloid follicles of the pars intermedia. Cysts lined with ciliated epithelium have been found in the par tuberalis close to the anterior lobe, in the anterior lobe and in the pars intermedia. The location of these cysts in the midline suggests their origin from the craniopharyngeal canal or from the nasopharynx. In rare instances, these cysts may enlarge to the size of a plum, causing severe symptoms. Also, rarely, the recessus infundibuli may extend as far as the hypophysis, and small cysts lined by ependymal epithelium in the infundibulum or hypophysial stalk may arise by partial obliteration of the recessus.

In about 10 per cent of pituitary glands, foci of lymphocytes may be seen in the pars intermedia, less often in the other parts of the anterior lobe or in the posterior lobe. They have been interpreted by some as derived from the buccal cavity and by others as sequelae of a chronic infection.

Persistence of Fetal Structures

Ribbonlike strands of narrow, high, cylindric cells closely attached to the capillary wall in the form of palisades are not uncommonly found in the anterior lobe, especially in the lateral parts. They apparently represent undifferentiated embryonic remnants ("fetal cells") and may give rise to tumors called "fetal adenomas," which may be benign or malignant.

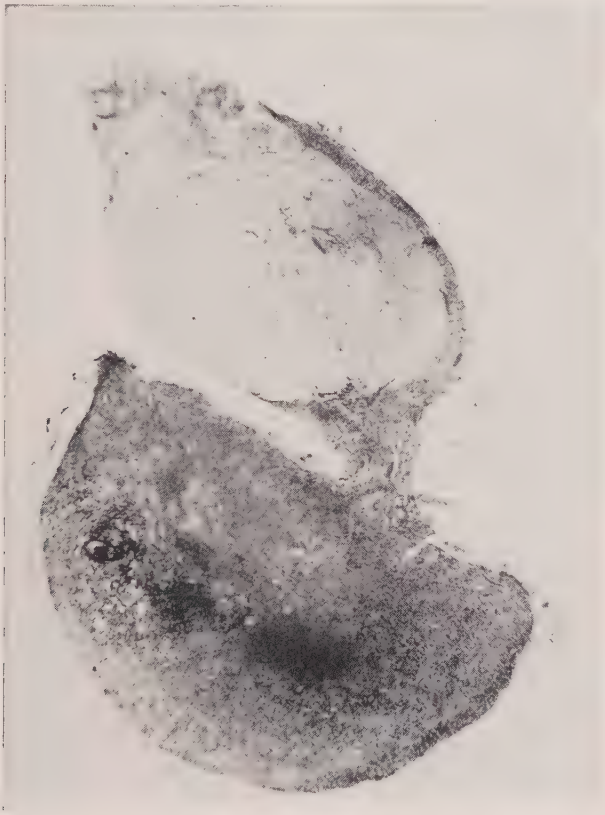

Fig. 837.—Dystopia of the neurohypophysis. The latter is lodged within the pituitary stalk.

The persistence of the craniopharyngeal canal is a rare event when there is normal skull formation, but is rather frequent in association with malformed skulls, especially in anencephaly. In a few cases of acromegaly and gigantism, the canal also has been found patent. The upper end of the canal is found at the bottom of the sella turcica and the lower end at the inferior aspects of the sphenoid bone. Lodged in the midline, it penetrates the sphenoid either completely or partially. In teratomas of the hypophysial region, especially those of the epignathic type, the craniopharyngeal canal usually is found open.

While in postnatal life the cyst of Rathke normally obliterates, being replaced by an area of colloid-filled follicles, in rare instances it may persist in the form of a spherical cavity filled with a gelatinous brownish mass. Severe functional disturbances may result because of the separation and compression of the two hypophysial lobes.

Agenesis and Hypoplasia of the Hypophysis Including the Changes in Anencephaly

Congenital absence of the hypophysis is a very rare anomaly. More frequent is hypoplasia of the entire organ or one of its parts. In anencephaly a severe involvement of the hypophysis is almost always found. The hypophysis is not absent, but easily overlooked. The shape of the hypophysis in anencephaly depends much on the form of the cranial base, which varies considerably. The most characteristic feature of the hypophysis in anencephaly is the underdevelopment or lack of the neural part and, of course, the lack of connection with the brain. Usually only the anterior lobe exists, and the posterior lobe is missing, or the posterior lobe is stunted and demonstrable merely microscopically. The pars intermedia may or may not be present.

Dystopy of the Hypophysis

Aside from the displacement of the hypophysis in certain cases of anencephaly (canal hypophysis), there is a special type of hypophysial dystopy involving exclusively the posterior lobe. The lobe may be fused with the tuber cinereum or displaced into the hypophysial stalk, thus causing it to have a spindle-shaped thickening. More rarely, the posterior lobe appears fused with the upper surface of the anterior lobe with thickening of the lower (distal) end of the stalk. Dystopy of the neurohypophysis may be important as a cause of hypophysial dwarfism or adiposogenital dystrophy.

Teratomas of the Hypophysis

The hypophysial region is a common location of teratomas because of the fact that in this region many different tissues come into contact. Most of the teratomas of the hypophysial region are epignathic teratomas, usually found in premature fetuses, and protruding into the pharynx or oral cavity, or extending out of the mouth. These tumors can be traced through the sella turcica into the intracranial space. Originating within the craniopharyngeal canal and growing in both directions toward the brain and toward the pharynx, these teratomas assume a typically hourglass shape with a waistlike constriction in the middle.[24] Some tumors described in the literature as teratomas appear to be craniopharyngiomas altered by old hemorrhages and degenerative or metaplastic changes.

RETROGRESSIVE CHANGES OF THE HYPOPHYSIS

Atrophy

In aged people, one may see the hypophysis decreased in size, sometimes with a concave depression of the upper surface around the insertion of the stalk. Usually late in the sixties, the eosinophilic cells show decrease in size and number with partial loss of their granulation, while the basophilic cells, as a rule, increase in number with age. A more marked invasion of the posterior lobe by basophilic cells and a more intense pigmentation of it also belong to the characteristics associated with aging.[11]

Under pathologic conditions, atrophy of the hypophysis may be found together with atrophy of the brain in senile dementia, paresis, dementia precox, severe arteriosclerosis, and in chronic wasting diseases such as tuberculosis and carcinoma. Prolonged starvation decreases the weight of the hypophysis to about 0.5 gram, with diminution in the number of eosinophilic cells.

Atrophy of the anterior lobe with increase of the interstitial tissue has been described in myxedema and cretinism. In Graves' disease, the hypophysis is decreased in weight and retrogressive changes may be found in all cell types.

Benda[12] described diminution of basophilic and chief cells (with apparent increase of the eosinophiles) in mongoloid idiocy.

Long-lasting pressure on the hypophysis may result in atrophy. The hypophysis is most affected by tumors which arise within the organ itself, the sella turcica, or above the hypophysis, as in the case of a suprasellar craniopharyngioma. Increased intracranial pressure due to space-occupying lesions, such as tumors of the brain and meninges, and chronic hydrocephalus usually does not cause atrophy of the hypophysis provided that the pituitary stalk is not destroyed.

While the hypophysis usually does not undergo atrophy due to increased intracranial pressure, the sella readily yields to the pressure and becomes wider and deeper with the floor markedly thinned, and even entirely destroyed.

Destruction of the hypophysial stalk, which may occur with suprasellar tumors, inevitably is followed by atrophy of the hypophysis, particularly the anterior lobe. Since the hypophysis and the diencephalon represent a functional entity, both parts being connected by nervous tracts and a special system of blood vessels, and as the hypophysial hormones pass through the

stalk to the diencephalon, it is easily understandable that destruction of one part results in retrogressive lesions in the remaining part of the system. Thus one sees atrophy of the hypophysis, not only in destruction of the stalk but also in destruction of the diencephalon if the lesion has lasted long enough.[13]

Circulatory disorders may lead to atrophy of the hypophysis, especially of the anterior lobe. Atrophy of the hypophysis may be the result of chronic inflammation, such as tuberculosis and gumma, or scars resulting from them. In rare cases, fracture of the skull base may give origin to atrophy of the hypophysis, the parenchyma of which becomes partially replaced by scar tissue. Unknown in etiology is the atrophy of the anterior lobe found in Falta's multiple sclerosis and in Lindemann's multiple atrophy of the endocrine glands.

Necrosis

Necrosis is not a rare lesion in the hypophysis. Severe retrogressive lesions, including cell necrosis, may be found in the hypophysis in diphtheria and other toxic and infectious conditions, and following intensive irradiation of the hypophysis. The majority of necroses result from vascular disorders. In addition to embolism, necrosis in the hypophysis arises from arterial thrombosis, vascular obstruction by syphilis and atherosclerosis, and also from thrombosis of veins or thrombophlebitis, particularly of the venous circle of Ridley. This has been described in cases of sinus cavernosus infection, purulent meningitis, and purulent osteomyelitis of the sphenoid bone.[14, 15]

It remains to be determined whether the necrotic foci sometimes seen in the anterior lobe in eclampsia are toxic or ischemic in nature. In toxic separation of the placenta and secondary to severe necrosis of the anterior lobe, hypophysial stalk, and tuber cinereum, together with bilateral cortical necrosis of the kidneys, obstetrical shock has been described.[14, 15]

Crooke called attention to certain retrogressive changes of the basophilic cells in Cushing's disease. Here the basophilic cells undergo hyalinization, which replaces the specific cell granules. (See page 985.)

CIRCULATORY DISTURBANCES OF THE HYPOPHYSIS

Chronic passive congestion, particularly marked in congenital heart disease, may cause atrophy of the parenchyma in the anterior lobe with narrowed cell strands separated by greatly dilated blood vessels. Marked hyperemia of the anterior lobe is seen in anencephaly where the capillaries may considerably exceed the cell strands in width. Another condition causing marked hyperemia in the anterior lobe is polycythemia.

Hemorrhage in the hypophysis may be seen in fracture of the skull base, in brain concussion, tetanus, sepsis, typhoid fever, miliary tuberculosis, etc. Most of these hemorrhages are small. Large hematomas are rare, but may be produced by a severe trauma.

Relatively frequent is the infarct of the anterior lobe characterized, apparently always, by anemic necrosis. It is yellowish-white in color and firm in consistency. The size ranges from tiny wedge-shaped areas up to infarcts that have destroyed the whole of the anterior lobe with the exception of the pars intermedia.

Symmetrically arranged infarcts commonly occupy the lateral parts of the anterior lobe, but the pars intermedia and the posterior lobe as a rule are uninvolved. Hypophysial infarcts are seen in generalized septic infections, in verrucous and ulcerative endocarditis, vessel sclerosis and syphilitic endarteritis, but mainly after parturition. While hypophysial infarcts developing in the puerperium were formerly considered embolic in nature, in many instances no embolism is demonstrable, and often there was a normal afebrile puerperium. The cause of the anemic infarcts may be thrombosis, which probably develops about the first day after delivery in connection with severe hemorrhages and vascular collapses, while puerperal sepsis is a less frequent etiological factor.[16-18] Scars in the anterior lobe without clinical symptoms found in multiparous women have been interpreted as secondary to a puerperal necrosis of small size.

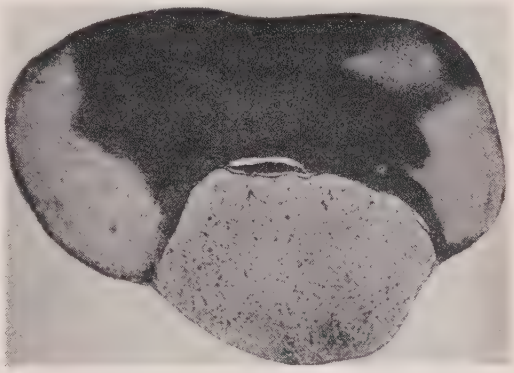

Fig. 838.—Symmetrically arranged anemic infarcts of the anterior lobe. (From Henke and Lubarsch, Handbuch der speziellen pathologischen Anatomie und Histologie, Julius Springer.)

INFLAMMATORY PROCESSES OF THE HYPOPHYSIS

Nonspecific Inflammation

Among inflammatory lesions of the hypophysis, the acute purulent inflammation probably is the most important, although hypophysial abscesses are not uncommon. In most cases, the abscesses are caused by staphylococci or streptococci, and occur in septic endocarditis, or in bronchiectasis and chronic inflammatory processes of the lungs and pleura.[19] These hematogenous abscesses are found, as a rule, in the posterior lobe and in the hypophysial stalk, whereas infected emboli in the anterior lobe usually cause anemic infarcts and, less often, abscesses. Very rare are embolic abscesses due to pneumococci.

Another mode of infection of the hypophysis is by extension from an adjacent area, as from purulent meningitis, suppuration of the cavernous sinuses, purulent osteomyelitis of the sphenoid bone, or purulent sphenoidal sinusitis, with the infection entering the hypophysis obviously along the blood vessels.[19] The entire hypophysis may be involved and converted into a sac filled with pus. Several cases of purulent inflammation of the hypophysis have been reported as originating from a suppurative otitis media. Nonpurulent inflammation of the hypophysis is rare.

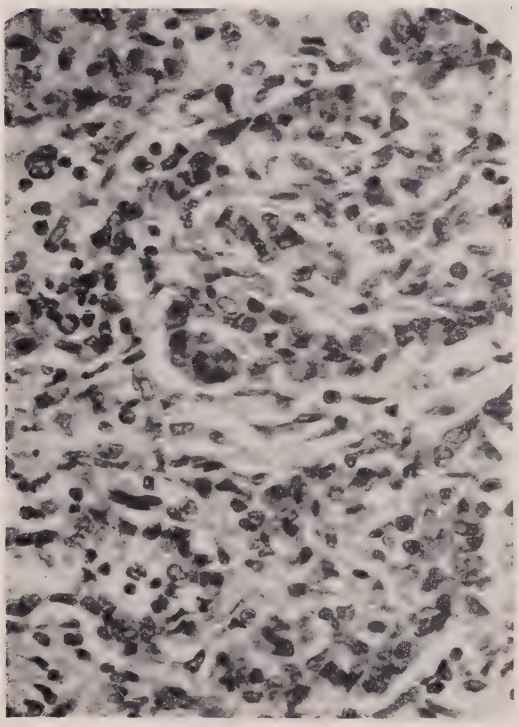

Fig. 839.—Interstitial hypophysitis in congenital syphilis. Notice the spindle cell proliferation and the stunted and entirely atypical glands of the anterior lobe.

Specific Granulomas

Tuberculosis of the hypophysis is not so rare as was believed formerly. Miliary and larger caseous tubercles occur. Tuberculosis of the hypophysis is either hematogenous in origin, or has extended to the organ from the neighborhood, e.g., from the meninges, the brain, or sphenoid bone. Chronic tuberculosis has been found to be a cause of Frölich's disease and pituitary cachexia. (For literature, see Kirschbaum and Levy.[20])

Syphilis of the hypophysis may be seen in congenital syphilis as an interstitial hypophysitis, chiefly characterized by an abundant spindle cell proliferation, just as is seen in the liver and other parenchymatous organs of syphilitic infants. Acquired syphilis or gumma of the hypophysis is rare.[21-24]

Sarcoidosis or Besnier-Boeck-Schaumann's disease may involve the hypophyseodiencephalic system, and has been reported with diabetes insipidus, and in one case with hypogenitalism and polyuria.[25] The granuloma may involve all parts of the hypophysis, first of all the neurohypophysis. This explains the relatively high incidence of diabetes insipidus in cases of generalized sarcoidosis. **Hodgkin's granuloma** in the hypophysis is rare, but adiposogenital dystrophy and diabetes insipidus have been caused by it. In **Hand-Schüller-Christian's disease,** involvement of the hypophysis is one of the characteristic features. The outstanding symptoms are multiple defects of the skull, exophthalamus, and diabetes insipidus. The last symptom is the result of the destruction of the posterior lobe by the granuloma extending to the hypophysis from the sella turcica, particularly the dorsum sellae. Rarely the granuloma causes adiposogenital dystrophy by destruction of the anterior lobe with or without involvement of the floor of the third ventricle. **Actinomycosis** of the hypophysis is rare.[26]

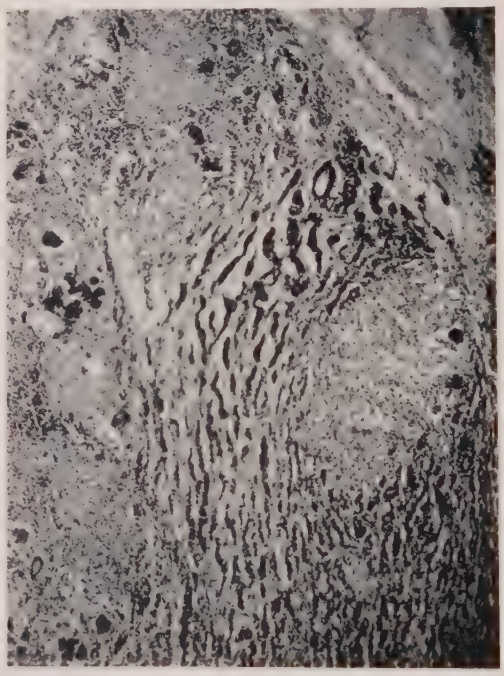

Fig. 840.—Sarcoidosis (Boeck) involving both lobes of the hypophysis.

HYPERPLASIA

The hyperplastic changes in the adenohypophysis may involve either one or more cell types, thus leading to enlargement of the organ, or the hyperplasia of one cell type may take place at the expense of other cell types, in which case the hyperplasia need not result in an enlargement of the organ.

The Hypophysis After Castration

Enlargement of the hypophysis in castrated animals has been known for a long time. The histologic picture of the hypophysis in castrated animals is not uniform, but increase in eosinophilic cells is common to most mammals. Castration in women is followed, as in experimental animals, by enlargement of the hypophysis with multiplication and heterotopy of the eosinophilic cells and with a decrease in the number of basophilic cells.[27, 28] In contrast to hypophysial changes, secondary to castration, the hypophysis was not altered in a case of agenesis of the ovaries studied by the author. Physiologic loss of the ovarian function in the climacterium is not followed by hyperplasia of the eosinophilic cells.

In cases of spontaneous myxedema in adults, observers have described enlargement of the hypophysis, increase in colloid, thickening of the cell cords, enlargement or proliferation of the chromophilic cells, proliferation of chief cells only, or proliferation of all cell types with the chief cells prevailing. In some reports, the hypophysis is called normal or only enlarged, but cytologically not altered. In other cases of myxedema due to fibrous atrophy of the thyroid gland, the hypophysis was found diminished in size, the stroma was thickened, calcium concretions were deposited in the pars intermedia, and colloid follicles were scattered through the anterior lobe. In postoperative myxedema and thyroprival cachexia the hypophysis usually is enlarged, but the histologic picture is variable.[29, 30, 31]

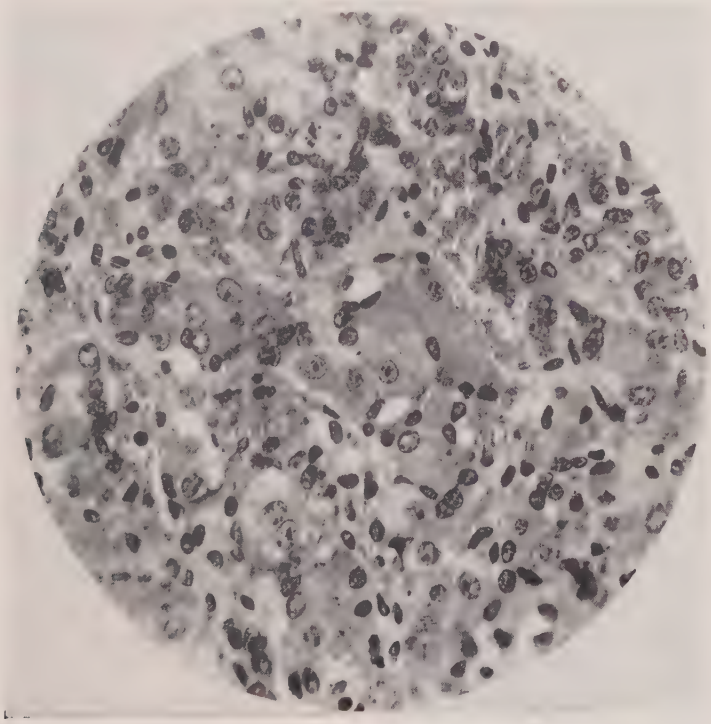

Fig. 841.—Pituitary gland. Thyroprival cells in a case of thyroaplasia. Notice the exceedingly large nongranular cells.

The Hypophysis in Hypothyroidism

Deficiency of function of the thyroid gland causes hyperplastic changes in the hypophysis. In cases of congenital absence of the thyroid, or thyroid hypoplasia with cretinism, the hypophysis appears enlarged. The increase in size is due to the proliferation of a special cell form which often has been compared with the pregnancy cell. This cell is larger than the eosinophile and is more numerous than the basophilic cell. It possesses an ill-defined cytoplasm and a very delicate eosinophilic granulation (Fig. 841).

The Hypophysis in Malignant Tumors

Several investigations have indicated that malignant tumors, both carcinoma and sarcoma, but especially the former, cause hyperplastic changes in the anterior lobe of the hypophysis. The chief cells have been reported to be increased in number in about 50 per cent of the cases. Kraus examined seven cases of carcinoma of the genitals in females, some of whom had excreted prolan (gonadotropic hormone) in the urine, and found the average weight of the hypophysis increased to 0.85 gram. This was associated with proliferation of

the eosinophiles especially. In cases of sarcoma and melanoblastoma, the hypophysis may be remarkably enlarged and show abundant eosinophilic cells.

Significant are the enlargement and cellular changes of the anterior lobe in cases of chorionepithelioma in women as well as in men. The histologic picture of the anterior lobe shows the chief cell converted into cells typical of pregnancy cells.[32] In cases of chorionepithelioma of the testis in which there are gynecomastia, secretion of colostrum, and elimination of follicle-stimulating and luteinizing hormones, the hypophysis has been found enlarged with the chief cells hypertrophic or transformed into cells very similar to pregnancy cells.[33]

The Hypophysis in Hypertensive States, Constitutional Obesity, and Some Other Conditions

Berblinger first noted increase of basophilic cells in the hypophysis in hypertensive individuals. He found it most frequently with uremia (87.5 per cent of the cases) and malignant nephrosclerosis (83.3 per cent). In benign nephrosclerosis, basophilic hyperplasia was found in 76.2 per cent of the cases, and in chronic glomerulonephritis in 61.5 per cent. The basophilic cells are increased also in individuals with so-called "constitutional" obesity, and in healthy men of the hypersthenic or athletic type.[35] These are also conditions in which the adrenals tend to be large, and there appears to be some correlation between adrenal hyperplasia and increase of basophiles in the hypophysis. The evidence suggests that the basophilic cells represent a part of the mechanism controlling blood pressure.

Also, in view of the possible significance of the blood cholesterol in hypertension, it is of interest to note that there seems to be a correlation between the concentration of that substance and the number of basophilic cells in the hypophysis.

The problem of the so-called basophilic invasion of the posterior lobe and its relation to hypertension frequently has been investigated and discussed in recent years. Some authors are inclined to attribute pathogenetic significance to the "basophilism" of the hypophysis in general or to the basophilic invasion of the posterior lobe in particular.[36] It appears probable that the inconstant "basophilism" of the hypophysis, including the posterior lobe, in cases of eclampsia is a secondary phenomenon attributable to the hypertension, to the renal disease, or to obesity. Though all investigators agree that the basophilic cells of the hypophysis are increased in the majority of hypertensive cases, most of them do not believe in the etiological significance of this finding. Rather, the "basophilism" in hypertensive cases might be a compensatory measure on the part of the basophilic cells, which seem to represent a part of the mechanism controlling the blood pressure.

Hyperplastic Changes of the Hypophysis in Cushing's Disease and Some Rare Types of Obesity

As far as Cushing's disease is concerned, hyperplastic changes of the basophilic cells have been observed in only a few cases, in which numerous small foci of newly formed basophiles, rather regularly scattered through the anterior lobe, were found. Against that, the majority of cases show a basophilic adenoma, and in a minority of cases no proliferation of basophiles whatever has been encountered.

In the syndromes to be discussed in the following paragraphs, hyperplastic changes of the hypophysis seem to be a rather constant finding. These conditions are the syndrome of Morgagni-Stewart-Morel, cerebral hyperglobulia, Dercum's adiposis dolorosa and the Laurence-Moon-Biedl syndrome.

Only scanty and rather conflicting reports on the hypophysis in the **syndrome of Morgagni-Stewart-Morel** or **Morgagni's syndrome** are found in the literature. This syndrome, which chiefly involves females, is characterized by obesity, amenorrhea, virilism, headaches, weakness, mental changes, visual disturbances, polyphagia, polydipsia, polyuria, and hyperostosis of the skull, either diffuse or more often limited to the frontal region and known as **hyperostosis frontalis interna.** The fact that, in some of these cases, acromegalic changes have been found and observed early called attention to the hypophysis. Henschen[37] found an adenomatous hyperplasia of the anterior lobe made up of eosinophilic as well as basophilic cells and, furthermore, reduction of the chief cells and basophilic invasion in the posterior lobe. According to Morel,[38] either hypertrophy or tumors of the hypophysis with damage to the infundibular region and the third ventricle are found in the hypophyseodiencephalic system.

Basophilic hyperplasia of the hypophysis and hyperplasia of the adrenal cortex have been found in **cerebral hyperglobulia,** a syndrome characterized by obesity, hyposexuality, narcolepsy, and polycythemia. Increase in weight of the adrenals and hypophysis, with excessive proliferation of basophilic cells in the anterior lobe of the latter, have been found in such cases. The changes found in the hypophysis and adrenals are not the cause of the syndrome but probably represent a part of the disturbance in the fat metabolism, which leads to the obesity. The same changes may be found in other types of obesity, such as constitutional obesity, Cushing's disease, Morgagni's syndrome, etc. The polycythemia may have a causal connection with the changes in hypophysis and adrenal cortex, since this sign is often associated with tumors of these structures. Polycythemia is not a rare finding in Cushing's disease, and several times has been associated with hyperfunction of the adrenal cortex.

There are numerous reports on findings in the hypophysis in **Dercum's disease or adiposis dolorosa.** They differ considerably and are mostly not very accurate. Some mention hyperplastic changes of the anterior lobe, but more

frequently tumors are reported. The disease, chiefly involving women, is characterized by huge, more or less circumscribed masses of subcutaneous fat tissue, which are very painful. In addition to the painful obesity, asthenia, fatigability epileptiform seizures and mental disturbances, bullae or ulcers on the extremities can be observed. Dercum and McCarthy[39] found an adenocarcinoma of the hypophysis and enlargement of the right adrenal; Burr,[40] a walnut-sized glioma of the hypophysis; Guillain and Alquier,[41] considerable enlargement of the hypophysis with increased fibrous tissue; Foot, Good, and Menard[42] described an adenomatous hyperplasia besides sclerosis of the hypophysis and bilateral suprarenal adenomas; and Winkelman and Eckel[43] saw an adenoma of the hypophysis with enlargement of the sella turcica and adenomatous hyperplasia of the adrenal cortex. No statement is made concerning the type of cells of which the hypophysial new growths (adenoma or hyperplasia) were composed.

Obesity and genital dystrophy are the two cardinal symptoms of the **Laurence-Moon-Biedl syndrome,** which in addition is distinguished by retinitis pigmentosa and a number of congenital anomalies, the most frequent being polydactylism and syndactylism. The disease shows familial occurrence. Other symptoms may be mental deficiency, bilateral cataract, skull deformities, and genu valgum. Until 1936, no autopsy findings were known. Then Bogaert and Borremans[44] reported an autopsy which revealed a slight enlargement of the sella turcica together with a small area devoid of nuclei within the hypophysial stalk, indicating apparently a circumscribed necrosis. In a case described by Loepp,[45] the sella was enlarged and contained a cyst with epithelial rests in its wall. In three other cases there was a strikingly high proportion of basophilic cells and relative paucity of eosinophilic elements. F. Anderson[46] found 42 per cent basophiles compared with the normal average of 15 per cent, and mentioned the absence of Crooke's hyaline change as seen in Cushing's disease. The fact that the syndrome is familial and displays so many malformations as regular findings, indicates that genetic factors play a decisive role in its pathogenesis and that it is not to be considered merely as an endocrine disorder.

The various types of obesity discussed in this section have a resemblance because of certain common features, such as disturbance in fat metabolism, hypogenitalism, proliferation of the basophilic cells in the hypophysis and hyperplastic changes of the adrenals. This fact suggests the importance of these two endocrine organs in the sexual sphere as well as in fat metabolism and its disorders.

Regenerative Hyperplasia

The regenerative power of the hypophysial parenchyma seems to be slight as is evident from the fact that cicatrizing lesions, such as result from infarcts, are not accompanied by any noticeable new formation of parenchyma.

NEOPLASTIC DISEASE OF THE HYPOPHYSIS

Adenoma

Adenomas of the pituitary are very common. Examination of 300 hypophyses in serial sections showed that 25 glands (8.3 per cent) were involved by adenoma, while 13 (4.3 per cent) showed adenomatous hyperplasia.[47] The greatest incidence of adenoma occurs in the sixth decade, males and females being involved about equally. The chromophobe type is about three times more frequent than the two chromophil types. According to Bailey's[48] statistics, hypophysial adenomas compose 17.8 per cent and the craniopharyngioma 4.3 per cent of all intracranial tumors.

Some adenomas are tiny and macroscopically hardly discernible, while others present a huge tumor mass protruding from an enormously enlarged sella turcica and destroying the neighboring parts of the brain and cranial base by pressure or infiltration. As long as the adenoma does not exceed a certain size, its growth takes place predominantly in the lateral direction and downward toward the bottom of the sella, since the diaphragm of the sella withstands the abnormal pressure longer than the osse-

Fig. 842.—Adenoma of the hypophysis. (From Henke and Lubarsch, Handbuch der speziellen pathologischen Anatomie und Histologie, Julius Springer.)

ous wall of the sella. As the adenoma grows, the entrance to the sella expands, and the tumor projects through the diaphragm into the cranial space. Thus an extrasellar portion of the tumor arises which sometimes considerably exceeds the intrasellar portion in size. The two portions may be differentiated by a circular ring of constriction resulting in an hourglass shape of the tumor. A larger adenoma may invade one or both cavernous sinuses, extend to the carotids, destroy the sella, break into the sphenoidal and ethmoidal sinuses and even into the nasopharynx and the maxillary sinuses. Tumors extending posteriorly destroy the dorsum sellae and the clivus; tumors having penetrated the dura mater sometimes grow outside the dura along the blood vessels and may re-enter the subdural space, forming nodules on the inner surface of the dura.

Growing toward the brain, the adenoma comes into contact with it either below or behind or in front of the optic chiasma. This is pushed upward and becomes flattened, together with the optic tracts and optic nerves. The optic nerves become atrophic, sometimes constricted and even severed by the medial cerebral artery or other branches of the circle of Willis. In rare instances the chiasma is perforated by the tumor. In its further growth, the adenoma burrows more and more deeply into the diencephalon, causing atrophy and destruction of the floor of the third ventricle. Destruction is due more to the pressure exerted by the tumor than to infiltration.

Besides the optic nerves, other nerves adjacent to the tumor, such as the oculomotor nerve and trochlear nerve, less frequently the abducent or trigeminal nerve, are crowded out, stretched, and flattened.

The injury done by the adenoma to the remainder of the hypophysis varies in severity. Even in large forms of adenoma the hypophysis, lying at the base of the deepened sella, may be in a fairly good condition, whereas in other cases the hypophysis is destroyed or reduced to a flat, atrophic structure. Concentrically arranged layers of atrophic cells forming a thin shell frequently are found surrounding the basal parts of the tumor. In case of predominantly extrasellar growth, the hypophysial stalk becomes destroyed at an early stage of the tumor. In the vast majority of cases, adenoma arises from the anterior lobe. Basophilic adenoma may originate from either anterior or posterior lobe. Occasionally the origin of adenoma can be traced to foci of anterior lobe parenchyma dispersed along the craniopharyngeal canal within the sphenoid bones.

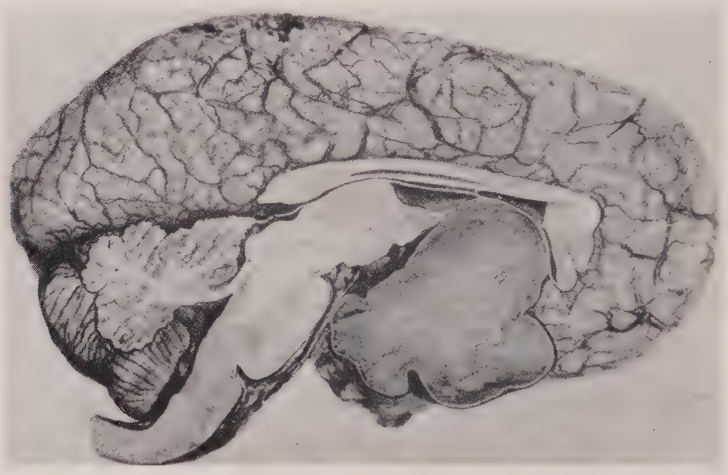

Fig. 843.—Eosinophilic adenoma of the hypophysis (associated with acromegaly). (From Henke and Lubarsch, Handbuch der speziellen pathologischen Anatomie und Histologie, Julius Springer.)

Although these tumors of the hypophysis frequently are malignant, metastases are seldom observed, although metastases to leptomeninges, cerebral tissue, lungs, and skeleton have been reported.

There are as many types of hypophysial adenoma as there are cell types in the

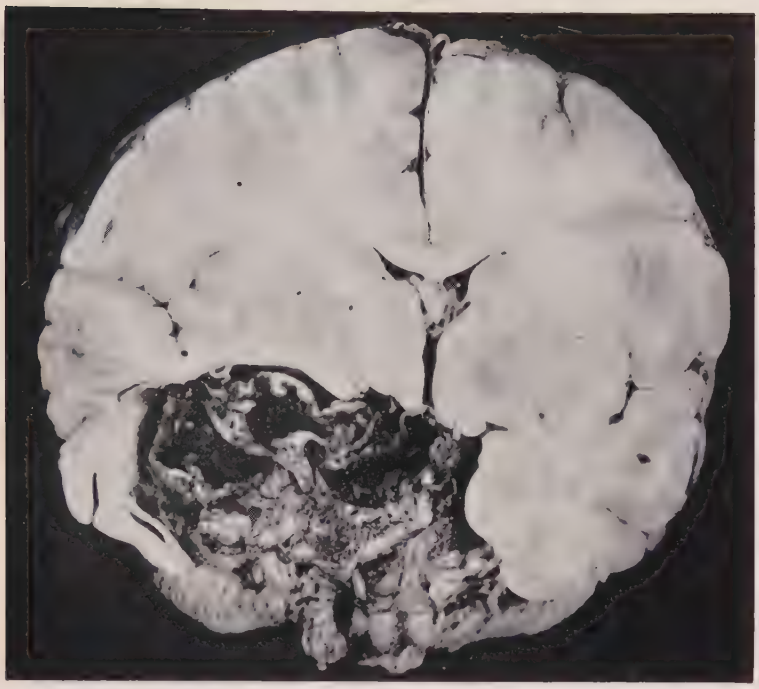

Fig. 844.—Expansion of a pituitary adenoma into right temporal lobe. (From Cushing, Intracranial Tumors, Charles C Thomas.)

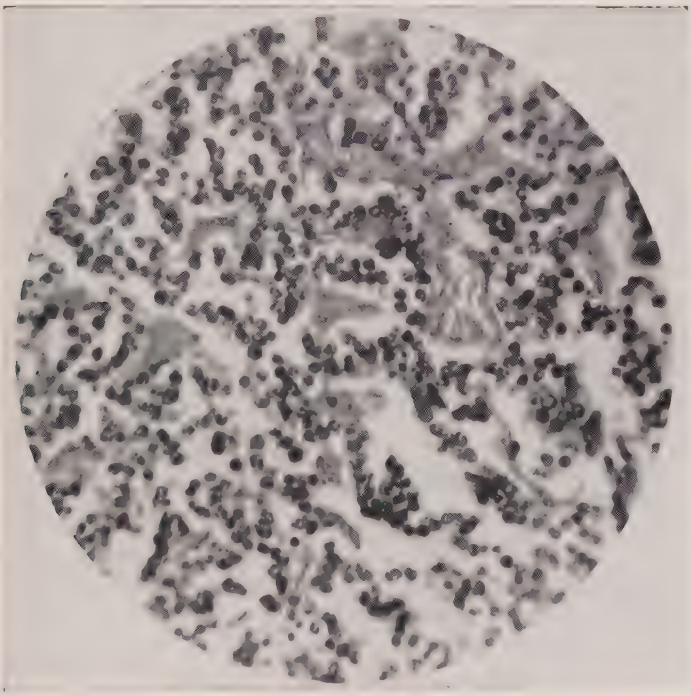

Fig. 845.—Chromophobe adenoma of the pituitary made up of chief cells characterized by very scanty cytoplasm.

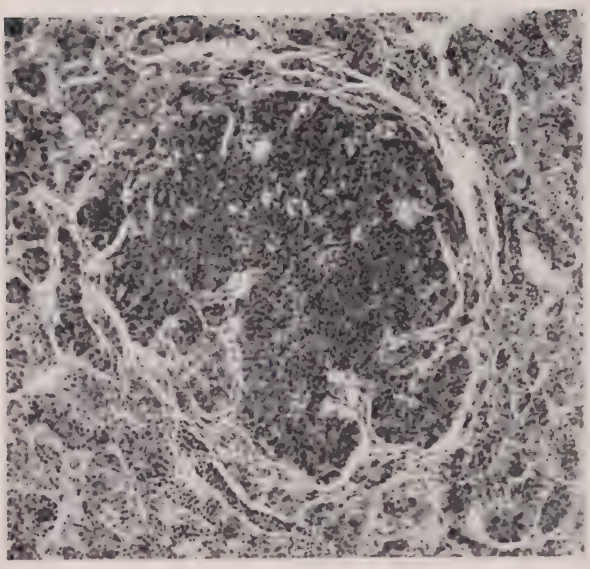

Fig. 846.—Small basophilic adenoma of the anterior lobe of the pituitary gland.

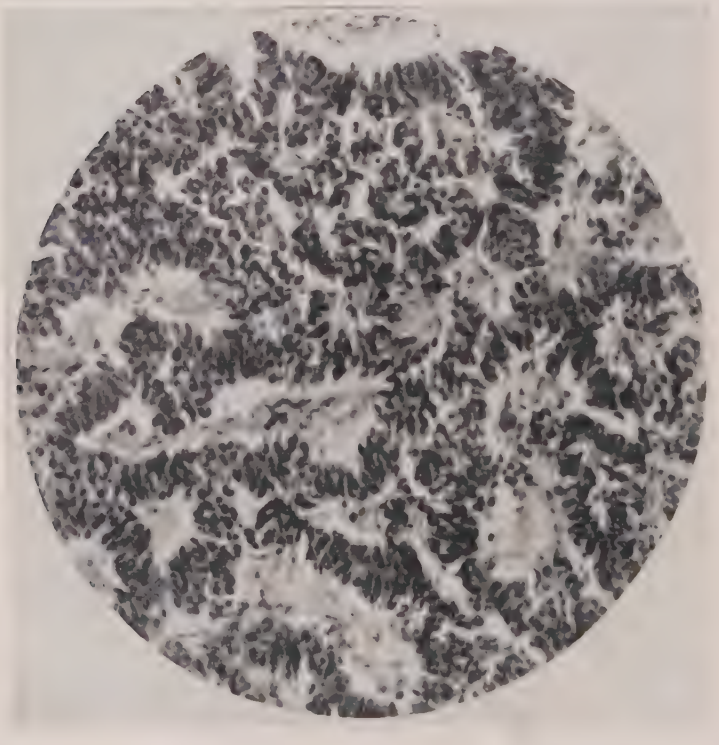

Fig. 847.—Fetal cell adenoma of hypophysis (Kraus). (The cylindric cells are arranged in palisades forming ribbonlike structures.)

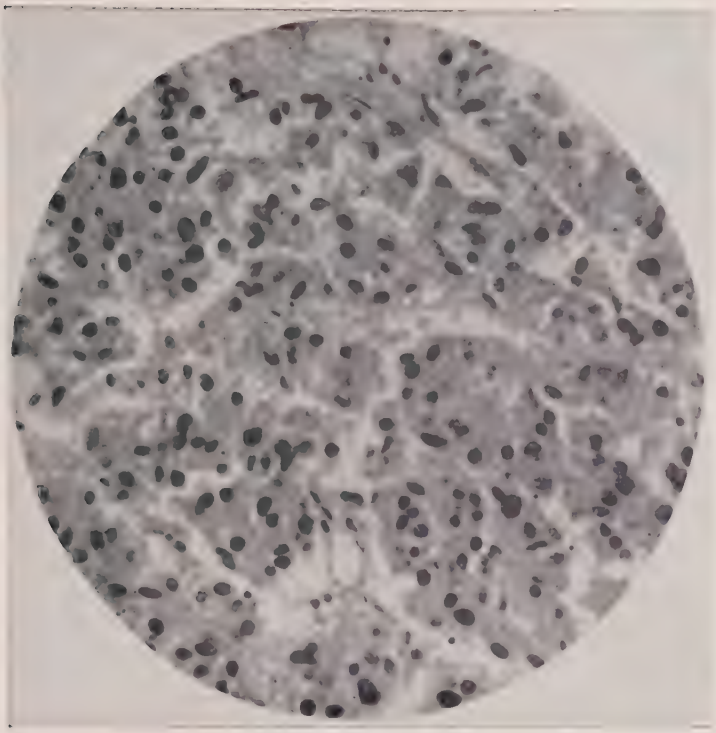

Fig. 848.—Malignant eosinophilic adenoma of pituitary gland in a case of acromegaly. The nuclei show considerable pleomorphism.

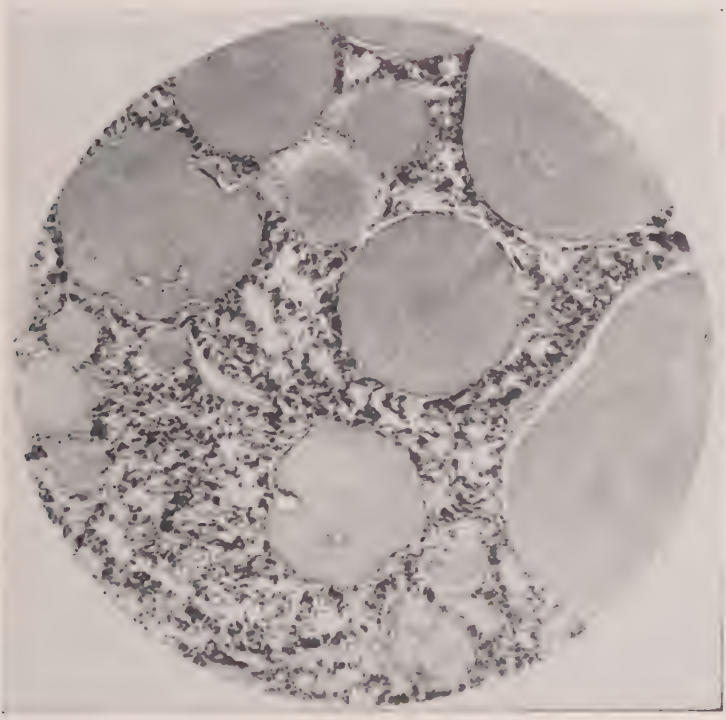

Fig. 849.—Psammomatous adenoma of the hypophysis (showing many concentric-layered corpora amylacea).

hypophysis. When more than one cell type is represented in the adenoma, the tumor is called a mixed cell adenoma. The cells in malignant adenoma are not always differentiated enough to reveal their true histogenesis. The tumor cells in an old eosinophilic adenoma may lose their specific granules to such an extent that, unless examined by specific methods very thoroughly, the eosinophilic character of the adenoma may be overlooked.

While eosinophilic and chromophobe forms of adenoma seem to arise almost exclusively in the anterior lobe, basophilic adenoma may be found in either the anterior or posterior lobe, in the former, however, much more frequently than in the latter. In Cushing's disease it has been seen in either lobe. Basophilic adenoma, as a rule, does not attain the size of chromophobic or eosinophilic adenoma.

There is one type of chromophobic adenoma in which the cells are similar in shape and arrangement to those in the anterior lobe during the very early stage of fetal life and called fetal or fetal cell adenoma. These tumors are characterized by high cylindric or fusiform cells arranged in bandlike interlacing strands. Thus arise cell palisades which, resting upon the septa and capillary walls, confer on the new growth a very characteristic appearance.

Another rare type is the so-called pregnancy cell adenoma, which is made up of cells morphologically corresponding to the normal pregnancy cells.

Adenomas in the hypophysis sometimes seem to spring from a local cell hyperplasia showing a well-defined contour only on one side, whereas on the other side the cells proliferate diffusely, merging into the adjacent hypophysial parenchyma. The new growth shows a lack of lipoids compared with a considerable lipoid content of the normal tissue.

In some cases chromophobic cells are present together with chromophils and transitional forms. This seems to indicate that in at least some cases chromophilic adenoma springs from chromophobic precursors which differentiate into chromophilic elements.

The most reliable sign of malignancy, aside from infiltrating growth, is anaplasia of the tumor cells, characterized by irregularity in size and shape of cells and nuclei and by the particularly large size of the latter, which exceeds the size of nuclei in adenoma. Alveolar arrangement of the tumor cells is usually found in adenoma, and a more diffuse arrangement suggests carcinoma.

Infiltrative growth of basophilic adenoma arising in the posterior lobe is not always a reliable criterion of malignancy. Only after it has invaded other structures can carcinoma be diagnosed.

Retrogressive and circulatory lesions are common in hypophysial adenomas. They are chiefly hemorrhage, infarction, necrosis, hyaline degeneration of the interstitial tissue and formation of hyaline concentric-layered bodies with or without calcification.

Craniopharyngioma

The tumor second in frequency to the adenoma is the craniopharyngioma, which is derived from the squamous epithelium of the former craniopharyngeal canal. In a great percentage of cases, small groups of these cells are found in the anterior and superior parts of the anterior lobe of the hypophysis as well as in the pars infundibularis. When the craniopharyngioma springs from cell groups dispersed into the anterior lobe, an intrasellar craniopharyngioma develops; when it arises from cell groups in the pars infundibularis, the result is a suprasellar craniopharyngioma. While craniopharyngioma in this location, especially above the sella, is not rare, there are only a very few cases known where the tumor has developed within the sphenoid bone, in the region of the former craniopharyngeal canal proper. According to Bailey,[48] 4.3 per cent of all intracranial tumors are craniopharyngiomas. Most frequently craniopharyngioma is found in children and young adults. According to Ingraham and Scott, 6.3 per cent of intracranial tumors observed in children under 15 years of age were craniopharyngiomata.[49]

There are benign and carcinomatous forms of craniopharyngioma, partially solid, partially cystic or cystic-papillary in structure. In many cases both solid and cystic parts are found. These tumors vary greatly in size, attaining, in rare cases, the size of a man's fist. The intrasellar craniopharyngioma crowds out the hypophysis, causing extreme atrophy, and widens and deepens the sella. Growing larger, it projects out of the sella and displaces the neighboring diencephalon upward. It may destroy the sella and even larger parts of the sphenoid bone. Growing toward the optic chiasma, it may invade the brain in front of the chiasma. If the craniopharyngioma is cancerous, it infiltrates the adjacent parts of the skull and brain. Metastases to the brain and to cervical lymph nodes have been described.

Different pictures result when the craniopharyngioma springs from the infundibular part of the hypophysis (outside of the sella turcica). These tumors lie within the circle of Willis and behind the optic chiasma and are attached above to the base of the brain and below to the hypophysis. The floor of the third ventricle is

Fig. 850.—Cystic suprasellar craniopharyngioma in a child 4 years of age.

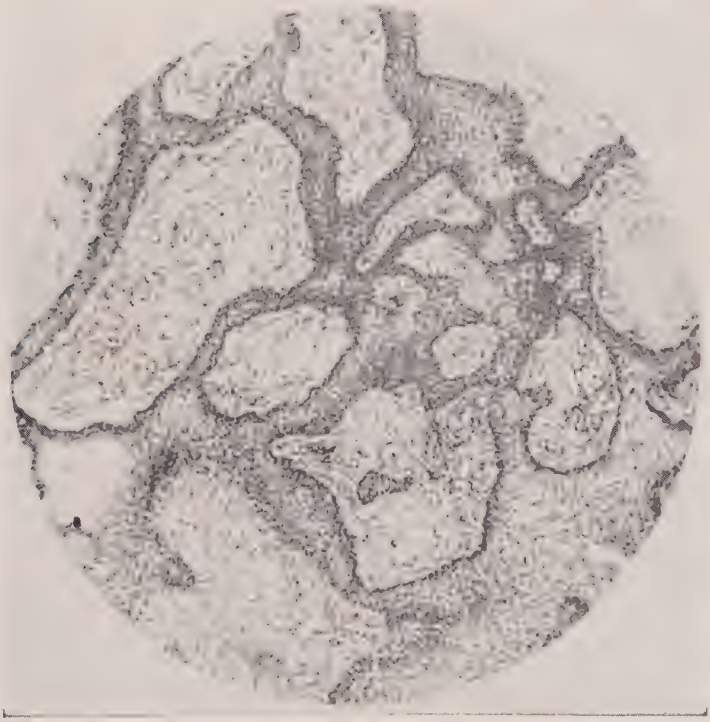

Fig. 851.—Craniopharyngioma. Notice the communicating strands of squamous epithelium.

pushed upward and is often extremely thinned or even destroyed, resulting in a large part of the tumor lodging within the ventricle. Sometimes the hypophysis is about normal, but more often it is compressed. The circle of Willis may be lifted and stretched by the tumor; the optic nerves may be indented by one of the arteries and pressed between the growing tumor and the big arteries, or they may even be severed.

Histologically, craniopharyngiomas are characterized by epithelium of prickle cell type but which lack keratohyaline granules as well as cornification. The solid parts of a craniopharyngioma are made up of squamous cell nests closely approximated and embedded in a fibrous stroma. The periphery of these cell nests is composed of a single layer of cylindric epithelium. Frequently there are regressive changes in both parenchyma and stroma, particularly hydropic degeneration, which by liquefaction often causes pseudocysts.

If the whole cell nest is liquefied, the necrotic mass, stained red by eosin, lies amid the stroma, often surrounded by foreign body giant cells, or else it undergoes calcification. Craniopharyngiomas may contain bone tissue which has developed from these calcified foci by metaplasia.

In cystic and cystic papillary craniopharnygiomas, the lining of the cysts is made up of two or more layers of epithelium, occasionally flattened by the cyst content. The lining shows a basal cell layer and layers of prickle cells, but without keratinization. Characteristic are shaggy vegetations budding from the wall, being attached to it either by a broad base or by thin stalks forming cauliflower-like structures. The papillae are covered by multilayered squamous epithelium and sometimes have an edematous stroma rich in blood vessels. Destruction of the epithelial lining by necrosis, foreign body giant cells, calcium and cholesterol deposits, and ossification are found in the cystic type as well as in the solid type. The cystic content may be colorless, yellow, brownish, or brown-green, and sometimes shows a large amount of glittering cholesterol crystals. Characteristic of the craniopharyngioma is its resemblance to the adamantinoma, which has caused many authors to call the craniopharyngioma an adamantinoma. Finally, it is quite typical of craniopharyngioma that the carcinomatous type occurs more often in young persons, whereas the benign form usually is found in older individuals. Both sexes are about equally involved.

Other Primary Tumors

Rarer primary tumors of the pituitary include fibromas, fibrosarcomas,[50] hemangiomas, chordomas,[51] gliomas,[52] and ganglioneuromas. Teratoma also belongs to the rare tumors of the hypophysis or hypophysial region.[53-55] Cholesteatoma has been described several times, but does not appear to occur in the hypophysis itself but in the infundibular region. It is of epidermal origin as proved by the presence of keratohyaline granules which are not found in craniopharyngioma.

True cysts of the hypophysis are infrequent. The macroscopic distinction from cystic craniopharyngioma may be difficult in some cases. Remnants of anterior lobe tissue lining the cyst facilitate the histologic diagnosis. Most of the pars intermedia cysts are intrasellar and separate the two lobes. They can be lined by ciliated or squamous epithelium. Whether or not there are clinical symptoms depends on the size of the cyst and the degree of compression and atrophy of the hypophysis itself. The size of these cysts varies; the majority of them are not very large. Another type of cyst is the ependymal cyst, usually located within the infundibulum and lined by ependyma.

Fig. 852.—Mature carcinoma of the thyroid metastatic to the posterior lobe of the pituitary gland.

Metastatic Tumors

Metastasis to the pituitary gland is not particularly rare, and is more often carcinomatous than sarcomatous. Pituitary metastases have been observed most frequently from carcinoma of breast, lung, and thyroid. (Fig. 852.)

THE DISORDERS OF THE ADENOHYPOPHYSIS

The disorders of the adenohypophysis can be classified as those caused by increased activity of the gland and those due to its partial or total deficiency. Hyperpituitarism and hypopituitarism are the terms that denote these conditions. Hyperpituitarism is represented by acromegaly and hypophysial gigantism, whereas hypopituitarism comprises hypophysial dwarfism, Fröhlich's disease, and hypophysial cachexia. Brugsch's acromicria or osteogenital dystrophy might be a form of hypopituitarism, but so far there seems to be no reliable postmortem findings indicating this. In Cushing's syndrome, called by Cushing himself "pituitary basophilism," the primary hypophysial origin of the disorder appears debatable.

Acromegaly (Marie's Syndrome)

Acromegaly is the result of a hyperfunction of the eosinophilic cells of the hypophysis, known as the producers of the growth hormone. Overproduction of this hormone causes enlargement of prominent body parts such as nose, lips, ears, lower jaw, hands, and feet. There are hyperplastic changes of the skeleton, macroglossia, and splanchnomegaly. Marked hairiness, with masculine type of hair distribution in females, cessation of the sexual functions, glycosuria, diabetes mellitus, visual disturbances (especially bitemporal hemianopsia), symptoms of increased intracranial pressure, mononucleosis and eosinophilia of the blood also may be present. The disease usually starts between 20 and 30 years of age. Not unusual is a beginning in puberty, but children are rarely affected. Acromegaly is a disease of long duration, lasting up to twenty-five or more years. The period of active growth, however, is relatively short. The two sexes are equally involved by the disease.

The morphologic basis of the hyperpituitarism causing acromegaly is an eosinophilic adenoma, benign or malignant, originating as a rule in the anterior lobe itself—in extremely rare cases, however, in the region of the former craniopharyngeal canal. In a few instances a diffuse or nodular hyperplasia of the eosinophilic cells has been observed.[56, 57]

The size of the eosinophilic adenoma varies, and the symptoms are not always in conformity with the size of the tumor. Thus, one can see a small eosinophilic adenoma accompanied by a fully developed classical picture of acromegaly, whereas in another case, despite a large tumor, the acromegalic symptoms are only slightly evident. The size of the eosinophilic adenoma is not as responsible for the severity of the acromegalic symptoms as is the degree of functional differentiation of its cells. The more the tumor cells simulate normal eosinophiles, the more severe is the endocrine dysfunction from the adenoma.

There are many statements, particularly in the older literature, about cases of acromegaly without eosinophilic tumor. This is partially explained by the fact that, because of exhaustion, the eosinophilic cells in old adenomas may lose, at least to a great extent, their specific granules.[58] Often the granules can be demonstrated reliably only by certain methods, such as the Azan-stain of Mallory or the chromium-hematoxylin stain of Kraus. In very rare instances, the eosinophilic adenoma may be hidden within the sphenoid bone while the hypophysis and sella turcica appear normal.[59]

In addition to the hypophysis, most of the other endocrine organs are involved. The pineal gland frequently appears enlarged; the thyroid gland often shows a nodular or diffuse goiter with colloid degeneration, atrophy of the parenchyma, and increase of fibrous tissue, sometimes complicated by myxedema.[60] The parathyroid glands, and also the thymus, may be hyperplastic. The pancreas, as a rule, is enlarged because of proliferated interstitial tissue. There may be hydropic degeneration, atrophy and depletion of the Langerhan's islets, as well as fibrosis and hyalinization. In the adrenals there is hyperplasia of cortex and medulla. Their combined weight may be as high as 25 grams and possibly more. In rare instances tumors may be found in several endocrine glands aside from the eosinophilic adenoma in the hypophysis; for instance in the pineal, the thyroid, the parathyroid, the adrenals, and the pancreas. The testes show, particularly in advanced cases, atrophy of the seminiferous tubules, and depletion of Leydig's interstitial cells, the disappearance of which, in early stages of testicular atrophy, is characteristic of the hypophyseo-diencephalic disorganization. Cystic

degeneration and atrophy of primordial and graafian follicles are typical findings in the ovaries. In other cases, however, many years after acromegaly has started, menstruation still may be present, just as in males spermatogenesis may be undisturbed despite many years of acromegaly. Hypoplasia of the genitals has been observed in cases of juvenile acromegaly.

Important for sexual function is the extent to which the hypophysial parenchyma is destroyed and the interbrain injured by the hypophysial tumor. Since in many cases of acromegaly the eosinophilic adenoma is not too large, there is often more surviving hypophysial parenchyma and lesser injury to the interbrain than is found in chromophobe adenomas and craniopharyngiomas. This may be the reason why genital disorders in acromegaly are less frequent than in other hypophysial tumors. The slow growth of many of these eosinophilic adenomas might explain why sexual insufficiency often is not found in the first years of the disease. Even signs of sexual hyperactivity, especially in males, can be frequently observed in early stages of the disease.

The enlargement of nose, ears, lips—particularly the lower lip—and the thickening of the eyelids is due mainly to proliferated fibrous tissue, but the epidermis also participates in the thickening of these structures. In nose and larynx the cartilage is hyperplastic. The low-pitched rough voice of acromegalic patients results at least partly from the thickening of the pharyngeal and laryngeal mucosa. The protrusion of the eyeballs, observed in some cases, is caused by an increase of retrobulbar tissue. Splanchnomegaly mainly results from the proliferation of interstitial tissue. In addition to the endocrine organs mentioned before, the organs usually enlarged are tongue, larynx, trachea, heart, liver, kidney, pancreas, and the gastrointestinal canal.

The skeleton shows thickening of the skull with the normally protuberant parts, such as the supraorbital margin, the zygomatic bone, the occipital protuberance, the osseous gyri, etc., strikingly prominent. The turbinates of the nose participate in the enlargement. The pneumatic nasal cavities are widened and the lower jaw enlarged, causing prognathism with the lower teeth overlapping the upper teeth sometimes as much as 2 cm. Separation of teeth, thickening of the collar bone, ribs, and epiphyses of the long bones are frequent. Osteophytic proliferation on the surface of the bones, exostoses at the ends of the bones close to the joints, thickening of the muscle insertions, of the manubrium sterni, the phalanges of fingers and toes are typical changes. The hands show two types of enlargement, one with the hands enlarged in length, the other one with the hands enlarged in width. Kyphosis in the lower cervical and upper thoracic spine and lordosis of the lumbar spine are frequent in acromegalic individuals. In later stages of the disease osteoporotic changes appear associated with atrophy

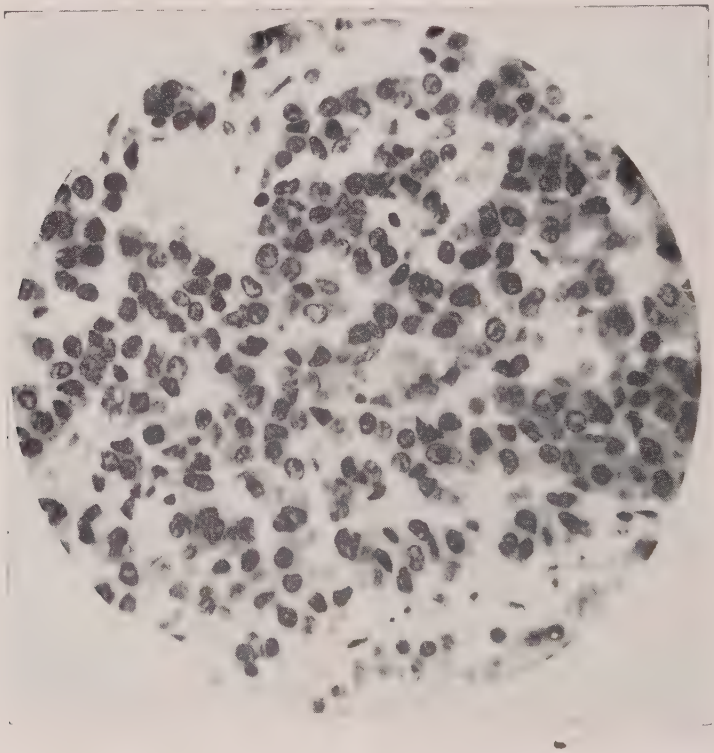

Fig. 853.—Eosinophilic adenoma of the hypophysis in a case of acromegaly.

Fig. 854.—Acromegaly.

of the musculature, especially of the arms and legs. Thickening of the bones can be found together with porosis. The spongy bone increases at the expense of the compact bone and the latter consists of concentrically arranged lamellae surrounding wide bone marrow spaces. Proliferative changes of the epiphysial cartilage followed by ossification of the new-formed cartilage may be found. The joint lesions associated with acromegaly resemble those of degenerative arthritis.[61]

The abnormally marked hairiness of acromegalic patients has been mentioned. The hair is thick, the eyebrows bushy, the beard rough; the trunk, extremities, genital regions, and linea alba appear very hairy. In the female, hair develops on the upper lip, the chin, the cheeks, between the breasts, at the linea alba, in the groins, the inner surface of the thighs and legs. Almost all acromegalic patients are brunets, and blond individuals developing acromegaly turn dark in the course of the disease.

Because of the fact that in acromegaly almost all of the endocrine organs are afflicted, it is not strange to see signs of pluriglandular insufficiency. Besides dysfunction in the sexual sphere, disorders of sugar metabolism are common, such as diabetes mellitus, xanthoma diabeticorum, and glycosuria.[62]

A frequently discussed question concerns the relative roles of the eosinophilic adenoma, destruction of the hypophysis, and pressure exerted on the interbrain in the pathogenesis of the various features of acromegaly. A case in which the eosinophilic adenoma developed within the sphenoid bone without secondary injury to the hypophysis and the interbrain at least partially illuminates the problem. In this case (observed by Erdheim[59]), the sexual glands and their function remained normal despite the long duration of the disease, and no cachexia was present. On the other hand, the acro- and

Fig. 855.—Enlarged feet of an acromegalic.

splanchnomegaly were just as strongly developed as in other cases of acromegaly. This fact permits the conclusion that the genital dystrophy and the cachexia, as well as the obesity observed in some instances, are due to injury within the hypophyseo-diencephalic system (hypophysis or interbrain or both). They apparently are not the result of eosinophilic hyperpituitarism per se, which is responsible only for excess growth by overproduction of growth hormone. Probably both hyperfunction of the hypophysis and of the adrenal cortex are responsible for the abnormal hairiness.

In some instances the picture of acromegaly does not appear fully developed, the enlargement being limited to certain organs. The changes in the hypophysis in these incomplete or fugitive cases have been described differently. A mixed cell adenoma, a fetal cell adenoma, or enlargement of the hypophysis with increase of eosinophilic cells are some of the findings reported. The acromegaloid features of some pregnant women may be due to action of the pregnancy cells, which appear to be functionally related to the eosinophilic cells.

A syndrome described by Brugsch[63] called **acromicria** or **osteogenital dystrophy** seems to be the opposite of acromegaly, although seemingly as yet uncorroborated by autopsy examinations. It is characterized by small stature, small fingers and toes with the cortex of the phalanges thinned, the spongy bone rarefied and the bone poor in calcium. Skull and mandibula may be similarly involved. Falling hair, headache, cessation of menses, tenderness of fingers and toes with acrocyanosis complete the clinical picture. Polyuria and obesity may complicate the disease.

Hypophysial Gigantism

Pituitary gigantism is characterized by excessive body height, a remarkable increase in the volume of the viscera and acromegalic aspects. Acromegalic features usually facilitate the differentiation between hypophysial and eunuchoid gigantism, though there are cases in which acromegalic and eunuchoid symptoms are combined. Some of these are primarily eunuchoid with acromegalic symptoms acquired at an older age. Infantile habitus, increase of the length of the lower over the upper segment of the body, hypoplasia of the sexual organs, especially the gonads, hypotrichosis, lack of beard, and patent epiphysial lines are the symptoms disclosing the eunuchoid origin of the gigantism. However, with overlapping symptoms, pertinent to each type, the differentiation and classification of the two forms of gigantism often may become difficult or even impossible. The relations between hypophysial gigantism and acromegaly also are very close, particularly inasmuch as acromegalic individuals often are very tall, and the border between hypophysial gigantism and acromegaly may not always be sharp.

It is probable that the hypophysial gigantism may be simply an acromegaly developing before the closure of the epiphysial lines,[64] i.e., the pathologic growth process begins while the individuals are still growing and extends into the period of finished physiologic growth.

Reliable histologic examinations of the hypophysis of hypophysial giants have been few, but it is probably correct to interpret this endocrine disturbance as an eosinophilic hyperpituitarism which either develops primarily in youth in a heretofore normal individual or, secondarily, superimposed upon eunuchoidism. The underlying pathologic process in the hypophysis is a hyperplasia or an adenoma of the eosinophilic cells.[65-68]

Hypophysial Dwarfism (Nanosomia Pituitaria)

The hypophysial dwarf is a person who was born normal in size and stopped growing in childhood. Body size and proportions correspond to those of a child; the epiphysial lines stay open until adult age; the external genitals are markedly underdeveloped; the gonads appear hypoplastic and atrophic; beard and body hair are lacking; the skin is dry, flabby, and often wrinkled, thus indicating the older age. The intelligence usually is fairly normal, though sometimes slightly below average. Blood pressure and basal metabolism tend to be below normal.

The hypophysis in nanosomia pituitaria is usually destroyed or severely damaged by an intrasellar or extrasellar craniopharyngioma which frequently shows marked retrogressive lesions indicating long duration of the new growth. Extensive calcification has often been observed. Hypophysial dwarfism as the result of a teratoma of the hypophysis (reported in the older literature several times) should be considered with caution, since old craniopharyngiomas altered by retrogressive changes often have been mistaken for teratomas.

Occasionally, the destruction of the hypophysis is due to a lesion other than a craniopharyngioma. Such have been

fibrosis of the anterior lobe probably secondary to ischemic necrosis, atrophy of the anterior lobe, colloid-cystic degeneration of the anterior lobe, congenital syphilis, chronic hydrocephalus, malformation of the hypophysis, etc.[69-72]

Changes in the testicles in typical cases of hypophysial dwarfism (which predominantly involves males) are not uniform, depending on the age at which the destructive process in the hypophysis begins. The final picture is a summation of hypoplasia and atrophy. While in younger individuals the hypoplasia usually is more distinct, in older dwarfs the atrophic lesions are predominant. The most characteristic feature shown by the testicles in hypophysial dwarfism is the lack of Leydig's interstitial cells, in contrast to other cases of testicular atrophy. The lack of interstitial cells, however, is also seen in adiposogenital dystrophy, and is characteristic of testicular atrophy of hypophyseo-diencephalic origin.

Fig. 856.—Hypophysial dwarf, 26 years of age. (Courtesy Drs. H. Selye and E. P. McCullagh, from Selye, Textbook of Endocrinology, Acta Endocrinologica.)

In hypophysial dwarfism, among other endocrine organs the thyroid gland shows atrophy, while the parathyroid glands usually do not appear affected. The adrenals are conspicuously small.

The skeleton, characterized by small size of the bones and open epiphysial lines, gives the impression of having been arrested in its infantile state, but there is a marked difference between the endochondral ossification zone of a child and that of a hypophysial dwarf. While in a child all processes of bone growth are in full swing, they appear completely arrested in hypophysial dwarfism. The spongy bone is separated from the cartilage by an uninterrupted plate of bone. Because of the lack of growth hormone, the proliferation of cartilage does not receive any stimulation, and, therefore, the bones do not grow and, since no vascular erosion and no formation of bone tissue take place, the epiphysial lines do not disappear. The degree of dwarfism depends on the age of the individual at the time when the destructive lesion of the hypophysis began and on the severity of the lesion. The farther back in youth the injury to the hypophysis goes, the more pronounced will be the dwarfism. The fact that the adult hypophysial dwarf as a rule is not obese results

Fig. 857.—Dystrophia adiposogenitalis (Fröhlich's disease). (Courtesy Drs. H. Selye and E. P. McCullagh, from Selye, Textbook of Endocrinology, Acta Endocrinologica.)

from the destruction of the anterior lobe, since the loss of anterior lobe function causes cachexia which counteracts the development of the obesity, produced by the injury to the interbrain. Hypophysial dwarfism in some instances may be associated with diabetes mellitus[73] or diabetes insipidus.

As to the pathogenesis of nanosomia pituitaria, there is no doubt that the lack of function of the anterior lobe is responsible for the arrest in body growth as well as sexual development. While the lack of eosinophilic cells causes the growth disturbance, the lack of basophilic cells seems to account for the genital dystrophy.

There seems to be a certain relation between hypophysial dwarfism and a peculiar disease described by Gilford[74] and called by him, **progeria.** The individuals are dwarfs; the skull is large; the face small; the fontanels are open; the head is bald; the eyes are large and protruding. Gilford described one of his patients, a boy 5 years old, as a "wizened dwarfish old man." Though several cases have been observed and published, autopsy findings are lacking.

Fröhlich's Syndrome (Adiposogenital Dystrophy)

In 1901 Fröhlich first recognized the causal connection between lesions of the hypophysis and the syndrome which is named after him, Fröhlich's syndrome or adiposogenital dystrophy. The condition is characterized mainly by obesity of eunuchoid type, by atrophy of the gonads and genitals, impotence, cessation of menses and sterility, loss of secondary sex characteristics, and sluggishness of metabolism. Headaches, vomiting, visual disturbances, somnolence, and often polyuria may be present in the clinical picture. Beginning in youth before the closure of the epiphysial lines and sexual maturity, the disease assumes features which represent a combination of obesity and dwarfism. There is no particular age involved by the disease, but the majority of cases occur during middle age and in women more frequently than in men.

The underlying pathologic basis of adiposogenital dystrophy is variable in nature, origin, topography, and extension, but common to all cases is location within the hypophyseo-diencephalic system. It might be practicable to set up four groups of pathologic lesions leading to dystrophia adiposogenitalis. The first group comprises cases with a destructive lesion limited to the interbrain; the second group involves cases with interruption of the continuity between anterior lobe and interbrain by partial or total destruction of the neurohypophysis. Cases with the primary lesion being limited mainly to the hypophysis form the third group, and cases with involvement of the entire hypophyseo-diencephalic system represent the fourth group.

The lesions of the interbrain underlying the adiposogenital dystrophy are suprasellar craniopharyngiomas, gliomas, meningiomas, cholesteatomas, exostoses of the dorsum sella or of the posterior clinoid processes which exert pressure on the region of the third ventricle. Tumors in the region of the third ventricle play an especially important part.[75] Furthermore, chronic hydrocephalus causes distention of the floor of the third ventricle, and depletion of ganglion cells in the nucleus paraventricularis and accumulation of lipoid in the ganglion cells of the nucleus basalis and nucleus tuberis have been found. In severe and long-lasting cases, the hypophysis shows depletion of the chromophilic cells in the anterior lobe and, finally, atrophy of the whole organ.

Cases of adiposogenital dystrophy caused by separation of the anterior lobe from the interbrain after destruction of the neurohypophysis or parts of it are rare.[76-80]

More frequent are those cases of adiposogenital dystrophy with the destruction involving the hypophysis itself. Chromophobic and basophilic adenomas, rarely eosinophilic adenomas, intrasellar and, exceptionally, intrasphenoidal craniopharyngiomas, angiomas, and gliomas of the posterior lobe are the tumors found in these cases. In addition, tuberculosis, syphilis (interstitial hypophysitis, especially in congenital cases, or more often gumma), colloid cysts in the pars intermedia, hypoplasia of the hypophysis, an old cystic hematoma apparently traumatic in nature, pressure atrophy by a meningeal cyst, compression of the hypophysis by a sphenoidal empyema, a chronic abscess involving the entire hypophysis, fibrosis of the anterior lobe, etc., have been reported in cases of adiposogenital dystrophy. In several cases, traumatic lesions by pistol bullets, shell fragments, etc., of the hypophysis were the cause of Fröhlich's disease.[81]

In the majority of cases the destruction involves hypophysis as well as variable parts of the interbrain. The destructive lesions consist of tumors of the hypophysis, such as benign and malignant adenomas and craniopharyngiomas, specific granulomas such as tuberculosis and gumma, brain tumors, meningiomas, cholesteatomas of the cranial base or third ventricle with compression of the hypophysis, etc.

The obesity in adiposogenital dystrophy is characterized mainly by the distribution of the fat tissue, with predilection particularly for the neck, chin, shoulders, breasts, lower part of the abdomen, and hips.

Loss of pubic as well as axillary hair, and in males the loss of beard on lips and cheeks, are typical features. The testicles show hypoplasia in those cases which have started in youth with the germinal tissue underdeveloped and the interstitial tissue increased. In cases of adiposogenital dystrophy beginning after sexual puberty has been reached, the testicles undergo atrophy. There is no spermatogenesis and the atrophy of the germinal tissue is accompanied by thickening and hyalinization of the membrana propriae of the seminiferous tubules. Leydig's interstitial cells are very sparse or entirely lacking in typical cases with hypophyseo-diencephalic lesions. In females the ovarian follicles disappear, or the ovaries show cystic degeneration with cessation of menses and resulting sterility. Simultaneously with hypoplasia or atrophy of the gonads, other parts of the sexual apparatus such as uterus, tubes, epididymis, prostate, and seminal vesicles exhibit changes either of underdevelopment or atrophy depending on the age in which the disease began. Injury by the space-occupying lesion to the basophilic cells, which allegedly are the producers of the gonadotropic hormone, has been held responsible for the loss of sexual function.

In cases of adiposogenital dystrophy, not all features in the clinical pathologic picture are equally developed. In some cases obesity is the prominent feature, and in many cases it appears to be due to injury of the vegetative center of the interbrain. In some cases of adiposogenital dystrophy, obesity is lacking and the picture is marked chiefly by the genital dystrophy. Some cases may finally develop cachexia. The great variability in the clinical picture of adiposogenital dystrophy becomes more understandable when the hypophysis and interbrain are regarded as one functional unit with close interdependence. This close relationship is proved not only clinically and experimentally but also morphologically, since changes in one part inevitably are followed by secondary changes in the other part. Any severe destruction within the hypophyseo-diencephalic system may cause the disease, the clinical features of which may vary as to the symptoms and their intensity, depending on the site of the destructive process, its nature, extension and rapidity of development, duration, and upon the age and sex of the individual involved.

Simmonds' Disease (Hypophysial Cachexia)

Simmonds[82] is credited with the discovery that lack of function of the anterior lobe of the hypophysis is followed by cachexia and finally death in coma. The first case upon which he based his opinion concerned a 46-year-old woman, who, after her fifth delivery, developed a puerperal sepsis from which she never recovered. Autopsy revealed absence of the posterior lobe, the pars intermedia represented by a few, small, colloid-filled cysts, and the anterior lobe was found to be converted into scar tissue containing a few strands of atrophic epithelium. Taking the patient's history into consideration, Simmonds interpreted the findings in the hypophysis as the result of necrosis due to a bacterial embolus.

The condition, today generally called Simmonds' disease, is characterized by chronic cachexia, a look of old age, wrinkled face, dry skin, falling hair and teeth, cessation of menses, loss of hair in axilla and pubic region, as well as diminution in size of internal organs (splanchnomicria). In addition, there are mental changes such as apathy, drowsiness, confusion, hallucination, delirium, dizziness, spells of fainting, and convulsions. The patients, the majority of whom are females, succumb to cachexia or intercurrent disease.

The pathologic basis of the disease is the destruction of the hypophysis or its anterior lobe by various processes. In

Fig. 858.—Simmonds' disease in a 42-year-old woman (case of Dr. B. Zondek). (From Henke and Lubarsch, Handbuch der speziellen pathologischen Anatomie und Histologie, Julius Springer.)

four of Simmonds' own cases a fibrous atrophy of the anterior lobe was found, whereas the posterior lobe was normal or slightly diminished in size. Only in one case (his first) was practically the entire organ destroyed. Usually the size of the organ is markedly decreased and weights of 0.3 down to 0.15 gram have been recorded. In the majority of cases, the disease begins following childbirth, often complicated by septic infection. This led Simmonds and others to the belief that the necrosis preceding the fibrosis of the organ is embolic in nature. But many of the patients had severe hemorrhages during or after delivery. The severe anemia with a vascular collapse is held responsible for vascular thrombosis in the hypophysis, which, in turn, causes the necrosis. Massive necrosis of the anterior lobe due to venous thrombosis associated with necrosis of the kidney cortex and central necrosis of the liver lobules were observed in a woman who died 7 days post partum after she had suffered a severe accidental hemorrhage.[83]

Tumors of the hypophysis also are important in the etiology of hypophysial cachexia. Most often, chromophobe adenomas and craniopharyngiomas have been observed.[84-89] Rare causes of the disease are a cyst in the posterior lobe or a colloid cyst in the pars intermedia separating the two lobes, with a secondary depletion of the chromophilic cells, especially the eosinophiles. Specific granulomas such as gumma, actinomycosis, etc., may produce hypophysial cachexia. Tuberculosis is a rarer cause of hypophysial cachexia.[89, 90]

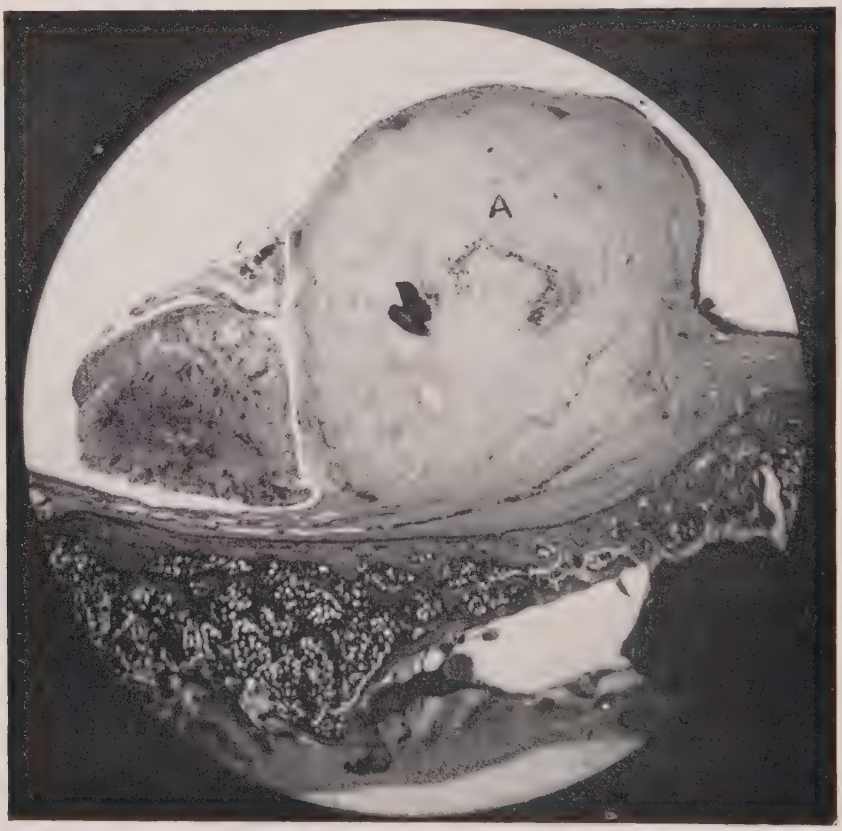

Fig. 859.—Hypophysis in a case of hypophysial cachexia. The anterior lobe (*A*) is replaced by partly calcified scar tissue.

Nonspecific inflammatory lesions and other rare lesions responsible for hypophysial cachexia are old encapsulated hematomas and injuries to the hypophysis by trauma, such as the fracture of the cranial base, causing hemorrhage in the hypophysis.

Not only the destruction of the hypophysis, but apparently also the destruction of the interbrain by a glioma or craniopharyngioma, may be followed by Simmonds' cachexia. Here, of course, it is not obvious whether the loss of the

vegetative centers of the interbrain or the separation of the hypophysis from the brain, leading to atrophy of the anterior lobe, is responsible for the cachexia.

In some cases of hypophysial destruction, the complete picture of Simmonds' disease does not develop, certain symptoms such as amenorrhea or falling hair not being present, or the emaciation does not reach the excessive degree found in classical cases. In other cases, however, cessation of the menses and falling hair are the only changes that call the attention of the physician to the hypophysial involvement. These incomplete or fugitive cases are sometimes hard to explain, particularly in view of the extensive destruction of the anterior lobe found in some of these instances. In a few cases of Simmonds' disease due to hypophysial destruction, the interbrain was examined microscopically, and glial proliferation and degenerative changes of the ganglion cells were found.

Aside from the hypophysis in Simmonds' disease, many other organs are involved by atrophy, as, for instance, the liver, spleen, pancreas, thyroid, adrenals, gonads, etc. The histologic picture shows atrophy with or without thickening of the interstitial connective tissue. The thyroid, particularly, exhibits fibrous atrophy, round cell infiltration, and chronic interstitial thyroiditis. In the ovaries the primordial follicles are lacking, there is no ripening of follicles, the uterus and the breasts are atrophic; the testicles do not show spermatogenesis, and the walls of the tubules are hyalinized and even a complete fibrous hyaline destruction occurs.

Hypophysial cachexia constitutes an important component of a syndrome, first described by Claude and Gougerot and called by Falta[91] **pluriglandular endocrine insufficiency** or multiple sclerosis of endocrine glands. This syndrome is caused by fibrous atrophy of several endocrine glands, such as the hypophysis, the thyroid gland, the adrenals and the gonads, simultaneously involved. Accordingly, the clinical picture shows a great variety of endocrine symptoms such as cachexia, hypothyroidism, signs of Addison's disease and late eunuchoidism. In the literature, the disease has been frequently confused with Simmonds' cachexia, but one fundamental difference is that in Simmonds' disease the primary lesion concerns only the hypophysis, and the changes in the other endocrine organs with their respective symptoms are secondary in nature and dependent on the hypophysial lesion. On the other hand, in Falta's multiple endocrine sclerosis the pathologic lesion involves several glands of the endocrine system primarily and simultaneously, and is characterized by atrophy of the involved glands with subsequent fibrosis. Only in cases where there is evidence that the pathologic process started simultaneously in multiple endocrine glands is the diagnosis of multiple endocrine sclerosis justified.

Anorexia nervosa easily can be confused clinically with hypophysial cachexia, but appears to have a psychiatric rather than an endocrine background, and no pituitary lesions have been found in fatal cases.[92, 93] The combined use of an insulin tolerance test and a 17-ketosteroid assay is now available for the diagnosis of Simmonds' disease.[94] After a normal initial fall of the blood sugar, there is a failure or delay in the usual spontaneous return. The elimination of 17-ketosteroid is, with exceptions in very mild cases, minimal (less than 0.5 mg. per 24 hours).

Cushing's Disease (Pituitary Basophilism)

Cushing[95-97] recognized as an entity a syndrome that is characterized by rapidly increasing (often painful) obesity, osteoporosis with a tendency to kyphosis of the thoracic spine, spontaneous fractures of bones, sexual dystrophy, hypertrichosis, and purplish striae, particularly on the abdomen. Whereas Cushing interpreted the new syndrome as a basophilic hyperpituitarism, some authors question its primary hypophysial origin while others regard it as a special form of hypopituitarism. The syndrome, which more frequently affects women than men, is often accompanied by arterial hypertension, glycosuria, erythrocytosis, leukocytosis, extreme dryness of the skin, pigmentation of the skin, acrocyanosis, and purpura-like hemorrhages. Cushing's disease in children has been reported in some instances.[98] The sexual dystrophy leads in males to impotence, and in females to amenorrhea and sterility. Subjective disturbances are pain in back and abdomen, fatigue, and weakness. Polyphagia, polydipsia, polyuria, and anasarca have been seen in some cases. Not always does the syndrome show all of these symptoms. The obesity, which in characteristic manner alters the face, neck, and trunk, but not the extremities, is always present together with the hypertrichosis, the kyphosis, and the purple striae on the greatly protuberant abdomen. These symptoms confer on the patient a very characteristic appearance, so that when the condition is fully developed, the correct diagnosis is rarely missed.

The pathologic observations include hyperplasia of the adrenal cortex, a basophilic adenoma of the hypophysis, and Crooke's "hyaline change" of the basophilic

cells. Hyperplasia of basophilic cells in the form of numerous ill-defined, microscopic nodules may be seen instead of an adenoma. Also found are marked lipomatosis of the parathyroid glands, atrophy of the thyroid as well as a diffuse or nodular colloid goiter, luteinization of graafian follicles in the ovary, atrophy of the testicles with a decrease of spermatogenesis and disappearance of Leydig's interstitial cells, osteoporosis, kyphosis, spontaneous fractures, arteriosclerosis, and central or diffuse fatty infiltration of the liver.

According to Cushing, the basophilic adenoma of the hypophysis represented the cause of the disease, while the changes of the adrenals and gonads might be secondary in nature. The obesity was supposed to be due to a disturbance in the tuberohypophysial mechanism, the osteoporosis due to the lesion of the parathyroid glands, and, finally, the arterial hypertension due to the basophilic invasion of the posterior lobe of the hypophysis. There are objections to this concept. Cases of Cushing's disease occur in which no basophilic adenoma or hyperplasia is found. In other cases, although basophilic adenomas are present, they are of tiny size (e.g., 1.5 or 2 mm. in diameter), despite long duration of the disease. Also, much larger adenomas of well-differentiated basophilic cells often have been found when there was no

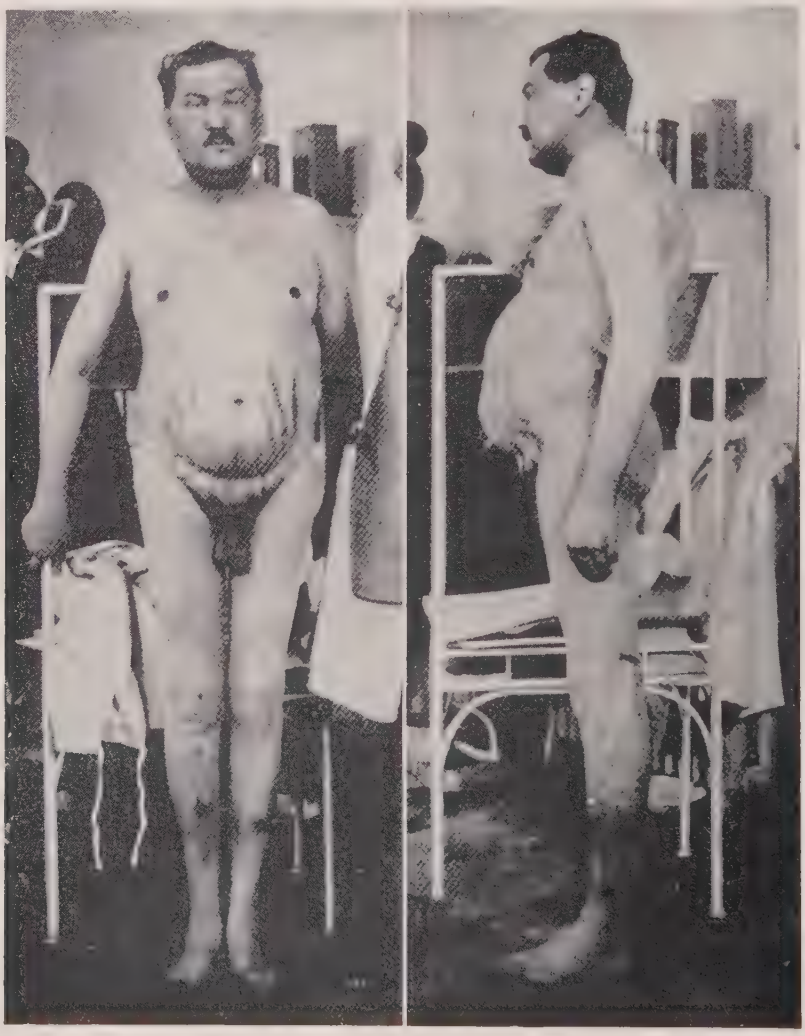

Fig. 860.—Cushing's disease in a 31-year-old man (case of Raab and Kraus). (From H. Cushing's monograph, the Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations, Bull. Johns Hopkins Hosp. 50: 137, 1932.)

evidence of Cushing's syndrome. And, finally, in cases of Cushing's disease, adenomas have been found in the hypophysis which were not basophilic in nature.

Basophilic adenoma in Cushing's disease probably represents a secondary feature, perhaps compensatory in nature. Certainly, a basophilic adenoma is not as essential in the pathogenesis of the disease as first was thought. On the contrary, it seems to be more probable that we have to deal in Cushing's disease with a condition of underactivity of the gland, rather than overactivity.

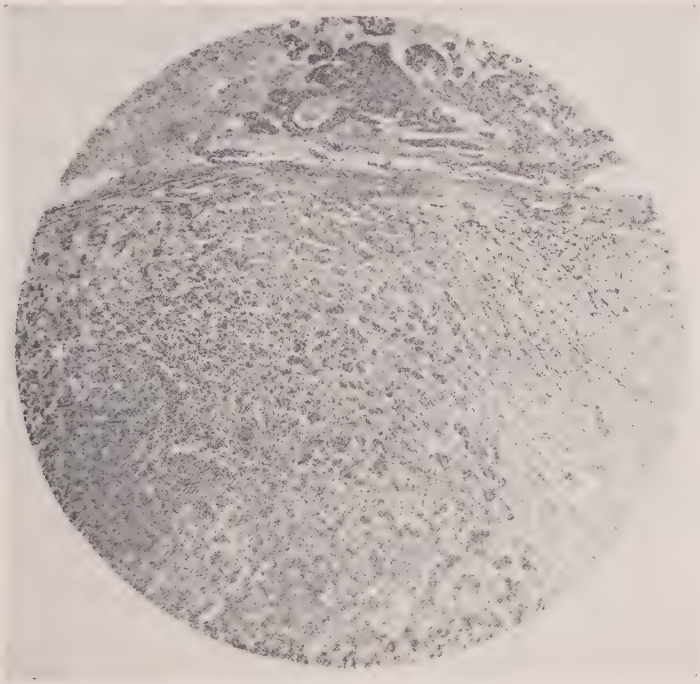

Fig. 861.—Malignant basophilic adenoma of the posterior lobe of the pituitary in a case of Cushing's disease. (Above there is a part of the anterior lobe, to the right a part of the posterior lobe, not yet invaded by the tumor.)

Besides the basophilic adenoma there is another lesion in the hypophysis, the so-called "hyaline change" of the basophilic cells, described by Crooke.[99] This lesion is characterized by a dense homogeneous hyaline cytoplasm replacing the basophilic granulation. This change is found in but few conditions other than Cushing's disease, and then merely to a slight degree. In addition to the hyalinization of the cytoplasm, the basophilic cells show, as essential changes, ballooning of the cell nuclei, excessive vacuolization and tendency to multinucleation and cell enlargement. Eisenhardt and Thompson,[100] who reviewed 63 cases of Cushing's disease found true basophilic adenomas in 33, chromophobic adenomas in 3, mixed cell adenomas in 2, and a malignant tumor with metastasis in one. Crooke's change was found in all these cases. The few cases reported in which Cushing's disease was fully developed in the absence of a tumor in the hypophysis and hyperplasia or tumor of the adrenals must be received with skepticism. Whereas some authors did not find any essential lesion of the hypothalamic nuclei, Heinbecker[101] reported in 4 out of 5 cases retrogressive changes especially in the nuclei and paraventriculares.

In contrast to the frequent absence of basophilic adenoma, hyperplasia of the adrenals seems to be rather constant and may reach a very remarkable degree. In some cases of Cushing's disease, adrenal cortical tumors have been found without adenoma of the hypophysis.[102, 103] Consequently, some have interpreted the disease as a hyperadrenocorticism.[104-106] It

seems that the hyaline change of basophilic cells in Cushing's disease represents injury resulting from hyperfunction of adrenal cortex, which, in the majority of the cases, though not in all, is followed by a regeneration and proliferation of the basophilic cells, usually in the form of a small basophilic nodule, or more rarely in the form of a diffuse or nodular hyperplasia. This conception seems to explain best the pathogenesis of the two hypophysial changes in Cushing's disease; Crooke's hyaline changes of the basophilic cell representing a retrogressive, and the basophilic adenoma a progressive and possible reparatory process. Recent studies seem to show that many features of Cushing's disease are attributable to overproduction of cortisone-like steroid hormones by hyperfunctioning adrenal cortices. Indeed large does of cortisone may produce in human beings symptoms found in Cushing's disease, such as muscular weakness, striae, decreased glucose tolerance, hypertension, amenorrhea, hirsutism, rounding of facial contours, and kyphosis.[107] (See also page 1038.)

Assays on the elimination of hormones in cases of Cushing's disease have revealed high, or normal 17-ketosteroids in the urine, high glycogenic corticoids, high 11-oxycorticosteroid, and tendency to increased elimination of gonadotropic and adrenocorticotropic hormones.[108, 109, 110]

Achard and Thiers[111] described a syndrome that they called **"diabète des femmes à barbe" (diabetes in bearded women).** Considering the essential symptoms, namely, the masculine hairiness of the face, the disorder in the sexual functions, the obesity involving the trunk but not the extremities, the striae, hypertension, and glycosuria, there seems little doubt that the syndrome is similar to or identical with Cushing's disease. In one case, autopsy revealed large adrenals, a colloid goiter, and fibrotic ovaries. In other cases, obesity, hypertrichosis, and osteoporosis were noted together with diabetes mellitus.

DIABETES INSIPIDUS

Diabetes insipidus is a disturbance of water balance characterized by excessive elimination of urine of very low specific gravity together with marked intake of water as the result of abnormal thirst. The pathologic changes forming the basis of diabetes insipidus are destructive lesions of variable nature located within the hypophyseo-diencephalic system, although there are cases which seem to be without any demonstrable morphologic alteration.

Various theories have been advanced concerning the nature of this disease, the predominant one being that there is lack of a hormone normally produced in the neurohypophysis and controlled by the vegetative centers of the hypothalamus, which, acting on the kidneys, promotes reabsorption of water in the renal tubules.

Diabetes insipidus develops when a destructive lesion involves the vegetative centers in the hypothalamus or the neurohypophysis or both. A cause of diabetes insipidus may be destruction of the posterior lobe by a metastatic tumor, e.g., from carcinoma of the breast, lung, or thyroid. Primary tumors of the hypophysis infrequently cause diabetes insipidus. Chronic inflammation and specific granulomas of the hypophysis, particularly gumma and tuberculosis, have caused some cases. In a few instances, Hodgkin's granuloma or sarcoidosis have been found in the hypophysis.[112] Diabetes insipidus may be an important feature of Hand-Schüller-Christian's disease (see pages 950 and 1215), due to extension of the lipoid granuloma from the sella to the neurohypophysis.[113-116]

Rarer are cases of diabetes insipidus in which both the hypophysis and the interbrain appear involved either by tumor or a specific granuloma. In these cases usually the diabetes insipidus accompanies another hypophysial disease, such as adiposogenital dystrophy, dwarfism, acromegaly, and Cushing's disease.

A third group of cases comprises those with the causal lesion being found exclusively in the interbrain, while the hypophysis shows only secondary changes due to the destruction of the vegetative centers.[117-119] Recently in a case reported by Gjersoe and Kjeruff-Jensen,[120] a hypothalamic lesion due to Boeck's sarcoidosis without any change in the hypophysis led to diabetes inspidus and hypogonadism.

Secondary degenerative changes of the nuclei supraoptici and paraventriculares have been found in diabetes inspidus as the result of the primary destruction of the neurohypophysis. Looking at the hypophysis and the vegetative centers in the interbrain as one physiologic unit, one may not wonder that the destruction of one of the two parts causes secondary changes in the other one.

In cases of diabetes inspidus reviewed by Jones,[121] the underlying lesion appeared to be a tumor of the hypophysis in 26 per cent, a tumor of the hypothalamus in 5 per cent, Hand-Schüller-Christian's disease in 10 per cent, chronic encephalitis in 16.6 per cent, syphilis and traumatic cranial injuries each in about 7 per cent, and various other types of hypophysial and hypothalamic injuries in but a small percentage of cases. In 19 per cent of cases, the underlying cause could not be determined.

Summarizing, one may say that the cause of diabetes insipidus is a destructive process within the nervous part of the hypophyseo-dien-

cephalic system, which is the posterior lobe, the hypophysial stalk and the floor of the third ventricle. The destruction of any one of these parts is able to produce the disease.

THE HYPOPHYSIS IN EXOPHTHALMIC GOITER

Examination of the hypophysis in cases of exophthalmic goiter has shown a decrease in the weight of the hypophysis and diminution in number and size of the eosinophilic cells, which frequently contain shrunken, dark-stained nuclei.[122, 123] In some cases there are severe changes of the basophilic cells such as decrease of size, poor staining ability, and pyknosis, but such alterations of the basophilic cells are not specific for exophthalmic goiter. The chromophobes are often proliferated at the expense of the eosinophilic cells and show partially shrunken, dark nuclei. Small chromophobes, seemingly without cytoplasm, and numerous small nongranulated cells similar to transitional cells may be present. The morphologic features of the hypophysis in Graves' disease indicates an injury to the parenchyma, as the lesions are degenerative in nature, whereas in hypothyroid conditions there occurs a proliferative process, causing enlargement of the organ, with retrogressive changes developing secondarily.

THE HYPOPHYSIS IN ADDISON'S DISEASE

In most cases of Addison's disease the basophilic cells show marked decrease in number, nuclear pyknosis, excessive diminution of granules, transformation into a honeycomb-like, almost confluent mass, small size, and irregular shape of the cell body and obscured cell contours. The chromophobes are usually increased in number at the expense of the chromophils. Frequently, they also show retrogressive lesions, such as pyknosis, etc.[124-129]

A close functional relationship between the basophilic cells in the hypophysis and the adrenal cortex is suggested, not only by the depletion of basophilic cells in adrenal insufficiency but also by the occurrence of increased numbers of basophiles in about 80 per cent of cases in which there is hyperplasia of the adrenal cortex. The findings suggest that both the adrenals and the basophilic cells of the hypophysis are part of a blood pressure regulating apparatus. (See also the discussion of Addison's disease on page 1034.)

THE HYPOPHYSIS IN DIABETES MELLITUS

The frequent occurrence of glycosuria or diabetes mellitus in acromegalic individuals has suggested a functional relationship between the eosinophilic cells of the pituitary and the pancreatic islets of Langerhans. Untreated juvenile diabetics have been found to have a decrease in size and weight of the hypophysis, with decrease in size and number of eosinophiles, and occasionally a peculiar hydropic change in basophiles. These findings, supported by certain experimental results, have suggested an antagonistic action between the anterior lobe of the hypophysis (probably by eosinophiles) and the pancreatic islets.[130-132]

THE HYPOPHYSIS AND LACTATION

Among individuals with lactation apart from pregnancy and the puerperium, many have been women with lesions in the hypophyseo-diencephalic system, and often cases of acromegaly.[133, 134] The relatively small amount of morphologic evidence available supports the hypothesis that the so-called "pregnancy cells" of the pituitary may be the source of a lactogenic hormone.[135]

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Chapter 35

THE PINEAL

W. A. D. Anderson

The pineal body (epiphysis) is a structure about which we have as yet little exact knowledge of any function. Incomplete evidence up to this time has pointed in the direction of its being a secretory organ concerned with sexual and somatic maturation. Pathologic changes in the pineal include tumors and cysts which cause disturbances mainly as space-consuming lesions, the nature of the effects largely being due to the anatomic situation of the organ. Surgical removal rarely has been successful, because of the hazards and difficulties involved in reaching and removing tissue from the pineal area.

Anatomy and Structure

The pineal is situated above the posterior extremity of the third ventricle with its base directed anteriorly, beneath the bulging portion of the corpus callosum, above and behind the posterior white commissure and resting on the groove between the quadrigeminal bodies. It is in a sagittal position, pointed backward and obliquely upward, and covered by pia mater. Laterally it is in relation to the choroid plexus and above borders on the vein of Galen. Thus its intimate relationship to essential vascular and cerebrospinal fluid channels and cerebral areas is such that its enlargement causes important disturbances from pressure, and at the same time makes operative removal difficult. Usual dimensions are 7 to 10 mm. in length, 3 to 6 mm. in width, and 3 to 4 mm. in thickness. In adults, the pineal averages about 0.154 gram in men and 0.159 gram in women.

During development of the pineal there may be a mosaic appearance histologically due to areas composed of pale cells separated by some irregular masses of small cells with dark nuclei. This appearance is also seen in some pineal tumors (see Fig. 864). The fully developed pineal is composed of masses of cells divided into lobules to a variable extent by connective tissue and vascular septa. The connective tissue septa and lobulated architecture tend to become more marked with increased age. The pineal parenchymal cells have pale nuclei, oval or round, surrounded by stellate or irregular cytoplasm, which takes ordinary stains poorly. Rio-Hortega[3] has described abundant cellular processes, revealed by silver carbonate staining, which seem to be directed particularly toward perilobular areas, where they end as terminal dilatations. These protoplasmic processes give the cytoplasm a pseudosyncytial aspect with ordinary stains. Small dark cytoplasmic granules are demonstrable, in the author's experience, after the age of 11 years, and are best seen after cresyl violet staining. Vesicular rounded masses or clear areas are occasionally seen in the nuclei. While these cytoplasmic and nuclear structures have been regarded by some as indicating secretory activity, evidence for this is incomplete. Neuroglial cells, mainly of astrocyte type, are scattered throughout the pineal.

Calcareous concretions (acervuli, brain sand) are rather constantly present in the pineal after the age of 15 years. Roentgenologic demonstrability of displacement of the pineal, made possible as a result of these deposits, sometimes assists in the clinical localization of intracranial lesions.[7]

Plaquelike areas of neuroglial hyperplasia or gliosis are frequent in the pineal, and seem to be more numerous in the older age groups. Small cavities often are seen within these glial areas, or lined by a layer of glial tissue with concentric fibrils, and also increase in frequency with age.

Function

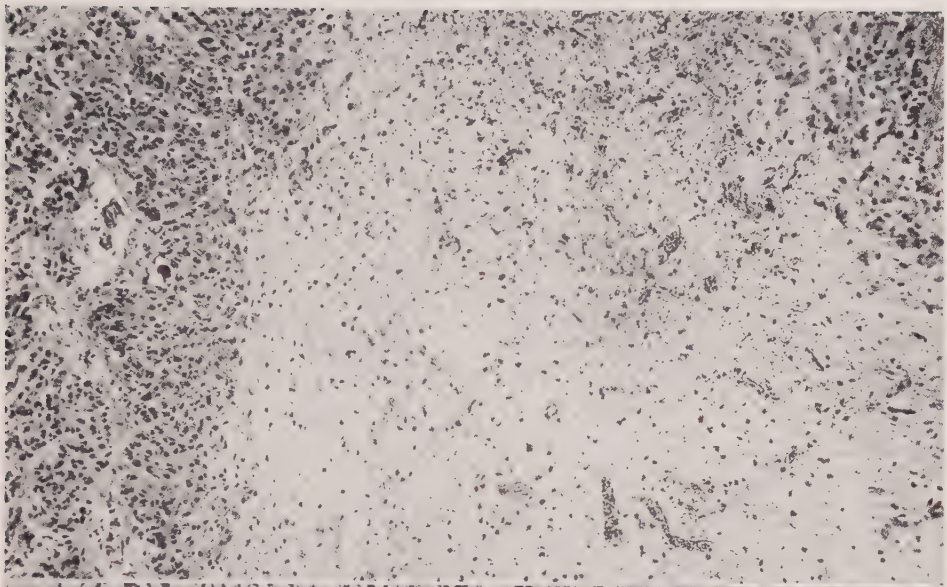
Experimental and clinical observations concerning any function of the pineal have been confusing and inconclusive. A popular theory has been that the pineal is concerned with controlling development to sexual maturity and the initiation of puberty, particularly in males. This idea has been based on the rare occurrence of precocious sexual maturation in boys with certain pineal tumors (see page 992), and on the interpretation of gliosis, calcium depositions, and other changes in the organ common after adolescent years, as of involutional nature.

The pineal is not essential to life nor to pregnancy and parturition. Experimental investigations by pinealectomies, pineal implants, pineal feeding, and injection of pineal extracts have produced conflicting results in different hands. Rowntree and associates[5] found that injection of pineal extracts retarded rate of growth but accelerated maturity of development and onset of adolescence in the offspring of treated rats, and that injection of succeeding generations amplified the effect.

Pathologic Changes

The only lesions of importance in the pineal are cysts and tumors. **Cysts of the pineal** are very common, usually being small cavities within areas of gliosis or having a glial wall. These are ordinarily small, do not cause enlargement of the organ, and are without any associated

Fig. 862.



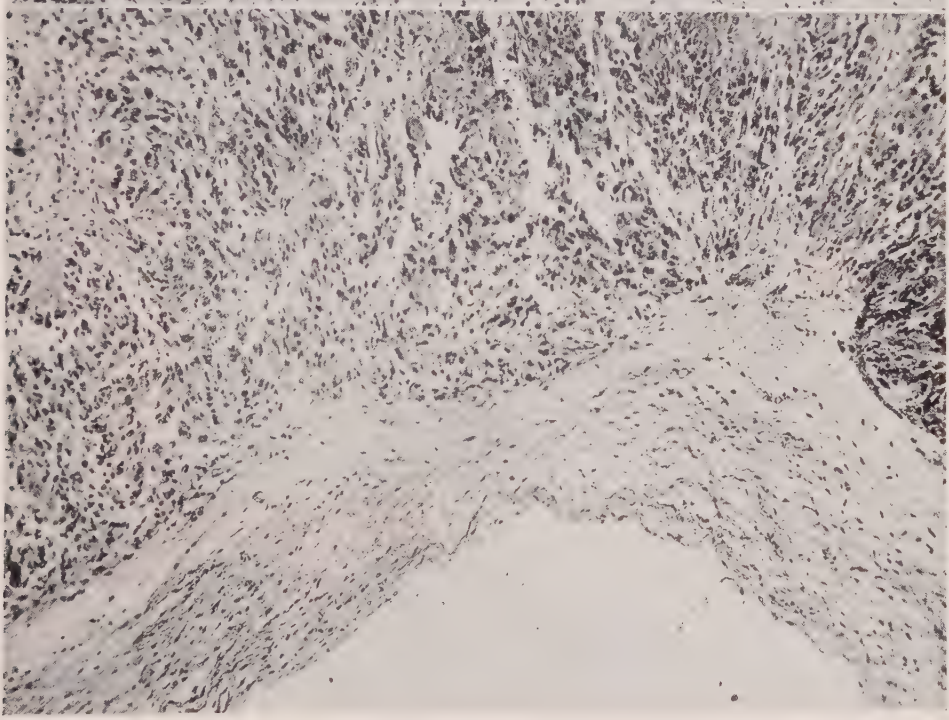


Fig. 863.

Fig. 862.—Adult pineal, showing plaque of neuroglial tissue.
Fig. 863.—Adult pineal, showing glial plaque with central cyst formation.

clinical disturbance. Much rarer are cysts which distend the gland, and cause pressure on adjacent structures *(cystic hydrops of the pineal),* and these likewise are lined by glial tissue. Inclusions of ependymal cells less commonly account for cyst formation. Some of the larger cysts have been associated with mental disorders and sudden death.[10]

Tumors.—Tumors of the pineal may be composed of pineal cells (pinealoma), of neuroglial cells, or may be of teratomatous nature. Because of the anatomic location of the pineal, the symptoms for the most part are due to increased intracranial pressure, the result of internal hydrocephalus secondary to obstruction of the aqueduct of Sylvius. Headache is usually the first symptom, followed at a later period by blurring of vision, diplopia (effect on oculomotor nuclei), Argyll Robertson pupils, papilledema, vomiting, drowsiness, change in mental outlook, and finally paralysis of extraocular muscles, particularly those necessary for conjugate upward gaze (indicative of involvement of the quadrigeminal bodies).[6, 14]

of these tumors to the seminomas of the testicle has been noted, and it has been suggested that they may arise from totipotent primordial germ cells.[26] There is considerable evidence that pinealomas are really atypical teratomas.[17, 24] Some pineal tumors extensively invade contiguous tissues or implant in the ventricles or on cranial nerves.[14, 19]

Gliomatous tumors of the pineal region have been of the nature of spongioblastomas[13] and ependymomas. While such tumors may be indistinguishable from their counterparts arising in other areas of the central nervous system,[12] it has been claimed that ependymal derivatives participate in the histogenesis of the pineal, and hence such tumors may be included as pinealomas[11] (e.g., pineal ependymoma, spongioblastic pinealoma). It is probable, however, that the spongioblastic pinealoma simply arises from the neuroglial cells found in the pineal.[14]

The pineal ependymomas are easily mistaken for adenocarcinoma because of a glandular structure in some areas and mucin production. They resemble ependymomas found elsewhere, but

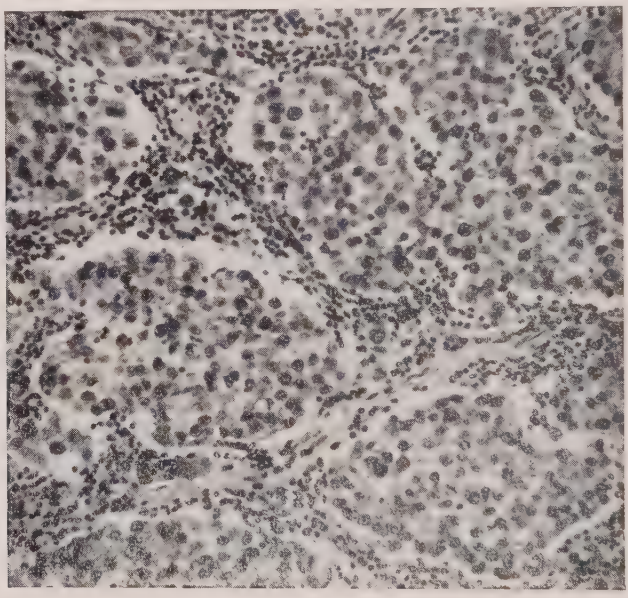


Fig. 864.—Pinealoma, showing the two types of cells usually present.

Pinealoma (pinealocytoma), the most frequent tumor of the pineal, is composed of pineal parenchymal cells, and usually reproduces in its appearance some stage in the development of the organ.[11] It occurs predominantly in males, and most often between the ages of 15 and 25 years.[12] In its most characteristic form it is composed of groups of the large pale parenchymal cells separated by smaller darker cells, and sometimes having as a result the mosaic pattern seen in the developing organ (Fig. 864). It has been felt by some that almost all pineal tumors may be identified with some developmental stage, and hence should be included under the term pinealoma.[11] The resemblance

have been said to be distinguished by the presence of large pale cells having the appearance of pineal parenchymal cells. They may have numerous mitoses and giant cells, indicating a high degree of malignancy.[14]

Teratomas of the pineal are rare but form a distinct group of tumors of the pineal region,[16] although the larger group of pinealomas has been interpreted by some as being also of teratomatous nature.[17, 24] In rare instances, teratomatous tumors of the pineal region in male children have been associated with precocious somatic and sexual development (macrogenitosomia praecox, pubertas praecox, Pellizzi's syndrome). While this often has been looked

upon as suggestive evidence of some relationship of the pineal to masculine sexual maturation, whether it is of an inhibitory or stimulative nature is a debatable point.[15] On the other hand, it has been pointed out that the precocious sexual development in such cases may have no direct relationship to the pineal, but may be a manifestation of vegetative disturbance resulting from hypothalamic disorder.[11] Similar precocious development has been found with an intact pineal and a tumor or lesion of adjacent cerebral areas.

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Chapter 36

THE THYROID

W. A. D. Anderson and Theodore Winship

STRUCTURE AND FUNCTION

The thyroid gland consists of two conical lateral lobes connected by an isthmus, wrapped partially around the upper end of the trachea, and extending from about the lower third of the thyroid cartilage to the fifth tracheal ring. Occasionally a third lobe, the "pyramidal lobe," extends upward from the isthmus or one of the lateral lobes, and sometimes is connected to the hyoid bone by a fibrous strand. The isthmus rarely may be absent. Each lateral lobe averages about 4 by 2.5 by 2 cm., and the isthmus is about 2 cm. high. The normal adult thyroid weighs about 25 grams on the average, but variations between 20 and 40 grams are common, depending on age, sex, geographic location, and other factors. The gland is enclosed in an intimate true capsule, which has firm connections with the trachea, and the cricoid and thyroid cartilages. The thyroid is very vascular, and the blood volume of a normal man moves through his thyroid once an hour. It is supplied by paired superior and inferior thyroid arteries, and sometimes by an additional artery, the thyroidea ima. The size of the thyroid vessels varies with the size and activity of the gland. In goiters the vessels may become large, show marked pulsation, and numerous small, irregular and unnamed vessels may become enlarged and prominent. The veins begin as a perifollicular plexus, travel beside small arteries to the periphery of the gland, and there develop a plexus covering the gland.

Development

The thyroid develops as a downgrowth from the region of the primitive pharynx. A mass forms at the base of the tongue and extends downward as a long tube, the thyroglossal duct, its final position being in front of the trachea and thyroid cartilage. The upper end of the thyroglossal duct is marked by a small depression at the root of the tongue, the foramen caecum. The elongated duct loses its lumen, is transformed into a cord and normally is obliterated during fetal life, beginning at about the fifth week. Failure of complete obliteration of the thyroglossal duct may leave a thyroid residue in the form of a pyramidal lobe or in any position along the course from the tongue to the final position of the gland. These nests of residual thyroid tissue may give rise to midline (thyroglossal duct) cysts, often attached to the hyoid bone, or some thyroid tissue may be found at the base of the tongue (lingual thyroid). Rarely there is complete failure of descent, and the main thyroid mass develops at the base of the tongue.

Some studies of thyroid development have suggested that a portion of the thyroid is formed from lateral anlages derived from the fourth or fifth branchial pouches.[5-7] While this conception may not be valid, it has been frequently referred to in explanation of aberrant thyroid tissue found in lateral parts of the neck[7] (see discussion of lateral aberrant thyroid tumors, page 1010). The parathyroids and thymus develop from branchial pouches independently of the thyroid and not in intimate association with it.

Microscopic Structure

The thyroid is composed of acini or follicles, of variable size and shape but tending to be spherical. In the normal gland, most follicles are between 0.05 and 0.12 mm. in diameter. Each follicle is a closed sac, lined by a single layer of epithelium, and containing colloid, a homogeneous gelatinous material. The follicles have no basement membrane. Between the follicles there is a small amount of interstitial connective tissue, with blood vessels, lymphatics, and occasionally some small foci of lymphocytes. When hyperplasia occurs in the thyroid gland, new follicles are formed by budlike proliferation of follicular epithelium, secondary acini being formed which communicate for a time with the primary follicle but eventually become isolated units. Small solid masses of interfollicular epithelium, which are encountered occasionally, have been interpreted as detached extrafollicular buds.[12]

The thyroid gland tissue appears to go through recurring cycles of secretion, colloid release, and resting or recuperation. Active functional units consisting of a main follicle and satellite follicles are found, and the form of follicular epithelium varies with its degree and type of function.[18] Tall columnar epithelium resorbs hormone from the follicular lumen and discharges it into the blood stream; high cuboidal epithelium actively produces colloid; low cuboidal epithelium produces colloid slowly; low, flat epithelium is inactive. Increase of secretion in small secondary acini gives rise to a papilla or bulging into an adjacent larger follicle which has been called a "Sanderson Polster." These apparently correspond to localized zones of functional activity.[18] Quantitative studies on the height of thyroid acinar cells have shown this to be an index of functional activity[16] or of stimulus by thyrotropic hormone.[17]

Intracytoplasmic colloid or secretion granules may be demonstrable during phases of activity of follicular cells.[11, 19] The Golgi apparatus of the follicular cells enlarges during secretory

activity.[13, 14] and some observations have suggested that its position indicates the direction of secretory activity.

The colloid within the follicles is most commonly a homogeneous eosinophilic material, but its consistency and staining properties, and presumably its chemical composition, show considerable variation. Thin colloid stains red with eosin and blue with azocarmine, while thick colloid is stained blue by hematoxylin and red with azocarmine. Functional and pathologic significance has been attached by some to the variations in staining properties. Thin, pale, eosinophilic colloid appears associated with functional activity, whereas the thick, deeply eosinophilic or basophilic colloid appears in inactive follicles.[14, 15] Crystalline materials have been demonstrated in the follicles by special technical methods.[19]

Function of the Thyroid

The thyroid produces a hormone which accelerates oxidative processes in body cells. The hormone appears to act on the cells themselves, perhaps primarily facilitating changes in protein metabolism, but directly or indirectly involving oxidation processes and increased use of oxygen. Thus, the thyroid influences or controls the rate of basal and general metabolism. The level of oxidative processes is most commonly measured by determining the level of basal or resting metabolism as evidenced by respiratory exchange of oxygen. Adequate amounts of thyroid hormone are necessary for normal growth and development in young animals and man. Failure of growth and development characterize deficiency of the thyroid hormone in infancy and childhood (cretinism, page 1001). Excess of thyroid hormone (hyperthyroidism) in childhood causes acceleration of growth.

Iodine and the Thyroid Hormone.—It has long been known that iodine is the important constituent of the thyroid hormone, and that it is the function of the gland to remove ingested iodine from the blood and elaborate it into the active hormone. Studies on the usage of iodine have been stimulated greatly by the recent use of radioactivated compounds of iodine, which can be traced and followed in the body.[23] When radioactive iodine is injected, it is detectable in the thyroid within two minutes, a much greater proportion being taken up by the thyroid than by other tissues. With very small dosage of iodine, the gland can abstract about 50 per cent of it, whereas it takes up relatively smaller proportions of larger doses. The amount of iodide taken up by the gland may be increased by injection of thyrotropic hormone.[32] When an insufficient amount of iodine is available to the gland, it is stimulated to undergo hyperplasia. About 0.1 to 0.2 mg. of iodine intake is necessary daily for normal hormone production, which is equivalent to about 0.3 mg. thyroxine.

The final chemical form of the hormone built by the thyroid is still undetermined. In 1915 Kendall isolated thyroxine, an iodine-containing amino acid, which exerted the physiologic action of whole thyroid, and the substance was later synthesized. The thyroid hormone is stored in the follicles in protein combination, as iodothyroglobulin. This can be broken down into two iodine-containing amino acids, thyroxine and diiodotyrosine, the latter being relatively inactive. The calorigenic action of whole thyroid appears to parallel the iodine content, but immunologic methods have shown that the hormone does not circulate in the blood as thyroglobulin, nor does it circulate as free thyroxine. It appears that the diiodotyrosine portion must be present in the body in some more active form.[30]

Iodinated proteins having a relatively low degree of physiologic activity similar to that of thyroid hormone have been formed in vitro.[33] It appears that iodine compounds with the activity of thyroid hormone can be and are made by tissues other than the thyroid gland, but only the thyroid gland produces active hormone with the necessary rapidity and efficiency.[30]

The protein-bound iodine of the blood can be used as a dependable index of circulating thyroid hormone.[27] The total blood iodine varies from 5 to 15 micrograms per 100 cubic centimeters in the normal person, in hyperthyroidism it may range as high as 110 micrograms, and in hypothyroidism as low as 2 to 5 micrograms. The active or T (thyroxine) fraction of protein-bound iodine of the blood ranges in the normal from 2.9 to 4.8 micrograms per hundred cubic centimeters, about one-third of the total iodine. It rises in hyperthyroidism, and in severe hypothyroidism may be almost zero.[24]

The rate of hormone production by the thyroid appears to be regulated by a complicated system of balances and controls, so that it is little to be wondered at that the rate and amount of hormone production is frequently disturbed, producing varying degrees of hyperthyroidism or hypothyroidism. The three important governing factors are (1) the supply of iodine available for synthesis, (2) the thyroid-stimulating hormone of the pituitary, and (3) the condition and activity of the thyroid gland itself.

Excess of iodine in the normal has little or no effect. A deficiency of iodine stimulates the thyroid gland to hyperplasia, with accumulation of an excess of iodine-poor colloid (colloid or endemic goiter). Prolongation of iodine deficiency tends to exhaust the gland, the large colloid-filled follicles becoming lined by flat and inactive epithelium. Increased supply of iodine allows iodination of the large accumulation of colloid to a form which can be liberated from the gland as active hormone. It appears that in some such cases administration of an excessive amount of iodine causes too rapid iodination and may lead to excessive formation of thyroid hormone and precipitate hyperthyroidism.[24]

In the hyperplastic condition of the thyroid gland in Graves' disease, administration of iodine for a time promotes storage of colloid in the follicles rather than release of hormone into the blood stream (see page 1000). Thus, there is a temporary decrease of circulating thyroid hormone, and corresponding clinical improvement.

Control of Thyroid Activity.—Although nervous regulation of the blood supply of the thyroid

has been looked upon as an indirect mechanism exercising some influence on the output of thyroid hormone, the activity of the gland appears to be controlled mainly by a thyroid-stimulating hormone of the anterior pituitary.[29] This pituitary factor is of protein nature.[30] It causes increase in height, secretory activity, and oxygen consumption of thyroid epithelium.

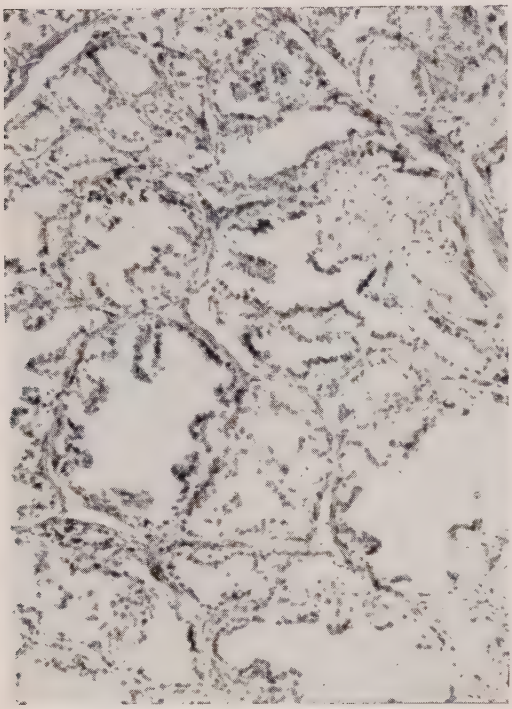

Fig. 865.—Thyroid following thiouracil therapy. Note marked hyperplasia and the almost complete absence of colloid.

Although the thyroid is the chief tissue on which this pituitary factor acts, there is evidence that in excess it causes swelling of orbital tissues and exophthalmos (see page 1000). The thyroid-stimulating hormone becomes oxidized and inactivated by its action on the thyroid, and appears in the urine in its inactivated form, but can be restored to activity by reduction. When the thyroid tissue is affected by pathologic lesions so that it cannot respond to the thyrotropic hormone, the thyroid-stimulating hormone appears in its active form in the urine.[30]

The amount of thyrotropic hormone formed by the pituitary tends to be regulated to some extent by the amount of thyroid hormone circulating in the blood. An increase of thyroid hormone in the blood depresses the pituitary output of thyrotropic hormone. Thus, the two glands normally tend to have a balancing or automatic regulatory effect on each other.[30]

Goitrogenic Substances.—The effects of certain chemicals on thyroid structure and function have confirmed the important influence of the thyrotropic hormone of the pituitary on the thyroid, and have great clinical and therapeutic importance. Cyanides and, later, sulfocyanates and thiocyanates have been shown to induce thyroid hyperplasia with enlargement of the gland, but decreased thyroid hormone production. Such goiters have been reported occasionally in patients receiving thiocyanate therapy for hypertension.[34] This effect appears to be preventable by iodine administration, and also as administration of thyroid substance will overcome the hypothyroidism, there is apparently no interference with the effect of thyroid hormone on end organs. It appears that there is a blockage of thyroid hormone formation by the thyroid, the consequent lowering of thyroid hormone in the blood stimulating the pituitary to produce an excess of thyrotropic hormone, which in turn leads to the thyroid hyperplasia and goiter.

Thiouracil and related substances (including sulfonamides) likewise appear to block at some point the formation of thyroid hormone, similarly leading to thyroid hyperplasia due to the unopposed influence of the pituitary thyroid-stimulating hormone. Marked degrees of thyroid hyperplasia with great diminution of colloid may be found in the thyroid gland as a result of thiouracil administration. Under such circumstances the degree of thyroid hyperplasia does not reflect the output of thyroid hormone, and so cannot be correlated with the clinical presence of hyperthyroidism or hypothyroidism. Certain thiouracil derivatives, such as 6-ethylthiouracil and 6-N-propylthiouracil, have been found to be even more active in their effect than thiouracil itself.[39] Used alone as preoperative treatment, without iodine, thiouracil decreases thyrotoxic reactions, but may increase technical difficulties of thyroidectomy because of the marked vascularity and friableness of the hyperplastic gland.[35, 38] There is some evidence that an undesirable effect of the unopposed thyrotropic hormone may be seen in an increase of exophthalmos.[34, 40] The exact mechanism of the antithyroid activity of thiouracil is uncertain, but some evidence suggests that it acts by inhibiting the cytochrome oxidase activity of thyroid tissue.[42]

GOITER

The term goiter, or struma, refers to an enlargement of the thyroid gland. Such enlargement may be related to several different etiological factors; it may be diffuse or nodular (adenomatous), and it may be associated with a deficient, normal, or excessive production of hormone. Many different classifications of goiter have been proposed and used, many of which have been made complex by fine subdivisions on the basis of gross or microscopic variations which have no etiological or clinical significance. For our purpose, five main types may be recognized:

1. Iodine deficiency goiter, also termed endemic, simple, or colloid goiter.

2. Diffuse goiter with hyperthyroidism (exophthalmic goiter, Graves' disease, Basedow's disease).
3. Nodular (adenomatous) goiter (with or without functional disturbances of hyperthyroidism or hypothyroidism).
4. Degenerative and inflammatory goiter:
   a. Amyloid goiter.
   b. Granulomatous thyroiditis (syphilis, tuberculosis, etc.).
   c. Lymphadenoid goiter (struma lymphomatosa).
   d. Riedel's struma.
5. Neoplastic goiter:
   a. Benign (adenoma).
   b. Malignant (carcinoma).

Not included in the above classification are the drug-induced hyperplastic goiters due to cyanates, sulfonamides, and thioureas. Although the above classification represents useful distinctions, it does not always indicate etiological or important biologic differences in the types of goiter, e.g., a later stage of an iodine-deficiency goiter may be a nodular goiter. Also, as far as the hyperthyroidism itself is concerned, there may be no difference between a diffuse goiter with hyperthyroidism and a nodular goiter with hyperthyroidism.

Iodine Deficiency Goiter

In certain regions of the world, goiter is present endemically in a relatively large proportion of the population. These districts are mainly mountainous areas of Europe, Asia, and America. The regions of the Alps, Pyrenees, Andes, Himalayas, and Rockies of northern United States and Canada have the highest incidence. However, certain nonmountainous inland districts of England, America, and elsewhere are affected. In America the goiter zone is found around the Great Lakes and St. Lawrence valley, extending westward through Minnesota, the Dakotas, and adjacent Canadian territory, and including Oregon, Washington, and British Columbia.

It seems reasonably well established that this endemic goiter is due to a relative deficiency of the amount of iodine available to the thyroid gland in relation to metabolic needs. While in most cases this is due to ingestion of insufficient iodine in food or water and may be prevented simply by increased intake of iodine, there is evidence that other factors play an important role in some areas, and the mechanism in all cases does not appear to be completely elucidated. However, some have felt that the evidence was sufficient to conclude that endemic goiter is not due to lack of iodine (Greenwald).[50b]

In most areas where endemic goiter is prevalent, there is a low iodine content of the soil and water of the district, and a low daily intake of iodine. Soil in high and inland areas has had much of its soluble iodine content drained away by water on the way to the sea. A clue to iodine intake is obtainable by measuring daily urinary excretion of iodine, which is excreted mainly through the kidneys. Such examinations have shown relatively small amounts of urinary iodine excretion in children in goitrous regions. In many areas an inverse proportion has been shown between the iodine content of the soil and water and the incidence of goiter in the population. The prophylactic addition of small amounts of iodine to the diet, by the use of iodized salt or other means, has been shown to lower the incidence of goiter among children in certain goitrous regions in striking fashion. In areas where there is a high intake of iodine in the diet, e.g., Japan, Iceland, and various coastal regions, the incidence of goiter is very low.

It is evident that other factors than a low intake of iodine may be of importance. The goiter tends to develop with especial frequency at times when there is increased demand for thyroid function, e.g., during puberty and adolescence, pregnancy, the menopause, with certain infections and intoxications, or when there is deficient oxidation as in anemias or at high altitudes. Under such circumstances the relative deficiency of iodine available to the gland becomes evident. Excessive calcium ingestion in the diet or excessive hardness of water also appears to be an important factor in some cases. In certain areas of India the endemic goiter appears related to bacteriologic contamination of water supply rather than to its iodine content. The experimental goiter which develops due to cyanides on a diet containing a large amount of cabbage or related plants is preventable by intake of sufficient iodine. It is thus possible that the nature of the diet may be a factor along with iodine deficiency in some cases.

The optimal daily requirement of iodine appears to be about 3 micrograms per kilogram of body weight (0.2 mg. for a 70 kg. individual) although the requirement in pregnancy may be greater. The addition of potassium iodide to sodium chloride for table salt to the extent of 0.01 per cent appears to be an effective prophylactic, and without danger of iodine overdosage.

Except in areas of high endemicity, the proportion of women who develop iodine deficiency goiter is two or three times the incidence in men.

The thyroid gland responds to deficiency or depletion of iodine in the gland by hypertrophy and hyperplasia.[47,52] In endemic areas this occurs most commonly about the age of puberty, and results in diffuse enlargement of the thyroid. Histologically, the appearance

may be similar to that in other goiters characterized by hyperplasia, and differing only in degree. Following this there occurs a stage of involution, the follicular cells become cuboidal or low, and abundant colloid accumulates within the follicles. Many of the follicles become very large and distended with colloid and may coalesce to form cysts. Seen most often in this phase, the gland grossly is diffusely enlarged and highly translucent due to its abundant colloid. With recurring cycles of hyperplasia and involution, unequal response by different portions of the gland results in gross nodularity, and different parts present different histologic pictures. It is particularly the simple goiters of long standing that are nodular.

Gross examination of simple goiters shows great variation in size. The whole gland may be involved diffusely, or it may be nodular, with patchy so-called "adenomatous" areas. Although the enlargement is diffuse in the beginning, successive cycles of uneven hyperplasia and involution give rise to the nodularity. The cut surface of the gland has a highly translucent appearance due to the abundant colloid. Degenerative changes are often evident, particularly in the nodular type, and there may be hemorrhage, cyst formation, and calcification. Coarse, irregular connective tissue trabeculae separate the adenomatous nodules.

Microscopically the goiter may be composed of large distended follicles, filled with abundant deeply-staining colloid and lined by low cubical or flattened inactive epithelium. Such a "colloid goiter" is in an involutionary phase, and has been preceded by a stage of hyperplasia in response to the iodine deficiency.

It has been emphasized particularly by McCarrison[49] and Hellwig[48] that the pathologic characteristics of endemic goiter vary with different geographic regions. The variety commonly found in mountainous regions such as the Alps and Himalayas is a diffuse type made up of small follicles, poor in colloid, and referred to as "parenchymatous goiter" or "microfollicular goiter." It develops in childhood, increases in incidence as age advances, reaching a peak incidence between 50 and 60 years, and is nodular in adults. Hyperthyroidism is rarely associated with this type of goiter, but congenital goiter, cretinism, and deaf-mutism are common in families in association with this condition. Endemic goiter in low inland districts, on the other hand tends to have abundant colloid, has its peak incidence in adolescence or early adult life, not infrequently develops associated hyperthyroidism but is uncommonly associated with congenital goiter and cretinism.

Hyperthyroidism

Hyperthyroidism is the result of a hyperplastic overactive thyroid which secretes an excess of hormone into the circulation. While it is possible that in some cases an abnormal hormonal product may be released, no proof of this has arisen, and the concept of a simple quantitative excess of thyroid hormone appears to fit the facts best. Hyperthyroidism may be of all grades of severity; those cases having diffuse thyroid enlargement (exophthalmic goiter) are in general more serious than those with nodular goiters. There appears to be no fundamental difference between the diffuse and the nodular hyperplastic goiters as far as the thyroid factor itself is concerned. While, as a general rule, the histologic changes of hypertrophy and hyperplasia within the thyroid indicate excessive secretory activity, functional interpretations from tissue sections are not always reliable. Graham[52] particularly has emphasized the lack of correlation which may exist between clinical evidences of hyperthyroidism and histologic evidence of hyperplasia. Therapeutic use of thiocyanates and thiouracil also may be associated with marked hypertrophy and hyperplasia of the thyroid, which appears to be correlated with the output of thyrotropic pituitary hormone, and without relation to the amount of thyroid hormone released. While quantitative studies of the height of thyroid acinar cells may in many cases be correlated with thyroid hyperfunction,[54] it is apparent that increased height of thyroid epithelium is more directly a measure of the amount of pituitary thyrotropic hormone.[56]

Hyperthyroidism is characterized by an accelerated rate of tissue oxidation, with increase of resting or basal metabolism, hyperactivity of the sympathetic nerv-

ous system, and negative iodine balance. Common manifestations are increased heat production, increased cardiac rate (tachycardia), nervousness, irritability, and tremor. These features may be reproduced by giving excess thyroid substance or thyroxine. Protrusion of the eyes or exophthalmos, which is common in diffuse goiter with hyperthyroidism (Graves' disease), does not appear to be due to an excess of thyroid hormone[57] (see page 1000). Some effects commonly observed in hyperthyroidism, such as weight loss, muscular weakness, disturbance of sex cycles, increased excretion of calcium, and creatinuria appear to be due in part or entirely to vitamin deficiencies, particularly factors of the B complex.[61] Growth acceleration may occur with hyperthyroidism in children.

Diffuse Goiter With Hyperthyroidism

Diffuse goiter with hyperthyroidism, also referred to as Graves' disease, Basedow's disease, or exophthalmic goiter, is the most serious and severe type of hyperthyroidism. Most cases are in young adults or occur in middle age, but childhood is not exempt. The incidence is sporadic; it is common in but not limited to zones of endemic goiter. The diffuse enlargement of the gland may be slight or marked, and the size of the goiter is not correlated with the severity of the disease. The nature of the hyperthyroidism itself is not different from that which may be associated with nodular goiter.

Although thyroid hyperactivity plays an essential role in Graves' disease and accounts for most of the symptoms, the exact etiology is not known. There is evidence of an underlying genetic basis, with a recessive factor favorable to the occurrence of exophthalmic goiter.[58, 58a] Warthin[59] also felt that there was an underlying "Graves' constitution" which was a necessary basis on which the disease developed as a result of some stimulus. He pointed to lymphoid follicles in the thyroid with exhaustion of their germinal centers, thymic hyperplasia, and hyperplasia of lymphoid tissue elsewhere as characteristics enabling recognition of this predisposing constitution. There is a disturbance of the delicate hormonal balance, particularly between the pituitary and the thyroid, and the actual stimulus for the hyperactivity of the thyroid probably is an excess of the pituitary thyrotropic hormone.

The clinical condition may develop slowly or suddenly, and proceed through a course which may be rapid or prolonged by a series of exacerbations and remissions. Eventually there may be an exhausted condition of the gland with actual hypothyroidism. The protein-bound iodine of the blood is increased. Plasma albumin is decreased and alpha-globulin increased.[62] The galactose tolerance test shows high values, apparently due more to increased intestinal absorption than to hepatic damage. However, injury to the liver is common, and evident in a large proportion of cases by the hippuric acid test. Cardiac damage also usually occurs, and cardiac failure is a common complication of late stages, often with auricular fibrillation. Calcium and phosphorus excretion is increased, and in prolonged cases there is demineralization of the skeleton, and, rarely, spontaneous fractures may occur.[63] Exophthalmos is common, but an inconstant feature. Its severity is not correlated with the degree of hyperthyroidism, and it sometimes becomes worse after the hyperthyroidism has been alleviated by surgical or other means.

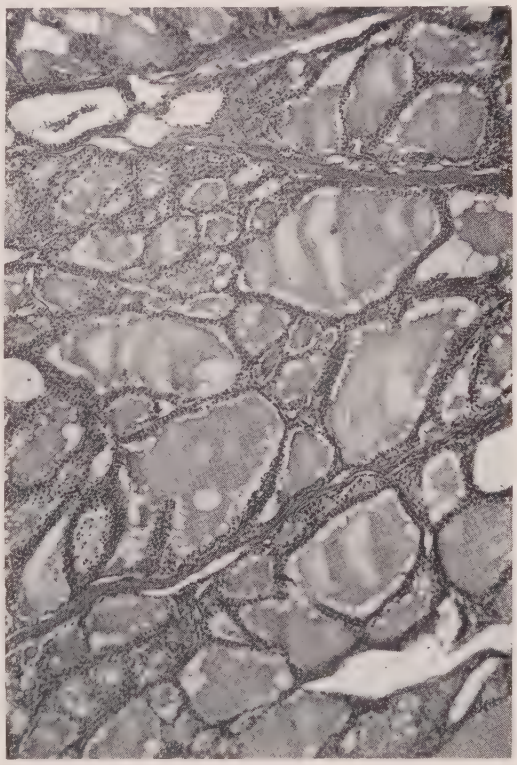

Fig. 866.—Hyperactive thyroid (Graves' disease). Note the tall epithelium lining the acini, with occasional papillary infoldings, and the marked peripheral vacuolation of the colloid.

The gross appearance of the thyroid gland is similar in all parts. Although it may not be much enlarged, it is highly vascular and has a characteristic meaty appearance and firm consistency. The cut surface has a solid, finely lobulated

appearance, without the translucence which would be imparted by a rich colloid content. By the promotion of colloid accumulation, preoperative iodine administration may change the aspect to a glistening translucence not unlike that of the normal gland.

Microscopically, characteristic features of thyroid hyperplasia are evident throughout the gland. The epithelial cells of the follicles are tall and columnar, their nuclei closely packed and basal in position. Papillary epithelial proliferation is often marked, with lacelike projections into follicular lumina. Hypertrophy of the Golgi apparatus is demonstrable by silver staining. New follicles with small lumina may be formed. The colloid is decreased in amount, thin, pale, and vacuolated or scalloped around the edges. Accumulations of lymphocytes, often with distinct germinal centers, are frequently prominent.

The preoperative administration of iodine usually causes a change in this picture before it is seen in the laboratory. In most cases iodine brings about a clinical improvement, with decrease of circulating thyroid hormone and alleviation of many of the evidences of hyperthyroidism. The effect usually lasts only a few weeks, after which there is refractoriness to iodine. The iodine content of the gland is increased, and microscopically there is seen an increase of colloid which stains well with eosin. The epithelium is changed to a cuboidal form, with less infolding and larger, more regular follicles. The mechanism by which iodine thus promotes colloid storage with decrease of hormone release into the blood stream has recently been studied by DeRobertis and Nowinski.[60] Follicular colloid has been shown to have proteolytic activity, and in reabsorption of colloid an enzymatic mechanism is involved which is responsible for proteolysis of thyroglobulin. Free iodine appears to inhibit this proteolytic enzyme system, and thus interferes with the release of follicular colloid. Hence there is decrease of circulating thyroid hormone and corresponding clinical improvement. Radioactivated iodine, exerting an "internal irradiation" after being taken up by the thyroid tissue, has been found to be an effective therapeutic agent in hyperthyroidism.[60a, 60b]

The inhibition of thyroid hormone production by thiouracil is evidently by a different mechanism. The thiouracil administration accentuates the hyperplasia of the gland, with decrease of colloid, a histologic effect directly opposite to that brought about by iodine.

Severe reactions (thyroid storm, thyroid crisis) follow thyroidectomy in some cases of severe hyperthyroidism, particularly if preoperative preparation has been inadequate. Severe hepatic injury is found in some of these cases (see below). Other operative reactions appear to be due to excessive adrenalin secretion, to which there is hypersensitivity.[64]

Lesions in other organs than the thyroid are often present in Graves' disease. Lymphoid hyperplasia tends to be generalized, and not simply in the thyroid itself. Thymic enlargement is frequent. The blood may show a relative lymphocytosis. Some skeletal decalcification is common. Voluntary muscles, such as the quadriceps, may show degenerative changes. Important damage of the eyes (exophthalmos and corneal ulceration), heart, liver, and adrenal may complicate Graves' disease.

Exophthalmos.—Various ophthalmic phenomena are frequently but not invariably associated with Graves' disease. These include exophthalmos, wide palpebral aperture, lid lag, a staring or frightened expression, limitation of upward movement of eyeball, diplopia, and swelling of lids and conjunctiva.[69] Except in Graves' disease, bilateral exophthalmos is uncommon, but may be encountered with skull deformities such as oxycephaly, Hand-Schüller-Christian's disease, and, rarely, in myasthenia gravis or hypertension.[69] Exophthalmos may appear before or after other evidences of Graves' disease. In some cases the ophthalmic phenomena overshadow those due to hyperthyroidism, and may be the most distressing feature of the case. Such severe ophthalmic complications occur more frequently in males and after thyroidectomy. While exophthalmos appears to have no direct relationship to hyperthyroidism, it has been brought about in experimental animals by injections of the thyrotropic hormone of the pituitary.[71]

The exophthalmos appears to be due mainly to swelling and edema of the orbital contents.[69] There occurs an increase of fat in the orbits and lids,[68] and the fatty tissue becomes swollen and edematous.[71] Extrinsic muscles of the eye also are swollen, particularly in severe cases, with increased water content, infiltration of lymphocytes, and degenerative changes.[66, 67] Compression of orbital veins by increased contraction of ocular muscles may be a factor in causing the increased accumulation of fluid.[72]

Hepatic Lesions in Hyperthyroidism.—Much clinical and postmortem evidence has indicated that damage to the liver is common in association with hyperthyroidism. The mechanism of this relationship, and whether it is a direct or indirect effect, is not clear. Depletion of protective glycogen storage in the liver occurs, although this appears to be an indirect effect due to commonly associated vitamin B deficiency. In experimental hyperthyroidism in animals, significant hepatic lesions are absent when nutritional requirements are adequate.[78] Nevertheless, various liver function tests, such as the hippuric acid test, indicate hepatic damage in hyperthyroidism.[74, 81] Abnormal values from the oral galactose tolerance test in hyperthyroidism appear to be explainable on

the basis of increased absorption, and do not necessarily reflect hepatic injury.[82] Occasionally in severe cases, jaundice may be present.

The hepatic changes seen at autopsy on hyperthyroid individuals include reduction in weight, fatty infiltration, increased periportal lymphocytic infiltration, and sometimes cirrhosis.[77] In patients dying of thyroid crisis, particularly postoperatively, severe acute degenerative hepatic lesions ranging up to actual necrosis and acute yellow atrophy have been found.[74] The hyperpyrexia and some other clinical features of thyroid crisis are similar to those found in so-called "liver-deaths" of different origin. Severe hepatic injury probably plays an important part in thyroid crisis (thyroid storm), contributing to the clinical picture and a fatal outcome.

Moschcowitz[82b] has recently described a type of hepatic cirrhosis which he considers pathognomonic of diffuse toxic goiter. It occurs predominantly in the subcapsular region of the liver, and is similar to that seen in chronic hepatic venous congestion and cardiac cirrhosis, but differs in that it is in the interlobular septa rather than around the central veins. It is suggested to be due to increased velocity of blood flow which alters the circulatory dynamics or normal pressure relationships between hepatic artery and portal vein.

The Heart in Hyperthyroidism.—Cardiac complications, as manifested by increase in size of the heart, disturbances in rhythm, and congestive failure, are common in hyperthyroidism. The cardiac manifestations tend to be seen in late stages or after prolonged hyperthyroidism, and at a time when the hyperthyroidism itself may not be of severe degree.

No specific type of damage or pathognomonic lesion of the heart has been demonstrated. A heart-accelerating substance has been demonstrated in hyperplastic thyroid tissue and in the blood of patients with Graves' disease.[84] The cardiac damage has been ascribed to overwork.[86] Cardiac muscle fibers appear to suffer glycogen depletion in hyperthyroidism, as do liver cells, possibly rendering them more vulnerable. The heart becomes hypertrophied, an effect reproducible in experimental hyperthyroidism in animals. Areas of myocardial fibrosis are common.[85] More severe degenerative changes and foci of necrosis have also been described in some cases.

Nodular Goiter

Nodular enlargement of the thyroid, the so-called adenomatous goiter, may be associated with an excess, a normal amount, or a deficiency of thyroid hormone production. The nodularity is the result of recurring cycles of hypertrophy and hyperplasia affecting the gland in irregular fashion. Hyperthyroidism sometimes appears in later life in association with what was originally a simple or colloid goiter, and for this reason is sometimes termed "secondary Graves' disease." The hyperthyroidism tends to be milder than in true Graves' disease, and exophthalmos is usually absent. A nodular goiter with hyperthyroidism is often called "toxic adenoma," although there is no good evidence that the gland produces an abnormal toxic product other than the thyroid hormone. Clinical distinction of a truly neoplastic adenoma in a nodular goiter is usually impossible. Large nodular goiters may cause disturbance by pressure on adjacent structures, e.g., the trachea.

In nodular goiters both the gross and microscopic appearance is extremely variable. The enlargement of the thyroid may be very marked and irregular. Areas of degeneration, hemorrhage, cyst formation, hyalinization, and calcification are very common. Nodular or adenomatous areas of varying size may show fibrosis around them. The cut surface may be meaty and firm, indicating hyperplasia, or soft and translucent, due to colloid storage. The appearance is often quite variable in different portions of the gland. Evaluation in terms of function is difficult and unreliable, as it depends upon the total balance of hyperplasia and involution.

Hypothyroidism

The condition of hypothyroidism or insufficient function of the thyroid gland may occur at various ages and from slight to extreme degree. Congenital thyroid deficiency results in a developmental and metabolic disturbance known as cretinism. A similar syndrome, known, as childhood myxedema, results from thyroid deficiency developing during infancy or childhood. The clinical effect of marked or severe hypothyroidism in the adult is termed myxedema, but there are many cases of mild deficiency of thyroid function in adults in which a well-developed picture of myxedema is not seen. In cretinism and childhood myxedema the most striking feature is retardation or halting of physical and mental development. In myxedema there is slowing and derangement of metabolic processes, and peculiar mucoid degenerative changes in subcutaneous and muscular tissues.

Cretinism.—Cretinism is congenital deficiency of thyroid function, the hypothyroidism existing at birth. This occurs

relatively frequently in certain areas where goiter is common, and the term endemic cretinism has been used in referring to such children of goitrous mothers. However, sporadic cases of cretinism occur also among children of apparently healthy mothers. When hypothyroidism develops in an infant or child through some cause acting after birth, the condition often is called childhood or juvenile myxedema. The effects appear essentially similar to cretinism, but response to treatment is said to be better. It is possible that in cretinism some defect other than simple hypothyroidism is present. There is evidence that the thyroid deficiency disturbs the normal interglandular and metabolic balance, and some of the effects seen may be but an indirect result of thyroid dysfunction.

Fig. 867.—Nodular (adenomatous) goiter. Areas of hemorrhage and degeneration are evident on the cut surface. (Courtesy Dr. H. C. Schmeisser.)

In cretinism and childhood myxedema there is a retardation of metabolism, and a failure of normal growth and development. Not only is

skeletal and somatic growth disturbed, resulting in dwarfism, but sexual and mental development also fails. In well-developed cases the stunted child is of stocky build, with broad coarse features, and dull expression. The long bones and the bones of the face particularly show defective development. In early or mild cases in which the diagnosis is in doubt, roentgenographic findings of the retarded skeletal development may be helpful evidence. The skin is dry, thick, and coarse; the circulation is poor; deafness is frequent. High serum cholesterol and low creatinuria are usually present.

The pathologic changes in the thyroid itself are quite variable. In endemic cretinism there is usually a nodular goiter, which may develop to considerable size. Microscopically, the nodular goiters may show areas of hyperplastic compensatory change. In some cases of sporadic cretinism the thyroid is absent or so defective in development that remnants are difficult to find. The gland tissue may appear inactive and atrophic microscopically. Changes in other organs may be similar to those in myxedema. The bone marrow tends to be hypoplastic. Muscular tissues may show fatty infiltration. Sexual organs, including gonads, fail in proper development and remain small. There appear to be no specific changes in the nervous system.

Myxedema (Gull's Disease).—The manifestations in adults of hypothyroidism of more than mild degree are known as myxedema, so termed because of accumulation of a mucoid substance in the tissues giving rise to a pseudoedema. It is most frequent between 30 and 60 years of age, and the frequency in women is four times that in men. In most instances the etiology is not clear, the condition appearing spontaneously and without obvious cause. Other cases have followed a thyroiditis[109] or a thyroidectomy for struma lymphomatosa. A too complete thyroidectomy for hyperthyroidism is sometimes followed by myxedema, or rarely it may occur in a late stage of Graves' disease. Cyanate therapy has resulted occasionally in myxedema.[99] Pituitary deficiency (Simmonds' disease) is associated with a secondary thyroid deficiency, presumably due to lack of the hypophyseal thyrotropic hormone, and in some cases the hypothyroidism dominates the clinical picture (pituitary myxedema).[96, 97] In primary myxedema, therapy with thyroid substance is very effective.

In myxedema there is a slowing of metabolism and mental reactions. The skin becomes rough and dry, the hair sparse and scanty. Puffiness of the face, eyelids, hands, and other areas appears. A flush or erythema may involve the cheeks and nose, but elsewhere the skin is often slightly yellowish, apparently due to carotinemia resulting from retarded conversion of carotene to vitamin A.[100] The voice is hoarse and the speech slurred due to swelling of larynx and tongue. Peripheral blood flow and cardiac output are decreased, and circulation time prolonged. Capillary permeability is increased.[104] Urea clearance tests indicate some depression of renal function.[98] A secondary or occasionally an aplastic[109] type of anemia is present. Decreased libido, menstrual irregularities, and sometimes sterility are present. Blood pressure may be increased, and vascular sclerosis promoted. The serum cholesterol is increased above normal, and the basal metabolic rate depressed to -20 or less.

The effectiveness of therapy with thyroid substance has resulted in scarcity of opportunity for autopsy study of advanced cases. The thyroid itself most often shows sclerosis and atrophy of its parenchyma. The small firm gland shows replacement of follicles by dense connective tissue, and lymphocytes are often abundant. In other tissues the most specific change is accumulation of a mucoid substance, most prominent in subcutaneous tissues, but in severe cases also found in skeletal muscles, muscle of bowel, and possibly in heart and blood vessels. The accumulated material has been described as an albuminous substance, as fibroblastic mucoid[105] and as a mucinous degeneration. In subcutaneous tissues there is an intercellular faintly basophilic material. In muscle, the mucoid substance may separate fibers or appear within the muscle fibers. Involvement of the intestinal wall causes weakness of musculature of the bowel, with disturbances varying from simple constipation to megacolon and paralytic ileus.[110]

In most cases the heart muscle shows loss of tone and there is dilatation of all chambers. Clinically, the cardiac dilatation is marked and associated with failure (myxedema heart). Interstitial edema and some scarring may be present. The author has observed basophilic degeneration of myocardial fibers in severe myxedema, a change which is neither constant in, nor limited to this condition. Specific changes in the heart muscle are not usually found except in advanced or

severe cases, in which it is claimed that mucoid replacement may be evident.[102, 103, 105] A similar mucoid degenerative change in the media of the aorta, leading to spontaneous rupture or dissecting aneurysm has been described in cases of induced hypothyroidism.[106] An advanced degree of atherosclerosis has been reported in young adults with myxedema.[105]

Localized areas of involvement of subcutaneous tissue by a change similar to that in myxedema have been described. Involvement of the anterolateral aspect of the legs (localized pretibial myxedema) has been described as associated with hyperthyroidism.[108]

Inflammatory and Degenerative Lesions of the Thyroid

The thyroid appears to be rather resistant to most types of infections, and inflammatory lesions are not common. An acute diffuse thyroiditis has been observed in association with acute infections and septicemias, with swelling, congestion, and tenderness of the gland. Abscesses may be found in cases of pyemia, or there may be extension from adjacent tissues. Gumma may be present in the thyroid in acquired syphilis.[117] Hemosiderin pigment becomes deposited in the thyroid in hemochromatosis.

Tuberculosis of the thyroid is distinctly rare, although it may occur either in the form of miliary tubercles or as a single large caseous lesion. Definite caseation necrosis should be seen before tuberculosis is seriously suspected, and proof of the nature of the lesion will depend upon demonstration of the organism. Pseudotuberculous lesions characterized by multinucleated giant cells are common in the thyroid,[133] and are easily mistaken for tuberculosis by the unwary. Such pseudotuberculous lesions with giant cells are a common finding in subacute thyroiditis, in Riedel's struma and sometimes in struma lymphomatosa.

Amyloidosis of the thyroid is an unusual condition which occasionally results in a goitrous enlargement of the gland and may be confused clinically with malignancy. The amyloid goiter is most often secondary to a pulmonary tuberculosis, but it also has been reported as part of a primary amyloidosis. In most cases there is a widespread amyloidosis. The thyroid gland is enlarged, firm, and has a fatty appearance. The amyloid is deposited mainly in the vascular interfollicular spaces.[118, 119]

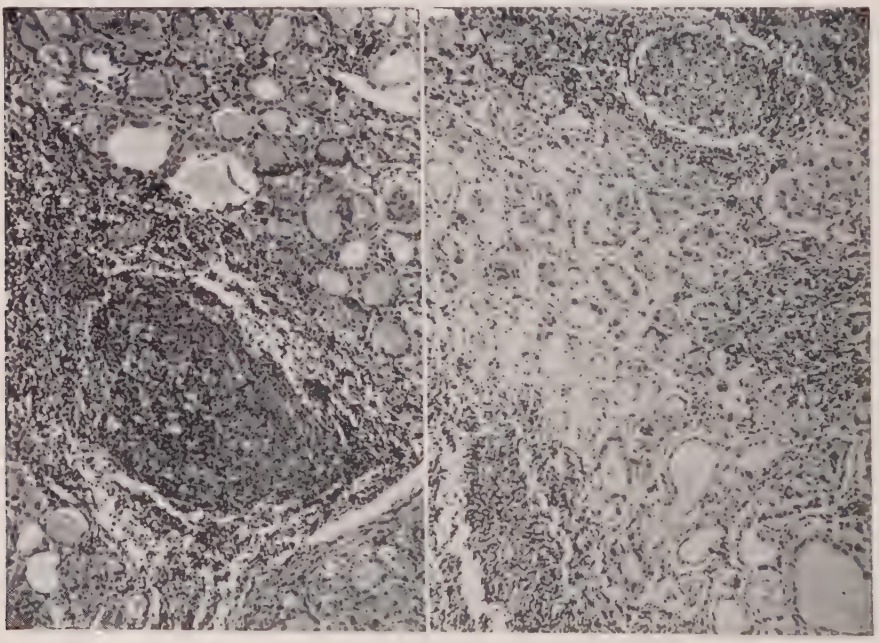

Fig. 868. Early struma lymphomatosa (Hashimoto's disease).

Struma Lymphomatosa.—Struma lymphomatosa (Hashimoto's disease, lymphadenoid goiter) is a condition of diffuse infiltration of the thyroid tissue by lymphoid cells, with associated atrophy of thyroid parenchyma and a varying degree of interstitial fibrosis. While the etiology is un-

determined, evidence suggests that the condition is a metabolic, constitutional or retrogressive change, rather than in the nature of a chronic inflammation. Although frequently confused with Riedel's struma, which has been considered by some as a late stage of struma lymphomatosa,[126] the two conditions appear to be distinct entities.[121, 128]

Struma lymphomatosa was described as a characteristic type of thyroid lesion by Hashimoto in 1912. The thyroid shows a uniform bilateral enlargement, sometimes to several times its normal size. A relatively normal contour is maintained, with a slight gross nodularity. The capsule is intact, and there is no adhesion to adjacent or overlying structures. It may be closely attached to the trachea, however, and the chief disturbance appears to be due to pressure on the trachea. The tissue is firm or rubbery in consistency, of a white or yellowish-brown color. Normal thyroid tissue or colloid usually cannot be recognized grossly. The cut surface appears divided into irregular areas by fibrous trabeculae. Areas of degeneration, necrosis, or hemorrhage are absent.

Microscopically there is an extensive diffuse lymphoid infiltration, which in localized areas is more condensed and shows formation of germinal centers. The thyroid follicles show atrophy, degenerative changes, and replacement, with marked diminution in colloid material. There may be increase of connective tissue, but usually without dense sclerotic scars. Evidence of acute inflammation, necrosis, or abscess formation is absent.

Most cases occur in women, usually after the age of 40 and at an average age of about 55 years. Functional disturbance is not constant, but most commonly there is a mild hypothyroidism. Pressure symptoms may be disturbing. The blood may show a slight relative lymphocytosis. The goiter often has been present for a prolonged period before the patient seeks relief, and has shown slow enlargement. Clinical diagnosis is rarely achieved. Subtotal thyroidectomy usually gives relief with recurrence, but leaves the patient with a mild hypothyroidism. As the nature of the condition is rarely recognized preoperatively, radiation therapy has had little trial, although a good response might be anticipated because of the sensitivity of lymphoid tissue. There is no tendency to malignant change.

The nature of the condition is not understood, but there is little to suggest that it is a chronic inflammation. Milder degrees of lymphoid infiltration are common in exophthalmic goiter, and no sharp line has been drawn between such cases and the slighter degrees of struma lymphomatosa. It has been suggested that the lymphadenoid goiter may be but the later stage of a diffuse goiter with mild hyperthyroidism which has become "burned out," or that it is but a more severe degree of the "lymphoid constitution" which has been looked upon as underlying Graves' disease. McCarrison[129] produced in rats by a vitamin-deficient diet, a goitrous condition having some similarity.

Riedel's Struma.—Riedel described a condition characterized by replacement of thyroid parenchyma by dense sclerotic

TABLE XII

DIFFERENTIAL FEATURES OF HASHIMOTO'S STRUMA LYMPHOMATOSA AND RIEDEL'S STRUMA (MODIFIED FROM JOLL[128])

HASHIMOTO'S STRUMA LYMPHOMATOSA	RIEDEL'S STRUMA
1. Occurs mainly in women from 45 to 60 years of age	Occurs in men and women of younger average age
2. Tendency to myxedema	Little tendency to myxedema except after radical operations
3. Diffusely involves all of thyroid, but no tissues around thyroid	Often unilateral or involving only a portion of thyroid, and extends to extrathyroid structures
4. Goiter may be large, but never very hard, and tends to be lobulated	Goiter is small, intensely hard, and smooth
5. Pressure effects seldom severe	Pressure effects are the rule
6. Diffuse lymphocytic infiltration, with prominent lymph follicles, and followed by fibrosis	Dense fibrous scar tissue, absence of diffuse lymphocytic infiltration and lymph follicles, sometimes giant cells, extension to surrounding tissues

scar tissue. The hard consistency has given origin to the terms "woody thyroiditis" and "iron-hard thyroid." Only a portion, rather than the whole gland, may be affected; there are commonly dense adhesions to adjacent surrounding tissue, which makes surgical resection difficult, and causes confusion with carcinoma.

The gland is not greatly enlarged, the condition often being unilateral or involving only a portion of the thyroid. The affected part is very hard, dense, and sclerotic. Microscopically there is a marked fibrosis, with dense, sclerotic scar tissue. The thyroid parenchyma is replaced to a variable extent, but areas containing small follicles often persist. Atrophic and degenerative changes are often evident in the thyroid follicles. Degenerating epithelial cells often fuse to form a syncytium around masses of colloid and appear as multinucleated giant cells." The formation of giant cells may give a pseudotuberculous appearance.[133]

Riedel's struma may be found at any age, but the average age is somewhat lower than in the case of struma lymphomatosa. Pressure symptoms are common, but any marked functional disturbance is unusual, and hypothyroidism is not usually troublesome even after surgical removal of the involved part of the gland.

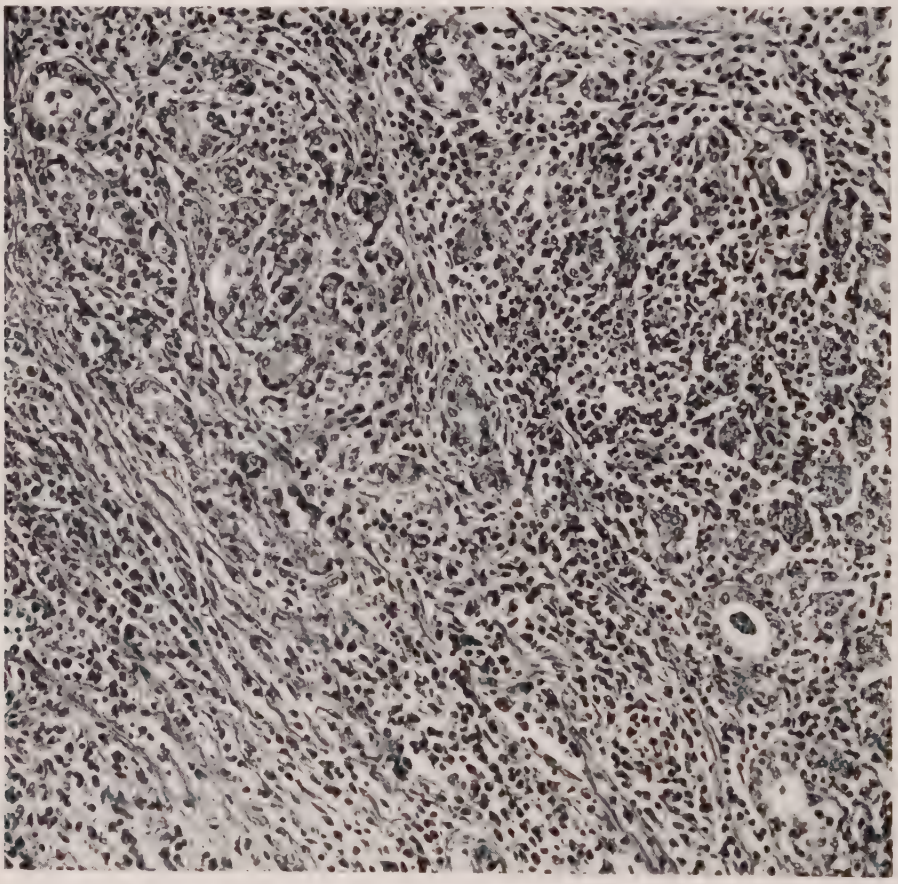

Fig. 869.—Chronic thyroiditis (Riedel's struma). Note the marked fibrosis and atrophy of thyroid parenchyma.

Although of unknown etiology, Riedel's struma appears to be a chronic inflammation with scarring, and an entity distinct from struma lymphomatosa. A clinical phase suggestive of acute perithyroiditis[112] or acute thyroiditis has frequently been noted to precede the development of Riedel's struma. Marked vascular sclero-

sis has been noted in association, and it has been postulated that the vascular changes may precede and promote the fibrosis of the thyroid.[112, 133]

Subacute Thyroiditis.—A granulomatous inflammatory process in the thyroid gland associated with distinctive clinical features has been termed subacute thyroiditis. Most cases have been in women in their forties, and have been associated with varying degrees of fever, pain, and tenderness in the thyroid gland, and prostration. The tender gland is enlarged, either in one area or generally, and hard. Recovery occurs spontaneously in a few weeks or months but is hastened by radiation therapy, and is not followed by hypothyroidism. The etiology is unknown, but a viral infection has been suggested.

The thyroid gland is usually diffusely involved by a granulomatous inflammatory reaction in which multinucleated giant cells and a tuberculoid appearance are prominent features. The giant cells appear to be a phagocytic reaction to colloid in degenerating follicles. There is usually little adhesion of the thyroid to surrounding structures. The relationship, if any, to other types of thyroiditis, such as Riedel's struma, is unsolved. It is probable, however, that many cases of subacute thyroiditis previously have been considered as early or more acute phases of Riedel's thyroiditis. The ingestion of colloid by macrophages (colloidophagy) has been suggested as an underlying cause of chronic thyroiditis.[115]

TUMORS OF THE THYROID

Reports of early thyroidectomies did not include detailed histologic descriptions of the tissue removed, and little was known of the pathology of thyroid tumors until the latter part of the nineteenth century. As surgery grew to be an accepted type of therapy for thyroid tumors, specimens became available in large numbers and information regarding thyroid neoplasms developed rapidly.[135, 136, 137, 138]

Thyroid tumors may be grouped into benign and malignant categories, and in some instances the distinction is difficult. Familiarity with the histologic types and a knowledge of the clinical peculiarities of these tumors are of considerable help in determining their benign or malignant nature.

Benign Thyroid Tumors

1. Colloid Adenoma
2. Fetal Adenoma
3. Hürthle Cell Adenoma

A thyroid adenoma is a true tumor, surrounded by a complete, distinct, fibrous capsule. Adenomas of the thyroid may occur at any age but are most frequent in the fourth and fifth decades. Approximately 65 per cent of all thyroid adenomas occur in women. They are usually single but may be multiple, and range in size from 1 to 10 cm. or more. The cause of thyroid adenomas is unknown, but the most widely accepted theories concerning their origin are those of Wölfler[141] and Wegelin.[142] Wölfler suggested that they arise from fetal rests, and Wegelin considered them to be the result of focal areas of hyperplasia secondary to thyrotropic hormone stimulation. Other existing hypotheses are merely modifications of these two basic concepts, and none has been proved. Frequently, a nodule described on physical examination as a discrete single adenoma, on laboratory examination is found to be merely the most prominent portion of a nodular goiter. A final diagnosis must, therefore, await the complete examination of the entire specimen.[143, 144, 145]

Colloid Adenoma.—Colloid adenomas (simple adenomas) are the most frequently encountered benign thyroid tumors. They are completely encapsulated and composed of colloid-containing follicles,* the lining cells of which are usually small, and cuboidal or flat. The follicles vary considerably in size. Macrofollicular and microfollicular varieties of colloid adenomas may be distinguished, but the differentiation has no clinical importance, for their treatment is the same.

Most colloid adenomas are nonfunctional and are known as nontoxic adenomas. Others, called toxic adenomas, contain actively functioning follicles and, at times, may be the cause of hyperthyroidism. The histologic changes seen in a toxic adenoma are the same as those in a hyperactive thyroid gland. Sudden enlargement of a thyroid adenoma is usually caused by hemorrhage, and degenerative changes are seen frequently. The cysts which may result from the degenerative process following repeated hemorrhage may contain fresh and old blood, or clear mucinous material, and deposits of calcium may be found in the walls of the cyst in the final stage of degeneration. Attempted regeneration of the thyroid tumor tissue following hemorrhage sometimes produces a pseudopapillary structure which may be confused, on occasions, with papillary carcinoma.

*The adjective "alveolar" has been used widely to describe acinar formation present in certain tumors. The term "follicular" seems more appropriate from a histologic standpoint[146] and is, therefore, employed throughout this discussion.

Fetal Adenoma.—Fetal adenomas are usually found singly in an otherwise normal thyroid gland. They are so named because they are composed primarily of minute follicles resembling those in the thyroid gland of a fetus. The follicles are lined by small, cuboidal cells with nuclei which may show considerable variation in size, shape, and staining quality. The lumens of most of the follicles are either completely closed or minute and empty, but a few may contain colloid. While there are many varieties of fetal adenomas, most of them have either a follicular or a trabecular pattern.

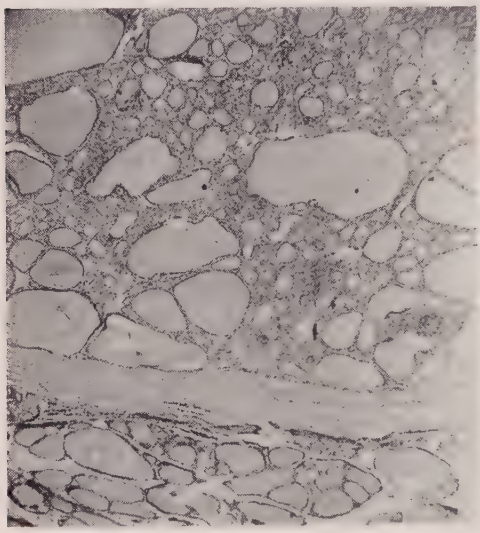

Fig. 870.—A portion of a colloid adenoma of thyroid.

Fetal adenomas are simulated occasionally by degenerating colloid adenomas because of small follicles found floating in the colloid freed by the breakdown of large follicles in colloid adenomas. The term embryonal adenoma is used by some to denote the presence of unusually small, immature follicles, but the distinction between fetal and embryonal adenomas is of no clinical importance. Fetal adenomas have a special significance since they are the only benign thyroid tumors which have been grown successfully in the anterior chamber of the eye of the guinea pig.[147] This suggests that some fetal adenomas have malignant propensities, especially those in which the cells are large and the follicular differentiation is minimal.

Hürthle Cell Adenoma.—Hürthle cell adenomas form a distinctive group comprising approximately 8 per cent of all benign thyroid tumors. Their origin has been the subject of extensive speculation, but no definite conclusions have been reached. These tumors differ from the other benign tumors in that they are usually small and firm and are tan or brown on cut section. Since degeneration seldom occurs in Hürthle cell adenomas, hemorrhage, cyst formation, and calcium deposits are rare.

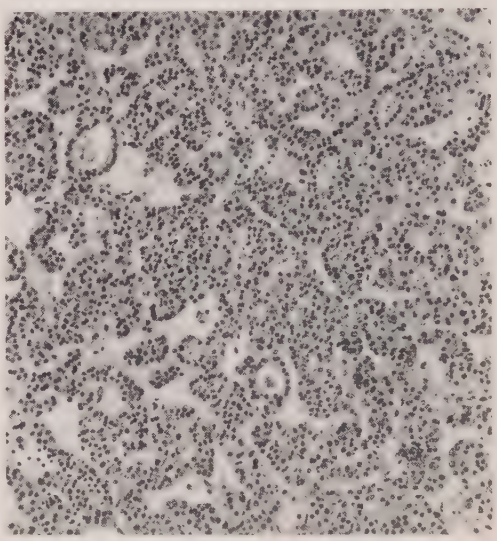

Fig. 871.—Fetal adenoma of thyroid.

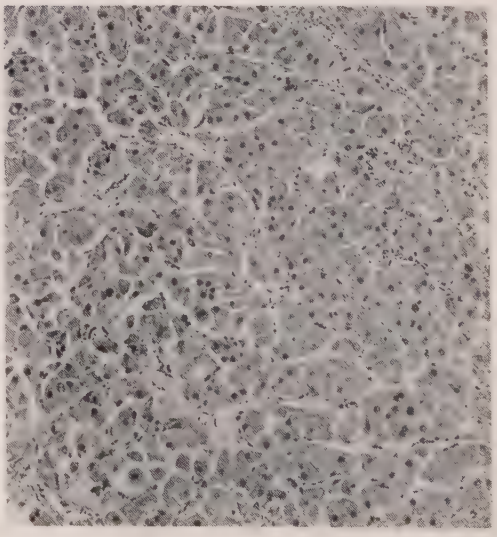

Fig. 872.—Hürthle cell adenoma of thyroid.

Microscopically, the cells are large with abundant, finely granular, distinctively eosinophilic cytoplasm and small, uniform, rounded, vesicular nuclei. There is considerable varia-

tion in growth pattern, but Hürthle cell adenomas usually form follicles, a few of which may contain colloid-like material. Others form trabeculae and, in rare instances, the cellular pattern is quite solid. The histologic distinction between benign and malignant Hürthle cell tumors is, at times, very difficult.

Other benign tumors occurring rarely in the thyroid gland are teratomas, fibromas, hemangiomas, chondromas, and osteomas.

Malignant Thyroid Tumors

1. Papillary Adenocarcinoma
2. Follicular Adenocarcinoma
3. Undifferentiated Adenocarcinoma
4. Hürthle Cell Adenocarcinoma
5. Lymphoma

Malignant tumors of the thyroid gland rank among the most interesting and controversial in the field of oncology because of their tremendous histologic variation and unusual clinical manifestations. Thyroid carcinoma can be detected early, offers the possibility of a high survival rate if therapy is prompt and adequate, is amenable to several types of palliative therapy and, unlike most carcinomas, is restricted to no age group.

Many theories have been proposed regarding the cause of thyroid carcinoma, but none has been proved. Two current hypotheses are based on the effects of radioactive iodine and thiouracil on animals. Although no similar histologic variations have been observed in man following the administration of either of these therapeutic agents, each has produced thyroid carcinoma in rats and mice in controlled experiments.[148, 149]

The incidence of thyroid carcinoma is difficult to determine because of variations in pathologic criteria and lack of uniformity in classification. Statistics from widely scattered areas of the United States show that approximately 18 per cent of all thyroid nodules considered clinically to be single, prove histologically to be carcinoma, and that from 4 to 6 per cent of all nontoxic nodular goiters contain carcinoma.[150, 151, 152] Malignant tumors may arise in toxic goiters, but the incidence is only about 1 per cent. Contrary to the repeated statement that approximately 90 per cent of all thyroid carcinomas arise in a previously existing adenoma, proof of this is lacking. A slow-growing, unencapsulated carcinoma often simulates an adenoma clinically, and this is the basic reason for advocating surgical removal of all single nodules of the thyroid.

Carcinoma of the thyroid gland is most common in the fifth decade of life but may be found at any age, and five cases of congenital thyroid carcinoma have been recorded.[153] Approximately 65 per cent of all patients with thyroid carcinoma are women; however, thyroid nodules are four times more likely to be malignant in men than they are in women. A safe rule to follow is to advise lobectomy for the complete removal of all nodules in men and young people and single nodules in women.[151]

Malignant thyroid tumors sometimes grow very slowly and apparently may lie dormant for years. Nevertheless, any type of thyroid carcinoma can be fatal. The prognosis for patients with thyroid carcinoma is dependent upon several factors, the most important of which is the stage of the disease. The type of therapy is the next most important factor in prognosis, and radical surgery is the treatment of choice. Another factor in prognosis is the type of carcinoma. In general, the results obtained are best in papillary, intermediate in follicular, and poorest in the most primitive type, undifferentiated carcinoma. The effects of irradiation cannot be evaluated properly since few patients are treated solely by this means, but preoperative irradiation has proved disappointing, and its value is primarily palliative. Radioactive iodine is of use in controlling inaccessible metastatic carcinoma which contains colloid-producing follicles.

Grossly, thyroid carcinomas are usually gray, firm, and unencapsulated, and they are extremely variable in size. Gross specimens should be examined carefully for tumor emboli because their presence indicates a grave prognosis. On microscopic examination, unless carcinoma is observed penetrating a vessel large enough to possess a muscular layer, blood vessel invasion has very little significance. A diagnosis of thyroid carcinoma based only on the apparent invasion of minute vessels is not reliable.[158] The usual criteria employed in establish-

ing a diagnosis of carcinoma (anaplasia, mitoses, disparity in size, shape, and staining quality of cells, metastasis, and invasion) must be relied upon. One of the distinguishing features of thyroid carcinoma is the occasional occurrence of psammoma bodies, and, as in benign tumors, the deposition of calcium may follow hemorrhage, degeneration, and cyst formation in malignant tumors.

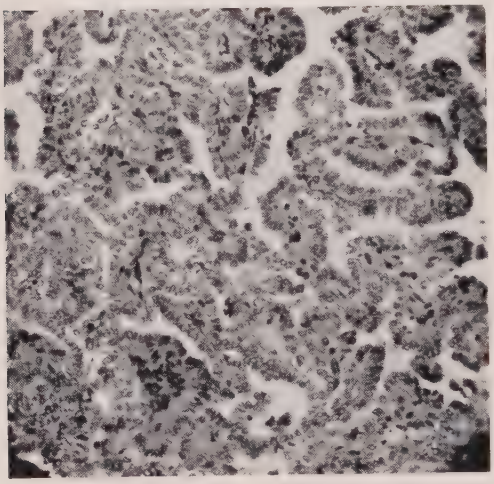

Fig. 873.—Papillary adenocarcinoma of thyroid.

Thyroid carcinomas frequently are composed of more than one histologic type; in fact, four distinct types have been encountered in the same tumor. Moreover, the histologic variability between different tumors is almost unlimited so differences in pathologic interpretation must be expected. In the classification presented here, some of the older terms encountered in the literature are omitted. The confusing and contradictory terms, "adenoma malignum" and "malignant adenoma," are not used. Since all malignant thyroid tumors, except lymphomas, hemangioendotheliomas, and fibrosarcomas, can be called adenocarcinoma, this term does not designate any special type of carcinoma, nor does carcinoma simplex (simple) have any descriptive value. The term squamous carcinoma is omitted since it has been shown that squamous cells in the thyroid represent either metaplasia or a carcinoma arising in a thyroglossal duct.[159] The term scirrhous simply means hard, and since any type of thyroid carcinoma can become fibrotic and hard, the term scirrhous has no diagnostic significance.

Papillary Adenocarcinoma.—Papillary adenocarcinoma is generally seen in a younger age group than are other types and is sometimes a very slow-growing tumor. Pure papillary adenocarcinoma comprises only about 25 to 30 per cent of malignant thyroid tumors. Tumors originally diagnosed as papillary carcinoma often are found, on thorough examination of multiple sections, to contain a follicular element. Even though the papillary pattern predominates, the accompanying element should be denoted in the diagnosis; i.e., a predominantly papillary tumor containing follicular elements should be labeled as papillary and follicular adenocarcinoma. This is of considerable prognostic importance since the follicular element is the more malignant of the two.

Pure papillary adenocarcinoma has an easily recognizable microscopic appearance. It consists of numerous, delicate, branching vascular strands of fibrous tissue covered by one or more layers of epithelium. The epithelial cells are somewhat larger than normal follicular lining cells and their cytoplasm is abundant and clear. The nuclei show little variation in size, shape, and staining qualities, and mitoses are rare. Despite their usually benign histologic appearance, it is now generally agreed that all papillary tumors found in the thyroid gland are malignant.[162, 163] Papillary adenocarcinoma rarely is seen arising in a previously existing adenoma, though a thin, fibrous pseudocapsule sometimes results from hemorrhage and cyst formation, and the term papillary cystadenocarcinoma has been employed for such structures. Papillary carcinomas may be either firm or soft but are seldom as hard as other types of carcinoma. They may be small, often measuring less than 1 cm.[164] Frequently they produce metastases in the cervical lymph nodes, enlarging them enough to disfigure the patient. Because these small primary thyroid carcinomas are not palpable, the enlarged cervical nodes were, until recently, fallaciously reported as "lateral aberrant thyroid carcinoma." This concept has been disproved, and it is now conceded that in

such cases a primary tumor can be found in the thyroid gland.[168] Though it is frequently the most slowly growing and the most easily controlled of all thyroid carcinomas, inadequately treated papillary carcinoma may cause death by invasion of vital structures or by metastasis. The frequent involvement of cervical lymph nodes indicates that metastasis from papillary adenocarcinoma occurs first by way of lymphatics. The lungs are the next most common site of metastasis, showing the frequency of venous invasion in this disease. Metastases in bone are seen occasionally, but when they occur there is usually an accompanying follicular element.

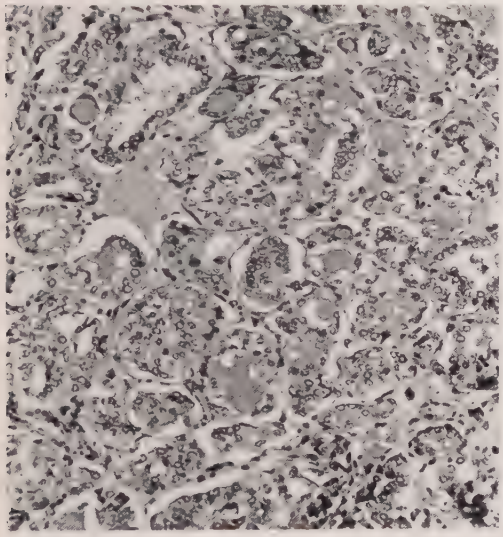

Fig. 874.—Follicular adenocarcinoma of thyroid.

Follicular Adenocarcinoma.—Tumors predominantly follicular in structure comprise the largest group of thyroid carcinomas but, like other categories, most of them are not of pure type. The majority are combined with papillary carcinoma, while others contain undifferentiated components. These tumors may contain follicles almost as well differentiated as those in normal thyroid tissue, or they may be composed of barely recognizable follicles without a lumen. The follicles vary considerably in size but rarely attain the dimensions of those in a normal thyroid. The follicular lining cells are usually large, with a glassy cytoplasm and nuclei which vary in size and shape, but mitoses are not numerous. While all tumors in this category contain follicles, not all of them produce colloid.

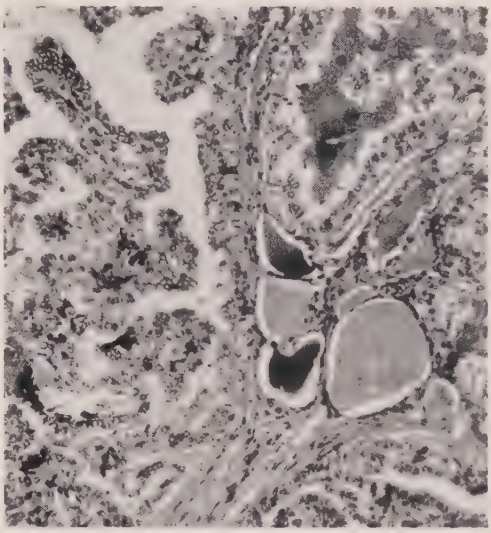

Fig. 875.—Papillary and follicular adenocarcinoma of thyroid.

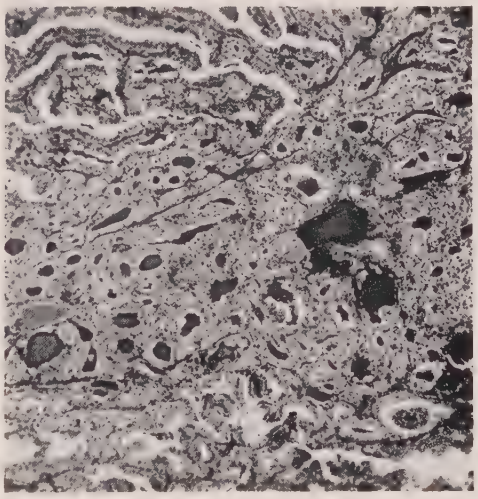

Fig. 876.—Follicular and papillary adenocarcinoma of thyroid.

In the category of follicular adenocarcinoma must be included a strange and rare entity, metastasizing struma—usually known as "benign metastasizing struma." This is a condition in which thyroid tissue of histologically normal appearance is found to have metastasized to the cervical lymph nodes, lungs, bones, or other distant organs. Despite the benign histologic appearance of the metastatic tissue, this paradoxical disease must be included with thyroid

carcinoma since death may be caused by the metastases. A primary thyroid carcinoma is often subsequently found in patients originally thought to have metastasizing struma.

Follicular carcinomas are of a moderate or intermediate degree of malignancy, and show a tendency to metastasize to bone and lungs. Such metastases cannot be treated surgically, but approximately 15 per cent of all thyroid carcinomas show some pick-up of radioactive iodine. Only the colloid-containing follicles show a radioactive iodine uptake, and the more the tumor simulates normal thyroid the greater is the uptake. The term follicular in the diagnosis indicates that metastases may be treated by the use of radioactive iodine.[171-174]

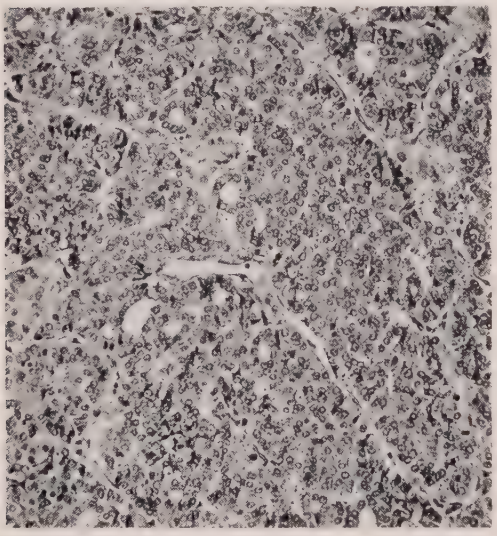

Fig. 877.—Undifferentiated adenocarcinoma of thyroid, solid and follicular type.

Undifferentiated Adenocarcinoma.—In this group are placed a miscellaneous assortment of tumors which are so primitive that the follicular structure is reduced or entirely lost. They consist of masses or strands of rapidly growing cells which show little evidence of differentiation. Like papillary and follicular adenocarcinomas, tumors in this category usually are not seen in a pure state but occur with one or more of the other elements, the most frequent of which is follicular. A wide variety of carcinomas, including some of the most malignant, are placed in this category. They occur predominantly in the older age group, and comprise approximately 20 per cent of malignant thyroid tumors. The two most frequently encountered tumors in this group are the solid and the spindle and giant cell varieties.

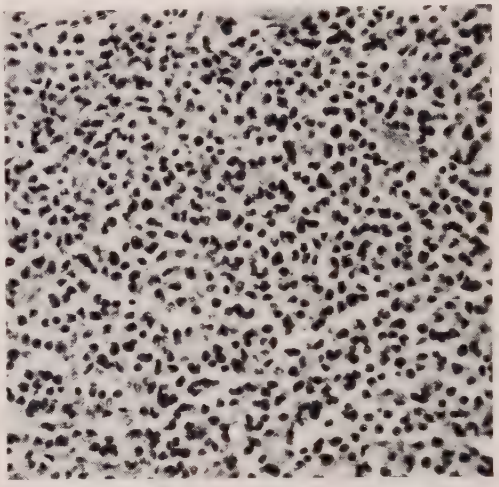

Fig. 878.—Undifferentiated adenacarcinoma of thyroid, small cell type.

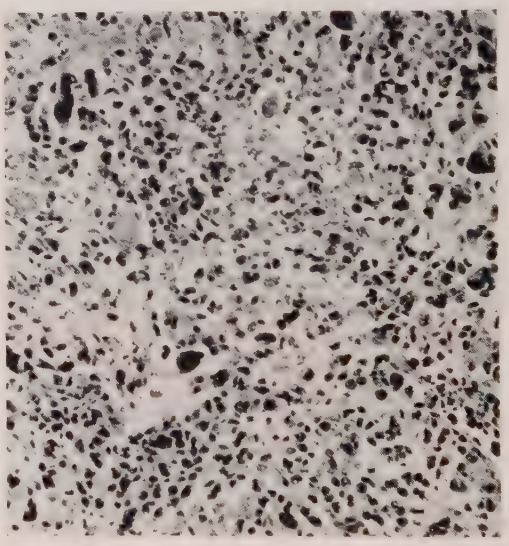

Fig. 879.—Undifferentiated adenocarcinoma of thyroid, spindle and giant cell type.

Solid adenocarcinoma is the most common of the undifferentiated group. These tumors are almost totally anaplastic, do not develop follicles, and tend to grow in broad, infiltrating sheets. The cells may be either large or small but are usually uniform. When composed of small cells, tumors of this nature have been referred

to as small cell carcinoma. The term spindle and giant cell adenocarcinoma is applied to a distinctive but rare type of tumor characterized, as the name indicates, by closely packed, spindle cells and cells containing large, irregular, hyperchromatic nuclei in a fibrous stroma. These tumors are highly malignant, rapidly growing carcinomas which metastasize promptly to the cervical lymph nodes, lungs, and bones and frequently invade the trachea or larynx. Spindle and giant cell adenocarcinoma often was mistaken for sarcoma by the pathologists of the nineteenth century. Other epithelial tumors encountered occasionally are anaplastic carcinomas which defy accurate classification, but because of their complete undifferentiation they are placed in this category.

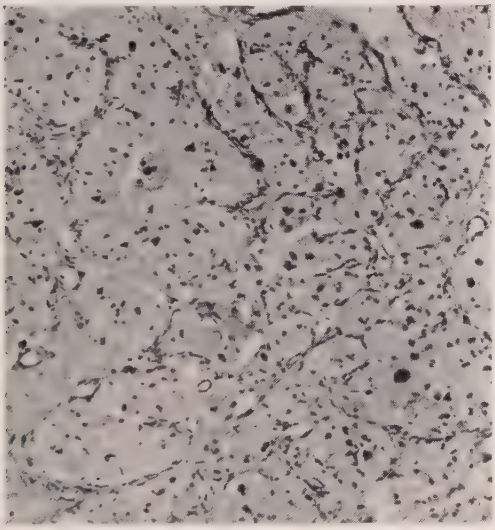

Fig. 880.—Hürthle cell adenocarcinoma of thyroid.

Hürthle Cell Adenocarcinoma.—Hürthle cell adenocarcinomas comprise approximately 5 per cent of thyroid carcinomas. They are found predominantly in women and occasionally are multiple. Grossly, these tumors are frequently solid and encapsulated, and, on cut section, are tan or brown. Microscopically, the cells are very large with eosinophilic cytoplasm and pleomorphic nuclei. The pattern of growth is usually follicular but may be tubular or solid. The follicles, when present, vary in size and in most instances are closed, but a few develop lumens and may produce colloidlike material. Hürthle cell carcinoma is a slow-growing tumor which, when not completely removed, may invade the adjacent cervical structures and metastasize to the skeleton, lungs or other organs.[178, 179, 180]

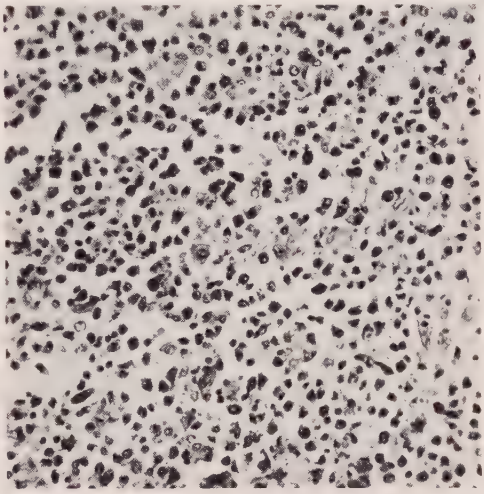

Fig. 881.—Reticulum cell sarcoma of thyroid. Note the similarity to the tumor in Fig. 878.

Lymphoma.—Lymphomas may be divided into three groups—lymphosarcoma, reticulum cell sarcoma, and Hodgkin's disease. Any of the three may be found in the thyroid when the disease is generalized, and they appear rarely as primary thyroid tumors.

Primary Hodgkin's disease of the thyroid is the least common of this group. The lesions, when found in the thyroid gland, are histologically identical with those found elsewhere in the body and may be confused with tuberculosis or Riedel's struma.

Primary lymphosarcoma and reticulum cell sarcoma in the thyroid gland are clinically and histologically similar. When a carcinoma is composed of small cells it may be confused with lymphosarcoma and reticulum cell sarcoma because they, also, are composed of small, rather uniform, closely packed, polyhedral cells supported by a delicate, fibrous network. Special stains are of doubtful value in differentiating between carcinoma and sarcoma in these cases.[186] In addition to thorough histologic study of the tissue, collateral clinical data and a knowledge of the anatomical distribution of the disease are essential in differentiating between lymphoma and undifferentiated thyroid carcinoma.

Lymphoma, when primary in the thyroid, occurs almost exclusively in elderly women and usually is rapidly

fatal. The only cases surviving five years are patients in whom the disease was localized and surgical and x-ray therapy was prompt and adequate.[182, 183, 184, 185]

Other malignant thyroid tumors, which occur too rarely to be included in the classification given here, are fibrosarcomas and hemangioendotheliomas. Tumors of these types have been noted more frequently in Europe than in the United States.

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Chapter 37
THE PARATHYROIDS

W. A. D. Anderson

The parathyroid glands produce a hormone concerned with the metabolism of calcium and phosphorus, and the maintenance of normal levels of these elements in the blood. Disturbances in parathyroid function may be in the direction of decreased activity (hypoparathyroidism) or increased activity (hyperparathyroidism). Hypoparathyroidism due to injury or removal of the glands results in tetany, a condition of neuromuscular hyperirritability. Hyperparathyroidism may be due to a functioning tumor (adenoma) of a parathyroid gland or to hyperplasia of all parathyroid tissue. It results in excessive mobilization of calcium from bones, leading to the skeletal condition of osteitis fibrosa cystica, and calcium depositions in the kidneys and other soft tissues.

Development and Structure

The parathyroid glands, usually four in number, are developed from endoderm of the third and fourth branchial pouches, in intimate relationship to portions of the thymus, but quite independent of the thyroid gland.[7] The superior pair of glands is derived from the fourth pharyngeal pouches, while the inferior pair, derived from the third pouches, outdistances the superior pair and the thyroid in caudal migration and hence takes the lower position. Their close connection with the development of the thymus explains the occasional occurrence of one or more parathyroid glands near or even embedded in thymic tissue. This possibility should be borne in mind during search for parathyroid tissue or a parathyroid adenoma by surgical procedures or at autopsy.

While four parathyroids are usually present, variations in number from two to ten have been reported.[9] The superior pair are situated rather constantly on the medial part of the dorsal surface of each lobe of the thyroid, about the junction of the middle and upper thirds. They are often embedded in thyroid substance, but separated by a connective tissue capsule. The inferior parathyroids, more inconstant in position, are found usually on the dorsal surface of the lateral lobes of the thyroid, near the lower pole.

The parathyroid glands are brownish-yellow, oval, somewhat flattened bodies, each measuring, in the adult, about 1.5 by 3.5 by 6.5 mm., and having a total weight of about 120 mg. (4 glands). The amount of interstitial tissue is quite variable, but the mean weight of parenchymal tissue has been estimated by Gilmour and Martin[8] to be about 82 mg. (4 glands).

Each parathyroid possesses a capsule of connective tissue, from which bands pass through the gland. The parenchymal cells may be arranged in solid masses, but frequently appear in cords or columns. Acinar or follicular structures may be found, tending to increase in frequency with age. Adipose tissue is present interstitially and in general tends to increase in proportionate amount with age. This interstitial fat is replaced and decreases or disappears when there is hyperplasia or adenomatous growth of the parenchyma. The parenchymal cells are of two main types, chief (principal) and oxyphil, each having varieties and transitional forms. The chief cells compose the bulk of the glands and, at early ages, practically the entire gland. Pale chief cells (*wasserhelle* or water-clear cells) are about 10 microns in diameter, with a small rounded nucleus and abundant "water-clear" cytoplasm. Dark chief cells are similar, but slightly smaller, with less abundant faintly staining cytoplasm. The oxyphil cells may be inactive or involuted chief cells. They are larger than the chief cells, polygonal, and contain acidophilic granules in their cytoplasm. Oxyphil cells appear to increase in number with age. The pale chief cell is considered to be a more active functional form of the darker chief cell. Glycogen is abundantly present in the parathyroid tissue, mainly in the chief cells. Brownish yellow pigment masses, colloid vesicles, and small cysts may be found in parathyroid tissue.[1, 7, 9]

Function

The parathyroid hormone appears to be of protein nature, with free amino groups necessary for physiologic activity, but its exact structure is not known.[2] While there is some inconclusive evidence that the pituitary produces a parathyrotropic principle influencing parathyroid function,[10] it appears that the relationship is not close or essential.[2]

The function of the parathyroids is concerned with the metabolism of calcium and phosphorus and the maintenance of normal concentrations of these elements in the blood. The mechanism by which this is accomplished and the point of action of the hormone are still in dispute. There is good experimental evidence that the parathyroid hormone has a direct effect on the resorption of bone, as well as stimulating osteoclastic resorption and raising

the level of calcium in the blood.[11, 12, 13] There is much evidence also to indicate that the hormone may regulate the renal excretion of phosphate.[3] Administration of parathyroid extract (parathormone) to a normal individual results in increased renal excretion of phophate (phosphate diuresis), lowering the level of serum phosphate, which in turn results in increased concentration of calcium in the blood and increased renal excretion of calcium.

The injection of parathormone in experimental animals results in marked initial diuresis with loss of electrolytes and water. If repeated, dehydration, urinary suppression, and death result, preventable by replacement of fluid and electrolytes. Somewhat similar instances of "acute hyperparathyroidism" or "parathyroid poisoning" have been reported in man.

Alkaline phosphatase activity in the serum and bone appears to be stimulated by parathormone activity,[2] but any relationship that this may have to shifts of calcium phosphate in relation to bone or to the renal excretion of phosphate has not been made clear.

Hypoparathyroidism

Decreased function of the parathyroid glands most commonly is due to accidental removal of some or all of the parathyroid tissue during thyroidectomy. In rare instances, hypoparathyroidism occurs idiopathically, and in such cases the parathyroid glands have been found to be replaced completely by fat,[14] or have not been identifiable at all.[15] A few cases have been reported of hypoparathyroidism in association with widespread moniliasis.[16]

In hypoparathyroidism the serum phosphorus is high (greater than 5.0 mg. and up to 12 mg.) and the serum calcium is low (down to 5 mg.), and little or no calcium is excreted in the urine. Absence of renal insufficiency and normal bones by roentgenogram are clinical features excluding other causes of hyperphosphatemia or hypocalcemia. There is a marked increase in neuromuscular excitability, apparently dependent on the hypocalcemia, and producing the clinical manifestations of chronic tetany. Tetany may result also from hypocalcemia due to other causes, such as rickets, osteomalacia, or steatorrhea, and from alkalosis, such as may result from hyperventilation. In hypoparathyroidism, the hypocalcemia may be overcome by administration of dihydrotachysterol (A.T. 10) a photochemical derivative of ergosterol, as well as by the use of parathormone.

Chronic hypoparathyroidism often is accompanied by trophic disturbances in tissues of ectodermal origin. Cataract is of frequent occurrence, and changes in nails, loss of hair, and skin lesions sometimes are found.[17] The bones may be more dense than normal. Calcification of brain tissue may occur. Some cases masquerade clinically as "epilepsy." Death directly due to the hypoparathyroidism is unusual.[18]

A condition of "pseudohypoparathyroidism" has been described[19] which resembles hypoparathyroidism but is not corrected by administration of parathyroid extract. It appears to be due to inability of the end organs to respond to the hormone, rather than to failure of hormone production. It is clinically differentiated from idiopathic hypoparathyroidism by failure to respond to injection of parathyroid extract of known potency by phosphate diuresis. The clinical features are similar to those of idiopathic hypoparathyroidism with similar blood chemical changes, chronic tetany, cataracts, etc. Intracerebral and skin calcification is more common, and short stature, stocky build, a rounded face, and short metacarpal bones have been frequent features in the cases of pseudohypoparathyroidism. Skeletal demineralization has been described in one case.[20]

Hyperparathyroidism

Excessive parathyroid function may be due to a benign or malignant neoplasm of parathyroid tissue, to a benign idiopathic hypertrophy and hyperplasia of all the parathyroid glands (rarely), or to a diffuse hyperplasia of parathyroid tissue secondary to a disturbance of calcium and phosphorus metabolism originating elsewhere in the body (e.g., renal failure, rickets, osteomalacia). The increased parathyroid hormone results in hypercalciuria and mobilizes excess calcium from the bones, bringing about the skeletal changes described as osteitis fibrosa cystica. The blood contains an increased concentration of calcium and sometimes of alkaline phosphatase, but a low level of phosphorus. The excess serum calcium tends to be precipitated in soft tissues, and may cause severe damage in such tissues as blood vessel walls and kidneys. Excessive amounts of calcium are excreted in the urine, and renal calculi are found in the majority of cases.

Tumors of Parathyroid Tissue.—Almost all cases of primary hyperparathyroidism are due to neoplastic overgrowth of functioning parathyroid tissue. Usually it is a benign adenoma limited to one parathyroid gland, or even a portion of one

gland, but in a few instances there have been multiple tumors and even more than one gland involved. The adenomas are composed most commonly of chief cells, but some have consisted of the large pale *"wasserhelle"* cells, and least commonly of oxyphil cells. Hyperparathyroidism is said to have been associated with adenomas composed of each of these types of cells, but oxyphil cell adenomas may be without activity. Usually an adenoma is composed almost exclusively of one type of cell, but transitional varieties of cells are common.

The size of the adenomas varies over a great range, an extreme of as much as 300 grams having been recorded. The degree of hyperfunction can be correlated roughly with the size of the tumor, but not with its histologic appearance.[21] Not uncommonly, the adenoma involves one of the lower glands and may be found in the mediastinum, where the gland has been carried during descent of the thymus.[22] The gross appearances of parathyroid tissue encountered at operation have been described by Cope.[22] The normal glands are irregular in size and shape, but have a variable brownish-yellow color due to their fatty interstitial tissue. Adenomas, which may vary from pinhead size to the size of a hen's egg, are browner than the normal glands due to absence of fat. Glands involved by primary hypertrophy (rare) are an even deeper brown color and grossly more irregular in shape than the adenomas. Glands involved by secondary hyperplasia are bulbous, more regular, and a lighter brown color. Uninvolved glands, in the presence of a functioning adenoma, undergo an atrophy of disuse, acquire a greater fat content, and hence are more yellow than normal glands.

Histologically, a parathyroid adenoma is composed of one cell form, i.e., pale or dark chief cells or oxyphil cells, but the cells are hypertrophied in comparison with corresponding cells in the normal gland. Cell size and structure show considerable variation. Cellular and nuclear gigantism and multiple nuclei are quite common. The stroma shows a scantiness or absence of fat cells, and irregularity in amount and distribution of fibrous tissue. The oxyphil cell adenomas usually are not functionally active[24] and only a few have caused hyperparathyroidism.[24a]

Carcinoma of parathyroid tissue is relatively uncommon. In some cases, however, metastases have occurred[27] and produced hormone which maintained hyperparathyroidism even though the primary tumor was removed.[25] Although not malignant, transplanted tissue of a parathyroid adenoma removed at operation has caused recurrence of symptoms of hyperparathyroidism.[29]

Cysts of parathyroid origin are quite rare except for small retention cysts of microscopic size. A few have been large enough to present as swellings in the side of the neck. They are lined by cuboidal or low columnar cells resembling those of the parathyroid, usually with parathyroid tissue identifiable in the wall.[31, 31a]

Primary Parathyroid Hypertrophy and Hyperplasia.—A relatively small proportion of cases of hyperparathyroidism has been associated with a primary or idiopathic hypertrophy and hyperplasia involving all the parathyroid glands. The glands vary greatly in size, the upper pair often being much larger than the lower pair. They tend to be a chocolate-brown color, with a little irregularity of the surface with small pseudopod projections or deep lobulations. The glands are composed exclusively of very large *wasserhelle* or water-clear cells, 10 to 40 microns in diameter, with fairly uniform nuclei about 8 microns in diameter. The arrangement of the cells may be in solid sheets, in acini with prominent basal orientation of nuclei, or in a somewhat irregular branching pattern. Most cases have been associated with renal stones, and a few with skeletal decalcification. Surgical resection of most of the involved parathyroid tissue has been helpful but not completely curative.[35]

Lesions Associated With Hyperparathyroidism.—Some, but not all, cases of primary hyperparathyroidism are associated with manifest osteoporotic lesions of the skeletal system, the fully developed condition being known as generalized osteitis fibrosa cystica. The level of phosphatase in the blood is increased when skeletal lesions are present. Whether or not skeletal lesions develop in a case of hyperparathyroidism may be influenced by the dietary intake of calcium. If this is sufficient, skeletal changes may be slight or absent. Probably more frequent and important as a manifestation of hyperparathyroidism are the effects on the kidneys. These effects are the deposition of calcium in the kidneys (nephrocalcinosis) and the formation of renal stones. Acute toxicity due to excess of parathyroid hormone ("parathyroid poisoning") particularly is manifested by calcification. Calcium deposits (metastatic calcification) occur in soft tissues, and may be especially damaging in blood vessel walls and in the kidney. Renal calculi are present in 60 per cent or more of cases of hyperparathyroidism, and may be the basis for the presenting symptoms. While hyperparathyroidism probably is responsible for less than 1 per cent of renal calculi, investigation for the presence of this condition should be part of the study of every patient with renal stones. In some clinics 5 per cent of individuals with renal stones have been found to be suffering from hyperparathyroidism.[3] The calculi are predominantly calcium phosphate or

TABLE XIII

POINTS IN THE DIFFERENTIAL DIAGNOSIS OF THE VARIOUS FORMS OF TETANY (FROM SHELLING[1])

TYPE OF TETANY	AGE DISTRIBUTION	CLINICAL HISTORY	DIETARY HISTORY	SEASONAL HISTORY	CATARACT AND OTHER ECTODERMAL CHANGES	BLOOD CHEMISTRY	Ca AND P METABOLISM	COURSE	X-RAY OF BONES
Parathyroprivic (postoperative)	Usually young adults	History of strumectomy	Worse after meals (high P)	Somewhat worse in winter	Very common	Ca low, P high, CO_2 normal	Urinary Ca excretion very low	Varies with diet	Normal
Parathyroprivic (idiopathic and traumatic)	Usually young adults and children	No definite history of trauma (hemorrhage ?)	Worse after meals (high P)	Somewhat worse in winter	Very common	Ca low, P high, CO_2 normal	Urinary Ca excretion very low	Varies with diet	Normal
Osteomalacic	Young adults	Poor hygienic conditions, pregnancy	Diet poor in Ca and in vitamin D	Worse in winter months	Common	Ca low, P low or normal	Negative Ca and P balance	Improves with Ca and vitamin D therapy	Osteomalacia, deformities
Chronic steatorrhea, sprue, celiac disease	Children and young adults	History of fatty stools	Disturbance of digestion rather than of intake	May improve during summer	Very rare (absent)	Ca low, P low, CO_2 normal, lipoids low	Negative Ca, P, balance	Usually chronic	Osteoporosis or rickets

Infantile (associated with rickets)	Usually between 6 months and 2 years	Presence of rickets	Usually artificially fed. Vitamin D inadequate	Worse from March to May	Very rare	Ca low, P increased (P normal or low if rickets is severe), CO_2 normal	Loss of Ca and P, mostly in feces	Responds promptly to Ca and vitamin D therapy	Rickets
At onset of infection (rickets absent)	Usually between 6 months and 2 years	Fever, prostration	No direct relationship	No relation	Absent	Ca and P normal, CO_2 low if acidosis, high if vomiting. Typical cytological changes for infection	No change from normal unless diarrhea is present	Tetany disappears with improvement of infection	Normal
Alkalosis (gastric retention, vomiting, Na HCO_3 therapy, hyperventilation)	All ages	History of vomiting or of gastric retention; bicarbonate medication, or hyperventilation	No definite relationship to Ca, P, or vitamin D intake	None	Absent	Ca normal, P normal or slightly increased, CO_2 high (Ca and Cl low, P and NPN high, if vomiting is persistent)	No definite disturbance in balance unless alkalosis is persistent	No recurrence if alkalosis is controlled	Normal
Chronic nephritis (P retention, renal rickets)	Renal rickets, common in children	History of nephritis or of congenital anomaly of urinary tract	Noncontributory	None	Very rare	Ca low, P very high, NPN high, CO_2 low	Urinary Ca and P low, Sp. gr. of urine low	Prognosis poor	Osteoporosis or rickets

TABLE XIV
DIFFERENTIAL DIAGNOSTIC FEATURES OF HYPERPARATHYROIDISM

	HYPERCALCIURIA	SERUM CALCIUM	SERUM PHOSPHORUS	SERUM PHOSPHATASE	SKELETAL LESIONS	NEPHROLITHIASIS
Primary hyperparathyroidism	Present	Increased	Decreased	May be increased (if bone lesions present)	May be generalized osteitis fibrosa	Frequent
Secondary (renal) hyperparathyroidism	May be absent	Low, normal or increased	Increased	May be increased	May be generalized osteitis fibrosa	May be present
Paget's disease (osteitis deformans)	May be present	Usually normal	Usually normal	Increased (very high)	Disseminated localized lesions	May be present
Osteoporosis	May be present in early stage	Usually normal	Usually normal	Normal or low	Generalized demineralization	
Osteoporosis with hypercalcemia in childhood (due to immobilization)	May be present	Increased	May be normal or increased	Normal or low	Generalized demineralization	May be present
Osteomalacia and rickets	Absent	Normal or low	Usually decreased (variable)	Increased	Generalized decalcification; in rickets, epiphyseal lines wide and irregular	
Osteogenesis imperfecta (fragilitas ossium)	Absent	Normal	Normal	May be increased	Thin cortex; fractures common	
Polyostotic fibrous dysplasia	Absent	Normal	Normal	Increased	Localized or segmented distribution	
Multiple myeloma	May be present	May be increased or normal	Usually normal, but may be increased or decreased	Normal	Localized	May be present
Sarcoidosis	May be present	May be increased	Usually normal	May be increased	May be localized decalcification with cystlike areas in bones of hands or feet	May be present
Metastatic cancer in skeleton	May be present	May be increased or normal	Usually normal	May be elevated	Localized; usually diagnostic	

calcium oxalate. In rare cases of hyperparathyroidism neither skeletal nor renal lesions have been manifest.[3]

Generalized Osteitis Fibrosa Cystica.—Osteitis fibrosa cystica (von Recklinghausen's disease) is characterized by distortion of the skeleton due to lack of sufficient mineralization as a result of osteoclastic resorption, and by replacement of the osseous tissues and marrow spaces by fibrous tissue. In advanced cases there are giant-cell tumors and cysts. Markedly involved bones are soft, and easily deformed or cut. The degree of skeletal change appears more closely correlated to the length of time that hyperparathyroidism has been present than to its intensity. The change is generalized throughout the skeleton.

The change is essentially an osteoclastic resorption of bone and its replacement by connective tissue in which there are abortive attempts at new bone formation. When mild, the gross change in the bones is merely a slight porousness, and microscopically, mild generalized osteoporosis and marrow fibrosis. As the condition progresses there is more loss of osseous tissue and replacement by connective tissue. Immature poorly calcified bone develops in the connective tissue. The newly formed bone soon may again undergo resorption. Osteoclasts are abundant. Large fibrous scars develop in the place of the original spongy bone. Some of these areas are brown due to blood pigment, and contain multinucleated giant cells (brown or giant-cell tumors). Cysts, lined by connective tissue, may result from degeneration or hemorrhage, but are not always present. (See also page 1219.) Characteristic roentgenographic changes include subperiosteal resorption of bone, most frequently seen along the margins of the middle phalanges of the hands.[54]

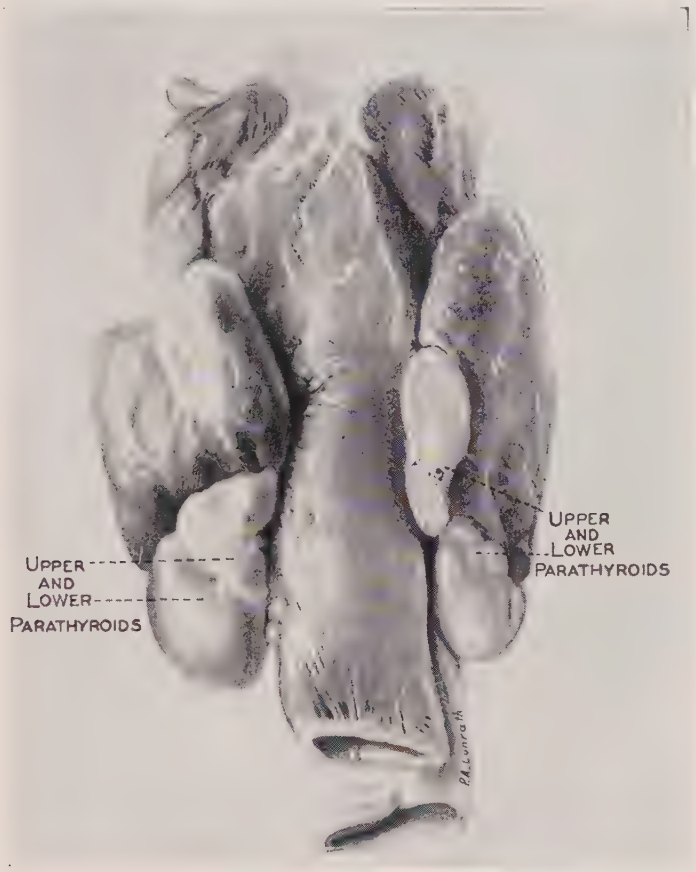

Fig. 882.—Parathyroid hyperplasia. Marked enlargement of all parathyroid glands in a case of renal dwarfism.

Metastatic Calcification.—Most cases of hyperparathyroidism have some deposition of calcium salts in soft tissues. The

kidneys and blood vessels are most frequently involved, but some deposits may be found, especially in acute hyperparathyroidism, in the lung, stomach, pituitary, and other areas. Calcium deposition is particularly abundant when there is renal functional failure and phosphate retention, resulting in high concentrations of both calcium and phosphorus in the blood.[48]

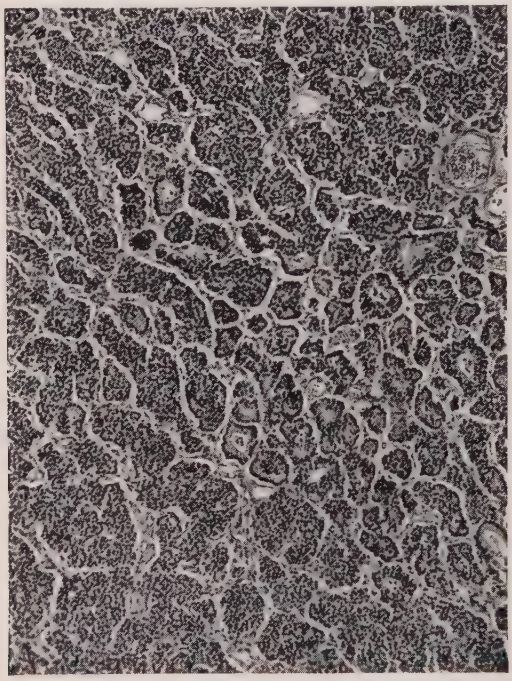

Fig. 883.—Parathyroid hyperplasia.

In the kidney in acute hyperparathyroidism there is calcification of tubular epithelial cells and formation of calcium casts. Tubular basement membranes also may be calcified. In the more long-standing cases the calcification is mainly peritubular and involves interstitial tissue. The formation of renal calculi appears to be on the basis of calcium deposits in the renal medulla.

In blood vessels the calcification is mainly in the media and particularly involves elastic tissue, so that the internal elastic lamella is often prominently calcified. The adjacent intima may be thickened by hyperplasia, but usually without calcification. Vascular calcification may be particularly severe in secondary (renal) hyperparathyroidism in which there is an increased level of blood phosphate. In some cases ischemic muscle pains in the extremities and even gangrene have resulted.[52]

The localization of metastatic calcification in the kidneys, lungs, and stomach has been ascribed to the fact that these are tissues which excrete acid, leaving the tissues in a relatively alkaline state favoring the precipitation of calcium salts from blood and tissue fluids. However, it is possible that the precipitation of calcium is preceded by some local tissue damage, so that it is more in the nature of a dystrophic calcification. This question is not yet settled, and the possible role of the excess alkaline phosphatase in hyperparathyroidism in promoting calcification is not known.

Renal Lesions in Hyperparathyroidism.—The kidneys may be severely damaged in hyperparathyroidism.[36] This is mainly the result of deposition of calcium in renal tissue, with resulting tubular obstructions and calculus formation. The parathyroid hormone appears to have a direct effect upon the kidneys, and excess hormone promotes diuresis and electrolyte loss with increased phosphate excretion. Whether excess of the hormone ordinarily causes damage to renal tissue other than that associated with calcification is not clear. In experimental animals, large doses of parathormone cause necrosis in renal tissue, followed by calcification.[37] Repeated administration of parathormone eventually results in severely damaged kidneys, with marked tubular dilatations and atrophy, and an appearance rather similar to that of advanced pyelonephritis. Tubules and interstitial tissue appear to be involved primarily, with later secondary effects on glomeruli and blood vessels. (See also page 584.)

Secondary Hyperparathyroidism.—Hyperplasia of all parathyroid tissue is a common accompaniment of renal insufficiency, rickets, and osteomalacia. It has also been found in association with extensive skeletal tumors such as multiple myeloma and metastatic carcinoma.[39] The hyperplastic glands are composed mainly of dark chief cells, are uniform throughout in their appearance, and have little or no interstitial fatty tissue. The actual stimulus which leads to the parathyroid hyperplasia is apparently some continued disturbance in the normally highly constant levels of calcium and phosphorus in the serum and perhaps is not identical in the various conditions. In rickets and osteomalacia the parathyroid hyperplasia appears to be a response to low serum calcium. In experimental animals, parathyroid hyperplasia may be brought about by injection of phosphates.[40]

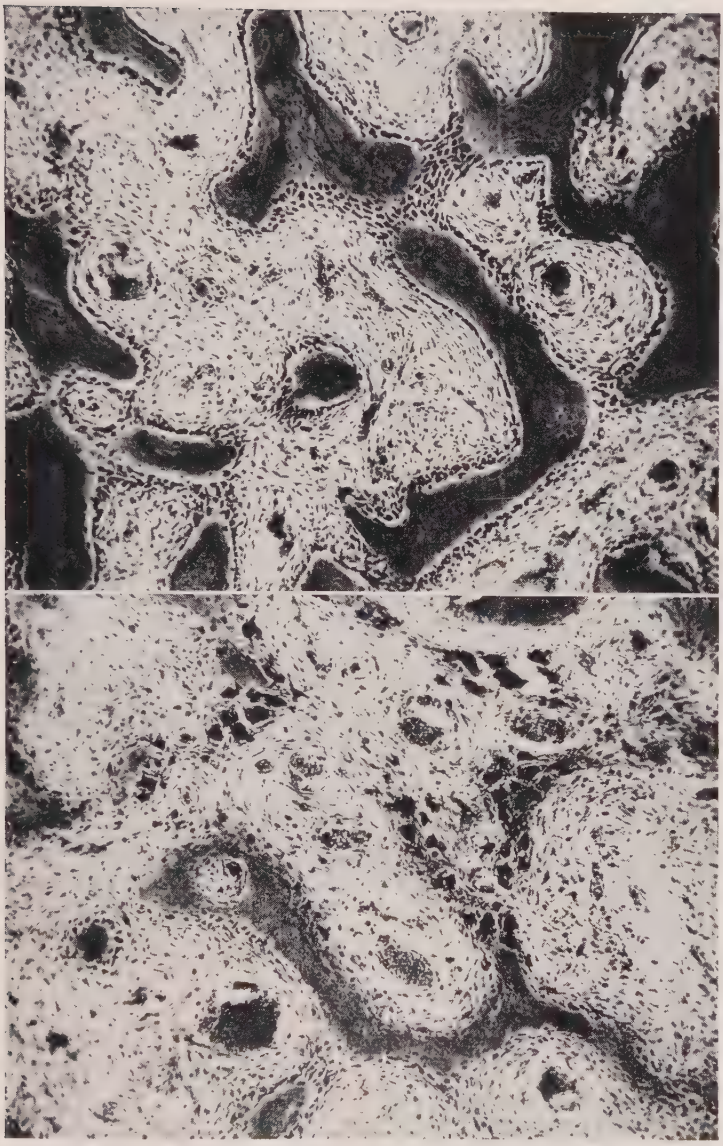

Fig. 884.—Osteitis fibrosa cystica (von Recklinghausen) in a case of hyperparathyroidism. Note the irregular arrangement of newly formed bone trabeculae, which exhibit narrow osteoid zones and osteoclastic resorption. The marrow is fibrous and hyperemic. (Courtesy Dr. W. H. Bauer.)

The characteristic features of the parathyroids in secondary hyperplasia have been given by Castleman and Mallory[33] as follows:

GROSS APPEARANCE:

Size: Slight to moderate enlargement of all glands, rarely reaching the size of the usual adenoma or primary hyperplasia; marked variation is not infrequent in the size of the individual glands, and one or all of them may be of normal size.

Color: The glands tend to be creamy gray rather than orange brown.

Consistency: Firmer and less pliable than the normal gland, the adenoma, or the primary hyperplasia.

High power:

1. Cells are normal-sized chief cells, unlike the adenoma or primary hyperplasia.
2. Tendency to vacuolization of the cytoplasm in less severe cases, producing slight cell enlargement.
3. No mitoses or hyperchromatism.
4. Oxyphil cells more numerous than expected for age of individual.
5. Glycogen content slightly higher than in adenoma or primary hyperplasia.

Others[51, 53] have found that clear cells rather than the dark chief cells are often predominant in parathyroid hyperplasia

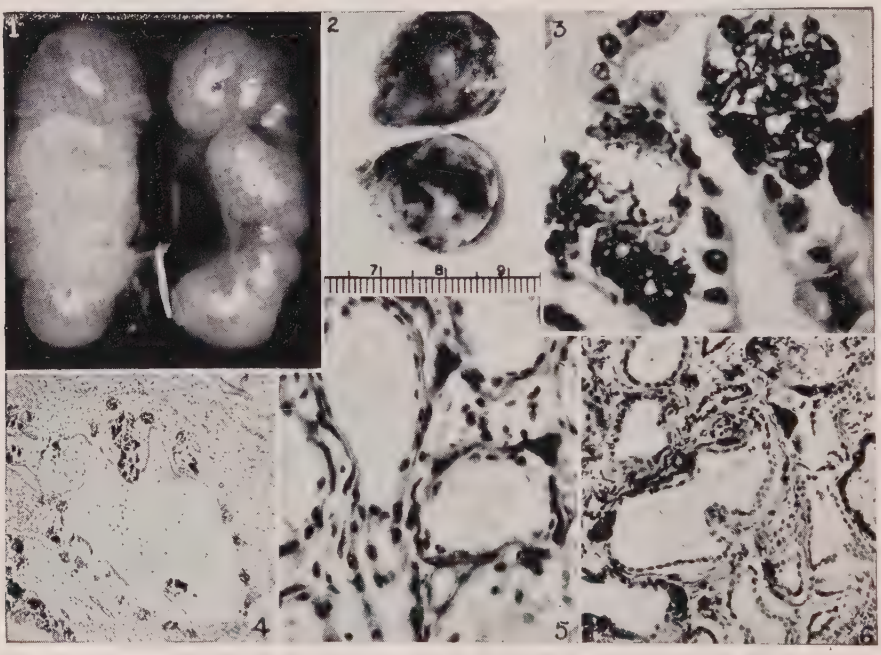

Fig. 885.—Hyperparathyroid renal disease. *1*, X-ray of kidneys, showing massive deposits of calcium. *2*, Parathyroid adenoma in this case, as seen from the external and cut surface. The dark area on the cut surface is an area of hemorrhage (scale in centimeters). *3*, *4*, *5*, and *6*, Interstitial and paratubular calcium deposits in the kidneys. (From Anderson, Endocrinology 24: 372, 1939.)

MICROSCOPIC APPEARANCE:

Low power:

1. Uniformity of all glands in a given case.
2. Absence or marked decrease of stromal fat cells.
3. Increase in number of cells as shown by widening of the epithelial columns.
4. Development of compact areas in which columnar arrangement is no longer distinguishable.
5. Tendency to acinar arrangement in the more advanced cases.
6. Uniformity of the whole gland except in more advanced cases where there is a tendency to adenomatous-like and papillary formations without real encapsulation.

secondary to renal disease, whereas oxyphilic cells are not increased or are scanty.

While parathyroid hyperplasia of some degree probably accompanies all cases of renal insufficiency,[8, 33, 41] it is only rarely that it is sufficiently prolonged and of a degree to produce clinical evidence of hyperparathyroidism. Renal lesions of a type in which large amounts of renal parenchyma are lacking or destroyed, and which are stationary or very slowly progressive (renal insufficiency over a prolonged period) may result in changes char-

acteristic of hyperparathyroidism in bones and other tissues. In adults, this rare condition (renal osteitis fibrosa cystica) is characterized by phosphate retention with a high serum phosphorus level, slightly high, normal, or reduced serum calcium, marked acidosis, calcium deposits in blood vessel walls and about joints, and generalized osteitis fibrosa cystica.[42] Skeletal changes also may be influenced by the chronic acidosis which accompanies the renal disease, but the roentgenographic changes are characteristic of hyperparathyroidism.[54] In children the condition is modified by its development before bone growth is completed and the epiphyses united, and has been termed renal rickets (renal dwarfism).[38, 43-46] Metastatic calcification is often a marked feature in secondary hyperparathyroidism due to the high levels and oversaturation of the serum with both calcium and phosphate.[48]

Renal Rickets.—Renal hyperparathyroidism is more common in children than in adults and remarkable skeletal deformities and growth disturbances (dwarfism) may result. The underlying renal lesion is most commonly a developmental imperfection in the kidneys or urinary tract, such as congenital hypoplasia, congenital polycystic disease, strictures of the ureters or congenital valves of the urethra. Infection (pyelonephritis) may be added to hydronephrotic atrophy in cases of obstructions in the lower urinary tract, and still further decrease the functioning renal parenchyma.

Some cases apparently are due to cystine-disease, a hereditary metabolic disturbance with failure of splitting up of a metabolic precursor of cystine, accumulation of crystals of cystine, and renal damage.[49, 50] The parathyroid glands show secondary (chief-cell) hyperplasia, and the changes in the shafts of the bones are those of osteitis fibrosa. Other factors to which bone changes have been ascribed in renal rickets are a persistent chronic acidosis[47] and retention of phosphate and its excretion by the bowel, where it combines with ingested calcium to be lost as the insoluble calcium phosphate.

While the changes in the shafts of the bones are similar to those due to hyperparathyroidism in the adult, characteristic changes occur in the epiphysial cartilages. The epiphysial cartilages are greatly increased in bulk, but show degenerative changes, defects of calcium deposition, and marked distortions. Stresses and strains cause the cartilage to be bent and twisted, and it may be partially or entirely pushed away from its normal position at the end of the shaft. Extreme deformity often results. The skull may be greatly thickened, and the appearance of the calvaria closely resembles that of Paget's disease of bone.

Metastatic calcification tends to be of marked degree in these cases, probably due to the high level of serum phosphorus. The media of arteries especially may be severely calcified. The kidneys, however, show less calcium deposition than in primary hyperparathyroidism, and renal calculi are less frequent.

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Chapter 38

THE ADRENAL GLANDS

W. A. D. Anderson and J. A. Saxton, Jr.

The adrenal glands, named from their locations next to each kidney, consist of two distinctive parts, cortex and medulla, which have different origins and functions. The cortex arises from mesoderm of the urogenital ridge, and is thus closely related in its origin to the gonads and other urogenital organs. The medulla is derived from the neural crest in common with sympathetic nerve cells. While anatomically associated in man, the cortex and medulla are largely distinct in their functions and pathologic disturbances, and are best considered as separate glands. A true anatomical separation is present in some lower species. The cortex, which is essential for life, secretes an unknown number of steroid hormones which are concerned with salt and water metabolism, carbohydrate metabolism, development and maintenance of secondary sexual characteristics, and resistance to various stresses. The medulla, which is not essential for life, secretes epinephrine (Adrenalin) and norepinephrine (Arterenol),[12] the combined effects of which are largely similar to sympathetic stimulation.

The adrenals are relatively largest at the time of birth, when they have an average combined weight of 4.7 to 5 grams. The large size is due mainly to a thick fetal reticular zone (androgenic or X-zone) of the inner cortex, which degenerates and disappears almost entirely in the first few months after birth.[13] There is a decrease in weight during the first six postfetal months, and just under 1 year of age the average combined weight of the adrenals is 3.3 to 4 grams. The weight at birth is again attained at about 12 years of age and increases to an average of 7 to 12 grams in the adult. The glands increase slowly in size during middle life and may decrease during senescence.[2]

The cut surface of the gland shows grossly three main layers. The inner portion, or medulla, is gray-white and constitutes about 10 per cent of the weight of the adult gland. The cortex is represented by a variably thin brown inner layer and a thicker peripheral layer which is bright yellow or mottled yellow and brown.

THE ADRENAL CORTEX

Structure and Function

The adrenal cortex is divided into zones descriptively named, from without inward, the glomerulosa, fasciculata, and reticularis. The thin outer zona glomerulosa is composed of cells grouped in irregular or ill-defined clusters. In the zona fasciculata, the widest layer, the cells are arranged in parallel strands. The thinner zona reticularis, next to the medulla, has cells arranged in an irregular network. Yellowish-brown pigment is often present in cells of the reticular zone. The nature and significance of the pigment, which stains with iron hematoxylin, are not well defined. The pigment has been considered by some to be a lipofuscin similar to that found in other organs of the body and referred to as a "wear and tear" pigment associated with a degenerative or ageing process. In support of this view are studies which suggest that the cortical cells originate in the glomerular zone and gradually progress to the innermost cortical zone, from which they eventually disappear.[14] Associated with this orderly migration are certain cytoplasmic changes which are thought to be related to the formation of a progressive series of steroid hormones. Attractive as this view may be, there is considerable evidence that cortical cells arise, function, and die in one zone.[15] The facts remain to be determined. Lipoid material (mainly cholesterol) is present throughout the cortex, but is most abundant in the cells of the zona fasciculata. Localization of lipoid and shift of lipoid patterns give some indication of adrenal cortical activity due to pituitary adrenotrophic hormone.[10] Ascorbic acid is stored in the reticularis and the inner part of the fasciculata. Its concentration parallels the cholesterol content of the cortex, and its presence is thought to be essential to the formation of steroid hormones.[1] The different zones of the adrenal cortex may have separate functions. The outer layers of the cortex appear to be concerned particularly with electrolyte and carbohydrate metabolism, and the inner or reticular zone with the androgenic sex hormones. However, until the exact nature of the secretion of the adrenal cortex is settled, it is difficult to assign distinct functions to the zones.[16]

An appreciation of the functions of the adrenal cortex is necessary to an understanding of their disturbances in diseases of the gland. At least 28 different steroids have been isolated from the adrenal cortex, and 6 of these have been shown to be biologically active. Whether

these are indeed the compounds secreted by the gland, or represent artefacts induced by chemical isolation, remains unknown. In either event some of these compounds have different biologic actions, which are evidenced in varying degree in the diseases associated with hypo- and hyperactivity of the adrenal cortex. No one compound which has been isolated has been found to have all the functions of the adrenal cortex, and an amorphous fraction of adrenal cortical extract also has marked physiologic potency. Adrenal cortical activity, evidenced by hypertrophy and the secretion of hormones, is stimulated only by the adrenocorticotrophic hormone (ACTH) of the anterior pituitary gland.[17] Under normal conditions, this secretion of the pituitary appears to regulate the activity of the adrenal cortex, and is itself dependent upon the circulating levels of cortical steroids. Augmented secretion of epinephrine by the adrenal medulla, besides its other effects, may stimulate the pituitary to greater secretion of ACTH and perhaps other hormones, by way of the hypothalamus. Stimulation of the hypothalamic center through sympathetic or cerebral pathways may also influence the secretory activity of the anterior pituitary gland.

All of the crystalline compounds isolated from the adrenal cortex have a common steroid nucleus, widely distributed in nature, and found in such compounds as cholesterol, sex hormones, vitamin D, and digitalis. The presence of certain radicals at the positions of carbon atoms numbered 3, 10, 13, and especially 11 and 17 seems to influence physiologic activity in the greatest degree. The active compounds may be grouped into three general classes according to biologic activity: glycocorticoids, mineralocorticoids, and those with androgenic activity. The first group, exemplified by 17-hydroxycorticosterone (compound F of Kendall) and 17-hydroxy-11-dehydrocorticosterone (compound E or cortisone), has mainly a sparing action on utilization of carbohydrate reserves, promoting gluconeogenesis and leading to a negative nitrogen balance. The second group, of which 11-desoxycorticosterone (compound A) is representative, possesses striking sodium- and chloride-retaining capacity with consequent influence on hydration, principally mediated through the kidney, with associated loss of potassium. The third group consists of androgen-like steroids such as adrenosterone, which, in addition to masculinizing effects, have an anabolic function resulting in synthesis of body protein, thus antagonistic to the catabolic effects of the glycocorticoids. Other activities associated with the adrenal cortex include an influence on fat metabolism favoring the deposition of body fat, a depressing effect on lymphoid tissue, circulating lymphocytes and eosinophiles, an inhibitory influence on mesenchymal responses, and influence on melanin pigment metabolism, calcium excretion, blood pressure, muscular response, growth of the young, and development of sexual characteristics in the fetus. The dissolution of lymphocytes may play a role in immunity.[18] From these varied actions and perhaps others appears a general pattern of resistance to stress, or homeostasis. Many of the effects of adrenal cortical activity directly or indirectly tend to maintain the steady state of the organism under most if not all adverse conditions.[16] These actions form the basis of Selye's concept of the alarm reaction and general adaptation syndrome.[19]

Loss of adrenal cortical function results in a striking depletion of sodium, chloride, and water from the body, which leads to dehydration, hemoconcentration, and shock. Serum potassium and blood nonprotein nitrogen levels become raised as renal failure develops consequent to dehydration, shock, and decreased renal blood flow. The effects of excessive adrenal cortical activity vary according to the proportions of the different types of active substances produced. Assays of the urinary excretion of 17-ketosteroids, especially the β fraction, and of 11-oxycorticosteroids, products of adrenal cortical activity, are of considerable value in the differential diagnosis of diseases associated with altered adrenal cortical function.[20]

Pharmacologic Considerations

To what has been said of the physiologic role of adrenal cortical hormones must be added a brief statement of the effects of ACTH and adrenal steroids (notably cortisone) on a large number of diseases of unknown cause.[21] These include principally the collagen diseases, which are thought to result from atypical responses of the body to subtle injurious agents. Both ACTH and cortisone have been shown to be remarkably effective in relieving the signs and symptoms of these conditions, at least temporarily, and their mode of action appears largely to be an inhibition of the bodily reactions which produce the symptoms. Since the diseases are not associated with evidence of pituitary or adrenal cortical deficiency, it is difficult to regard the therapeutic or palliative effects of adrenal cortical hormones, exogenous or produced by ACTH stimulation, as replacement phenomena. Nevertheless, knowledge of the functions and interrelations of the adrenal cortex is by no means complete, and it is possible that further studies will show a physiologic basis for this important contribution to therapy. At the present time the action must be regarded as an augmentation of the natural capacity of tissues for homeostasis, which may or may not be ultimately beneficial depending upon the cause of the disease. In this sense, the action of ACTH or cortisone is pharmacologic.[16] It is noteworthy that in bacterial disease, inhibition of tissue responses has been found to be harmful. Inhibition of normal healing is also a highly undesirable effect of excess of cortical hormones.[22] Of especial interest are the physiologic effects of prolonged administration of large doses of ACTH or cortisone to patients with rheumatoid arthritis[22] and other diseases.[23, 24] All the clinical and metabolic manifestations of Cushing's syndrome were observed, including Crooke's hyaline changes and pituitary basophile hyperplasia, supporting the concept that this syndrome is due to overproduction of certain adrenal cortical steroids.

Developmental Disturbances

Developmental anomalies of the adrenals, although not rare, are not often of great importance in themselves. Variations in size, shape, and position are not uncommon. Unilateral absence of an adrenal occasionally occurs, usually involving the right side, and with hypertrophy of the opposite gland.

Hypoplasia of the adrenals is a common finding in cases of anencephaly.[25] The glands may be normal in shape despite their small size, which is due mainly to lack of development of cortical tissue. Histologically, the hypoplastic cortical tissue is more like that of the adult gland than of the infantile type. The adrenal hypoplasia has been considered to be secondary to the failure of proper development and function of the pituitary. Adrenal hypoplasia is said to occur also in individuals with the so-called status thymolymphaticus (see page 956), and it has also been noted in cyclopia.[26]

by some as a possible origin of the so-called hypernephroma of the kidney (see page 598).

Cysts of the adrenal glands are very rare. Reported cases have been mainly hematocysts and lymphangiectatic cysts.[29]

Myelolipoma is a term used for tumorlike nodules of bone marrow structure in the adrenal, although it is probable that the condition is not truly neoplastic. The lesion has been seen mainly as an incidental finding in individuals of middle or older age. There may be no anemia and no other foci of extramedullary hematopoiesis. The nodules may be yellowish-orange color, and microscopically show predominance of adipose tissue, with some erythroblastic tissue and less myeloid tissue. Other nodules are dark red or reddish-brown, cellular rather than fatty, and have predominantly myeloid elements and fewer erythroblastic cells. It has been suggested[30] that they are derived from proliferation of reticuloendothelial cells of the blood sinuses as a result of some unknown stimulus.

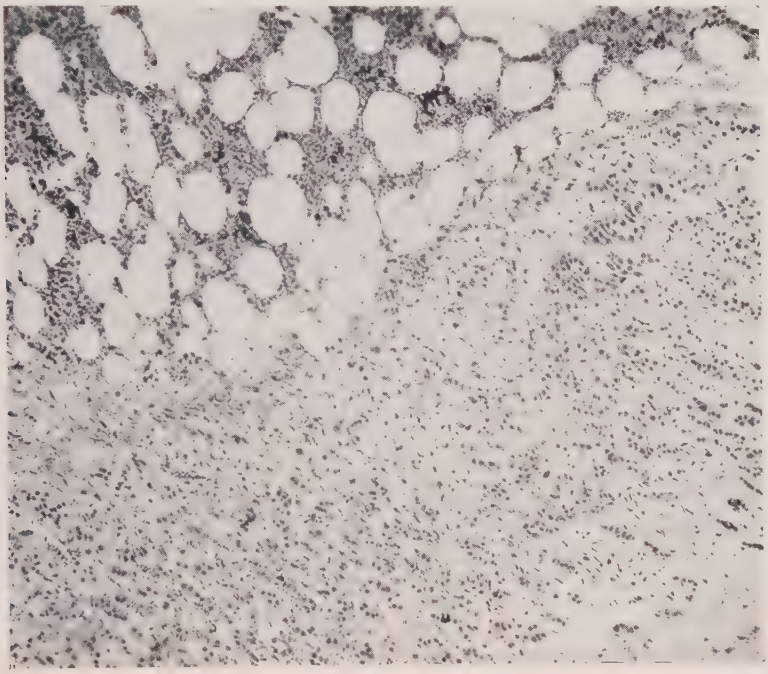

Fig. 886.—Myelolipoma of adrenal. The fatty and myeloid tissue, resembling bone marrow, formed a tumorlike nodule enclosed by adrenal cortical tissue.

Malposition of the adrenals (complete heterotopia) is rare, whereas heterotopic rests of accessory adrenal cortical tissue are common. O'Crowley and Martland[27] encountered adrenals beneath the capsule of the kidney with no adrenals in their normal position 8 times in 5,000 consecutive autopsies. Accessory adrenal cortical tissue is quite common beneath the capsule or in the cortex of the kidneys, and in the connective tissue or fat around the adrenals. It has also been found in many places in the abdominal cavity, along the genitourinary tract, scrotum, broad ligaments, and vaginal wall. Ectopic adrenal rests in the kidney have been considered

Regressive and Destructive Lesions

The more important pathologic changes in the adrenals may be classified broadly into two groups: (1) those which are degenerative or destructive, and in general associated with some or a severe degree of adrenal cortical hypofunction; and (2) those which are in the nature of hyperplasias or tumor formations, characterized by an excessive amount of adrenal cortical tissue, which in some, but not all,

cases produce in turn an excess of adrenal cortical hormone and may be associated with clinical evidences of hyperfunction.

The degenerative and destructive lesions include idiopathic atrophies, variations in lipoid content and distribution, nonspecific degenerative changes due to toxemias or infections, destruction by specific infections involving the gland parenchyma, infarcted areas due to vascular disturbances, and hemorrhage. The lesions range in severity from small focal involvements, which have little effect on function, to massive bilateral destructive changes.

The Adrenal Cortex in Infections.—In a variety of infective or inflammatory conditions, as well as in cachexia and protracted vomiting, a depletion of lipoid or a change in the lipoid pattern of the adrenal cortex is common.[31] Severe degenerative or destructive lesions are associated with pemphigus.[32] Rich[33] directed attention to a severe degenerative change of the adrenal cortex associated with acute severe infections. It is characterized by necrosis of occasional isolated cells, and particularly by a change of the normally solid cords of the zona fasciculata into tubular structures containing an inflammatory exudate.

Focal or extensive areas of the adrenal cortex may become involved by infective lesions. Tuberculosis, histoplasmosis, syphilis, tularemia, and other infections may involve the adrenals. Particularly in the case of tuberculosis, extensive bilateral destruction of the adrenals may lead to insufficiency of function (Addison's disease, see page 1034).

The Adrenal Cortex in Shock.—The clinical picture of acute adrenal cortical insufficiency (crisis of Addison's disease, see page 1034) is similar to that of shock (page 100); but there is little evidence that the adrenal cortex plays an important role in the pathogenesis of ordinary cases of shock. Histologic changes, particularly lipoid depletion, which have been described in cases of shock,[34] suggest exhaustion of a gland which has been stimulated to meet excessive immediate requirements of the body tissues for cortical secretion. However, the effects of administering cortical extracts on the course of experimental and clinical shock have been too variable to warrant conclusions.[1]

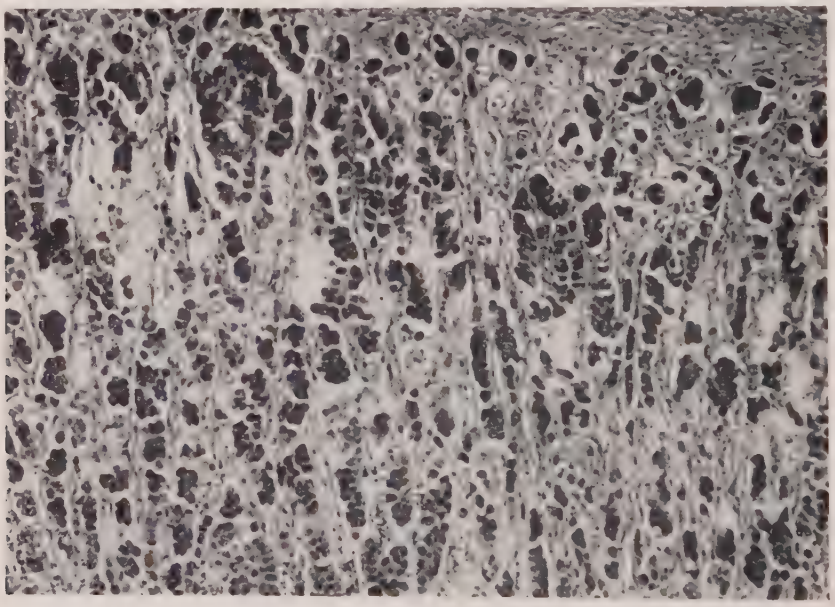

Fig. 887.—Tubular degeneration of adrenal cortex in acute infection. (AFIP No. 82923.)

Vascular and Hemorrhagic Lesions of the Adrenal Cortex.—The small arterioles about the adrenals are commonly involved by hyaline arteriolosclerosis, particularly in essential hypertension. Small adrenal or periadrenal vessels may be affected in polyarteritis nodosa, and small focal areas of infarction may be found in the cortex.

Small hemorrhages in the adrenal cortex may be found in various acute infections, such as diphtheria, influenza, typhus, scarlet fever, and meningococcus meningitis, as well as in severe burns, blood dyscrasias, hemorrhagic diseases, and vitamin deficiencies. These are not often sufficiently extensive to have functional or clinical significance.

Adrenal Hemorrhage in the Newborn.—Extensive hemorrhage of one or both adrenals is occasionally found in infants who die within the first few days after birth. In many cases this appears to be the result of trauma during birth to the very vascular cortex. Symptoms of adrenal hemorrhage in the newborn may be those of acute adrenal insufficiency, such as high temperature, rapid respiration, purpuric rash, cyanosis, and hypoglycemia, or signs of internal hemorrhage, such as shock and collapse, may predominate. Sometimes a mass is palpable in one or both kidney regions.

Waterhouse-Friderichsen Syndrome.—Earlier reports of fulminating purpura associated with bilateral adrenal hemorrhages were summarized by Waterhouse in 1911[36] and Friderichsen in 1918.[37] The syndrome is now known by their names, and it is nearly always due to a meningococcus septicemia. The syndrome is most common in infants and young children, but is not rare in adults.[41] The condition is one of severe and overwhelming sepsis, which pursues a rapid course, with death occurring usually within twenty-four hours after onset. The invasive phase is characterized by malaise, chills, fever, headache, and generalized aching, and vomiting. In a period of hours petechiae of the skin occur, which coalesce into large purpuric areas associated with marked cyanosis, cardiorespiratory collapse, severe shock, convulsions, and coma. Almost no other infection kills with such rapidity. Smears from the purpuric areas may show the causative organism and enable early diagnosis.

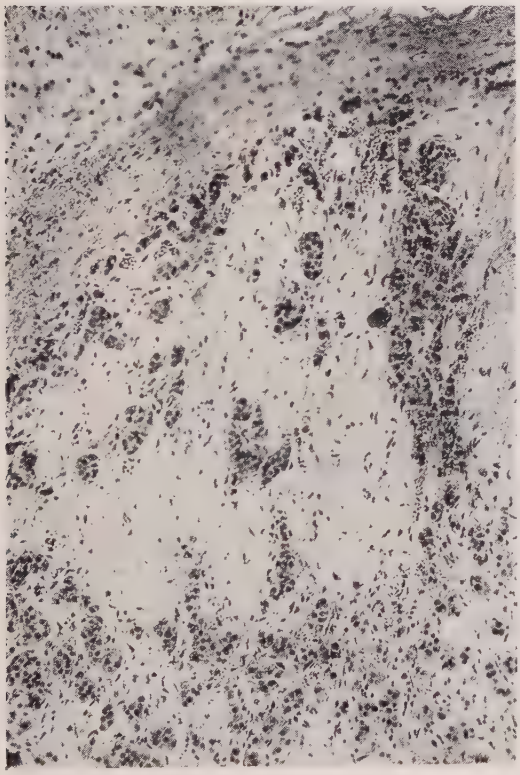

Fig. 888.—Amyloidosis of adrenal cortex. The capsule of the adrenal is at the top. Adrenal cortical cells are largely replaced by the amyloid material.

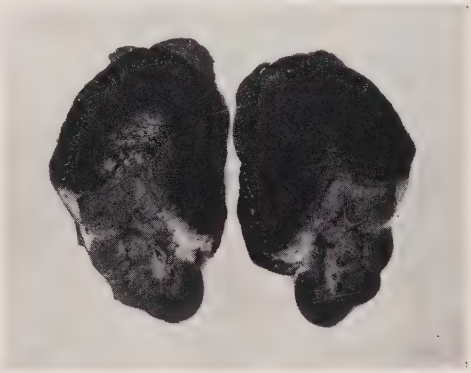

Fig. 889.—Bilateral adrenal hemorrhage in the newborn. The kidneys are seen below the massive, dark hemorrhagic adrenals.

Postmortem examination shows marked cyanosis and purpuric lesions of the skin, conjunctiva, and serosal surfaces. Gross evidence of meningitis is usually absent, and in many cases microscopic evidence of meningeal involvement is also lacking. In nearly all cases the most striking finding is the massive bilateral adrenal hemorrhage. The glands are swollen and purplish red but usually retain their shape. The cut surface may show many small hemorrhagic areas, or the whole gland may be a mass of blood with individual hemorrhages or parts of the gland grossly indistinguishable. Rarely the hemorrhage ruptures through the adrenal capsule into the peritoneal cavity. Microscopically, the most severe damage appears in the middle and inner layers

of the cortex. The glomerulosa may escape damage or be involved only in patchy fashion (see also page 209).

The significance of the adrenal damage in the pathogenesis of Waterhouse-Friderichsen syndrome is doubtful. Whether the adrenal hemorrhage is only the manifestation of generalized purpura in a highly vascular organ or is associated with destruction of a vital source of hormone needed by the body to combat acute severe infection has not been settled. Nevertheless, many feel that administration of cortical hormones is indicated and beneficial in cases of this syndrome.[45]

Addison's Disease.—In 1855 Addison[46] gave a masterly account of the clinical picture associated with destructive disease of the adrenals. The condition is characterized by marked weakness, low blood pressure, loss of weight, pigmentation, gastrointestinal disturbances of anorexia, nausea, vomiting, and constipation, and metabolic disturbances. The metabolic disturbances include a decreased serum sodium and chloride concentration, an increased plasma potassium level, and elevation of blood urea and nonprotein nitrogen. Evidences of disturbance in carbohydrate metabolism may include a low fasting blood sugar, a flat glucose tolerance curve, a tendency to hypoglycemic reactions, and increased sensitivity to insulin. An increased concentration of the blood may be shown by decrease of plasma volume, increase of packed red blood cells, and increased concentration of total serum proteins. The urinary excretion of 17-ketosteroids is decreased below normal values.

Pigmentation of skin and mucous membranes due to increased deposition of melanin in the basal epithelial layer is a striking part of the clinical picture in a high percentage of cases. The pigmentation may precede the development of other evidences of Addison's disease by some time, and its degree and intensity generally have no reliable close correlation with the severity of the disease. Those cases in which pigmentation appears early and is marked have been claimed to have a longer survival time than those in which pigmentation is less prominent. Pigmentation of oral mucous membranes, scars, and pressure areas may be especially striking. Jet black spots or freckles may develop. Areas of vitiligo in the hyperpigmented skin are common.[61] The pigmentation is entirely due to melanin, and so on biopsy is distinguishable from the pigmentation of hemochromatosis which shows some iron-containing hemosiderin pigment in addition to excessive melanin.

The cause and mechanism of the pigmentation are obscure. According to one hypothesis, injury of the medulla is important in this manifestation of Addison's disease. An excess of the precursor of adrenaline, no longer being acted upon by the cells of the adrenal medulla, becomes transformed to pigment by the melanogenic enzymes of the skin (the "dopa" reaction, see page 1166). The weakness of this theory lies in the fact that there is no difference in the pigmentation in those cases in which the medulla of the glands appears unaffected and in those wherein the medulla is destroyed.

Addison's disease tends to be of insidious onset and slow course, although often marked by recurring acute crises. A crisis may be precipitated by an acute infection or by cessation of salt or adrenal extract therapy. It is marked by a sudden intensification of symptoms and signs, and resembles shock in that there is fall of blood pressure, reduction in circulating blood volume, hemoconcentration, increased nonprotein nitrogen of blood, and vasomotor collapse.

Most cases of Addison's disease occur in adult life, with the greatest incidence in the third and fourth decades. However, childhood is not exempt, and a number of cases in children, due mainly to tuberculosis, have been recorded.[57] There is little difference in the sex distribution, although some series of cases have shown a slight preponderance in men, particularly in those cases due to tuberculosis. The duration of life with the disease is from one to three years in the majority of cases. Those caused by tuberculosis have a shorter life expectancy than those due to adrenal cortical atrophy.

Thorn and associates[60] have pointed out that certain cases of renal damage may be associated with excessive loss of sodium, chloride, and water, resulting in collapse, and simulating Addison's disease so far as the disturbance of electrolyte and water metabolism is concerned. In such cases the adrenals are not involved, and administration of adrenocortical hormone is of no value. The response (percentage fall) of circulating eosinophiles following injection of Adrenalin or of ACTH, which depends upon adrenal cortical function, is of value in the differential diagnosis of Addison's disease.[61]

The pathologic basis of Addison's disease is a bilateral destruction of the cortex of the adrenal glands. The medullary portion of the glands, which may or may not be destroyed as well, appears to play little or no part in the production of the clinical disturbance. The two major causes of the adrenal cortical destruction are tuberculosis and idiopathic atrophy.

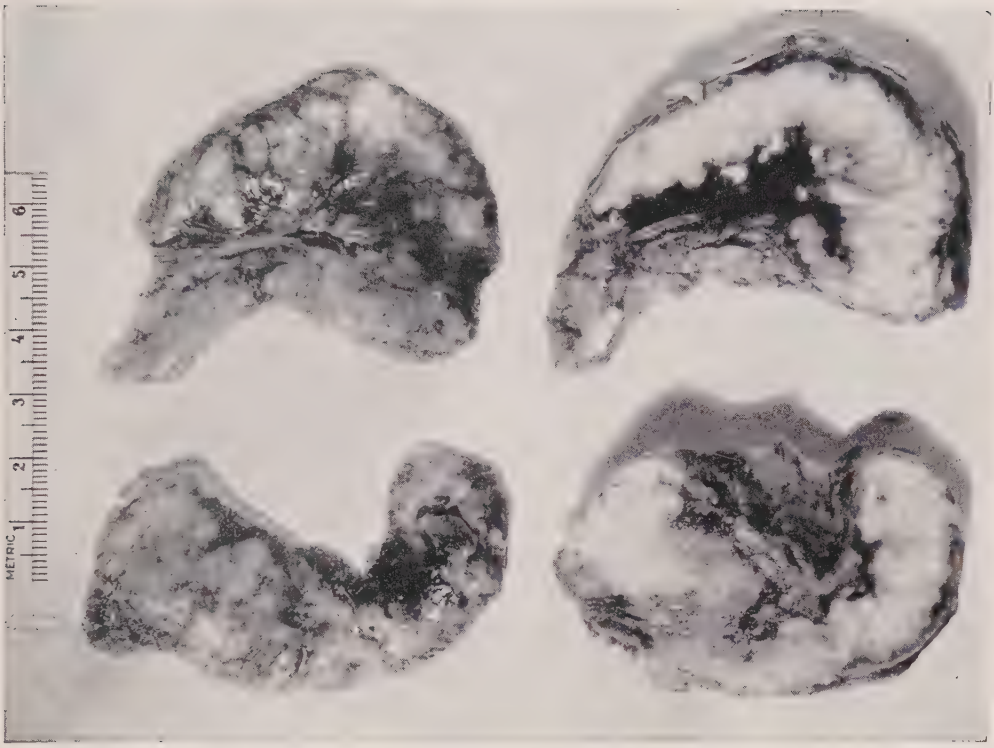

Fig. 890.—Tuberculosis of the adrenal glands in Addison's disease. (Courtesy Dr. H. C. Schmeisser.)

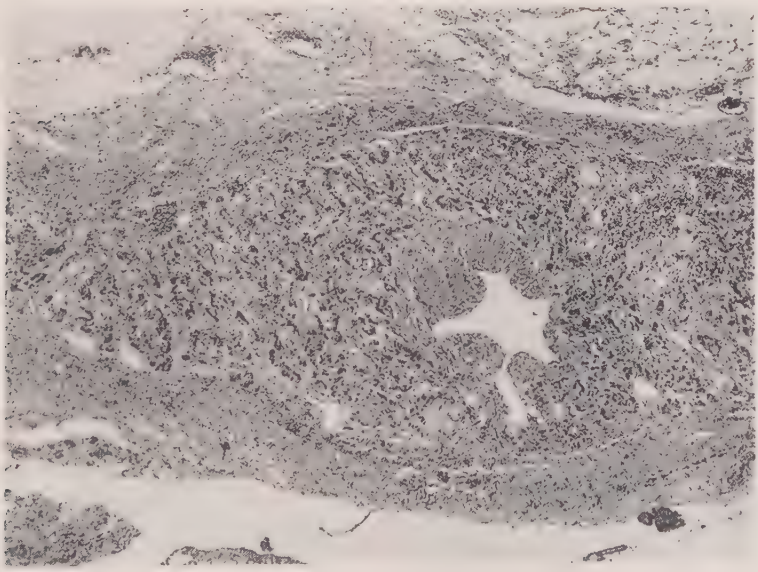

Fig. 891.—Adrenal in Addison's disease showing cortical atrophy. Only the medulla is seen, which is focally infiltrated with lymphocytes.

In older records tuberculosis was the predominant cause, particularly in continental Europe, accounting for about 80 per cent of cases. In the United States the relative incidence of cortical atrophy as a cause of Addison's disease has been increasing in recent years, and now appears the basis of almost 50 per cent.[47] Rarer causes include amyloidosis, histoplasmosis, bilateral metastatic tumors, and other destructive toxic or inflammatory lesions.

Bilateral tuberculous involvement of the adrenals in Addison's disease is a progressive caseating process which destroys the medulla and cortex. The yellowish caseous glands are usually enlarged. Some tiny remnants of cortical tissue may be found in the outer part of the cortex or as peripheral nodules of cortical tissue adjacent to the outer margins in the tuberculous inflammation. Calcification of the necrotic areas is not usually prominent. Active and progressive tuberculosis elsewhere, as in the lungs, may or may not be present.

In Addison's disease due to adrenal atrophy or selective cortical necrosis, the adrenals are very small and their remnants may be difficult to locate and identify. The cortical tissues may be completely gone, or only isolated remnants of somewhat pleomorphic cortical cells remaining. The zona reticularis disappears first, and the zona glomerulosa persists longest. Collapse of the stroma results in an apparent increase of fibrous tissue. There may be some lymphocytic infiltration among remnants of the cortex and in the medulla. Nuclear inclusions have been noted in remaining cortical cells in at least one case.[58] The medulla is usually relatively intact. The nature and cause of the process are not known and it is not an atrophy in the true sense of the word. Toxic injuries of the adrenal cortices due to chemicals, infections, interference with circulatory supply of the glands, and a slow chronic inflammatory process have all been postulated.

Other organs which show lesions in Addison's disease include the pituitary (see page 987), thyroid, heart, skin, and sometimes testes or ovaries. The hypophysis shows a decrease in the number of basophiles, and a relative increase in the number of chromophobe cells. Remaining basophiles may be large and vacuolated. The thyroid sometimes is small and atrophic, with lymphocytic infiltrations of the stroma. The heart often is small, and shows increased lipochrome pigment. Patchy myocardial degeneration without any inflammatory infiltration is sometimes present, and may be quite severe. An enlarged thymus and generalized hyperplasia of lymphoid tissue have been prominent in some cases. Occasionally there is fibrosis of testes or ovaries.

Hyperplasia and Neoplasia of the Adrenal Cortex

Adrenal cortical hypertrophy may be a diffuse enlargement or a focal nodular hyperplasia. Diffuse hypertrophy of one adrenal is common after injury or destruction of the other. A congenital hyperplasia of the cortex is present in female pseudohermaphrodites, and has been described in hydrops fetalis and erythroblastosis, and in a case of bilateral testicular tumors.[65] Adrenal cortical hyperplasia in infants without stigmata of hyperactivity, but with signs of intestinal obstruction, has been described.[63]

Nodular hyperplasia is common in adults. The small focal areas of hyperplasia are usually less than 1 or 2 cm. in diameter, and situated in the outer part of the cortex or within the capsule. Their functional significance, if any, is not determined, and they have been interpreted by some as focal regenerative areas following some injury. It has been claimed that nodular hyperplasia is more frequent and marked in hypertensive than in nonhypertensive individuals (see page 1041) and in diabetes mellitus.[64] Larger nodules are usually considered true adenomas, and are composed of cortical cells of more atypical appearance. However, no sharp dividing line can be drawn between the nodular hyperplasias and true adenomas.

Tumors of the adrenal cortex consist of benign adenomas and adenocarcinomas. Either may or may not be associated with functional disturbances and there appears to be no reliable morphologic distinction between those which have and those which are without endocrine function. Broster and Vines[5, 6, 7, 66] have emphasized the presence of fuchsinophilic

granules in the cells of those tumors which have androgenic functional activity. Blackman,[62] pointing out that Vines' pouceau-fuchsin stain is essentially similar to Masson's trichrome stain, has noted that it tends particularly to stain cells derived from the reticular zone of the adrenal cortex, which contain little lipoid, and which seem to be concerned particularly with the metabolism of masculinizing sex hormones.

Fig. 892.—Bilateral cortical adenomas of the adrenals, showing their situation in relation to the kidneys. (Courtesy Dr. H. C. Schmeisser.)

Adenomas occur as yellowish or yellowish-red rounded tumors which may grow to considerable size. Although well circumscribed, they press upon and deform the remainder of the gland. Microscopically, they are composed of cells similar to those normally found in the adrenal cortex, and have a variable lipoid content. The cells may be arranged in cords similar to those of the zona fasciculata, or may be without any particular architectural arrangement. *Carcinomas of the adrenal cortex* contain areas of atypical and anaplastic cells, and they metastasize readily. Signs and symptoms of the nonhormonal tumors do not appear until the tumor has become evident because of its size or until metastases occur.

Endocrine Disturbances.—Hyperplasias and tumors of the adrenal cortex associated with functional disturbances due to hormone production by the hyperplastic or neoplastic tissue are less common than nonfunctional overgrowths. The hyperplasias are usually bilateral,

Fig. 893.—Carcinoma of the adrenal cortex. The tumor cells show marked variation in size, shape, and intensity of staining.

but the functioning tumors, with rare exceptions, are unilateral, and the opposite adrenal is often markedly atrophic. Such an atrophic adrenal may be unable to assume immediately the whole burden of essential adrenal cortical function on surgical removal of the tumor. Hence, preparations should be made for therapy of acute adrenal insufficiency on surgical treatment of such cases. Hypofunction of the adrenal cortex manifested as symptoms of Addison's disease also has been reported as secondary to hyperplasia of the androgenic zone.[57]

The endocrine disturbances associated with adrenal cortical hyperplasias or tumors can be divided roughly into three groups of cases, which intergrade according to the functional activities of the glands.

1. Pseudohermaphroditism and Precocious Development.—Those cases occurring in infancy or childhood are characterized by precocious sexual and physical development. They are more commonly associated with hyperplasia of the "androgenic" (reticular) zone of the cortex than with tumors. In females, hyperplasia in utero results in pseudohermaphroditism. In male children precocious physical and sexual development results from cortical hyperplasias or tumors. Adrenal lesions are not the exclusive causes of such clinical syndromes in childhood. Similar precocious sexual development in boys has been associated with pineal and other midbrain lesions and tumors involving the hypothalamus, and with interstitial cell tumors of the testicle, and in girls with granulosa cell tumors of the ovary.

2. Adrenal Virilism.—This condition, known as the adrenogenital syndrome or adrenal virilism, is due to production of an androgenic hormone by hyperplastic adrenal cortical tissue or by an adenoma or carcinoma of the adrenal cortex. The prognosis as to life is good except when due to a malignant tumor, which is the commonest underlying lesion. Atrophy of the contralateral adrenal is less common in cases of adrenal virilism than in the following group (Cushing's syndrome). These cases are characterized by evidences of masculinization in a female child or adult. Such changes in the child include the development of hirsutism, enlargement of the clitoris which is usually less pronounced than in the congenital form, deepening of the voice, rapid early growth with premature closure of epiphyses, masculine body contour and impaired development of the breasts. In the adult female there are cessation of the menses, atrophy of ovaries and uterus, and other evidences of defeminization. The urinary excretion of 17-ketosteroids is elevated. The clinical condition may be simulated in the presence of a masculinizing tumor of the ovary (arrhenoblastoma, see page 1055).

In rare cases in adult males impotence and feminization have accompanied a malignant adrenal cortical tumor. In such cases estrogenic rather than androgenic material has been a product of the tumor tissue.

3. Cushing's Syndrome.—In these cases the principal manifestations are hypertension, obesity of trunk, face, and neck, purplish striae and cyanotic discoloration of the skin, osteoporosis, a tendency to polycythemia, and decreased glucose tolerance with glycosuria. The syndrome occurs in women with about four times the frequency found in men. It may occur at any age but has its highest incidence in early adult life. Some manifestations of the adrenogenital syndrome, such as hirsutism, are commonly present. The prognosis is poor, the average duration of untreated cases being about five or six years, or less when the adrenal lesion is cancerous. Dramatic recoveries have resulted from complete removal of an adrenal tumor. Death is usually due to infection, to which these patients are highly susceptible, or to a complication of the hypertension, such as cerebral hemorrhage or cardiac failure (see Fig. 860, page 984).

The genesis of Cushing's syndrome is obscure. Originally, Cushing attributed the syndrome to a functioning basophilic adenoma of the pituitary.[77] Subsequent observations have cast doubt on this view, emphasizing the role of adrenal cortical secretions in the development of the syndrome. The occurrence of all of the manifestations of this syndrome following prolonged massive dosage with cortisone,[22, 23, 24, 78] and the regression of signs and symptoms after removal of an adrenal cortical tumor point to the importance of the adrenal cortex in the pathogenesis of the syndrome. Heinbecker[79] has observed atrophy of the hypothalamic nuclei in cases of Cushing's syndrome, and has shown in the dog that denervation of the entire neural hypophysis, or interruption of the paraventricular hypothalamic pathways, results in the syn-

drome, presumably by producing an imbalance of pituitary-adrenal function. Whether the primary change is in the pituitary, adrenals, or hypothalamus, or if it varies in different cases is not known. Pituitary changes, in nearly all cases a hyaline change or vacuolization of the basophilic cells described by Crooke,[80] with or without an adenoma of basophilic or rarely of other cells of the hypophysis, are usually found in Cushing's syndrome. No change in either the pituitary or adrenals appears to be constant, and in many cases both pituitary and adrenal abnormalities are found. There is usually increased excretion of 11-oxycorticoids and 17-ketosteroids. The urinary levels of the latter may depend upon the type of adrenal lesion present, being highest in the presence of adrenal carcinoma.[86]

A somewhat similar clinical picture occurring at an older average age (fifth decade), characterized by obesity, virilism, and hirsutism, has been found associated with bony thickenings of the skull (hyperostosis frontalis interna, metabolic craniopathy, see page 966).

THE ADRENAL MEDULLA

The medulla of the adrenal has an origin from ectoderm in common with sympathetic nerve tissue. The cells of the medulla stain with chrome salts as do certain other tissues such as abdominal paraganglia. Their function of epinephrine and norepinephrine production is not essential to life.[12] In destructive adrenal lesions, any functional disturbance caused by injury of the medulla is overshadowed by the effects of cortical involvement, as in the tuberculous type of Addison's disease. The only lesions of the adrenal medulla of known practical importance are tumors. Using size of the nuclei and cells of the medulla as measured by a micrometer as an index of functional activity, Drake and associates[91] observed evidence of decreased activity in neoplastic diseases and prolonged infections. High activity was observed with cerebral injuries, diabetes, obesity, hypertension, and hyperthyroidism.

Tumors of the Adrenal Medulla

Tumors of the adrenal medulla are composed of immature or mature cell types comparable to those which occur in embryonic development of medullary and sympathetic nerve tissue. The most immature cell forms, the precursors of the other types, are the sympathogonia, small, dark lymphocyte-like cells, which differentiate into sympathicoblasts and pheochromoblasts. The sympathicoblasts mature as ganglion cells, and the pheochromoblasts develop into pheochromocytes, the mature cells of the adrenal medulla. Tumors composed of the immature forms (sympathicogonioma and neuroblastoma) occur almost exclusively in early life and are highly malignant. Those composed of mature forms (ganglioneuroma and pheochromocytoma) are benign and occur mainly in adult life.

Sympathicogonioma.—Sympathicogoniomas usually develop during intrauterine life or in early infancy, are highly malignant and invasive, and metastasize early. They are composed of small, round, dark cells resembling lymphocytes, some of which group to form rosettes. No neurofibrils are formed.

Neuroblastoma.—Adrenal neuroblastoma or sympathicoblastoma is a highly malignant tumor which occurs almost exclusively in infants and young children. It arises either in the adrenal medulla or the immediate neighborhood. Microscopically, it is extremely cellular, composed of small, dark cells resembling lymphocytes, and it has the characteristic feature of a circular grouping or pseudorosette formation around a fine fibrillar network. It differs from the sympathicogonioma only in its somewhat greater maturity, and some differentiated ganglion or pheochrome cells may be present. The cells tend to be larger, irregular, or oval in shape, and some may have elongated cytoplasmic processes. The medulloblastoma of the midbrain and the retinoblastoma of the eye are also malignant tumors which arise from undifferentiated neural elements, have a similar histologic structure and occur in childhood. Cultivation of cells of sympathicoblastomas in vitro has been advocated as a help in identifying this tumor, and in differentiating it from lymphosarcomas or Ewing's tumor, which may be similar histologically.[99]

Two clinical groups of neuroblastomas have been proposed on the basis of the distribution of metastases. In the Pepper group there is early and extensive metastasis to the liver, which results in abdominal enlargement. In the Hutchinson type there is prominent metastasis to the skull, dura, long bones, and sometimes lungs. Although it has been claimed that the Pepper type usually arises from the right adrenal and the Hutchinson type from the left, this has not been found to be true, and it appears that the position of the metastases is not determined by the site of the primary tumor.[95] There is much overlapping of the two groups of cases. There does appear to be a difference in age incidence, neuroblastomas which metastasize to the liver and soft tissues being in general in younger children than those which metastasize to the skull and bones. Those cases with extensive skeletal metastasis may show marked anemia.

Ganglioneuroma.—Ganglioneuroma is a rare benign tumor composed of differen-

tiated, large, sympathetic ganglion cells, and often a few nerve fibers. It may occur in either child or adult, but is more frequent in the latter. While the common origin is from the adrenal medulla, it may arise in any part of the sympathetic system, or rarely in the central nervous system. It produces symptoms only by virtue of the large size to which it may grow. Small neurofibromas of the medulla are occasionally an incidental finding at autopsy.

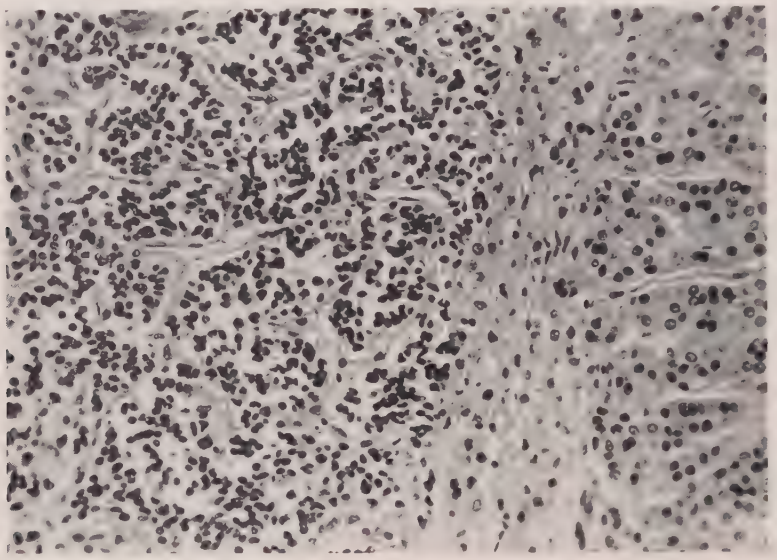

Fig. 894. Sympathicoblastoma of adrenal in newborn infant.

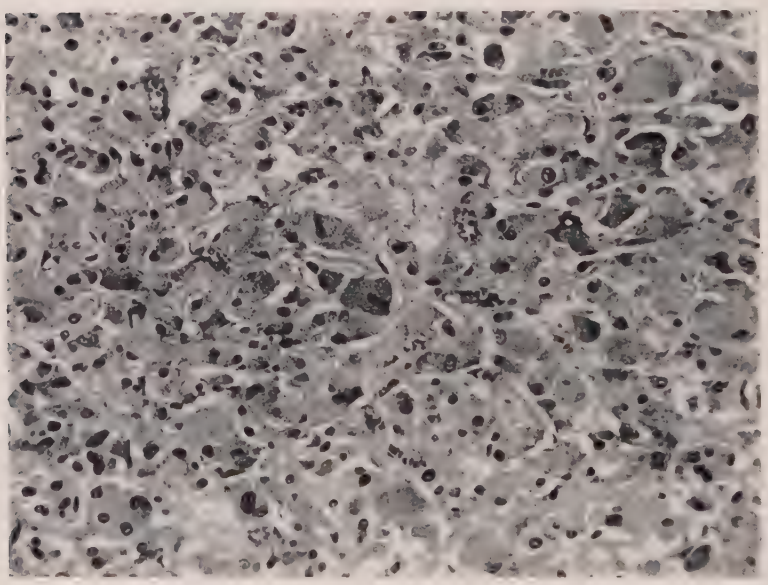

Fig. 895.—Pheochromocytoma of adrenal medulla.

Pheochromocytoma (Chromaffinoma).—Pheochromocytoma is a rare tumor, usually benign, composed of a differentiated mature type of cell resembling those which compose the adrenal medulla. The tissue of this tumor, like

other chromaffin tissue stains brown when fixed in bichromate solution. The reaction is due to the presence of a reducing substance, probably Adrenalin or noradrenalin.

Chromaffinomas usually occur in early adult life or middle age. In a small number of cases the tumors are bilateral.[74] They are sometimes associated with neurofibromatosis.[103] Chromaffinomas which arise in extra-adrenal chromaffin tissue have been referred to as paragangliomas.

Fig. 896. Small neurofibroma of adrenal medulla.

Pheochromocytomas are usually small tumors less than 10 cm. in diameter, circumscribed, yellowish-brown in color, and frequently with cystic, necrotic, or hemorrhagic areas. The tumor cells are large, irregular, or polyhedral. Some of the tumor cells are stained brown after fixation in bichromate. A vascular fine connective tissue stroma surrounds groups of cells. Epinephrine and norepinephrine, the latter having mainly the effects of increasing the blood pressure and peripheral vascular resistance rather than the metabolic effects of epinephrine, have been found in these tumors.[12]

The clinical syndrome associated with pheochromocytoma is characterized by paroxysmal attacks of hypertension, palpitation, anxiety, headache and precordial pain, vomiting, hyperglycemia, pallor, and other vasomotor effects. The picture is similar to that produced by a large injection of epinephrine and/or norepinephrine, and variations in the clinical picture are thought to be due to differences in the proportions of the two hormones in the tumor or in rate of secretion.[12] In some cases the hypertension is sustained, rather than occurring in episodes, and in others, glycosuria and hypermetabolism may be persistent, with intermittent hypertension.[12] As time progresses, the attacks increase in frequency and severity. Surgical removal of the tumor relieves the symptoms. The diagnostic use of adrenergic blocking agents, such as benzodioxane (933F), Dibenamine, and imidazoline derivatives may be helpful in distinguishing this syndrome from essential hypertension.[12]

THE RELATION OF THE ADRENALS TO HYPERTENSION

The known association with hypertension of tumors of both the adrenal cortex (in Cushing's syndrome) and adrenal medulla (pheochromocytoma)[115] has led to considerable investigation of the gland as to its possible role in the still unsolved problem of essential hypertension. The subject has been reviewed in detail by Selye[107] in his discussion of the "adaptation syndrome" and by Corcoran.[108] A nodular hyperplasia of the adrenal cortex has been

claimed by some to be regularly associated with hypertension,[110] but the association has been denied by others.[111] Similarly a high lipid and cholesterol content of the adrenal has been noted in hypertensive individuals. The urinary excretion of 17-ketosteroids appears to be lower in hypertensive than in normal individuals.[112] Desoxycorticosterone acetate has been found to bring about a gradual increase of blood pressure both in patients with Addison's disease and those without adrenal lesions.[114] The medulla of the gland also has been incriminated, and evidence of increased activity of the medulla in hypertensive individuals has been claimed.[91] In patients with pheochromocytoma and sustained hypertension, it is possible that the adrenal cortex has been secondarily stimulated by the effects of medullary secretions on the pituitary.[108] Goldzieher[3] has emphasized the finding of hyperplasia of the medulla in hypertensive disease, and also the muscular hypertrophy of adrenal veins. Experimentally, a prompt and sustained hypertension has been produced in dogs by unilateral subtotal ligation of periadrenal blood vessels and tissue.[113] The bulk of evidence would certainly suggest that the adrenal glands have some part, and perhaps an important one, in the pathogenesis of hypertensive disease.

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Chapter 39

THE FEMALE GENITALIA

WALTER SCHILLER

The important pathologic conditions of the female genitalia are inflammations, endocrine disturbances, tumors, and cysts. Many gynecologic diseases are closely related in both functional and morphologic aspects to hormonal imbalance. The endocrine factors important in gynecologic pathology are the pituitary gonadotropic principles and the ovarian and placental hormones.

Hormonal Relationships

Pituitary Gonadotropic Hormones.—There are two pituitary principles which act on the ovaries: (1) a follicle-stimulating hormone (prolan A), which controls maturation of the ovarian follicles, and hence in turn the production of follicular hormone (estrogen); and (2) a luteinizing hormone (prolan B) which controls luteinization of the ruptured follicle, and hence in turn the production of the luteal hormone (progesterone). The nature and chemical structure of these pituitary principles are still unknown. Gonadotropic hormones act on the uterus, vagina, etc., only indirectly through their ovarian stimulation. After castration or the menopause, they have no action on the uterus and vagina. Gonadotropic hormones in general are not specific for the sex.

Ovarian Hormones.—The two ovarian hormones which normally are controlled in this fashion by the pituitary are of known chemical nature and structure, and they exert pronounced effects on the endometrium, vagina, and other tissues. Menstrual changes and periodicity are dependent on these hormones.

Maturing ovarian follicles produce a hormone, estrogen *(theelin)*. This has been isolated in a number of closely related forms, all characterized by the ability to produce estrus (heat) in castrated animals. Various names given to these estrogens are estradiol, estrone, and estriol. Certain estrogenic substances can be derived synthetically (e.g., stilbestrol). Although stilbestrol has a different chemical structure from theelin, its biologic action is identical. The basic chemical structure of estrogens is the phenanthrene ring system. Thus there is a chemical structural resemblance to certain naturally occurring sterols and to some potent carcinogenic materials, a relationship which has caused much interesting speculation.

Estrogen, formed by the mature ovarian follicle, is a sexual growth-stimulating substance which acts especially on the uterus and vagina. It brings about the proliferative endometrial growth characteristic of the first half of the menstrual cycle. In addition, it controls the rhythmic activity of the uterine musculature, causes cornification of the vaginal epithelium, and growth of the duct system of the breast. At puberty, estrogen is responsible for the appearance of the various secondary sexual characteristics. Estrogen is not specific for the female, but it is also produced, circulated, and excreted by the male organism. It is also produced by plants and, for instance, is present in the roots of turnips. It probably is a general growth-stimulating hormone, and as such is produced in large quantities during pregnancy to support growth of the embryo. Progesterone, on the other hand, is specific for the female sex.

The ovarian follicle ruptures about the middle of the menstrual cycle and then forms the corpus luteum. This luteinized follicle produces not only estrogen, but also a new and characteristic hormone, *progesterone.* In animals the corpus luteum contains only progesterone. This latter substance also is a sterol, of known chemical formula, and has been isolated, crystallized, and synthesized. It has a close structural relationship to the male sex hormone, testosterone.

Progesterone also affects the endometrium, vagina, and breast. In the endometrium it brings about a secretory phase. The endometrium remains thick, but the glands become very tortuous in outline and secretory in function. The stromal cells of the endometrium begin a decidua-like change. These changes are in preparation to receive the fertilized ovum. If conception fails to occur, the corpus luteum atrophies, the endometrium breaks down, and menstruation occurs. However, if pregnancy occurs, the corpus luteum continues to develop and produce progesterone, its effects being important in maintenance of the pregnancy in its early phases.

In addition to its effect on the endometrium, progesterone reduces or even inhibits contractility of the uterus, suppresses ovulation and menstruation, causes a proliferative phase in vaginal epithelium and a lobular proliferation of the breast.

Hormones of Pregnancy.—During pregnancy chorionic gonadotropic hormones are produced in large quantities and are found in the urine (urinary prolan). The biologic pregnancy tests (Aschheim-Zondek, Friedman) are based on demonstration of such hormones in the urine. These substances are "anterior pituitary-like" (A.P.L.) in their action. The placenta also seems capable of producing progesterone, an action important in maintenance of later stages of pregnancy.

OVARIES

Development and Structure

The ovaries develop from the Wolffian body, along with other portions of the reproductive and urinary system. The ovary and testis have a similar anlage. In the early undifferentiated ovary, medullary cords form, similar to those of the early testis which later form the seminiferous tubules, but from the beginning each single cell of the embryo, and consequently each cell of the growing gonad, is through chromosomes either male or female. Enormous numbers of primordial germ cells develop as the ovary differentiates. The cortex of the ovary is composed of these primordial germ cells and a dense connective tissue stroma. The so-called epithelial cells of the follicles (i.e., granulosa cells) and the stromal cells (including theca cells, which are specialized stromal cells around follicles) have a common mesodermal origin. Their close relationship is evidenced in certain tumors (e.g., combined granulosa cell and theca-cell tumors). The so-called primordial follicles consist of a central ovum surrounded by a layer of low cuboidal or flat cells, the prospective granulosa cells. As the follicle matures and enlarges under the influence of the pituitary follicle-stimulating hormone, the granulosa becomes more cuboidal and several layers thick. A central cavity appears, the ovum being at one pole, surrounded by a pile of granulosal cells, the discus proligerus. Around the follicle is a specialized layer of connective tissue cells, the theca interna. *Call-Exner bodies* are small, rounded, clear glandlike areas found in the granulosal layers, and similar structures appear in tumors composed of granulosal cells. About the middle of the intermenstrual interval the follicle ruptures, after having reached a diameter of about 8 mm., and the ovum is extruded. The ruptured follicle develops into a corpus luteum under the influence of the luteinizing hormone of the pituitary.

At the time when the mature follicle ruptures, many other follicles are approaching maturity. Their further development is stopped by the hormone of the corpus luteum, and they undergo regression. These atretic follicles may form cysts, and in some cases the cysts reach a considerable size. Usually the cystic stage is promptly followed by fibrosis, forming a small hyaline node, the corpus candicans.

In development of the corpus luteum following follicular rupture, the granulosa is vascularized, and the cells become large and polyhedral, with abundant cytoplasm. They are then called granulosa lutein cells and form a bright yellow zone. Hemorrhage into the follicular lumen usually occurs in the premenstrual phase, and in some cases is abundant. The mature corpus luteum is much larger than the follicle, measuring up to 10 or 15 mm. in diameter.

If fertilization does not occur, regression of the corpus luteum begins shortly before menstruation. Fatty change of the lutein cells is followed by atrophy, fibrosis, and hyalinization. This results in a convoluted hyalinized mass, the corpus candicans, which slowly regresses further and may disappear. Occasionally the corpus luteum fails to regress but develops into a cyst *(corpus luteum cyst)*. Also, if pregnancy occurs, the corpus luteum does not regress but becomes even larger and more prominent.

Surface Epithelium.—At some time the surface epithelium of the ovary has been credited with numerous important functions, such as production of germinal cells, germinal cords, and even the rete ovarii. While formation of ova in the adult appears to occur in certain mammals, normal function of the surface epithelium appears to be limited in the human to production of the secondary germinal cords. Pathologic changes produced by the surface epithelium include the formation of small inclusion cysts by infolding and downgrowth, which in turn may give rise to cystomas, endometriomas, or Brenner tumors.

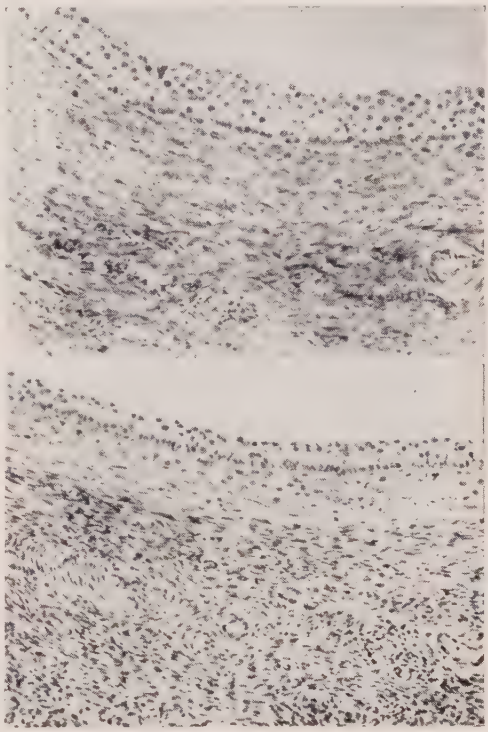

Fig. 897.—Theca. Upper: Normal, inactive, with border between ovarian stroma and theca. Lower: Luteinized theca during pregnancy showing sharp demarcation of ovarian stroma and theca.

Interstitial Tissue of the Ovary.—Two different functional systems have been distinguished in the ovary, (1) the generative system consisting of granulosa cells and ova (epithelial), and (2) the interstitial system, of connective tissue character, and consisting of unspecific stroma and theca cells. Unspecific stroma, theca-granulosa and surface epithelium originate from the same matrix, from celomatous tissue. The interstitial tissue plays an important role in the production of hormones. Because of the hormone production by luteinized

theca cells, the term "interstitial gland" of the ovary has been used. This tissue reaches its maximum activity physiologically during pregnancy, and pathologically in cases of hydatidiform mole and chorionepithelioma. The endocrine function of the ovary before puberty is carried out by the luteinized theca of atretic follicles (i.e., by the "interstitial gland"), and not by the granulosa.

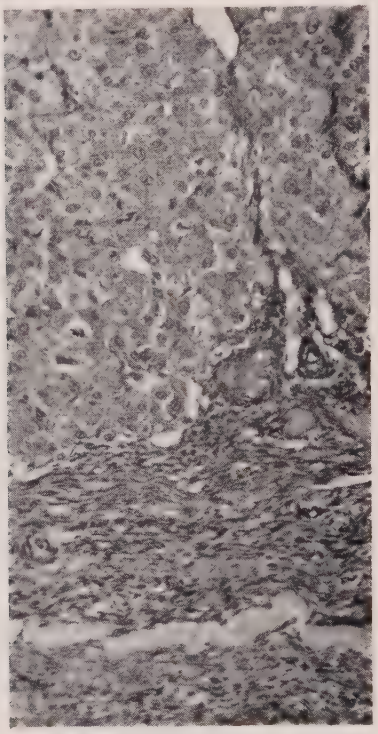

Fig. 898.—Corpus luteum of pregnancy (full term). The granulosa, at the top, composed of large fat-containing epithelioid cells, and the theca, below, almost completely "deluteinized."

Leydig Cells; Hilum Cells.—These cells have been a problem to investigators for decades, but recently a solution has been found. In 1850, Leydig described interstitial cells producing and storing lipoids in the testicles. Later the problem of Leydig cells became associated with the problem of cells located in the hilum of normal ovaries which were discovered by Kohn of Prague. They are large lipoid-producing and lipoid-storing cells found close to sympathetic nerves, a high percentage of which demonstrated a chromaffin character. Berger proved that the presence of these sympathicotropic or hilum cells is not limited to a certain age. Reinke demonstrated crystalloids in Leydig cells, and similar crystalloids are present in virilizing ovarian hilum cell tumors. A functional identity is indicated by Berger's finding of a virilizing tumor composed of hilum cells with regression after surgery. It can be accepted that the same cells are a constituent of the male and the female gonad, being called Leydig cells in the testis, and hilum cells or sympathicotropic cells in the ovary, and producing virilizing changes in tumors and hyperplasia.

The **Sertoli cells** of the testicle were suspected to be of female character and endocrine activity. This assumption was proved right when testicular tumors composed of Sertoli cells were found with a feminizing effect on the bearer with regression after surgery. Thus it is as follows:

Leydig cells of the testis Hilum cells of the ovary	virilizing
Sertoli cells of testis Granulosa cells of ovary	feminizing

Oophoritis

Inflammation of the ovary, or oophoritis, occurs in many cases of mumps, and occasionally follows measles or scarlet fever. Reversible degenerative changes occur in the granulosa or in the theca, and may be accompanied by hyperemia, edema, and leukocytic infiltration of the stroma.

In oophoritis due to bacterial invasion, the organisms reach the ovary from an infective focus elsewhere in the body

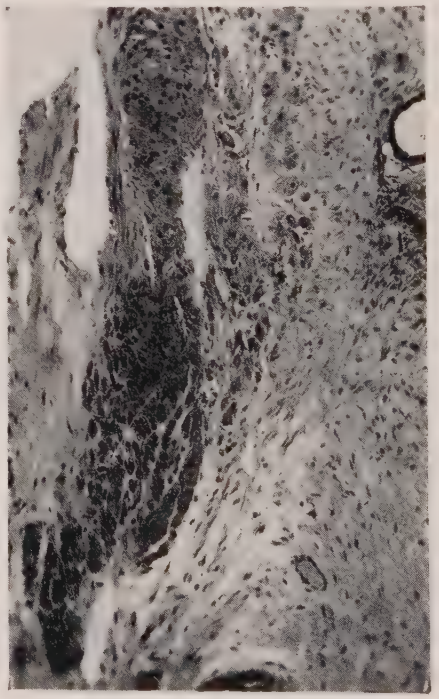

Fig. 899.—Hilum (sympathicotropic) cells in the ovary of an adult woman. The cells are polyhedral and have a dark protoplasm with brown granules.

either by way of the blood stream or by direct spread from an adjacent organ. Hematogenous infection of the ovary is uncommon, although in any case of generalized pyemia, abscesses may develop in the ovary as well as in other organs such as the liver, lungs, kidneys, etc.

Infection of an ovary from adjacent tissues may occur from the uterine tube, uterus, or peritoneum. Gonococcal salpingitis frequently spreads to the peritoneum around the ovary and causes a perioophoritis. In some cases the infection spreads to the ovarian parenchyma. Ruptured follicles present a favored portal of entry for the bacteria. Infected follicles or corpora lutea soon are transformed into abscesses. Their origin is recognizable only when some remnant of the former lining remains. Mixed infections, in which staphylococci or streptococci as well as gonococci are present, tend to cause a greater and more persistent involvement of the ovary.

Spread of bacteria to the ovary from the uterus occurs mainly in cases of puerperal endometritis or infected endometritis following an abortion. Spread occurs to an ovary by veins or lymphatics, the infection starting at the hilum or in deeper parts of the ovary and spreading outward to more superficial strata. Abscesses in the ovary in such cases bear no constant relation to follicle or corpus luteum.

Microscopically, acute oophoritis shows hyperemia, edema, and diffuse or focal inflammatory infiltration by neutrophilic leukocytes and plasma cells, with focal suppuration or abscesses.

Perioophoritis and subsequently oophoritis may develop as a special localization of a general peritonitis. The right ovary is exposed to local peritonitis arising from acute appendicitis, and the left ovary from perforating diverticulitis of the colon.

Mild oophoritis may subside without leaving persistent structural or functional damage of the organ. In more severe or chronic cases adhesions about the ovary are common. Probably the formation of adhesions or membranes on the ovarian surface in oophoritis is not a common cause of sterility by mechanically preventing rupture of follicles. But oophoritis seems to interfere with ripening of follicles, which undergo cystic changes. The ovary may contain numerous small cysts, 5 to 15 mm. in diameter, lined by a thin layer of granulosa. Such small cystic degeneration is probably caused more commonly by disturbances of endocrine balance or other causes than by chronic oophoritis.

Cysts and Tumors of the Ovary

The ovary is not only a frequent site of tumor formation, but the neoplasms are of great variety and may contain tissues not among the normal components of the ovary. Many attempts have been made at classification or grouping of ovarian tumors, and no classification is universally used or accepted. Some groupings have been on a clinical basis, and others on a purely histologic basis. The classification used here, on a basis of histogenesis and morphology, is presented with the realization that the origin and histogenesis of some ovarian tumors are unknown or in dispute. Tumors of doubtful origin are grouped according to the most probable theory, and reclassification may be necessary with the acquisition of new knowledge.

Classification

Cysts

1. Follicular cyst
2. Corpus luteum cyst
3. Luteinized or lutein cysts (from atretic follicles)

True Tumors

A. Ovariogenic—derived from ovarian tissue
   1. Granulosa cell tumor
      a. homogeneous immature
      b. trabeculated, immature and mature
      c. homogeneous mature and folliculoid (folliculoma)
      d. luteinized (luteinoma of granulosa origin), folliculome lipidique (ovarian Sertoli cell tumor)
   2. Fibroma
      a. simple
      b. luteinized—xanthofibroma thecacellulare, theca cell tumor
   3. Lymphangioma, hemangioma, luteinoma (of other than granulosa origin)
   4. Hilum cell tumor

B. Heterotopic—derived from tissues not normally present within the ovary
   1. By pathologic differentiation
      a. from surface epithelium—prosoplasia in direction of Müllerian epithelium
         (1) serous cystoma and derivatives (tubal type of epithelium)
         (2) endometrioma (uterine type of epithelium)
         (3) pseudomucinous cystoma and variants (uterine cervical type of epithelium)

b. from mesenchymal (ovarian) core by error in sex chromosomes
   (1) arrhenoblastoma (from male-directed elements)
      —homogeneous
      —trabeculated
      —adenomatous, canalicular
   (2) disgerminoma (from neutral or germinal elements)

2. From tissues displaced
   a. in fetal life
      (1) early—teratoma
         —immature—embryoma
         —mature—dermoid
      (2) late—from tissues in vicinity of ovary
         —hypernephroma
         —mesonephroma
         —Brenner tumor (from urogenital anlage)
         —ganglioneuroma
   b. in adult life
      (1) by implantation—endometrioma
      (2) by metastasis—Krukenberg tumors, etc.

Ovarian tissues develop from mesodermal cells, the celomatous mesenchyma, and when undifferentiated and immature present mesodermal characteristics, but when mature and differentiated have an epithelial appearance. Thus tumors of immature undifferentiated granulosa cells have a sarcomatous appearance, while tumors of granulosa cells of higher maturity appear carcinomatous.

A pitfall in the estimation of malignancy of ovarian tumors lies in the misinterpretation of immature tumor tissue as malignant. Diagnosis of malignancy in ovarian tumors should be based on atypical cytologic characteristics, polymorphism, and evidence of invasion or metastasis, and not on developmental immaturity of the component tissue.

Ovarian malignancies do not appear to originate directly from normal tissues, but by a malignant transformation in a benign tumor.

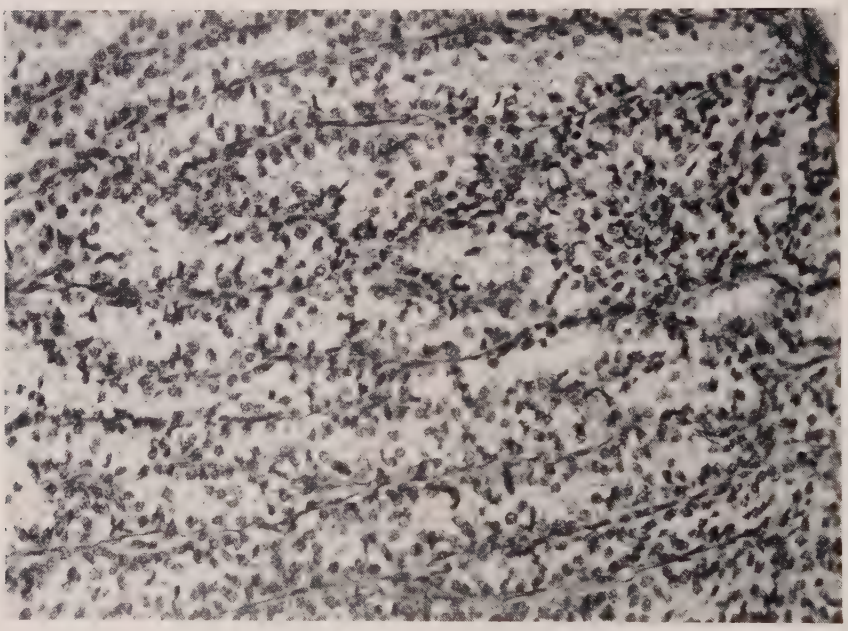

Fig. 900.—Testicular tumor classified by Teilum as Sertoli cell tumor analogous to folliculome lipidique. (Courtesy Dr. G. Teilum.)

Certain peculiarities of ovarian tumors must be kept in mind, particularly the tendency to apparent change from carcinomatous to sarcomatous character, and vice versa, in granulosa cell tumors and in arrhenoblastomas, due to erroneous interpretation, and a frequent discrepancy between a histologic appearance of malignancy and a benign clinical behavior.

Teilum uses the term "gonocytoma" for gonadal tumors of endocrine activity developing in ovary as well as testis. Having found arrhenoblastomas and mesonephromas of the testis and a testicular tumor analogous to the ovarian folliculome lipidique, missing links in the classification of gonadal tumors, he suggested a grouping into a seminoma series and an androblastoma series.

Thus, the folliculoma lipidique Lecène (page 1054) which could not be placed in any previous classification finds an appropriate place in Teilum's table as a feminizing Sertoli cell tumor.

Some ovarian carcinomas are undifferentiated, and have lost all cellular or structural characteristics of their matrix. Since the origin of such carcinomas cannot be determined, they cannot be fitted into a histogenetic classification, and must be grouped simply as undifferentiated carcinomas.

the absence of proliferative activity of their lining cells so that they never become papillomatous or multilocular, the epithelium rather tending to become flattened or lost from pressure of increased distention; in the absence of any tendency to undergo malignant change; in their size, rarely becoming larger than 5 to 10 cm. in diameter; and in the fact that they may carry on endocrine secretion and disturb normal endocrine balance. When the

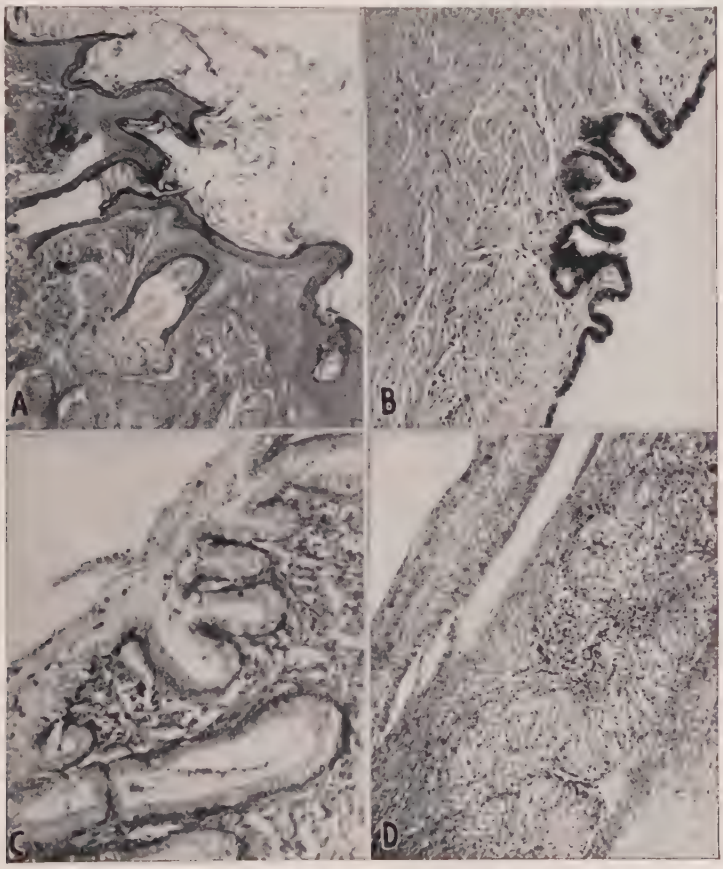

Fig. 901.—Ovarian cysts showing characteristic linings. *A*, Dermoid cyst, with keratinizing squamous epithelium and sebaceous glands; *B*, serous cystoma, lined by dark-staining cuboidal cells; *C*, pseudomucinous cystadenoma, lined by pale columnar cells with basal nuclei; *D*, corpus luteum cyst, lined by a thick layer of large luteal cells. (From Berman, Synopsis of the Principles of Surgery, The C. V. Mosby Co.)

Cysts of the Ovary

Ovarian cysts develop by cystic distention of follicles, corpora lutea, or luteinized corpora atretica (called theca lutein or, by abbreviation, lutein cysts). Cysts differ from cystomas in their origin by pathologic dilatation of a physiologic cavity due to increase of retained fluid; in

epithelial lining becomes destroyed, serous fluid content tends to be absorbed by the denuded wall, the cavity is narrowed, collapses, and the cyst disappears. Thus, cysts have a limited growth, and eventually may heal spontaneously.

Follicular Cysts.—Follicular cysts may occur either as a single large cyst in one

ovary, or as multiple smaller cysts, usually bilateral. The solitary cyst, which may reach the size of a large walnut, appears to originate from a mature follicle which, failing to rupture at ovulation, persists and grows larger. The lining consists of stretched and compressed granulosa cells attached to a wall consisting of a thinned regressing theca. With increased size and persistence for several weeks, the granulosa lining becomes partially or completely shed and the theca undergo fibrosis or replacement by nonspecific connective tissue. At this stage the nature of such cysts may be recognizable only if some remnants of granulosa or theca can be found in the wall. Differentiation from cystomas is usually readily made, however, by the absence of a typical epithelial lining. The fluid in follicular cysts often, but not invariably, contains estrogenic hormones.

Multiple small follicles, 5 to 15 mm. in diameter, lined by a thin layer of granulosa and theca, are usually bilateral and located at or bulging over the ovarian surface. They may or may not contain a flattened cumulus and degenerated ovum. These cysts are not derived from mature follicles, but are immature follicles dilated by some hormonal or inflammatory stimulation. Such small cystic degeneration of the ovary is to be distinguished from multiple inclusion cysts resulting from infolding and downgrowth of surface epithelium. The latter have a nonspecific connective tissue wall lined by a single row of cuboidal or low columnar epithelium, lack hormones in their fluid content, and have been supposed to undergo neoplastic transformation into cystomas. They are called "serosa cysts," "surface cysts," or by the name of the first investigator, "Walthard cysts."

Corpus Luteum Cysts.—Corpus luteum cysts, which develop from cystic change of a corpus luteum of either menstruation or pregnancy, are usually solitary and unilateral. They are usually less than 6 cm. in diameter, but may reach the size of a small orange. The wall consists of a thin, vascularized and luteinized granulosa which grossly appears as a yellow coat around the cavity. In small cysts the wall under this lining may still show the character of theca. The fluid content is often mixed with blood, and appears brownish and turbid. It usually contains estrogenic hormone, but a progesterone content is doubtful. Hemorrhage into the cyst cavity may lead to rupture into the peritoneum, an event often misdiagnosed as a ruptured tubal ectopic pregnancy.

Lutein Cysts.—Luteinization of the theca of atretic follicles during pregnancy is caused by the presence of large quantities of gonadotropic luteinizing hormone (prolan B). This is produced early in pregnancy by the pituitary and later by the placenta. In pathologic proliferation of the chorion, as occurs in hydatidiform mole and chorionepithelioma, this hormone production is increased to many times normal amount, and provokes a proliferation of the theca and transformation of corpora atretica into nodes with a diameter of several centimeters. There is no actual cystic distention by increased fluid, although hemorrhage usually distends the cavities. The walls of these lutein cysts frequently fuse. The ovaries become enlarged to several times normal size, present firm masses with a lobulated surface, and on cut surface show a yellowish-gray homogeneous parenchyma, interspersed with small blood-containing cavities a few millimeters in diameter. Lutein cysts or masses develop in 15 to 40 per cent of cases of hydatidiform mole and chorionepithelioma, but almost never occur in the absence of such abnormalities of the placenta. Involution occurs within two or three months after removal of the diseased placenta.

Chocolate Cysts.—This term is used for ovarian cystic cavities filled with smeary, soft masses of chocolate brown color. The term is a purely descriptive one and not a diagnosis. It is not a pathologic entity. Three different changes may give origin to chocolate cysts: (1) endometriosis developing at the surface of the ovary or in the albuginea; (2) a cystic corpus luteum; (3) a cystic follicle after luteinization of the granulosa. This change is microscopically easy to differentiate from a normal corpus luteum. In the luteinized follicle which generally originates from a mature follicle ready to burst for ovulation but failing to do so, the luteinized granulosa does not show the folds and frills nor the triangles of luteinized theca between the folds of the granulosa as always seen in a corpus luteum.

Cystomas of the Ovary

Cystomas of the ovary are true neoplasms; the newly formed tissue of the epithelial lining may tend to proliferate toward the lumen with papillomatous formations or toward the wall to produce an adenocystic character and additional cavities. Such new cavities formed by the epithelial projections causes the cystoma to become multilocular. Cystomas are not limited in their growth as are re-

tention cysts, but may reach a giant size. The epithelium of cystomas does not produce hormones, so that they do not interfere with endocrine balance except by their destruction of adjacent ovarian tissue. Malignant change often occurs in cystomas. Three distinct types of cystomas occur, usually referred to as pseudomucinous, serous, and endometriomatous, and differing in their type of epithelial lining and fluid content.

Pseudomucinous Cystoma.—Pseudomucinous cystomas have been estimated to compose more than half of ovarian tumors, and about 70 per cent of ovarian cystomas. They are lined by high columnar epithelium with basal nuclei and pale or clear cytoplasm, similar to the epithelium of the uterine cervix or of the large intestine. Pseudoxanthoma cells are sometimes present beneath the columnar epithelium, a change not found in serous cystomas. The secreted fluid is thick, mucinous, translucent and colorless or gray and opaque, and contains a mixture of glycoproteins. The cystoma is unilateral in about 80 per cent of cases, multilocular in 30 per cent, and papillomatous in 20 per cent.

There are two types of pseudomucinous cystomas: (1) of teratomatous origin, being the intestinal part of a mixed teratoma; (2) of Müllerian duct origin. The gross appearance is similar in both, and differentiation is possible only microscopically by special staining. The intestinal character of the first group is proved by the presence of argentaffin cells which are present in the intestinal mucosa, but are never found in the cervical epithelium and its derivatives. Thus, the pseudomucinous cystomas which have no argentaffin cells among their epithelium can be classified as of Müllerian origin.

Serous Cystoma.—Serous cystomas are lined by two types of columnar epithelium: high columnar ciliated cells and cylindrical cells with a dome-shaped outer border which secrete the serous fluid. The combination of ciliated and serous columnar cells and the occasional presence of intercalary peg cells and interepithelial cells, duplicates the composition of fallopian tubal epithelium, and has led to the term "endosalpingioma" for these cystomas. Serous cystomas compose 25 per cent of ovarian cystomas. They occur mainly during the reproductive age, and are usually unilateral. Most serous cystomas are multilocular, but with fewer, less deformed cavities and thicker septa than in pseudomucinous cystomas. Papillomatous growth is more frequent than with pseudomucinous cystomas, often has a multicentric origin, and forms low, whitish, brittle projections from the lining. Fibrous stromal thickening of the wall and septa often occurs, and may be of marked degree, a change not seen in pseudomucinous cystomas.

Endometriomatous Cystoma.—See page 1079.

Histogenesis of Ovarian Cystomas.—The theory of origin of ovarian cystomas from the surface epithelium of the ovary is supported by a number of observations. The striking similarity of the epithelial lining of the serous cystomas with the epithelium of the uterine tube, and of the epithelium of the pseudomucinous cystomas with the epithelium of the uterine cervix, tends to relate them as derivatives of the Müllerian duct. Latent Müllerian potentialities of surface epithelium may become awakened, and development proceed to formation of epithelium of tubal type (serous cystoma), endometrial type (ovarian endometrioma), or cervical type (pseudomucinous cystoma). This does not preclude the probability that some cases of ovarian endometriosis may be due to endometrial implantation following retrograde menstruation, nor that some pseudomucinous cystomas may result from exclusive proliferation of intestinal components of an ovarian teratoma.

Malignant Change in Ovarian Cystomas.—Malignant change is more frequent in papillary serous cystomas than in pseudomucinous or in simple serous cystomas. Malignancy in a papillary cystoma may be difficult or impossible to discern grossly. A malignant change is unlikely to have occurred if a hydropic change of the tips of the papillae can be seen, or if the papillary projections cover only a portion of the surface. Microscopically, malignant change is characterized by proliferation of the epithelial lining to several rows of cells, from which may originate irregular projections consisting only of epithelial cells and lacking a stromal core. Epithelial growth may form solid masses in the folds between papillary projections. Carcinomatous epithelial cells show variability in size, shape,

and staining characteristics. Coordination in the development of degenerative changes in epithelium and stroma may no longer be present.

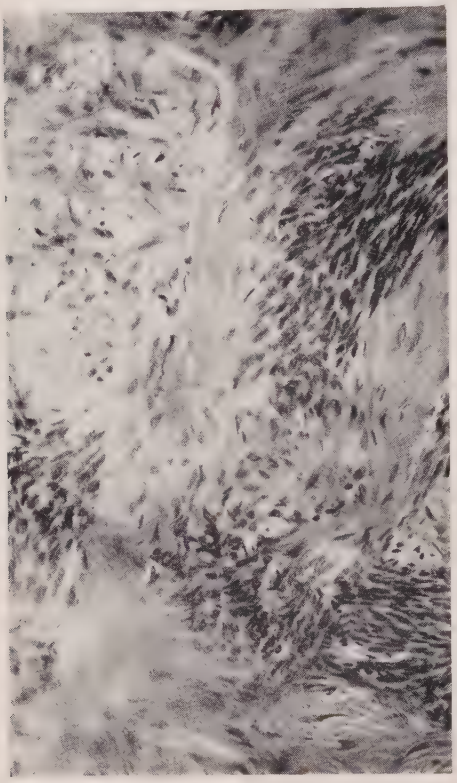

Fig. 902.—Fibroma of the ovary. Note the alternating cellular and hyalinized bundles.

Peritoneal implants of benign papillomas, particularly of the serous type, may undergo spontaneous involution. Peritoneal implantation of papillary serous cystadenocarcinomas have been observed to regress following removal of the primary tumor, both spontaneously and following irradiation therapy.

Surface Papilloma.—In some papillomas there is a tendency for proliferation of epithelium on the outer surface as well as in the cyst cavity. Hence it is erroneous to assume that every case showing surface papillary growth is due to carcinomatous penetration of papillary epithelium from inside the cyst. In some cases a few small, low, papillomatous projections may be found on the surface of an ovary which contains no cystoma.

Parvilocular Cystoma.—A rare variety of cystoma is characterized by only very small cavities, embedded in and separated by a dense fibrous stroma. The microscopic cysts are lined by high columnar cells producing a thin mucinous fluid. Papillomatous proliferation of the epithelium may occur and be followed by a malignant change.

Peritoneal Pseudomyxoma.—Peritoneal implantation and spread of a ruptured pseudomucinous cystoma with production of large quantities of mucinous secretion has to be differentiated from a similar change called "pseudomyxoma," which originates not only from the ovary but also from the appendix, and consequently is also encountered in males. The former secretion is a thick fluid, whereas in "pseudomyxoma" the secretion is jellylike and cannot be poured or filtered. The low columnar mucinous epithelium is not malignant, does not invade but only proliferates and expands, and has a tendency to be shed off and dissolve in its own secretion.

Fibroma of the Ovary

Fibromas account for about 2 to 5 per cent of ovarian tumors, most cases occurring between 40 and 60 years of age. Fibromas are not known to originate before puberty. They form very firm solid tumors, most of which are of small size, only a few centimeters in diameter, although giant examples have been reported. They may be composed of the nonspecific supporting connective tissue of the ovary, or of the more specific structural type of connective tissue which forms the tunica albuginea of the outer cortex of the ovary. Fibromas are quite often multiple either in one ovary or bilaterally, and may be found with cystomas. They have a dense fibrous structure, with only moderate vascularization. Hyalinization, edema, and cystic degeneration are quite common.

Clinical symptoms and signs produced are due mainly to the firm consistency of the tumor and depend on the tumor's size and consistency. No hormone production or endocrine disturbance occurs. Large ovarian fibromas become mobile by stretching the ovarian ligament and may cause pain or disturbing subjective sensations by pressure on neighboring organs. Edematous fibromas may be associated with ascites, and sometimes with hydrothorax (Meigs' syndrome). The ascitic fluid arises by transudation from the tumor itself, and not from the peritoneum by mechanical irritation. The pleural fluid apparently is derived from the ascitic fluid by transmission through diaphragmatic lymph channels, blockage of which has been shown to prevent development of hydrothorax.

Xanthofibroma of the Ovary

Theca cell tumor or xanthofibroma thecacellulare is an ovarian fibroma composed of cells with the potentialities of theca cells and which may become lutein-

ized. Such tumors may produce estrogenic substances and so produce changes of hyperestrinism similar to those found with granulosa cell tumors, i.e., endometrial hyperplasia with amenorrhea and subsequent hemorrhage during reproductive years or irregular hemorrhages after the menopause, and enlargement of the uterus and breasts. Most cases occur about the menopause or in the early postmenopausal period, and only rarely in young women. Ascites and hydrothorax (Meigs' syndrome) may be present. Malignant (sarcomatous) change is rare.

Theca cell tumors do not become as large as simple ovarian fibromas, and rarely exceed 12 to 15 cm. in diameter. They are usually unilateral. They are similar to fibromas on gross appearance except for a yellowish color due to a lipoid content. Microscopically, they are composed of spindle-shaped cells, the appearance being similar to that of a cellular proliferating fibroma. Fat stains show the cells to be studded with fine droplets of fat and lipoid. Chemical tests show the presence of comparatively large quantities of cholesterol, cholesterol esters, phospholipids, fatty acids, and neutral fats. A high phospholipid content usually corresponds to marked estrogenic activity. Sometimes there is advanced focal hyalinization. In some areas of luteinization the cells may become round or oval and epithelioid in appearance.

Sarcoma of the Ovary

True sarcoma of the ovary is rare, forming less than 1 per cent of ovarian neoplasms. Most cases occur during the reproductive age period. It appears as a solid massive tumor, with a slightly lobulated outer surface, a thin capsule, and a pale soft cut surface. Necrosis and cystic degeneration may be present in the tumor tissue. Microscopically, it is similar to fibrosarcomas originating elsewhere, and is composed of spindle-shaped or round cells, sometimes combined with giant cells. Extension occurs by direct spread and hematogenous metastasis.

A sarcomatous component may be present in some highly malignant mixed tumors of the ovary in which tissues of mesodermal origin predominate (desmoblastoma ovarii malignum).

Granulosa Cell Tumors of the Ovary

Granulosa cell tumors form about 10 to 15 per cent of solid ovarian tumors. In 1 to 10 per cent of cases they may be bilateral. Their age incidence shows a wide range, and they may be found any time from infancy to old age. Their clinical features arise more from their production of sex hormones than from their size or consistency. Granulosa cell tumors produce estrogenic hormones, and mature, luteinized forms may produce progesterone as well. In children before puberty, granulosa cell tumors provoke precocious pubertal changes, with or without menstruation. Premature development of sex organs and secondary sexual characteristics occur. When precocious menstruation also occurs, it is probably due to an associated production of gonadotropic hormones by the pituitary. During the reproductive period of adult life, the hyperestrinism produced by a granulosa cell tumor results in enlargement of the breasts and uterus, hyperplasia of the endometrium, and periods of amenorrhea followed by hemorrhage. In the postmenopausal period granulosa cell tumors may be a cause of uterine bleeding by preventing senile involution of the endometrium.

Grossly, granulosa cell tumors vary from microscopic sizes up to giant tumors, but most are 10 to 20 cm. in diameter. They are usually rounded or oval, with a smooth or slightly lobulated surface. Those composed of immature tissues tend to be firmer. The mature types frequently present cystic cavities, which may contain clear or hemorrhagic fluid. The color of the cut surface varies from grayish-pink to grayish-white or, if luteinization is present, may be pale yellow.

Microscopically, granulosa cell tumors show great variation, but may be classed in four groups:

1. *Homogeneous immature*—solid, sarcomatous in appearance, and apparently corresponding to the mesenchymatous core of the ovary prior to formation of sex cords.
2. *Trabecular (cylindromatous)*—cords of cells, corresponding to the sex cords, first still connected with the adjacent stroma (immature type), and later sharply demarcated from it (mature type).
3. *Homogeneous mature*—solid or with cavities (folliculoid form) corresponding to the granulosa of the follicle prior to or after formation of the follicular cavity. In the folliculoid form, the so-called Call-Exner bodies may be found.

4. *Luteinoma (luteoma)*—supposed to correspond to the corpus luteum phase of development of the normal granulosa, and originating from advanced luteinization of a mature folliculoma. The origin and even the existence of this tumor are controversial.

Frequently two, or all three types of granulosa tumor tissue can be found in a single tumor, the most immature types of tissue tending to be found at the periphery.

tumor may be incorrect. There is evidence that it may be analogous to feminizing Sertoli cell tumor (see page 1046). In most cases evidence of hyperestrinism has been present, and in some there has been a pigmentation of the face and of the linea alba of the abdominal wall, a change similar to that in pregnancy and not found with any other ovarian tumor.

Relatively few granulosa cell tumors are malignant. At least 70 to 80 per

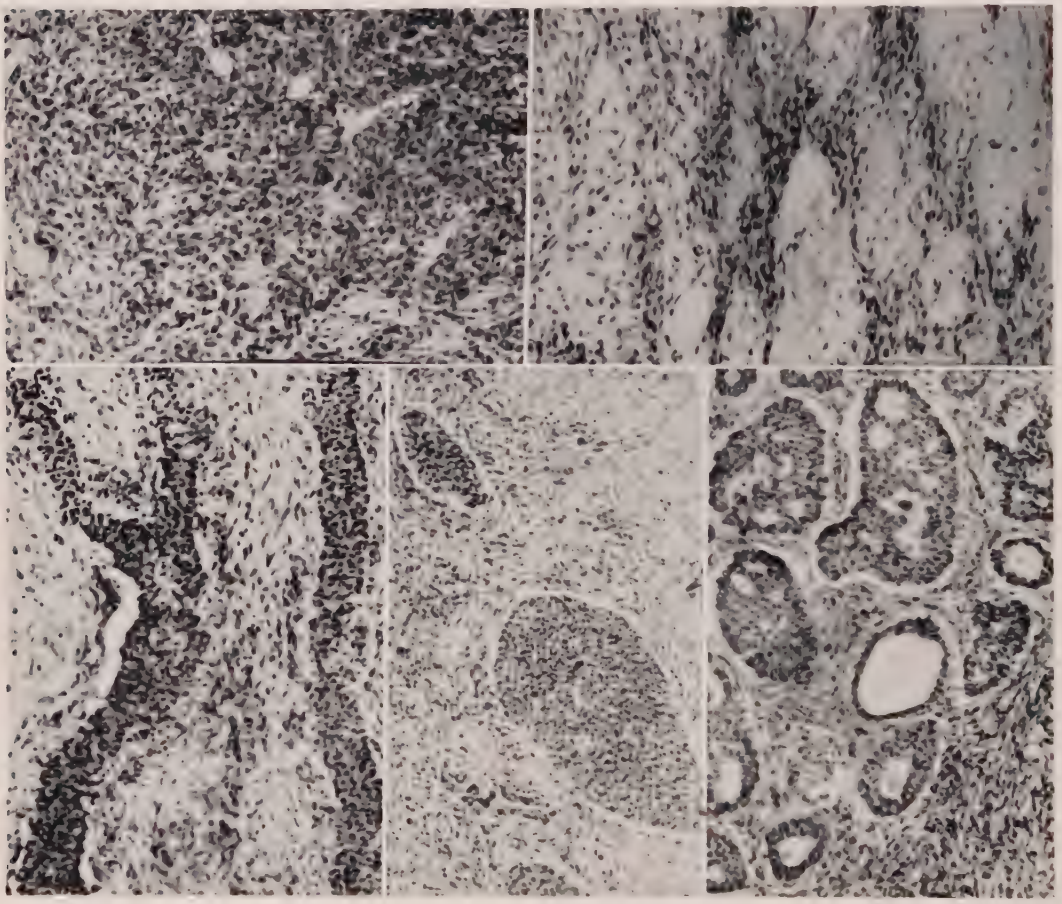

Fig. 903.—Development of granulosa cell tumor. *A*, Immature solid; *B*, immature trabecular; *C*, mature trabecular; *D*, mature solid; and *E*, mature folliculoid.

A rare special tumor is that described by Lecène (1910) and termed **"folliculoma lipidique."** In addition to parts which duplicate more or less a mature homogeneous granulosa cell tumor, there are nests and rows of high columnar cells of typical epithelial character, the cytoplasm of which is laden with doubly refractive lipoids. Such cells cannot be referred to any phase of the normal granulosa, and its classification as a form of granulosa cell

cent follow a benign course. The immaturity of some forms has been confused histologically with malignancy, and the trabecular form often simulates and may be mistaken for an invading carcinoma. Histologic identification of malignancy in a granulosa cell tumor is very difficult, as it cannot be based on

immaturity of the tissues. Some ovarian carcinomas may simulate the trabeculoid or folliculoid forms of granulosa cell tumors, and yet such features as secretion of mucin or true epithelial structure exclude a granulosa cell origin. On the other hand, some undifferentiated ovarian carcinomas may be of granulosa cell origin, but due to undifferentiation may be difficult to identify.

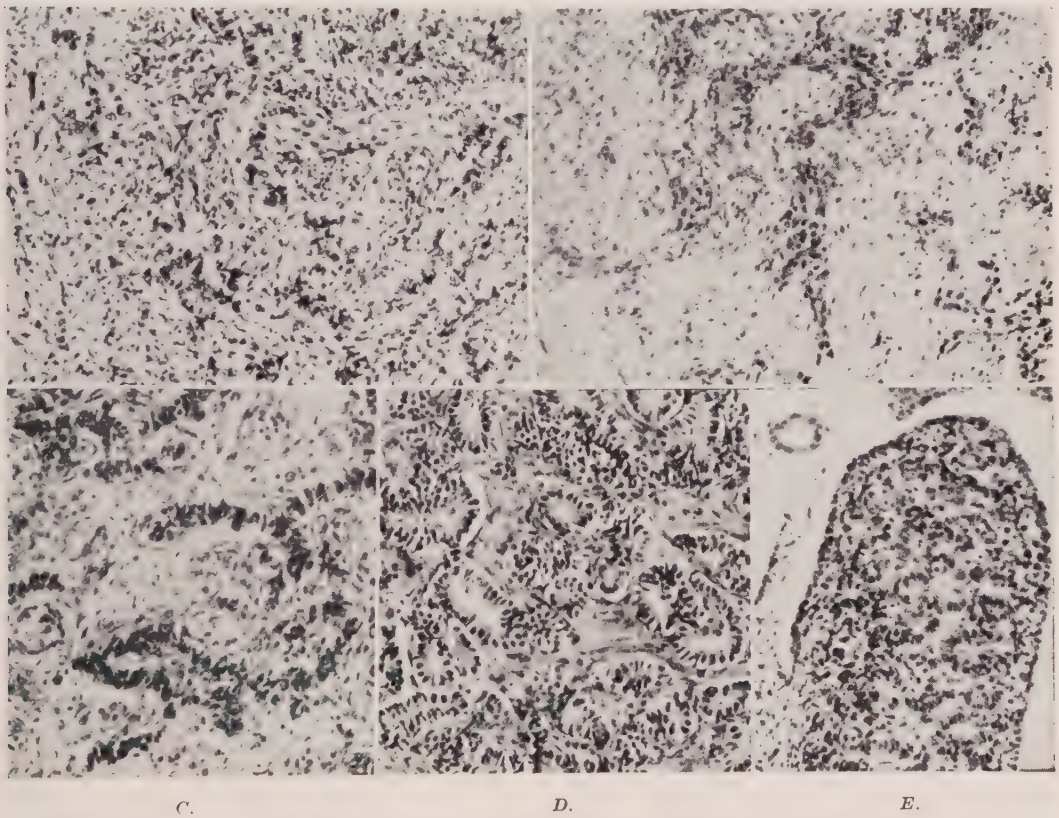

Fig. 904.—Development of arrhenoblastoma. *A*, Immature solid; *B*, immature trabecular; *C*, mature trabecular; *D*, mature canalicular; and *E*, Germinal cords of testicle, embryo, 19 mm.

Combinations of granulosa cell tumors with theca cell proliferation are frequent. These have been interpreted by some as a thecomatous change in the stroma caused by the proliferating granulosa, and by others as a combination of independent theca cell and granulosa cell neoplasms.

Arrhenoblastoma

Arrhenoblastomas are ovarian tumors which by hormone production bring about masculinizing changes, such as excessive growth of hair with a masculine distribution, enlargement of the clitoris, and changes in dimensions of the larynx associated with deepening of the voice. This masculinization, like that provoked by other ovarian tumors, is reversible. After removal of the tumor the feminine character is restored to the extent that pregnancy may occur. Local symptoms may be present with larger examples of arrhenoblastomas due to pressure. Most cases have occurred between the ages of 20 and 50 years. Malignant character is rare in an arrhenoblastoma, although histologically immature examples are easily misinterpreted as malignant. A possible origin of arrhenoblastomas has been considered to be from stromal cells which on the occasion of a mitotic division have lost one of the two female X chromosomes, thus acquiring male character, and becoming potential Sertoli cells such as are present

in the fetal testicle of the analogous phase of development.

The gross appearance of an arrhenoblastoma is similar to that of a granulosa cell tumor, so that gross distinction is usually not possible. Arrhenoblastomas usually are unilateral, and vary in size up to a diameter of 15 to 20 cm. The outer surface is smooth, sometimes slightly bosselated, and covered by a thin fibrous capsule. The cut surface is whitish-gray, and may be solid or show areas of cyst formation or necrosis and hemorrhage.

The trabecular form of arrhenoblastoma shows an irregular trabecular network of cells of epithelial appearance. The trabeculae usually consists of two or three layers of high columnar cells, with long oval nuclei, the long axis of which runs parallel with the long axis of the cells. This appearance differs from that of the trabeculae of granulosa cell tumors, which consist of several indistinct layers of rounded cells with round nuclei. Also helpful in differentiation is the presence of large polyhedral cells with lipoid-containing cytoplasm, similar to the Leydig cells of the testicle. They may be single or in groups attached to the trabeculae of the

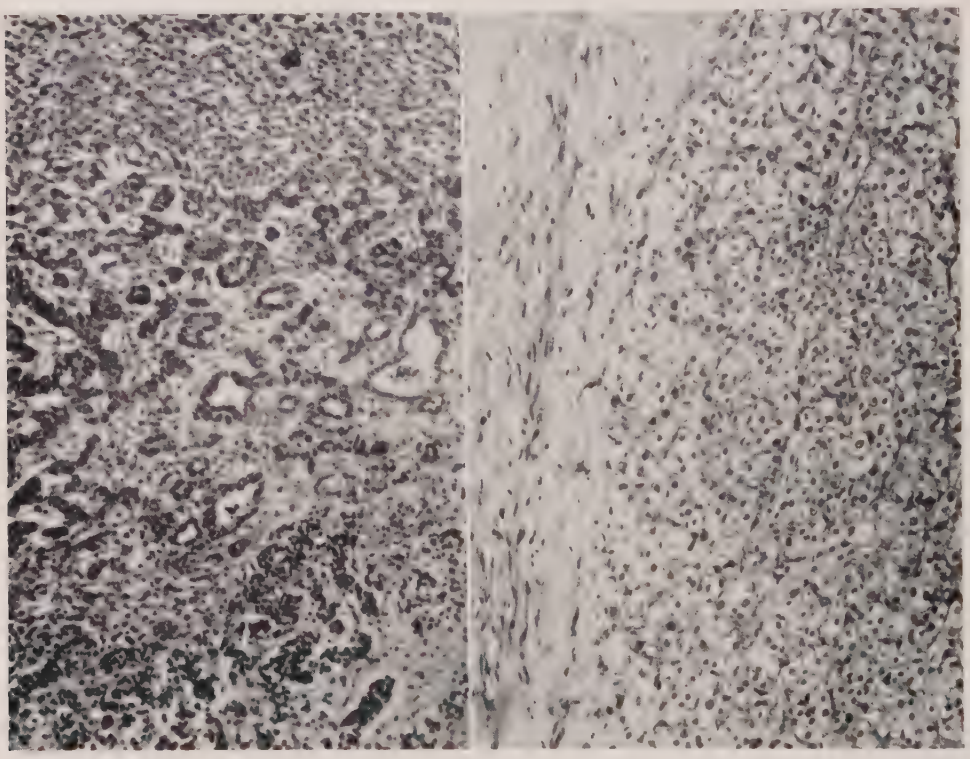

Fig. 905. Fig. 906.

Fig. 905.—Virilizing benign arrhenoblastoma. Some of the anastomosing thin trabeculae show early lumen formation. A few cells of Leydig type, with clear cytoplasm and small dark central nuclei, are present around the trabeculae.

Fig. 906.—Virilizing solid hypernephroid tumor of the ovary.

Histologically, arrhenoblastomas may be classified as of homogeneous immature, trabecular, and adenomatous (mature) types, (roughly corresponding to the three similar histologic varieties of granulosa cell tumor—immature, trabecular, and folliculoid).

Arrhenoblastomas of lowest differentiation are composed of a dense cellular tissue, similar in histologic appearance to a cellular fibroma, or a sarcoma, and very similar to the immature forms of granulosa cell tumors. This tissue has been considered analogous to the mesenchyme of the gonad prior to formation of the germinal cords.

arrhenoblastoma, but are never seen in a granulosa cell tumor. The trabecular form of arrhenoblastoma has been likened to the germinal cord phase in the development of the testicle.

In the most differentiated histologic form of arrhenoblastoma, the trabeculae have developed lumina, and are transformed into canaliculi which have been likened to testicular tubules. This similarity of glandular structure to testicular tissue led to the term "adenoma testiculare" for this tumor (Pick). The tubules of the arrhenoblastoma are devoid of germinal cells or spermatogonia, and consist only of cells corresponding to the accessory Sertoli cells.

The degree of masculinization provoked by arrhenoblastomas is greatest with the trabecular types, and may be slight or absent with either the immature or the adenomatous type. An explanation of the apparent paradox of comparatively little hormone production by the most mature histologic variety of arrhenoblastoma has been advanced by comparison with the development of the testicle. The main source of testicular male hormone is believed to be from the interstitial cells of Leydig, which are present in greatest relative number during fetal development of the testicle before the germinal cords become canalized. In arrhenoblastomas, the degree of masculinization produced appears to correspond to the number and development of cells of interstitial Leydig type, which are usually, but not invariably, most numerous in the trabecular variety.

Hypernephroid Tumors of the Ovary

Masculinization may be produced by ovarian tumors having histologic resemblance to adrenal cortical tissue or to the so-called hypernephromas of the kidney. The degree of masculinization produced may be even greater than that with arrhenoblastomas, but regresses after removal of the tumor. Grossly, the tumors may be small, firm and bright yellow in color, or larger, pale yellow, softer, and often cystic. Microscopically, they consist of large polyhedral cells with a pale vacuolated cytoplasm containing abundant lipoidal material. An adenopapillary or cystic structure similar to that of the renal hypernephroma may be present. Differentiation from lutein cell tumors is by the lack of syncytium-like connections between the cells, by the presence of glycogen in the tumor cells, by the sharp demarcation of the tumor tissue from the normal ovarian parenchyma, and by absence of theca reaction. A theory of origin from rests of adrenal cortical tissue in the hilum of the ovary receives some support from a similar masculinization produced by certain adrenal cortical tumors.

Gynandroblastoma

Gynandroblastoma is a rare ovarian tumor containing both arrhenoblastomatous and granulosa cell tumor tissue in an individual showing evidences of masculinization. Clinical evidence of overproduction of female hormone may be absent or slight, or may be manifested by hyperplasia of the endometrium.

Disgerminoma

Disgerminomas are uncommon solid ovarian tumors which occur mainly between the ages of 10 and 25 years, and are rare in later life. They do not produce or store hormones, and hence are not associated with endocrine disturbances. However, most girls with disgerminoma have a genital hypoplasia and the general habitus of infantilism. Sterility is also common with disgerminoma, even though the menstrual cycle may not be disturbed. Sexual maturity may develop and sterility be overcome following removal of a disgerminoma. Tumors which develop in hermaphroditic ("intersexual") gonads are most commonly disgerminomas. Forty to sixty per cent of disgerminomas involve both ovaries. In rare cases an extraovarian origin of disgerminoma has been in the uterus, tube, or broad ligament. About 20 to 30 per cent of disgerminomas are malignant, as judged by evidence of invasion and metastasis. Disgerminomas are highly radiosensitive. A histologically similar tumor occurs in the testicle (seminoma), mainly after the age of 40 years, and is almost always highly malignant.

Disgerminomas are solid massive tumors, varying up to 30 cm. in diameter. They may be irregular but most of them are kidney-shaped, the mesovary being attached to the concave hilum of the tumor. The capsule is thin

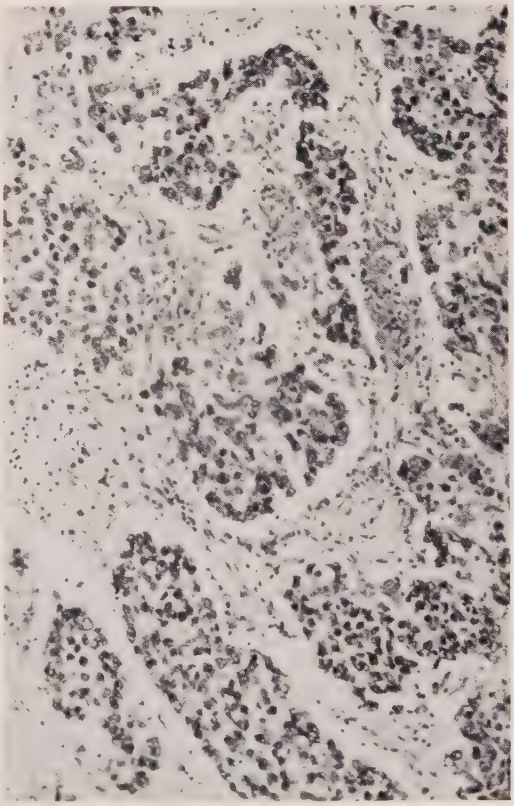

Fig. 907.—Disgerminoma of the ovary. There is alveolar structure and lymphocytic infiltration of the septa.

and the surface smooth or slightly lobulated. The cut surface shows a grayish-white soft tissue, often with irregular, sharply demarcated yellowish areas of necrosis, and sometimes cystic degeneration. They often remain about the same size over a period of several years, or grow only slowly.

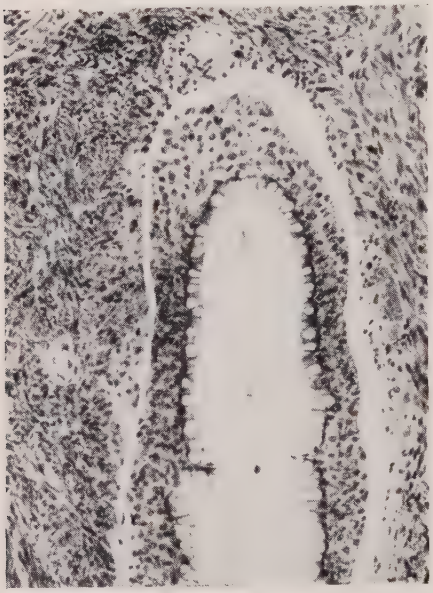

Fig. 908.—Brenner tumor of ovary, showing epithelial island with central cavity lined by columnar cells of mucinous type.

Histologically, disgerminoma is composed of strikingly uniform large round cells with large vesicular nuclei and pale homogeneous cytoplasm. These cells lie in loosely arranged groups or in thin rows separated by stromal connective tissue fibers. The connective tissue stroma may be infiltrated by lymphocytes. Pseudotubercles often are found within the tumor tissue, composed of foci of caseous necrosis, surrounded by epithelioid cells, lymphocytes, and some multinucleated giant cells. Giant cells containing small lipoid droplets may be found among tumor cells far from any necrotic focus. Actual tuberculous infection is not demonstrable in these tubercle-like foci.

Histologic diagnosis of malignancy of a disgerminoma may be difficult in the absence of invasive growth or metastasis. It must be based on polymorphism of the tumor cells, and on the presence of numerous atypical or irregular mitoses.

A theory of origin of disgerminoma is that it develops from sexually neutral elements of early phases of the embryonal gonad, either from germinal cells of abnormal neutral character, or from abnormal neutral cells of the mesenchymatous core of the gonad. Some authors have traced the origin of the disgerminoma cells to the germinal cords of the embryonal testis. This has been confusing, as the germinal cords are composed of two types of cells, potential spermatogonia and potential Sertoli cells. Evidently the correct interpretation would be from the former type, as the latter, the Sertoli-type cells, have a potential feminizing endocrine activity. Niedner, a German gynecologist, has recently suggested that the disgerminoma cells arise from the mesenchymatous core of the gonads by an abnormal process of differentiation. It is particularly in hypoplastic gonads or in hermaphroditic (intersexual) individuals that the abnormal differentiation tends to occur.

Brenner Tumor

Brenner tumors are benign ovarian tumors characterized by islands of epithelial cells in a dense fibrous stroma. They are usually seen as a small, white, firm, nodule embedded in an otherwise normal ovary, or as a small white firm node in the wall of a pseudomucinous cystadenoma, or a dermoid. A few large examples have been described, but most Brenner tumors are less than 5 cm. in diameter. The firm white cut surface is similar in appearance to that of a fibroma. Areas of hemorrhage or necrosis are unusual.

Microscopically, the Brenner tumor shows oval or rounded islands of squamous epithelium of transitional cell type, similar to the lining epithelium of the urinary bladder. The epithelial cells throughout each island are of similar size and shape, without transformation of basal cells to prickle cells, or of prickle cells to keratinizing cells. The epithelial islands are embedded in a homogeneous stroma of mature connective tissue, similar to that composing a fibroma. Frequently small cavities appear in the centers of the epithelial islands, lined by columnar epithelium of mucinous type.

Most Brenner tumors occur beyond the age of 40 years, and a majority after the menopause. They are not associated with any hormone production or endocrine disturbance. Clinical effects produced by larger tumors are similar to those from ovarian fibromas; small Brenner tumors usually escape clinical detection. The Meigs' syndrome of ascites and hydrothorax is rarely associated with large Brenner tumors. With the exception of one doubtful case, malignant change has not been reported.

There are three main theories of origin of Brenner tumors: (1) From islands of prosoplastic epithelium described by Walthard, and seen quite commonly beneath the surface epithelium of the ovary and the serosal endothelium of the tubes, broad ligament, and uterine ligaments. Against this origin is the fact that Brenner tumors are restricted to the ovary. (2) Origin from a teratoma from which all other tissue components have disappeared is suggested particularly by the frequent occurrence of Brenner tumors in the wall of dermoid cysts or pseudomucinous cystadenomas. (3) An origin from remnants of urogenital tissue in the rete of the ovary is suggested by the

type of epithelium and particularly the combination of transitional and mucinous epithelium which is not found in the normal female genital organs, but regularly occurs in the urinary tract in the mucosa of the urethral orifice.

Mesonephroma

Mesonephromas are soft, solid or semisolid tumors with a tendency to focal necrosis and liquefaction. They vary in size up to a diameter of about 20 cm. Although examples have been found at all ages, about one-third have been in infancy. About 70 per cent have been highly malignant, and have spread early by invasion and metastasis.

Microscopically, the mesonephroma is characterized by small cystic cavities separated by a thin delicate stroma and lined by flat or low cells of endothelial appearance. There is no mucin production. Proliferation of the endothelial lining of the small cavities produces solid masses of asteroid elements, devoid of stroma, but connected with each other by long thin projections of their protoplasm. In about 60 per cent of the tumors, cystic spaces are produced which contain "glomeruloid" structures, similar in appearance and structure to an embryonal or developing renal glomerulus.

A suggested hypothesis of origin of this tumor is from mesonephric tissue misplaced during development into the ovarian parenchyma, and which has potentiality for developing renal structures.

Teratoma of the Ovary

Teratoma is a tumor consisting of a combination of various tissues not normally found at that site. The tissues forming the teratoma may have the character of normal tissues, mature or immature, but usually are mixed together in proportions and architectural relationships unlike the normal. However, in some teratomas there is a tendency toward normal form and structural relationships. Although most teratomas arise in male or female gonads, they also originate in many other organs, a fact which must be considered in any classification or theory of histogenesis.

Classification.—For practical use, the common types of ovarian teratomas may be classified as (1) solid teratomas (malignant), (2) cystic dermoids (benign), (3) struma ovarii, and (4) chorionic epithelioma (choriocarcinoma) of the ovary. However, various qualities of the tumors may enable further distinction: (a) the tissues composing the tumor may be of mature and fully differentiated type, or may be of embryonal or immature nature (embryomas); (b) teratomas may be grouped according to whether one, two, or three germinal layers are represented in the tissues composing the tumors as monophyllomas, diphyllomas, and triphyllomas respectively; (c) teratomas may be benign or malignant. In malignant teratomas, it is difficult to tell in an advanced stage whether malignancy was present from the beginning, or malignant change developed in one or more foci in an originally benign tumor. It is important to avoid confusing immaturity of tissues in a teratoma with malignant character. Immaturity of tissues in a teratoma is no more indication of malignancy than in immaturity of tissues in an embryo, although the immature tissues do have a greater tendency to undergo malignant change than is exhibited by mature tissues.

Teratomas thus may be classified according to (a) the mature or immature nature of their tissues, (b) whether they have tissues of one, two, or three germinal layers, and (c) their benign or malignant character. While all combinations of these three characters occur, most ovarian teratomas are either (1) immature triphyllomatous malignant solid or pseudosolid teratomas (embryomas) or (2) composed of mature tissues of one, two, or three germinal layers, benign and cystic (dermoid cysts).

The Solid Immature Teratoma or Embryoma.—The solid ovarian teratoma is usually composed of very immature cells of embryonal character. Frequently there is so little differentiation that even those familiar with embryonic tissues may be uncertain of the type. Usually all three germinal layers are represented.

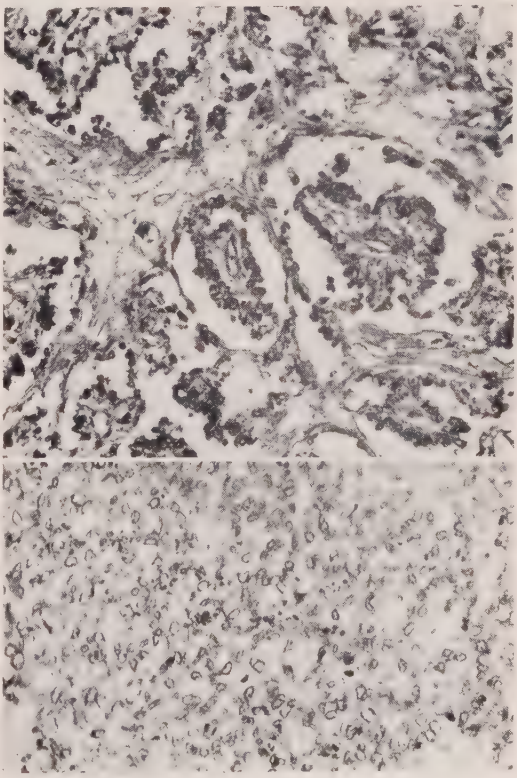

Fig. 909.—Mesonephroma. Upper: Glomeruloid structures. Lower: Solid area in a malignant mesonephroma, consisting of stellate cells.

The tumor is solid, or may be termed pseudo-solid because of numerous cystic spaces of microscopic size. The consistency is soft and the color white or a light gray or yellowish. A thin capsule of connective tissue forms a smooth, slightly lobulated or bosselated surface. The cut surface is often marked by necrotic areas,

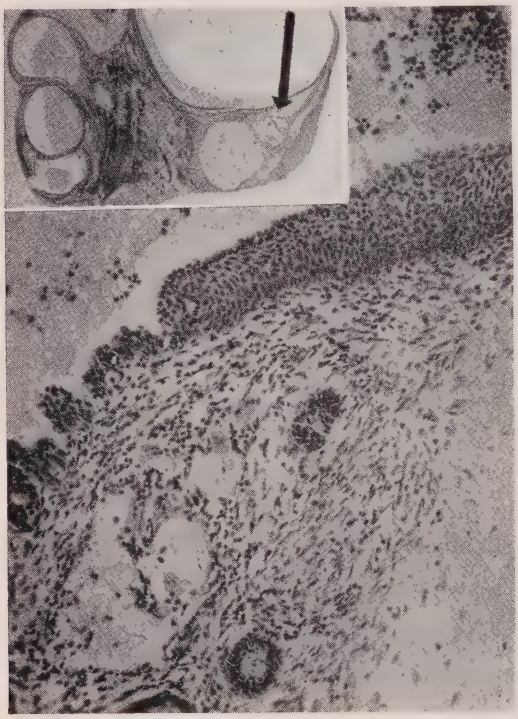

Fig. 910.—Small teratoma in the wall of a cystic ovarian follicle. It consists of dense stroma, several glands, and a central cavity lined by epithelium of various types.

hemorrhage into which results in dark brownish discoloration. The tumor may vary from the size of a plum to as large as a man's head. It is more common in the first half of the reproductive years, and is very rare after the menopause. Usually the tumor has a high degree of malignancy, as manifested by rapid invasion of neighboring organs and rapid metastasis to lungs and pleura as well as to abdominal organs. Generalized spread may be rapid, and in some cases no more than four to six weeks elapse between the first clinical evidences leading to discovery of a small ovarian tumor and the fatal ending with widespread extensions of the tumor. Frequently the metastases have less differentiation than is found in the primary tumor, so that it may be impossible to determine the tissue component from which they originated. However, in some cases studied by the author, it was possible to identify the metastatic tissue as coming from a mesonephric component of the primary tumor.

Choriocarcinoma of the Ovary.—Mature teratomas and dermoids never contain placental or chorionic tissues. Rarely, triphyllomatous embryomas may contain chorionic tissues, and exhibit rapid growth and metastasis to lungs and brain just as in the case of chorioepitheliomas of uterine origin. In other cases of malignant embryomas with chorioepitheliomatous components, metastases may be of somatic components only (carcinoma or sarcoma) or of chorionic tissues also. There is also a primary chorioepithelioma of the ovaries, in which chorionic tissues only compose the primary tumor and metastases. The occurrence of some of these tumors before puberty disposes of the possibility that all such cases may have followed a pregnancy or abortion. Similar types of chorioepitheliomas arise in the testicle, where their incidence is greater than in the ovary.

Struma of the Ovary.—Some teratomas show structures of an organoid type. Wilms suggested that all teratomas start as triphyllomas, but in the course of development only tissues of greater vitality and resistance survive. This is probably not true for all, as some very early dermoids show evidence of only one or two germinal layers. However, in some tumors, one tissue component does become predominant and others tend to disappear. Such appears to have occurred in the so-called struma of the ovary. These tumors vary from the size of a walnut up to that of a man's fist, and are composed of typical thyroid tissue. In some cases thyroid tissue is present alone, and in others there is connection with a small dermoid. Thyroid tissue is a common component tissue in dermoids (found in up to 15 per cent of dermoids). Iodine has been demonstrated in ovarian struma in a concentration equal to that in normal thyroid tissue. That ovarian struma may have functional activity is also evidenced by the occasional case in which its removal has resulted in decrease of hyperthyroid symptoms, or development of hypothyroid (myxedematous) changes.

Dermoid of the Ovary.—

Incidence.—The most common teratoma of the ovary is the so-called dermoid cyst, which occurs 120 to 200 times as frequently as the solid embryoma, and accounts for 10 to 15 per cent of all ovarian tumors. Its highest incidence is between puberty and 30 years of age. Rarely, it has been found before the usual age of puberty, and in some such cases precocious puberty has been associated. In such cases the dermoid probably has had the same cause as, or has been a sequel of, the precocious puberty, as no endocrine tissue which could cause onset of puberty has been found in the dermoid. Ovarian dermoids often develop during pregnancy, with which they do not interfere, although incarceration of the tumor in the pouch of Douglas during the third or fourth months of pregnancy may

necessitate its immediate surgical removal.

Dermoid cysts do not tend to grow indefinitely, and usually do not continue to increase in size after becoming as large as a man's fist or a child's head. In 2 to 15 per cent of cases there are bilateral ovarian dermoids, but more than one arising from a single ovary is rare. Dermoids often become pedunculated by stretching of the ovarian ligament and mesovary, which allows torsion and may lead to spontaneous amputation. If there were previously formed adhesions to the omentum, the dermoid may become a so-called parasitic tumor (60 to 70 per cent of parasitic tumors are dermoids).

Appearance and Structure.—The ovarian dermoid is a cystic tumor, the cavity containing an oily substance produced by sebaceous glands of skin linings, which is fluid at body temperature but solidifies on cooling to room temperature. At one point in the lining of the cyst there is always a node or thumblike projection called the nipple or dermoid tubercle. This and adjacent areas are covered by skin having stratified squamous epithelium, hair follicles, sebaceous glands, and sweat glands. Opposite this area the cyst is lined by flattened squamous epithelium usually without glands or hair. The core of the nipple contains a characteristic mixture of heterotopic tissues, usually of one germinal layer (ectodermal), but less commonly of two or rarely of three germinal layers. The ectoderm is commonly represented by skin and accessory structures, salivary glands, pigmented retinal cells, teeth, etc. Mesodermal tissues often present are cellular connective tissue, bone, and cartilage, and the entoderm may be represented by bits of tracheal or intestinal mucosa. Desquamated keratinized material and hair may provoke formation of phagocytic giant cells, the horny fragment being demonstrable in their cytoplasm.

Among the tissue components of dermoids, those of the skull are most frequent and frequency of the various tissue components decreases corresponding to the lower location and distance from the head. The skin structures of a dermoid usually duplicate the scalp, the bones usually duplicate flat bones of the skull or jaws, and only rarely fragments of long bones of the extremities, ribs, or vertebral column. In unusual cases organoid structures may be produced, such as rudimentary fingers or extremities.

Pigmentation of the skin in a dermoid is similar to that of the skin of the bearer. In light-complexioned white women the dermoid epithelium usually contains no pigment. In dark-complexioned white women a few pigment granules are found in the basal layer of dermoid epithelium. In such darker women the dermoid epithelium during pregnancy may develop a pigmentation corresponding to a chloasma of pregnancy, which, like chloasma, fades on termination of the pregnancy. In Negro women there is an abundance of granules of melanin pigment in the basal layer of the dermoid skin. The hair of a dermoid likewise usually corresponds in color to that of the bearer, although it may be lighter from bleaching or unpigmented but is never darker.

Teeth found in a dermoid may correspond to those of a first or of a second dentition, more often the latter. Usually they are well formed, and may have normal root structures if they are inserted in a piece of bone corresponding to an upper or lower jaw. Periosteum, nerves, and pulp usually are of normal size and form. If two or more teeth are present, all are either of the left or of the right side. A combination of teeth from the left and right sides has never been observed. Tissues which originate by a complicated interplay of organizer and organized elements, such as the persistent kidney (metanephros), are not found in teratomas.

Malignant Change in Dermoids.—Tumors which develop from the skin, such as nevi and papillomas, have been observed in the skin of dermoids. Secondary malignant change may occur in ectodermal compounds of dermoids, well-differentiated squamous cell carcinoma being the most frequent. Glandular or papillary carcinomas are rare, although they may arise from bits of mammary gland, sweat gland, thyroid, etc. Sarcomas may develop from mesodermal components. Benign dermoids have been found associated with an adjacent malignant embryoma.

Origin of Teratomas.—There are two main theories of the origin of teratomas: (1) that they arise by parthenogenesis from an unfertilized ovum, or (2) that they arise from misplaced blastomeres.

The ovulogenic theory assumes that a teratoma rises from an unfertilized ovum following its stimulation by an unknown and probably nonspecific stimulus. Hence the tumor has the same genetic relationship to the bearer as a child to its mother. There are various direct and indirect arguments against this theory. Parthenogenesis in mammals has never been found to go beyond the production of a small number of undifferentiated cells. In atretic follicles the ovum can be found sometimes to consist of three to six necrobiotic cells. In experiments with rodents, parthenogenesis has not been found to go beyond a few undifferentiated cells, duplicating an early morula.

In neoplastic proliferation of benign tumors, types of cells produced do not vary from normal potentialities, but the change is only in the structure and relationships of the tissues produced. In normal growth of a fertilized ovum, development of chorionic tissues at first surpasses development of fetal tissues. Hence it might be expected that if a teratoma represented a neoplastic development of an ovum, there would be a large proportion of chorionic or placental tissue. On the contrary, dermoids, even early tiny ones, never contain chorionic or placental tissue, so that it might be concluded that they originate from cells having no potentialities to form such tissues. Only the rare primary chorionic epitheliomas of the ovary are consistent with the parthenogenetic theory in this regard, although the same theory will not explain the chorionepitheliomatous components of testicular embryomas.

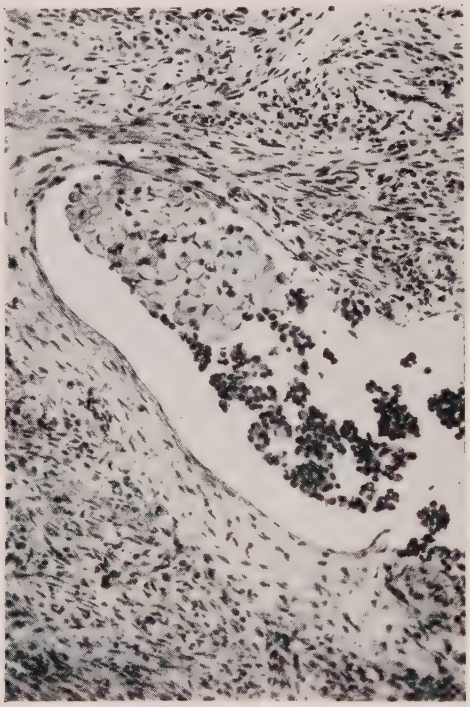

Fig. 911.—Krukenberg tumor of the ovary. The tumor cells are seen in a distended lymph vessel of the hilum. The primary tumor was in the stomach.

Early in embryonic development there is segregation of somatic blastomeres, destined to form the body of the individual, from the primordial genital cell. No observation has shown the presence of primordial genital cells from which a teratoma, of ovarian, testicular, or extragenital origin, could have developed. Also, in the theory of development from an ovum, there is no explanation of the fact that in a dermoid the tissues are of one side of the body only, either right or left.

There are three parts of the blastomere theory:

1. In the morula phase of embryogenesis totipotent cells are present which have the prospective potentiality to form (a) placental-chorionic, (b) primordial-germinal, and (c) somatic cells of all three germinal layers. Under normal conditions they first split into cells with placental-chorionic potentialities and cells with primordial-germinal plus somatic potentialities. The second cells again split into two cells, one with primordial-germinal, and one with somatic potentialities. The latter form the embryo, the first enter the gonad to be organizing germ cells. If by error the splitting occurs not before but after the cell has entered the gonad, the cell with the somatic potentialities later may give origin to a primary triphyllomatous teratoma which in the course of its development may become reduced to a biphylloma or even a monophylloma. This theory, proposed by Ingier, holds not only for the ovary but also for the testicle.

2. If a totipotent cell is misplaced into the area of the prospective gonad it may later on give origin to a chorionic-epitheliomatous tumor by the placental-chorionic component or to a triphyllomatous teratoma by the somatic component, or of both mixed. This part also holds for the testicle.

3. The third part of the blastomere theory holds that somatic blastomeres of a later stage, at the time of or after differentiation into three germinal layers, become misplaced into the parenchyma of the gonad. Thus somatic potentialities of one, two, or three germinal layers may be possessed according to the time of displacement, and hence determining the possible components of a resulting teratoma. As somatic potentialities only are possessed, there is no production of chorionic tissue or primordial genital cells. If the blastomere is misplaced to other than a gonadal area, an extragenital teratoma may develop. The greater frequency of tissues from the head region in dermoids points to the blastomere displacement occurring early in embryogénesis when the prospective gonadal tissue is located nearer the head pole of the body than it is later when a descent toward the pelvic region is under way.

Metastatic Tumors of the Ovary

Many types of malignant tumors, may, on occasion, metastasize to the ovary. Of particular frequency and significance, however, are ovarian metastases of primary tumors of the gastrointestinal tract. Carcinomas of the uterine cervix almost never and carcinomas of the endometrium rarely metastasize to the ovaries. Primary carcinomas of the fallopian tube often spread to the adjacent ovary, and in advanced cases it may be difficult to determine whether the tumor began in the tube or the ovary.

Krukenberg Tumor.—The most frequent metastatic tumor of the ovary is a type described by Krukenberg in 1896, and characterized by mucin-producing epithelial cells having a "signet ring" form. The primary tumor is most often in the gastrointestinal tract, but may be in the gall bladder, bile ducts, or pancreatic duct. In 60 to 90 per cent of cases there is bilateral ovarian involvement, the tumors varying in size up to 20 or 30 cm., and usually having smooth surfaces. The cut surfaces are grayish-white, soft, elastic, and may show cystic cavities of minute to moderate size with smooth linings and a thick, sticky, mucinous content.

ovary. This has been confirmed by failure to find any other primary site on thorough autopsy examination, and also by cases of apparent cure following surgical removal of only the involved ovary.

Parovarian Cysts

Cysts of the broad ligament can develop from the epoophoron, the paroophoron, the Wolffian duct, the rete ovarii, and from incidental remnants of the Müllerian duct. When the cysts are small, their localization gives a clue as to their origin. Products of the Wolffian duct and its tubules have a lining of columnar

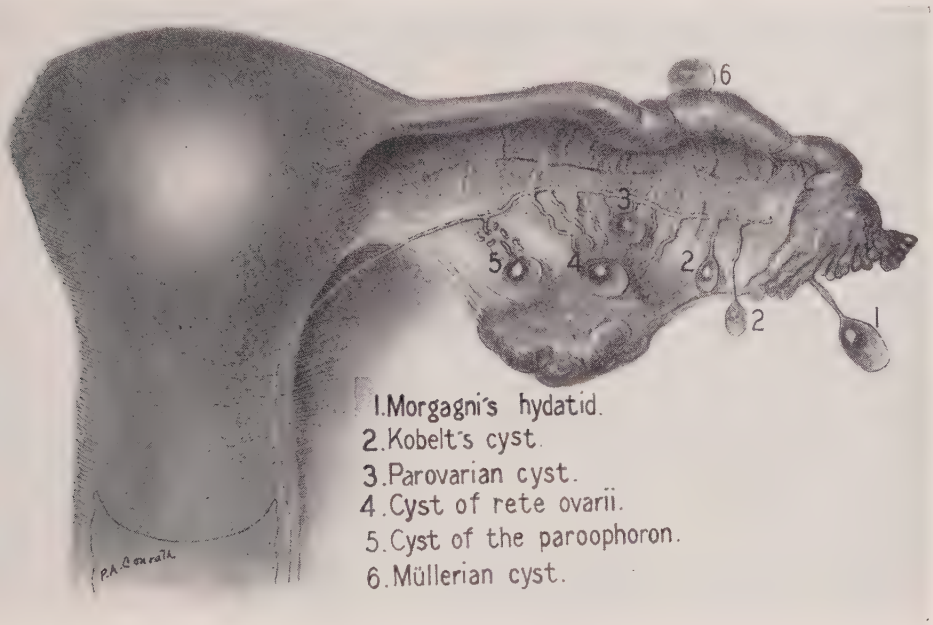

Fig. 912.—Vestigial structures of the broad ligament.

Microscopically there is a great variation in appearance. The characteristic tumor cell contains abundant cytoplasmic mucin, which distends the cell and pushes the nucleus to one side, giving the signet ring appearance. Such cells may be present singly, in columns, or in irregular masses. The characteristic signet ring cells are not specific for Krukenberg tumors, and are sometimes absent. Dense fibrous stromal proliferation is often present. Occasionally there is cavity formation, with mucinous secretion into the cavity.

The route by which the tumor cells reach the ovary appears to be most commonly by retrograde lymphatic extension, the carcinomatous cells entering the ovary from the hilar side. Direct spread to the ovary occasionally occurs from a carcinoma of the sigmoid colon. Spread to the ovaries by transperitoneal migration and implantation, or by the blood stream is uncommon.

There is evidence that in rare cases a tumor of Krukenberg type may be primary in an

cells which may be ciliated, surrounded by a well-developed muscular coat. Cysts from the junctional tubules of the rete have thin walls, low cuboidal epithelium, and no muscular coat. Cysts of Müllerian origin have a lining similar to tubal epithelium. The differences in microscopic structure are lost when the cysts become large and the wall is stretched.

Cysts which are attached to the tubal fimbriae are of pronephric origin. They are called hydatids of Morgagni. They rarely become very large. Clinically of importance are the so-called parovarian cysts, which may reach the size of a fist. They are ovoid, have a paper-thin wall, and contain clear watery fluid. They develop "intraligamentarily" between the two leaves of the broad ligament. When growing larger they separate the two leaves of the mesosalpinx and the tube gets attached to and stretched by their upper circumference. This true intraligamentary location is not to be confused with the pseudo-ligamentary location of ovarian cystic tumors,

which originates from inflammatory adhesions between the anterior wall of the ovarian tumor and the posterior aspect of the broad ligament.

FALLOPIAN TUBES

The fallopian tubes have a muscular wall covered on the outer surface by peritoneum, and lined by a mucosa which is thrown up into intricate papillary arborescent folds. Some of the cells lining the mucosa are ciliated, while others are nonciliated and appear to have a secretory function. The tubal epithelium undergoes some cyclical changes with the menstrual cycle.

Salpingitis

Intended as a passage for the spermatozoa to reach and fertilize the ovum, and for the fertilized ovum to pass to the uterus, the fallopian tubes at the same time establish a passage of communication by which bacteria may reach the peritoneal cavity from the outside. Salpingitis, or inflammation of a fallopian tube, may be classified according to the infecting organisms, according to the method by which the infection reaches the tubes, or by the area of the tube first infected.

Salpingitis may be due to gonococci, staphylococci, streptococci, colon bacilli, tubercle bacilli, or other organisms. The bacteria may reach and infect the tube by spread from the uterus (endometritis), from the peritoneum in either general or pelvic peritonitis, or by the blood stream from some distant focus of infection. Most often the infection first involves the mucosa (endosalpingitis), but may start in the serosal part (perisalpingitis) by spread of organisms from the cervical or lower uterine part of the myometrium via the blood and lymph vessels of the broad ligament.

Acute Salpingitis.—Nongonorrheal acute salpingitis most often is a spread from an infected endometrium following parturition or an incomplete abortion. The salpingitis may persist after the uterine infection has cleared up. The involved tube is enlarged, the serosa reddish from congestion, and the mucosal folds thickened by the inflammatory edema, congestion, and exudate. The lumen in this acute phase is not distended but may contain a few drops of purulent exudate. Microscopically the mucosa shows edema, congestion, and infiltration by neutrophilic leukocytes and some plasma cells. The lumen contains some pus cells but no plasma cells.

Gonococcal salpingitis arises by spread from a gonorrheal endometritis, the latter usually clearing up spontaneously after a short duration. The tubal mucosa forms a favorable medium for the gonococci which tend to persist, so that the inflammation becomes chronic. The gross and microscopic appearance of acute gonococcal salpingitis is similar to that from other pyogenic organisms and described above. Special staining methods may reveal gonococci within the cytoplasm of neutrophilic leukocytes in the lumen. From the fimbriated end of the tube the infection may spread to cause a localized pelvic or generalized peritonitis. A generalized peritonitis due only to gonococcal infection usually clears up in a few days without permanent residua such as adhesions.

Chronic Salpingitis.—If the fallopian tube remains patent, particularly in the proximal intramural portion, acute salpingitis may subside without persistent chronic inflammation or permanent residual damage remaining. In severe infections the lumen of the tube may be blocked by the inflammatory changes at both the fimbriated and uterine ends, transforming the infected tube into a closed cavity (pyosalpinx). The sealed tube becomes dilated by the accumulation of exudate, and the infection persists and becomes chronic. Adhesions developing between the mucosal folds converts the mucosa into a multilocular polycystic or pseudofollicular structure. Eventually after some weeks or months the bacteria are destroyed and the purulent exudate becomes converted to a serous watery fluid.

In some cases exudation predominates over the tendency to form adhesions, the mucosal folds become flattened out, and the sealed tube becomes distended into an ovoid or egg-shaped structure. At first, this type of pyosalpinx may show a few projections which are remnants of the compressed mucosal folds, but eventually these disappear and the wall is lined by a smooth layer of cuboidal or flat epithelium. The wall becomes thinner as distension progresses and the inflammatory process subsides. Eventually the contents become sterile, and the purulent exudate is replaced by a watery fluid (hydrosalpinx).

Salpingitis isthmica nodosa is a type of salpingitis in which the mucosa of the proximal

portion of the tube near the uterus shows inflammatory hyperplasia and tends to invade the muscularis. Glandular islands lined by tubal epithelium are located in septa between muscle bundles. The proximal portion of the tube shows nodular thickenings.

Chronic salpingitis may cause impaired fertility or sterility by obstruction of the lumen. It also may cause ectopic tubal pregnancy by the formation of blind pouches in the lumen of the tube due to adhesions between folds.

Tuberculous salpingitis is the most frequent type of tuberculosis of the female genitalia, and is almost always due to hematogenous spread from a distant focus, and only rarely to direct extension. There is a moderate diffuse thickening of the tube as a whole, with a swelling and reddening of the mucosa. Larger tuberculous foci in the mucosa appear as pale, demarcated, nodular areas surrounded by a hyperemic halo. Adhesions may form between folds, but the fimbriated end rarely becomes sealed off. Extension often occurs to endometrium and to pelvic peritoneum.

The growing carcinoma of the tube forms soft papillomatous masses which grow toward the lumen, distending and enlarging it. The diameter of the tube becomes considerably enlarged, and the wall thinned. Spread to peritoneum through the distal opening of the tube may occur before there is much invasion of the tubal wall. In addition to peritoneal spread, extension may occur to regional lymph nodes and by the blood stream to liver and lungs.

Microscopically, carcinoma of the tube often maintains a glandular or papillary architecture, but eventually forms solid masses of undifferentiated polymorphous malignant epithelial cells. In rare cases it may be of squamous cell type.

No etiological relationship to hormonal disturbance or previous inflammation has been proved.

Ectopic Pregnancy

Ectopic pregnancy is the embedding and development of a fertilized ovum in an abnormal location outside the uterine cavity. The most frequent site is in the tube (tubal pregnancy). Peritoneal embedding may occur either primarily or secondarily after abortion or rupture from the tube. Ovarian embedding also occurs, but rarely. The incidence of ectopic pregnancy has been estimated as 1 to 200 or 300 normal pregnancies. The maximum incidence is between 24 and 33 years of age. Parity appears to have no influence, and 10 to 15 per cent of ectopic pregnancies occur in primiparas.

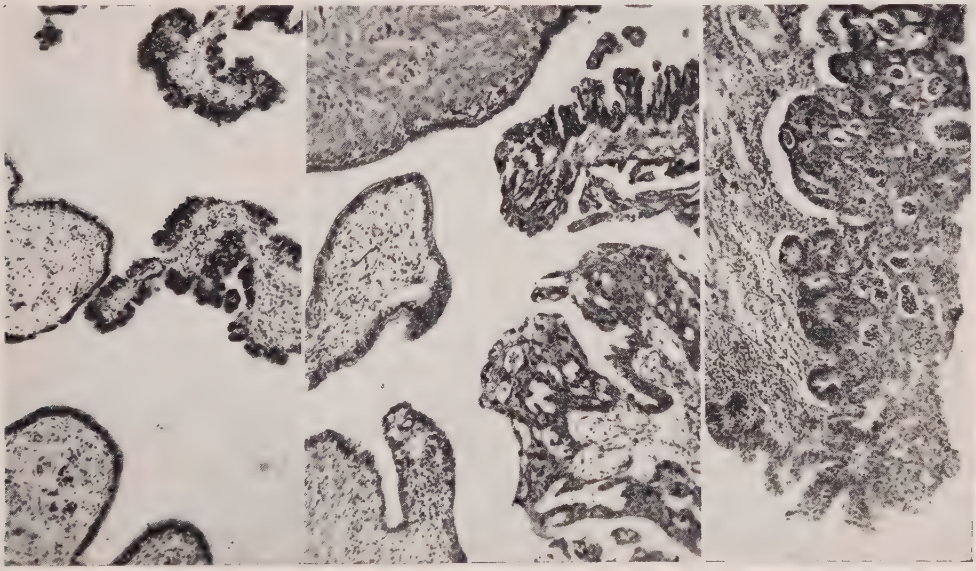

Fig. 913.—Early carcinoma of the fallopian tube. Left: Early preinvasive stage. Center: Advanced stage showing adenopapillary masses in the lumen. Right: Advanced carcinoma showing edge of tumor and adjacent tubal epithelium.

Carcinoma of the Fallopian Tube

Carcinoma of the tube is rare, but of a high degree of malignancy. Most cases occur about the menopausal age. About one-third appear to arise simultaneously in both tubes. In advanced cases with considerable spread and involvement of pelvic organs, the tubal origin may be difficult to determine. Investigation of the borderline zone between the tumor and tubal mucosa indicates tubal origin when there is transformation of normal epithelium into carcinomatous tissue without break of continuity.

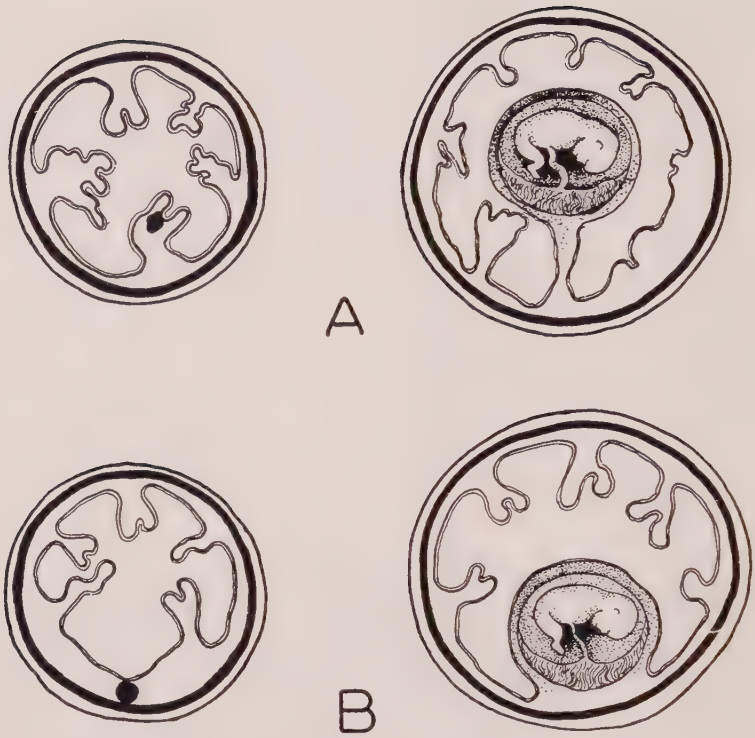

Fig. 914.—Ectopic tubal pregnancy. *A*, Columnar embedding (in tip of a fold). *B*, Intercolumnar embedding (in the mucosa between two folds). Left side: The black point shows the area of embedding. Right side: Advanced phase; formation of placenta.

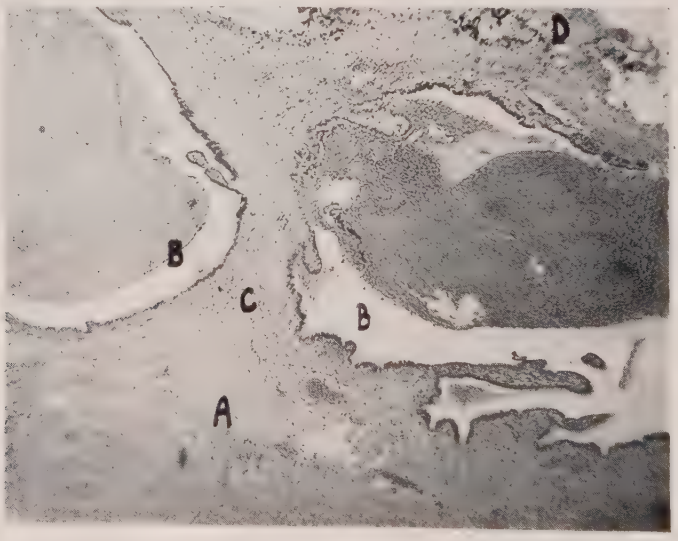

Fig. 915.—Ectopic tubal pregnancy. Columnar embedding. *A*, Inner part of the wall of the tube with involuted folds. *B*, Lumen of the tube with recent blood clots. *C*, Basal part of the fold into which the ovum embedded. *D*, Placenta of the ovum.

The fertilized ovum normally is transported to the uterus by the ciliary and peristaltic activity of the tube, the time consumed by this migration normally allowing sufficient development of the ovum for it to be capable of embedding on reaching the uterus but incapable of embedding during its tubal phase. Hindrances to transportation of the ovum allow it to become capable of embedding before the uterus is reached. Such hindrances are most commonly adhesions or other effects of tubal inflammation (about 60 per cent of cases). Other causes are congenital malformations of the tube, perisalpingitis, causing kinking of the tube, and possibly external or transperitoneal migration of the ovum (corpus luteum found in opposite ovary) or ovary on same side has been removed.

Most tubal pregnancies are in the distal half of the tube, and the proximal uterine portion of the tube is only rarely the site. Embedding may occur in a mucosal fold (columnar embedding) or in the groove between folds (intercolumnar embedding). Local decidual formation is defective as compared with intrauterine pregnancy. Particularly with columnar embedding, the basal part of the fold tends to rupture, the ovum comes to lie free in the lumen surrounded by blood clots, and may be extruded through the peritoneal opening of the tube (tubal abortion). In intercolumnar embedding the placenta invades and erodes the muscularis of the tubal wall, which eventually ruptures and allows escape of the ovum into the peritoneal cavity (tubal rupture). Tubal abortion appears to be considerably less frequent than tubal rupture. Particularly severe hemorrhage following rupture may occur when embedding has occurred in the lower half of the tubal circumference (basiotropic embedding) near vessels of larger caliber in the broad ligament. Embedding in the upper half (called "acrotropic") is supposed to cause moderate hemorrhages only.

Fig. 916.

Fig. 917.

Fig. 916.—(Inset.) Tubal ectopic pregnancy with intact amniotic cavity and beginning rupture of the tubal wall. In the amniotic cavity is the intact fetus cut obliquely.

Fig. 917.—Tubal ectopic pregnancy. Decidual transformation of the stroma of the folds, with involution of the epithelium.

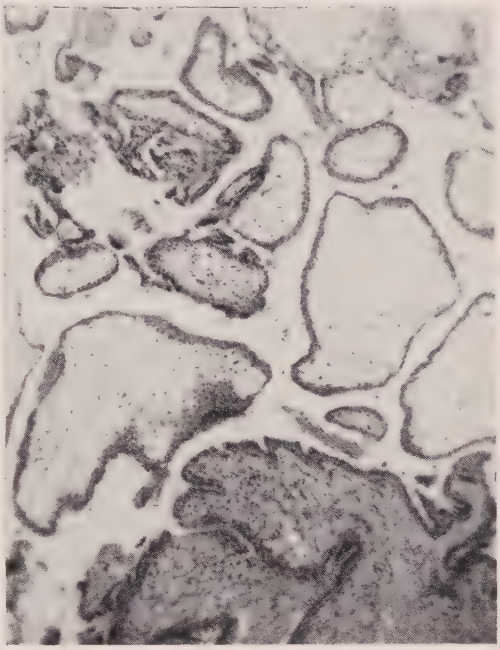

Fig. 918.—Placental villi in a tubal pregnancy. Some villi show stromal edema, proliferation, and vacuolization of the chorionic lining, similar to changes in a hydatidiform mole.

The tubal mucosa is not capable of much decidual transformation. Small islands of decidual cells may be found in the mucosa, often in areas a centimeter or more from the site of embedding. Also islets of ectopic decidua may be found in the serosa of the wall of the uterus, around the appendix, ovaries, etc.

Abdominal pregnancy may be primary, or secondary after tubal abortion or rupture. Ovarian pregnancy with embedding inside the ovary may occur when the ovum does not escape following rupture of the follicle, but is retained and becomes fertilized within the follicle.

In ectopic pregnancy, wherever located, the uterine endometrium undergoes decidual transformation does not differ from the change in uterine pregnancy. This decidua is cast off when the extrauterine placenta is separated from its insertion. In many cases the decidua is not thrown out piecemeal, as in menstruation, but as one triangular sac with three openings. Micro-

scopically it shows decidua more or less involuted, but neither fetal nor placental elements. The absence of these makes the case suspicious for ectopic pregnancy but may also indicate previous complete abortion.

UTERUS

Structure and Development

The uterus develops by fusion of the lower parts of the bilateral Müllerian ducts into a single symmetrical organ. It consists of an epithelial mucosal lining, a muscular wall, and a serosal covering (perimetrium) which is part of the peritoneum. All parts develop from celomatous mesenchyma, the endometrial and cervical mucosa developing from mesoderm, not from ectoderm or entoderm, and having a close relationship to the underlying muscularis without separation by a submucosa (as is the case in the intestinal tract).

The uterus consists of two parts, the body (corpus), having a narrow triangular cavity, and the cervix, with a channel connecting the uterine cavity and the vagina. The two upper symmetrical outlets of the uterine cavity, which communicate with the lumen of the tubes, are guarded by circular muscle bundles which morphologically do not form a distinct sphincter but function as such by closing the tubal openings on contraction of the uterus. The cervix has fewer circular muscle bundles, but at its lower end are longitudinal bundles which cause shortening and slight widening of the cervical opening on uterine contraction. This muscular distribution promotes emptying of contents into the vagina on uterine contraction (e.g., at menstruation) and protects against regurgitation into the fallopian tubes.

The endometrium, the lining mucosa of the uterine cavity, consists of straight tubular glands and a specific stroma (the so-called cytogenic tissue) in which they are imbedded, and which separates their basal blind end from the myometrium. The line of demarcation between the endometrial stroma and myometrium normally is straight and even. The stromal cells participate and function in the changes of the menstrual cycle and pregnancy. In pregnancy the stroma is transformed into decidua, which surrounds and embeds the ovum. At the time of delivery it allows separation of the placenta by the normal mechanism, and if it is missing, the placenta becomes anchored to the myometrium (placenta accreta) and normal separation fails. With menstruation, the inner two-thirds of the endometrium (the so-called "functionalis"), both glands and stroma, are cast off, and regeneration occurs in the postmenstrual phase from the retained basal portion.

The cervical canal is lined by columnar mucinous epithelium which forms racemose glands embedded directly in the cellular connective tissue of the cervical wall. Specific stromal tissue is not present in the cervical mucosa. The demarcation between endometrium and cervical mucosa (histologic internal os) lies somewhat lower than the border between the triangular uterine cavity and the cylindric cervical canal (anatomical internal os), the intervening part (isthmus) having an endometrial character but with fewer glands and participating only slightly in the changes of the menstrual cycle. Abnormal embedding of the ovum in the region of the isthmus may result in placenta praevia. But this is not the specific or exclusive cause of placenta praevia, which may originate also from other causes. During the fourth or fifth month of pregnancy the isthmus becomes incorporated into the uterine wall to form the lower uterine segment.

Prolapse and Procidentia

The terms prolapse and procidentia are used by many in the same sense. Others use the term prolapse when the uterus has descended but remains inside the peritoneal cavity, and the term procidentia (synonymous to total prolapse) when the uterus has descended to a location outside the pelvis. The uterine descent may be due to damage to the pelvic floor inflicted at the time of delivery, or may be part of a generalized "enteroptosis" in which all intraperitoneal organs are displaced downward due to constitutional weakness of the suspending ligaments. Normally the body of the uterus is held in position both by ligaments and by the peritoneal covering, and the cervix of the uterus is held by the floor of the pelvis and the pelvic fascias.

Malformations of the Uterus

As the uterus develops by fusion of the lower parts of the two Müllerian ducts, malformations may be classified according to the ways in which this developmental process fails. Four groups of uterine malformations depend on (1) aplasia or hypoplasia of one of the Müllerian ducts, (2) failure of attachment or incomplete fusion of the Müllerian ducts, (3) atresia or failure of lumen formation, and (4) reduplication.

Many of the uterine malformations involve loss of uterine function due to lack of a uterine cavity or an endometrium suitable for embedding of the ovum. In the unicornuate or bicornuate uterus, there may be normal embedding and pregnancy in one horn. In a bicornuate uterus, the endometrium of one horn undergoes full decidual transformation with pregnancy in the other horn, and the shedding of this decidual lining may erroneously suggest a tubal ectopic pregnancy.

Cervix

The cervix is that part of the uterus extending downward from the histologic internal os. The stroma contains semicircular spiral and also longitudinal muscle bundles, the latter becoming increasingly predominant toward the lower end. On myometrial contraction, the longitudinal fibers cause the cervix to be shortened, and lifted up, and the cervical canal opened slightly. The cervical canal is lined by a mucous membrane having racemose glands with tall columnar epi-

thelium, basal nuclei, and pale homogeneous cytoplasm. The epithelium is of the goblet cell type, producing one large droplet of secretion.

Erosion of the Cervix

The vaginal surface of the cervix is lined by stratified squamous epithelium, similar to that of the vagina, which develops from the urogenital sinus. The histologic external os of the cervix is the line of demarcation between the columnar epithelium of Müllerian origin and the stratified squamous epithelium of urogenital sinus origin. In the early part of fetal development, this line of demarcation is higher up in the canal, above the anatomical internal os. Such squamous epithelium lining the lower cervical canal may persist in cases of genital infantilism, although normally replaced later in fetal development by columnar glandular epithelium. Erosion refers to loss of epithelium only, whereas loss of epithelium and stroma is termed ulcer.

Acquired erosions result from inflammation of the cervix, or laceration at childbirth. Tears in the lower end of the cervix at childbirth expose the endocervical mucosa to the vagina due to change in configuration of the cervical wall, even though the distribution of epithelium is

Fig. 919.—Congenital malformations of the uterus. I, Aplasia of one duct: *A*, Uterus bicornis unicollis. Dysplasia of one duct. *B*, Asymmetrical uterus bicornis with rudimentary horn. *C*, Asymmetrical uterus bicornis with partially atretic rudimentary horn. *D*, Asymmetrical uterus bicornis with atretic rudimentary horn. II, Deficient contact of the Müllerian ducts: *A*, Uterus duplex or didelphys with double vagina. *B*, Uterus bicornis duplex. *C*, Uterus bicornis unicollis. *D*, Uterus arcuatus. III, Deficient fusion of the Müllerian ducts: *A*, Uterus septus duplex with septate vagina. *B*, Uterus septus duplex. *C*, Uterus subseptus. *D*, Uterus biforis.

normal (laceration ectropion). Inflammatory or mechanical injuries remove the surface epithelium but usually there is no destruction of the underlying denuded stroma. Both columnar and squamous epithelium from the edges tend to grow over the area, but first the simpler columnar epithelium by its more rapid growth succeeds in covering most of the denuded region, which then acquires a smooth, glistening, dark red appearance. In a second phase of healing, squamous epithelium covers the area, creeping either beneath or over the columnar epithelium, which is eventually eliminated.

As in the endometrium, the surface epithelium of the cervical canal and the glandular epithelium are identical and reproduce each other. Glandular reproduction may occur in the congenital eversions, during the first stage of healing of a glandular erosion, or due to stimulation by chronic inflammation of the cervix. Such proliferating glands, extending beneath the squamous epithelium, dilate due to retention of their contents and form small cysts (Nabothian cysts). Secreting glands left beneath the recovered squamous epithelial surface of an erosion tend to cause desquamation of the surface epithelium and a recurrence of the erosion. Recurrent erosions with focal proliferation and involution cause unevenness of the cervical surface. Histologically, the intermixtures of columnar and squamous epithelium which may result must be distinguished from carcinomatous proliferation. In healing of a glandular erosion, plugs of squamous epithelium grow into and fill the lumen of the glands, causing compression and atrophy of the lining columnar cells.

In erosions of the cervix, the two types of epithelia, columnar and squamous, may become intimately mixed or replace each other, but there is no transformation of one type into the other.

Cervicitis

The cervical canal ordinarily is protected from infection caused by bacteria from the vagina by a thick, sticky mucoid secretion which closes the external os. When this is ineffective, organisms which are harmless to the more resistant vaginal epithelium enter and infect the cervix. The cervical mucosa becomes swollen, hyperemic, and velvety. The common infecting organisms, staphylococci and streptococci, present the same type of inflammatory reaction as gonococci, so that bacterial rather than histologic differentiation of the type of infection must be made. Microscopically, there are focal infiltrations of lymphocytes and shrunken, scarred areas of stroma.

Tuberculosis of the cervical canal is infrequent, and tuberculous ulcers of the vaginal portion of the cervix are rarer still. Cervical tuberculosis is usually an extension from endometrial tuberculosis, which may have originated from a tuberculous salpingitis.

Cervical Polyps

Polyps of the cervix may originate from the vaginal surface of the cervix or from the mucosa of the cervical canal. The less frequent former type, which arises from an area covered by squamous epithelium, is a small dome-shaped projection a few millimeters in length, with a solid core of cervical stroma containing a few thin vessels, and covered by squamous epithelium. The solid polyps usually are not pedunculated.

Much more frequent are elongated soft pendulant polyps which originate from the mucosa of the cervical canal by a form of local hyperplasia. By growing longer they may reach the lower end of the cervical canal and protrude from the external os. They consist of a core of loose connective tissue with numerous thin-walled blood vessels, and a covering similar to the mucosa of the cervical canal. Glands rarely are absent, and tend to undergo cystic dilatation. Kinking or compression of the pedicle leads to vascular congestion and stasis, sometimes with hemorrhagic infarction or necrosis at the tip of the polyp. Sometimes when the tip of a polyp projects from the external os, squamous epithelium may replace the columnar epithelium, plug the outlets of underlying glands, and changes similar to those seen in erosions are found.

Cervical polyps, unlike those of the intestinal tract, have little tendency to undergo malignant change.

Carcinoma of the Cervix

Cancer of the uterus is of great importance because of its high incidence. Carcinoma of the cervix is the most frequent type of cancer of the female genital organs and also, along with cancer of the breast and of the stomach, is one of the most common types of malignancy. Regular gynecologic examinations enable carcinoma of the cervix to be discovered at an early stage of development, and hence the chance for successful therapy is better than with cancers of some other internal organs.

The uterus has three types of epithelium: (1) columnar epithelium of the endometrium; (2) columnar epithelium of the cervix canal; and (3) squamous epithelium of the vaginal aspect of the cervix. From each arise distinctive carcinomas which differ in their location, type of component cells, and in mode of proliferation and spread. An uncommon fourth type of carcinoma may arise from remnants of Gartner's duct.

Carcinoma of the cervix composes about 90 per cent of all uterine cancers, and, among these cervical carcinomas, only about 2 per cent arise from the glandular epithelium of the cervical canal. Carcinoma of the cervix occurs mainly between the ages of 40 and 60 years, but during the last two decades there has been a disturbing shift to younger-aged groups which cannot be entirely accounted for by progress in accuracy of examination.

Types and Grading of Carcinoma of the Cervix.—The squamous cell or solid carcinoma of the cervix can be divided into two gross types which vary in their manner of growth and extension: (1) Cervical carcinomas which grow outward and project beyond the level of the surface epithelium from which they originated. These form dense cauliflower-like projections of a pale gray to light pink color. These projecting growths may be referred to as exophytic. (2) Cervical carcinomas which on proliferation invade the underlying stroma and have little or no tendency to grow out beyond the surface. These invasive carcinomas soon become ulcerated and may be termed endophytic. Some cancers of the cervix are entirely endophytic and exhibit no tendency to grow outward from the surface. However, all primarily exophytic carcinomas have a tendency for invasion and eventually manifest endophytic growth. The endophytic carcinoma of the cervix appears grossly as an area of ulceration, beginning usually near the external os and extending over the vaginal surface of the cervix. The involved area appears dark red, rough, and bleeds easily on being touched, and eventually, spontaneously. The surface area undergoes necrosis and so is soft in consistency, but the deeper parts tend to be indurated and resistant.

The exophytic type of tumor, which grows by a piling up of tumor tissue on the surface, has a better prognosis if treated in an early phase than has the endophytic invasive growth which extends early into the lymph spaces around the cervical vessels.

Microscopically, carcinoma of the cervix consists of islands or strands of malignant epithelial cells separated by a connective tissue stroma. The stroma often shows a tendency to infiltration by leukocytes, and this leukocytic accumulation often is particularly marked at the edge of the advancing tumor and involves adjacent normal tissue. The malignant epithelial cells may present variable degrees of differentiation, those which are most undifferentiated corresponding to cells of the basal layer of the squamous epithelium. The most highly differentiated cells may form keratin pearls with concentric lamellation. About 5 per cent of squamous carcinomas of the cervix show keratin pearls and thus present a high degree of differentiation, the squamous epithelium of the cervix under normal conditions never showing this keratinization. In other tumors there may be a marked degree of anaplasia, cells which are produced varying from their normal size and in the staining reactions of the nucleus and cytoplasm. The carcinomas may be classified or graded, as suggested by Broders, according to the relative proportions of undifferentiated cells. For instance, grade I is 0 to 25 per cent undifferentiated cells; grade II, 25 to 50 per cent undifferentiated cells; grade III, 50 to 75 per cent undifferentiated cells; and grade IV, 75 to 100 per cent undifferentiated cells. In general, the prognosis becomes worse with the increase in the proportion of undifferentiated or immature cells. On the other hand, the cells of lower differentiation and maturity are more sensitive to irradiation. In any one tumor the degree of differentiation which is evident may vary in biopsies taken at intervals of a few weeks from the same tumor.

Two methods of invasion and proliferation may be distinguished. Some carcinomas of the cervix grow as solid masses of tumor cells so that the demarcation line between the tumor and the adjacent noninvaded tissue is a continuous and uninterrupted one, even though it may show irregularities of projections and indentations. In other carcinomas of the cervix there is proliferation and invasion by smaller groups or single lines of tumor cells apart from the main mass of the tumor. In such cases there is no definite border line or line of demarcation between the tumor and adjacent normal tissue, but rather there is a zone in which there are found island groups of tumor cells. This latter method of spread results in a poor outlook as advanced groups of tumor cells or single malignant cells relatively soon reach lymphatic spaces and thus in an early phase may spread to neighboring tissues.

The infiltration of leukocytes, which is noticeable particularly at the advancing border of a tumor, apparently depends on a biologic difference between the carcinoma and the invaded normal tissue. The degree of this inflammatory defense reaction is variable, and in cases in which it is marked, the prognosis appears to be better than when it is slight or absent.

Thus, the microscopic features of a cancer of the cervix on which a prognosis may be based include the degree of differentiation, the manner of spread and invasion at the advancing age of the tumor, and the degree of leukocytic or inflammatory reaction at the border of the tumor. Gross characteristics which may be correlated with prognosis include the type of growth, that is, whether fungating (exophytic) and extending on the surface, or ulcerative and invasive (endophytic), and the degree of extension.

Histologic grading indicates rate of growth and degree of radiosensitivity but is probably less important in prognosis and as a guide to treatment than is the degree of extension of the tumor at the time examined. In this regard, certain stages of the disease have been designated as a guide.

Group I. Carcinomas limited to the cervix; the uterus is mobile. About 80 per cent obtain five-year cures.

Group II. Carcinoma spreading upward into uterus is partially mobile. About 40 per uterus and downward into vagina; the cent have five-year cures.

Group III. Carcinoma extending outward into the parametrium, with beginning fixation of the uterus. About 12 per cent have five-year cures.

Group IV. Carcinoma massively invading parametrium and extending to wall of pelvis, with complete fixation ("frozen pelvis"). No five-year cures.

Combined consideration of the histologic grade and the degree of extension leads to the most accurate prognosis.

Extension and Causes of Death.—The main direction in which an advancing carcinoma extends is laterally toward the parametria. Advanced carcinoma infiltrates the parametria and forms a continuous mass which eventually extends over the floor of the pelvis from the uterus in the midline up to the iliac bone. Generalization by metastases to remote organs is rare, and the cause of death is very rarely due to such generalized spread of the tumor. A fatal ending is usually due to one or more of three complications: (1) extension of the carcinoma into the parametria which may compress one or both ureters and cause hydronephrosis and infection; (2) septicemia from local infection of the ulcerated surface; (3) hemorrhages from eroded uterine vessels or parametrial vessels.

Early Diagnosis of Carcinoma of the Cervix.—Analysis of groups of cases have indicated that the chances of cure vary with the earliness of the phase of development of the carcinoma. This indicates the value of finding and recognizing carcinoma of the cervix at the earliest possible stage of development. Advanced obvious carcinoma of the cervix can be recognized and identified by ulceration, by invasion, and by the cytological changes in the cells which form the tumor. Ulceration is not a specific change, the important criterion being invasion and the character of the tumor cells. In most of the advanced carcinomas the demarcation between the tumor cells and the normal surface epithelium is marked by a small zone (neutral zone or groove of demarcation) in which no epithelial lining covers the surface of the inflamed stroma. In about 4 per cent of early cervical carcinomas this zone contains epithelium which is in direct and uninterrupted connection with both the normal epithelium and the tumor cells. This zone of epithelial cells is about the same thickness as the normal surface epithelium, but it is composed of cells which show the same irregular polymorphous atypical character of the cells of the carcinoma. Because of the character of these cells, they were interpreted as being a part of the carcinoma but without invasion, and have been referred to as surface extension. Microscopic studies of cervices which grossly appeared perfectly normal have led to the discovery of small early carcinomas in an early phase at a time when there was no ulceration, no invasion, and only a malignant transformation of the surface epithelium. Whether this earliest phase should be called carcinomatous or precancerous, or otherwise, has been the subject of much discussion. In advanced carcinomas, the surface extension is definitely a part of the tumor, differing from it only by its position at the surface and lack of invasion, and is composed of cells apparently the same as those which form the bulk of the tumor and connected with the tumor cells without any line of cleavage or demarcation. In such cases it is generally accepted that these cells form a part of the tumor. Hence when this early phase of preinvasive growth only is seen, it is felt that it should be considered carcinoma and not a precancerous change. The evidence indicates that the surface change of the epithelium in these early cases is always followed later by downgrowth, and invasion, although the interval before downgrowth occurs may amount to several months or even several years. From a practical point of view it is, of course, to be emphasized that from a single slide which shows the surface change only, it cannot be concluded that invasion has not already taken place in an adjacent area. Removal or destruction of the whole area has to be carried out whether it is classified as a carcinoma or considered as a precancerous condition.

Comparison with a similar affection of the skin, Bowen's disease, may be useful. However, there are certain cytological differences between the surface carcinoma of the cervix and the epithelial cells of Bowen's disease of the skin.

Although the invasive and surface parts of a carcinoma of the cervix have identical cytological character, there is an important biological difference between the two components. The invasive part proliferates in the stroma, a medium to which it is not normally related, replacing and eventually destroying the stroma and growing larger by increasing its own cellular material by mitotic or amitotic divisions. In the carcinoma confined to the surface epithelium, there is no area which shows a gradual transformation from the normal to the malignant type of epithelium, but the line of demarcation often presents a sharp and sudden change in the type of cells although there is no break in the epithelial structure. A normal cell and a malignant cell are side by side at the margin of the tumor and are connected with each other in the normal fashion. The line separating the tumor cells and the normal epithelium is an oblique one, the carcinoma side projecting in the basal part into the normal epithelium, and the normal epithelium in the superficial part overlapping the carcinomatous cells. This has suggested that the carcinoma grows not by increase of its own cells and corresponding destruction and elimination of the normal epithelium, but rather by malignant transformation of adjacent normal epithelial cells into cells of

carcinomatous character. Such growth by assimilation can take place only in the less differentiated basal cells and not with the already functionally differentiated prickle cells, and still less with the fully differentiated cells of the higher strata. Following a malignant transformation of basal cells, it takes an interval of time for these basal cells to replace the whole thickness of epithelium above them by cells of carcinomatous character, and for this reason, at the demarcation line the youngest cells and the carcinomatous basal layer are still overlapped by normal prickle cells and normal surface cells.

Surface extension of the tumor progresses very slowly and takes months or even years to extend a few millimeters, whereas once invasion downward has started, progressive proliferation becomes rapid and leads to early replacement of normal tissue and extension of the tumor.

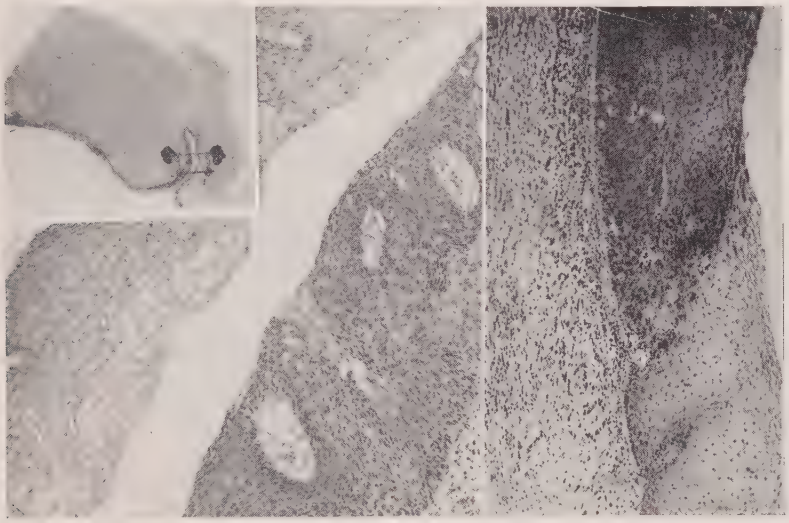

Fig. 920. Fig. 921.

Fig. 920.—Preinvasive carcinoma of the cervix (right) and adjacent normal vaginal epithelium (left). Note the sharp demarcation of the carcinomatous surface cells from the underlying stroma, which always shows inflammatory infiltration. (From area indicated in low-power view [inset].)

Fig. 921.—Preinvasive carcinoma of the cervix. The oblique cleavage line between the carcinoma (above) and the normal epithelium (below) represents an abrupt change without gradual transition. Inflammatory infiltration is present beneath the surface carcinoma.

The advanced stage accompanied by ulceration needs no special method for diagnosis. The reddish ulcerated area adjacent to the external os cannot escape detection on examination of the cervix although differentiation must be made between erosion and carcinoma. Biopsy and microscopic examination of tissue from the suspicious area is necessary to distinguish with certainty between carcinoma and inflammatory erosion. In the preinvasive phase of carcinoma of the cervix in some cases it can be discerned as a slightly elevated area with a dull wrinkled surface of lighter color, thus appearing as a white patch or "leukoplakia." Such white areas are not necessarily of carcinomatous character, and distinction can be made only by histologic examination. Biopsy from suspicious areas should, if possible, include a borderline between the normal and the leukoplakic epithelium to permit a microscopic comparison.

In the majority of early carcinomas of the cervix in which such suspicious areas are not evident, the iodine test (Schiller test) founded on a biologic difference between normal and malignant epithelium may be useful. Normal cervical epithelium stores glycogen in the cells of its superficial layer. This glycogen differs from that of liver and muscle in that it is not soluble in water. The faculty of glycogen storage is absent from carcinomatous epithelium. The glycogen storage in a normal epithelium is demonstrable in microscopic preparations by staining with iodine or Best's carmine. The use of a watery iodine solution with a concentration of ⅓ to 1 per cent is best for demonstrating the glycogen content of the living cervical epithelium.* Such application to the cervical tissue within half a minute stains the surface covered by normal epithelium a deep mahogany-brown color. Carcinomatous epithelium, on the other hand, remains unchanged and white. An area which fails to be stained by iodine may be an area of early surface carcinoma or an area of hyperkeratosis such as occurs in prolapse of the uterus or, less frequently, as a result of syphilis or as a constitutional abnormality. Although the areas of hyperkeratosis are assumed by some to predispose to malignant change, there is little evidence for this. Areas which fail to be stained by iodine also may be produced by trau-

*Iodine—1 Gm. Potassium iodide—2 Gm. Water—300 c.c.

matic removal of the upper glycogen-storing layer of the epithelium. Also, in the postclimacteric senile involution, after certain infections, or in generalized cachexia, it may be found that regressive changes of the cervical epithelium are associated with decrease or absence of glycogen content. In such cases the failure to stain with iodine normally is not limited to certain areas but tends to be diffused over the cervix and the vagina. Failure to stain with iodine has also been considered, particularly in France, to indicate estrogen deficiency. The iodine test is not applicable to differentiation of ulcerative carcinoma and erosion, both of which remain red after the application of iodine. Proper use of the iodine test as a routine procedure will result in discovery of some early carcinomas, and diagnosis in this stage gives a good chance of complete cure.

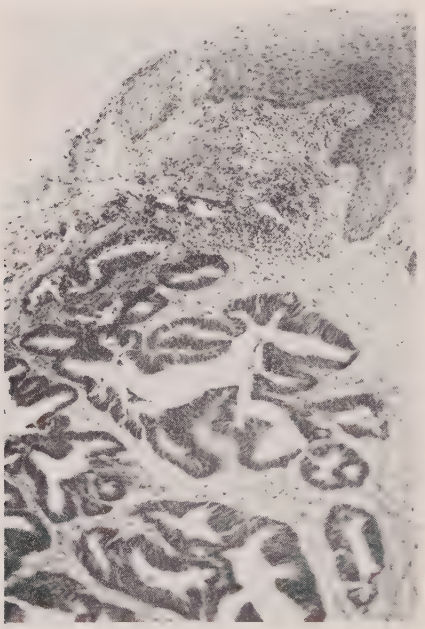

Fig. 922.—Adenocarcinoma of the cervix.

Vaginal smear methods for diagnosis of uterine cancer have been developed, and may be helpful, particularly as a screening procedure. In certain vertebrates, such as mice, vaginal smears have been of value in determining the phase of estrus cycle in experimental studies. In the human, Papanicolaou has devised a method of fixation and staining of vaginal smears which preserves excellent cellular detail. Such vaginal smears may not only be useful in determining the hormonal status of the individual but also sometimes reveal carcinomatous cells desquamated from a tumor in the cervical canal or the uterine cavity, even when the vaginal portion of the cervix appears normal. In such smears may be seen single cells or groups of cells which differ from the normal, are elements of bizarre shape with hyperchromatic nuclei and irregular cytoplasm staining in atypical fashion. A modification of this technique is suspension and fixation of material from the vaginal cervix in formalin, centrifugation, embedding of the sediment in paraffin, and cutting and staining by ordinary methods. Positive smears or sections which contain recognizable cancer cells are of diagnostic importance. Negative smears or sections do not rule out cancer, as some carcinomas do not shed tumor cells in all stages.

Etiology.—The high incidence of cancer of the cervix, which in this country causes more than 10,000 deaths per year, makes it important to investigate any possible etiology of this particular tumor. For many years it has been assumed that the chronic irritation of the cervix associated with erosions and lacerations is important as a cause of carcinoma, but increasing experience has failed to support this concept. The initial phases of carcinoma have not been found in the areas of erosions or lacerations. In the cases of early carcinomas which have been discovered, they do not appear to have originated from an area of inflammation.

Multiparous women appear to have a higher incidence of carcinoma of the cervix than women who have had few or no children. This does not appear to be explainable on the basis of lacerations of the cervix as carcinoma of the cervix is found in as high a percentage of multiparous women who have had no lacerations, and in those cases with lacerations the tumor is not found localized within the lacerated area. The high incidence of cancer of the cervix in multiparous women would appear to be related more probably to the higher content of estrogenic hormones during pregnancy as there is evidence that estrogenic substances have some carcinogenic activity. However, the high proportion of carcinomas of the cervix which occur after the menopause or after castration seems to indicate that the sex hormones play no very important etiological role. The greatest degree of prolonged irritation of the cervix occurs in cases of uterine prolapse where there may be not only mechanical irritation of projecting cervical tissue, but also thermic irritation due to exposure to the lower temperature of the air and chemical irritation by urine. However, the incidence of cancer of the cervix is not only relatively lower in cases of prolapse than in uteri in normal position, but actually the occurrence of carcinoma of the cervix is uncommon in cases of prolapse.

Adenocarcinoma of the Cervix.—Adenocarcinoma originating from cervical glands is much less frequent than the solid carcinoma which develops from the squamous epithelium, being found in a ratio of from 1:50 to 1:80. This relative incidence would be expected to be reversed if chronic irritation due to inflammation were important etiologically, as it involves the area lined with columnar epithelium more frequently and severely than the squamous epithelial portion. The simultaneous presence of an adenocarcinoma and a squamous carcinoma of the cervix is not more fre-

quent than would be expected from a coincidence. Early adenocarcinomas of the cervix appear to originate from the depths of glands and not from superficial areas where inflammation is most prominent.

Adenocarcinoma of the cervix shows the same variations of differentiation as does adenocarcinoma of the endometrium and may be described and classified in a similar fashion. Those which are most differentiated show secreting cells arranged around the lumen and so reproducing glandular structures. Those which are less differentiated show production of solid masses of tumor cells without polarity or glandular structure. In those cases in which there is little gland formation, there is similarly little production of mucin, although in some cases such mucin production may be continued and distend the cytoplasm of cells. As most of the adenocarcinomas of the cervix originate deep in the cervical wall and reach the surface only after they have infiltrated and penetrated the entire wall, they tend to become clinically evident only at an advanced stage and hence give less opportunity for cure. In most cases when adenocarcinoma of the cervix is clinically manifest, the tumor cells have already invaded the perivascular lymphatics of the large vessels and thus have gained access to the parametrium.

Some of the adenocarcinomas differ from the others in that they are composed of smaller lower cells with dark-staining cytoplasm and little or no tendency to mucin production. These tumors appear to develop from vestigial remnants of Gartner's duct which are located in the lateral part of the cervical wall. These tumors are usually characterized by the formation of narrow ducts lined by low columnar or cuboidal cells having deeply staining cytoplasm. The ductlike structures form a network by anastomosing with each other at acute angles.

Carcinoma and Pregnancy.—Clinical observations have tended to indicate that carcinoma of the cervix grows and spreads more rapidly if associated with pregnancy. This may be due to stimulation of the tumor tissue by the large quantities of hormones present during pregnancy. However, it is more likely that the stimulation of the tumor is brought about by the hyperemia and edema of tissues in and around the uterus during pregnancy.

Endometrium

Normal Endometrium

In the fallopian tubes and uterus, organs which originate from the Müllerian duct, both the lining epithelium and the wall originate from the same celomatous matrix. During fetal development, the lining epithelium and the subepithelial stroma of the wall reproduce one another, and it is probable that, in adult life, there may similarly be reproduction of epithelium by stroma, and vice versa. The relationship between the lining mucosa and the muscular wall is much closer than in the case of the intestinal tract, and there is no separation of the mucosa from the muscular wall by a submucosa. In the endometrium the glands are embedded in a specific stroma which normally is well demarcated from the muscle bundles and connective tissue septa of the uterine wall. The specific stroma of endometrium is traditionally referred to as cytogenic tissue.

The endometrial glands differ in several respects from cervical glands. The endometrial glands have a straight course without ramifications, and they are roughly parallel to each other at right angles to the mucosal surface. The columnar cells of the endometrial glands are lower than the cervical epithelium and have a deeper staining cytoplasm. The epithelial cells produce fine droplets of secretion which, on discharge, leave the upper edge of the cell jagged.

The most important function of the endometrium is to provide a matrix for the embedding of a fertilized ovum. During normal, regular ovulation, which occurs at intervals of about four weeks, the endometrium after each ovulation undergoes changes in preparation for embedding of an ovum. If, however, the ovum is not fertilized, the prepared endometrium becomes cast off by menstruation, following which it is again regenerated. The intermenstrual interval of about four weeks begins by one or two days of regeneration, during which the rough surface becomes covered over by epithelium which originates from the epithelium of stumps of glands remaining after menstruation. Initial phases of this regeneration appear to be independent of hormonal stimulation, and a similar type of regeneration may be observed following endometrial curettage in a castrated woman. During later phases of this regeneration, the endometrium becomes stimulated by estrogen from the ovary. The estrogen stimulates the glands to become longer, and the endometrium as a whole thickens. This period of change from the time of early regeneration up to ovulation is called the proliferative phase. After ovulation, which usually occurs 14 to 16 days after the onset of the last menstruation, the ruptured follicle is transformed into a corpus luteum which releases progesterone into the circulation. The progesterone stimulates the endometrial glands to active function, their effect being characterized microscopically by tortuosity of the glands and evidences of secretion. This phase of secretion is evident about two or three days after ovulation, which is the time required for transformation of the ruptured follicle into a corpus luteum which produces suf-

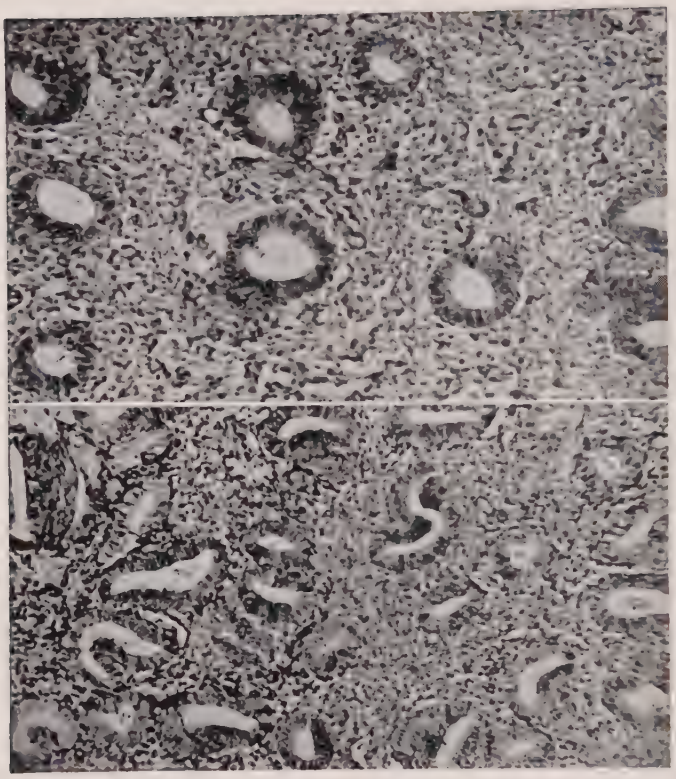

Fig. 923.—Endometrium in proliferative phase. The rounded and regular glands in some areas are lined by several layers of cells. (From Anderson, Synopsis of Pathology. The C. V. Mosby Co.)

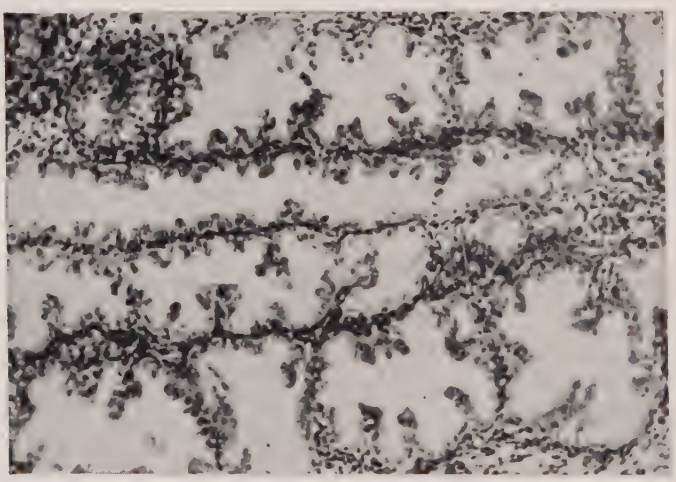

Fig. 924.—Endometrium in secretory phase. Note the irregularity of the glandular linings. (From Anderson, Synopsis of Pathology.)

ficient progesterone. The first progesterone produced by the corpus luteum is derived from theca cells, the luteinization of which precedes the luteinization of the granulosa cells, but which is temporary and ends two or three days after ovulation when luteinization of the granulosa is completed. The corpus luteum not only produces progesterone but also continues to form estrogen so that the stimulation to proliferation of endometrium by estrogen continues after ovulation, as is evident by increased thickness of the endometrium and increased length of the glands. Prior to actual secretion, the cells of the endometrial glands undergo distinct histologic changes. The nuclei of the epithelial cells, which previously were at the base, ascend to the middle part of the cells and the underlying basal part of the cells becomes pale and translucent. This midposition of the nuclei is found usually about two days before the onset of secretory changes.

If the ovum fails to be fertilized, the corpus luteum ceases production of progesterone about ten days after ovulation, and about two or three days later the effects of the withdrawal of progesterone are evident in the endometrium.

The cyclic changes of the endometrial mucosa affect the stromal tissue as well as the glands. In the proliferative phase the stroma consists of densely arranged oval or round cells with deeply staining rounded nuclei. In the secretory phase the stromal cells become larger and rounder and tend to be separated from each other by spaces bridged over by fine protoplasmic projections connecting the cells. The nuclei of the stromal cells become vesicular and are paler than in the proliferative phase.

The cyclic changes of the glands and stroma do not involve all layers of the endometrium as the basal part remains inactive. This inactivity is particularly evident in the small extensions or projections of the endometrium which are often seen extending from the innermost part of the mucosa into the underlying endometrium. These small endometrial projections and the adjacent inner layer of endometrium is referred to as the inactive basalis, whereas the upper layers which undergo changes are called the active functionalis. Within this latter functional layer, different portions show varying degrees of response to progesterone. Tortuosity and distention by secretion normally are found only in the middle zone of the endometrium where the distention of the glands and reduction of interstitial tissue may result in an appearance simulating adenoma. This middle zone of the endometrium has been called the spongiosa. In a small zone beneath the surface epithelium the glands remain straight and inactive during the secretory phase so that the stromal changes here predominate over the glandular changes, and this zone has a compact appearance (zona compacta). The inactivity of the basal layer evidently serves to preserve this region as a basis for postmenstrual regeneration. The inactive outer compact zone has been thought by some to prevent the escape of glandular secretions before menstruation.

TABLE XV

HISTOLOGY OF THE MENSTRUAL CYCLE

DAY OF CYCLE	OVARY	ENDOMETRIAL PHASE	ENDOMETRIAL HISTOLOGY
1 to 4	Degenerating corpus luteum	Menstrual	Infiltration of leukocytes, degeneration and breakdown of endometrium; hemorrhage and sloughing of endometrium
5 to 12	Developing follicle Mature follicle	Proliferative (estrogen)	Regeneration of endometrium from basalis. Glands rounded, regular, with piled-up cells; mitoses; stromal cells elongated, spindly with scanty cytoplasm
13 to 15	Ovulation	Secretory (estrogen plus progesterone)	Glandular epithelium lines up in single layer; subnuclear vacuolization, followed soon by peripheral vacuolization of glandular epithelium with basal nuclei, glands tortuous, saw-toothed; stroma edematous in early stages, later stromal cells swollen, rounded, finally decidua-like; congestion of blood vessels and infiltration of polymorphonuclears and lymphocytes in final stages
16 to 28	Corpus luteum		

ANOVULATORY MENSTRUATION

The endocrine mechanism of menstruation by growth and regression of a corpus luteum formed from the empty follicle after ovulation is not the only one possible. There are menstruations which are not preceded by ovulation and consequently not controlled by a corpus luteum.

They otherwise clinically duplicate postovulatory menstruation so completely that differential diagnosis between the two types cannot be made by clinical observation, but only by special tests, such as suction currettage in the premenstrual period. The endometrial glands if not stimulated by progesterone show neither tortuosity nor secretion. Anovulatory menstruation in the normal individual is frequent after the menarche and in the premenopausal period.

The mechanism of menstruation as far as the endometrium is concerned is founded on its specific type of vascularization. The lower strata of the endometrium have a network of thin-walled anastomosing capillaries. For the upper layers small arterioles ascend from the subendometrial myometrium. They pass the lower strata without branching. This they do only after having reached the upper strata. These branches do not anastomose with other arterioles, and thus are real endarterioles. They are called spiral arteries, because when the endometrium becomes thinner they shorten by forming spiral tours. In menstruation they contract so that the upper strata of the endometrium receive no blood, and become first ischemic, then necrotic, and finally are shed.

Some observers do not admit the menstrual character of the anovulatory cycles, and suggest that they should be called "cyclic bleedings."

Ectopic Endometrium

Endometrial mucosa, characterized by its glands and specific stroma, normally is limited to the lining of the uterine cavity, developing only in the upper part of the area along which the two Müllerian ducts fuse to form the body of the uterus.

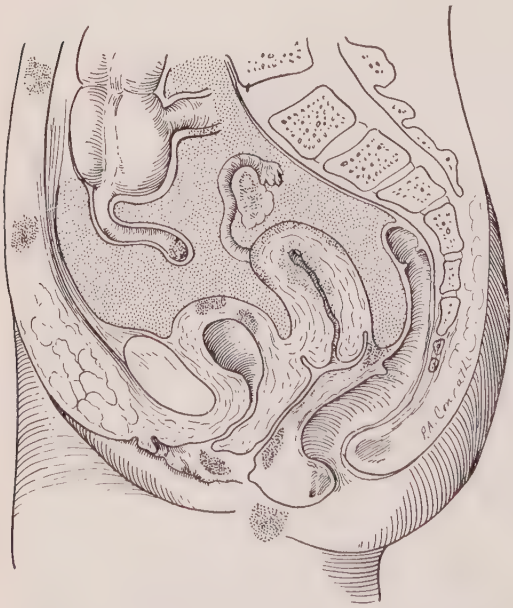

Fig. 925.—Common locations of ectopic endometrium in the abdomen are shown by the areas of stippling.

Many abnormal locations of endometrial tissue have been observed since Recklinghausen in 1893 published a monograph about endometrial inclusions in the wall of the uterus and tube, which he erroneously believed to derive from remnants of the mesonephros. All of these may be included under the term "ectopic endometrium," signifying endometrium in locations other than the lining of the uterus. Two terms commonly used in referring to ectopic endometrium are "endometrioma" and "endometriosis." While, strictly speaking, endometrioma should be used for focal, local endometrial neoplastic changes only, it is often used for single foci of ectopic endometrium without neoplastic character, whereas endometriosis refers to multiple foci without neoplastic character.

Ectopic endometrial tissue has never been found in the male, but in the female occurs in the uterine wall, in leiomyomas of the uterus, in the fallopian tube, the peritoneum, the ovary, the vagina, in extraperitoneal tissues such as the umbilicus, in laparotomy scars, in the groin, the vulva, the perineum, and the extremities.

Ectopic Endometrium in the Uterine Wall (Endometriosis or Adenomyosis Uteri Interna).—Spreading of the uterine mucosa into septa of the underlying myometrium is referred to as "adenomyosis," i.e., proliferation of glandular tissue in the muscularis, as well as by the more specific term endometriosis. Invasion of myometrium from intrauterine mucosa and involving the inner layers of the myometrium is called adenomyosis uteri interna, and is to be distinguished from endometriosis uteri externa, which is an invasion of the outer part of the myometrium from the peritoneal ectopic endometrium located at the uterine perimetrium. In endometriosis uteri interna the ectopic glandular islands develop directly from and are identical with the endometrium lining the uterus.

Adenomyoma of the Uterus.—Some myomas possess multiple endometrial inclusions between the muscle bundles, and are termed adenomyomas. Usually they do not grow very large, have no capsule, and are not sharply demarcated from the surrounding myometrium. The endometrial inclusions do not develop from the endometrium lining the uterine cavity, nor do they derive from the perimetrium. For their origin local foci of undifferentiated cells with the latent potentiality for producing endometrium must be assumed. Adenomyomas must be distinguished from a focal or localized adenomyosis.

Endometriosis and Adenomyosis of the Fallopian Tube.—Adenomyosis of the tube refers

to islands of tubal mucosa in the muscular wall of the tube, developed from the tubal mucosa by downgrowth.

Endometriosis of the tube signifies islands of endometrial character in the muscular wall of the tube developing by local downgrowth from tubal mucosa of abnormal endometrial character, or by local transformation of the islands of a tubal adenomyosis into endometrial character.

Endometrial lining of the tube may originate:

1. From developmental error. The portion of the Müllerian duct destined to form the tubal mucosa may assume the properties of the lower end of the ducts which form the endometrium, so that the tubal mucosa may duplicate uterine mucosa. From this there may be invasion of underlying tubal muscular wall. Such developmental origin of tubal endometriosis is doubtful or at least very rare.

2. From postfetal extension. Such overpassing of a border line frequently occurs where two types of mucosa meet. Also, there may be an extension of an adenomyosis of the uterus into the adjacent muscularis of the central part of the tube.

3. From implantation. Sampson developed a theory that ovarian and peritoneal endometriosis originates from implantation of endometrial fragments from retrograde menstrual flow, as he found fragments of endometrium and blood clots in the lumen of the tubes during or after menstruation. Novak doubted this origin, as he considered the fragments too large to have passed through the narrow intramural part of the tubal lumen. He suggested that they arise from ruptured peritoneal or ovarian endometrial cysts and enter the distal end of the tube. With either interpretation, it is assumed that endometrial fragments become implanted in the tubal mucosa, and by invasion of the muscularis give rise to tubal endometriosis.

Local transformation of tubal adenomyosis into endometriosis may occur in chronic salpingitis. The tubal mucosa frequently exhibits a tendency to invade the muscularis, particularly in the intramural and the adjacent interstitial portions of the tube, and is referred to as "salpingitis isthmica nodosa." Some observations indicate that there may be a secondary change of the inclusions from tubal to endometrial character. If such is the case, it would be referred to as a primary tubal adenomyosis of inflammatory origin with secondary change to endometriosis.

Peritoneal and Subperitoneal Endometriosis.—Small islands of endometrial tissue may be found in the peritoneal serosa of the anterior abdominal wall, the intestines, the uterus, or the uterine ligaments, extend to the peritoneal subserosa and finally invade the muscle wall. Peritoneal endometriosis does not involve the upper or supra-umbilical portion of the abdominal cavity. Common pelvic locations are the ovaries and the cul-de-sac. Involvement of the serosa of the uterus (endometriosis uteri externa) is of higher incidence on the posterior than on the anterior wall. About one-fourth of all cases of pelvic endometriosis are located in the cul-de-sac. In upper parts of the pelvis, endometrial islands are rarer, and usually are observed only in advanced cases of diffuse endometriosis. In the typical case of peritoneal endometriosis there are numerous tiny dull brownish foci, 0.5 to 10 mm. in diameter. If superficial and covered by intact serosa, the surface of each focus appears black or bluish and glistening.

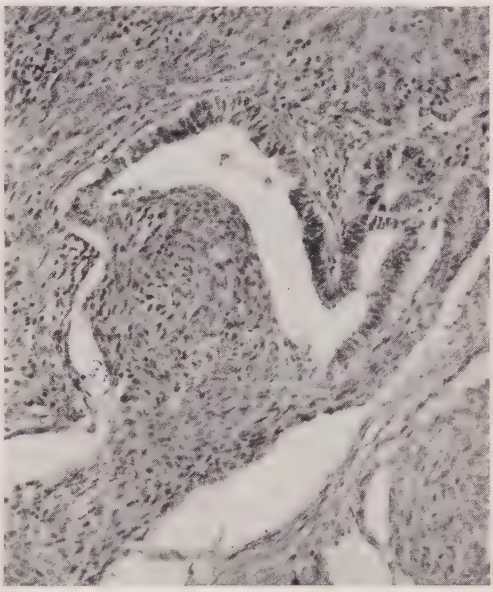

Fig. 926.—Endometriosis of fallopian tube, showing squamous metaplasia.

Endometriosis (Endometrioma) of the Ovary.—Ovarian endometriosis and endometrioma are important because of their high frequency. Unilateral ovarian endometriosis and endometriomas account for 36 per cent of all cases of pelvic endometriosis, and bilateral ovarian endometriosis for 28 per cent. Although morphologically and histogenetically analagous to or even identical with peritoneal endometriosis elsewhere, ovarian endometriosis, has been classed as a separate type because the surface of the ovary is covered, not by peritoneum, but by cuboidal cells without a subserosa, formerly referred to as "germinal epithelium."

Endometriosis of the Vagina.—Vaginal endometriosis may appear in women in the child-

bearing age as multiple, dark brown nodules, 1 to 4 mm. in diameter. Microscopically, they show glands of endometrial character surrounded by stromal tissue. There is evidence that they may arise by implantation of endometrial fragments shed during menstruation. Similar endometrial foci are sometimes found in areas of the vulva contacted by menstrual flow.

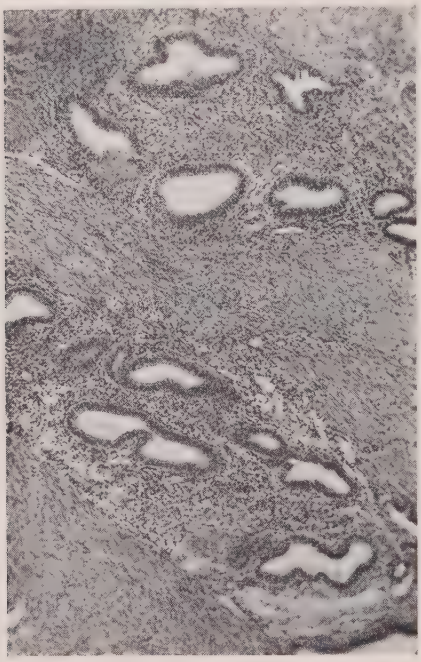

Fig. 927.—Subperitoneal endometriosis. Endometrial islands beneath the serosa of the sigmoid consisting of inactive glands and dense cytogenic tissue.

Endometriosis of Extraperitoneal Tissues.—Extraperitoneal endometriosis (1) may develop by extension from subperitoneal foci or by direct implantation from the peritoneum, or (2) may have no relation to the peritoneal serosa. Most of the former develop in the umbilicus and in laparotomy scars of the anterior abdominal wall. The latter are less frequent and involve locations near the peritoneum, such as the groin, the perineum, and the pelvic retroperitoneal connective tissues.

Endometrial inclusions of the umbilicus appear as slightly projecting brown or bluish nodes. They may or may not have narrow fistulas, which bleed at the time of or shortly before menstruation. There is evidence in some cases that the endometriosis started in the peritoneum by implantation or by local prosoplasia, and extended by proliferation through the abdominal wall to the external skin surface.

Fistulas developing in operative scars of the abdominal wall, from a few weeks to several years after the operation, on microscopic examination may show endometrial tissue adjacent to the fistulous tract. Some occur after operations which involve opening the uterine cavity, e.g., Cesarean section, when direct implantation of endometrial fragments is possible. Such foci and fistulas have developed after surgical fixation of the uterus to the abdominal wall, the endometrium proliferating along the silk sutures. Others develop after laparotomies in which the uterus was not involved, e.g., after appendectomies, some in young girls before the menarche. Implantation during menstruation cannot be the only mechanism to produce endometriomas.

Identification of Ectopic Endometrium.—Extrauterine glandular inclusions may be identified as ectopic endometrium by morphological or by functional criteria. While some accept them as ectopic endometrium if the glandular epithelium is similar to endometrial epithelium, others require that there be typical cytogenic tissue around the glands also. Still more controversial are the physiologic criteria. Many consider that true ectopic endometrium must be functionally identical with intrauterine endometrium, by duplicating its cyclic changes and its pregnancy changes.

The intermenstrual cyclic changes are frequently absent in ectopic endometrium, a fact which is not a decisive argument against their endometrial nature. Endometrial tissue of abnormal origin and location may be unable to respond to hormones as does normal endometrium.

Ectopic endometrium does not always participate in menstruation. If enclosed ectopic endometrium goes through a cyclic bleeding, the blood cannot escape, and remains as an old blood clot or as blood pigment. In many cases no such traces of previous hemorrhages are discernible.

Cyclic bleeding from extrauterine organs may be a vicarious menstruation, and as such not related to the presence of ectopic endometrial tissue.

Changes in ectopic endometrium associated with pregnancy are more often decidual transformation of the stroma than the presence of Opitz pregnancy glands in the glandular component. Changes with pregnancy are more frequent than intermenstrual cyclic changes. The presence of cells of decidual type is not by itself complete evidence for the endometrial nature of the tissue, as ectopic decidua can be found during pregnancy in various, mostly subperitoneal, locations as produced by changes in the stroma of various organs without ectopic endometrium.

Functional identity of ectopic endometrium with intrauterine endometrium also may be indicated by involution and atrophy at the menopause or after surgical or radiologic castration. Most ectopic endometrial foci show dependence on ovarian hormones. However, some cases of endometriosis of the rectovaginal septum continue to show proliferation and invasion after withdrawal of ovarian hormones. Such tissue behaves like an autonomous malignant neoplasm, but without malignant appearance microscopically, and without a tendency to metastasize.

The response of ectopic endometrium to the administration of male sex hormones is in many cases like that of uterine endometrium, as it undergoes regressive changes.

In summary, it may be said that evidence of functional identity with uterine endometrium gives strong support to the morphological evidence of the endometrial character of the tissue, but absence of such functional identity is insufficient to prove that the tissue is not of endometrial nature.

Etiology of Ectopic Endometrium.—Various theories of the origin and histogenesis of ectopic endometrium have been offered. It is likely that no one single origin accounts for all cases, and that the same final result may be accomplished in different ways. The theories are of two types: (1) that ectopic endometrium is identical with and derived from intrauterine endometrium, i.e., it is dislocated intrauterine endometrium, or (2) that it is locally produced in the site in which it is found, by metaplasia or prosoplasia (adenscerositis theory of Meyer).

That ectopic endometrium is nothing but dislocated uterine endometrium, holds for endometriosis uteri interna, where direct extension from the endometrium can be shown by serial sections.

Sampson originated the concept that backflow of menstrual blood with lumps of endometrium may occur through the tube (retrograde menstruation), and that the fragments may become implanted in the tubal mucosa, or be carried through the distal opening of the tube to become deposited on the ovary or on adjacent serosal surfaces. Implantation on the cul-de-sac gives origin to the frequent endometriosis of that area, and by downgrowth it may extend to the rectovaginal septum. The ovarian implants may form cysts, often filled with old blood of brownish color, and hence referred as chocolate cysts. Such cysts may rupture, and viable endometrial tissue from their lining start new endometrial foci on other areas of the pelvic peritoneum. Some structures which appear grossly as chocolate cysts prove on microscopic examination to be cystic corpora lutea with hemorrhage into the lumen. Novak rejected Sampson's theory of origin from menstrual endometrium, believing that the endometrial fragments encountered in the tubal lumen were too large to have passed through the narrow interstitial part. He suggested that such fragments might arise from foci of peritoneal endometriosis of local origin, and enter the tubal lumen in a fashion similar to that of the ovum. Other observers, such as Philipp and Huber, assumed that the endometrial implants may arise from abnormal endometrial mucosa of the tube, shed off either at the time of menstruation or possibly in the intermenstrual interval, rather than from uterine endometrium. The theory of retrograde tubal transportation from the uterine endometrium receives some support from the fact that small groups of tumor cells have been found in the tubal lumen in cases of carcinoma of the endometrium.

Direct implantation from menstrual flow has been considered in cases of endometriosis of the vagina and of parts of the vulva exposed to the menstrual outflow.

There have been many arguments for and many against the implantation theory of endometriosis. The frequency of involvement of the ovary (60 per cent) and of the cul-de-sac (25 per cent) has favored the tubal implantation theory as these areas are the nearest to the distal opening of the tube. But such preferential localization is explainable also on the basis of local prosoplasia, since these areas are near to Müllerian duct tissue which possesses latent metaplastic and prosoplastic potentialities.

Animal experiments have not tended to support the menstrual backflow theory. Dissemination of endometrial tissue by lymphatics or by the blood stream, in a fashion similar to that of malignant tumors, has been suggested, but there is insufficient evidence that this occurs.

A great part of ectopic foci of endometrial tissue may develop locally from the involved tissue, rather than be the result of implantations of cells from the uterine endometrium. Cells forming the lining of the coelomic cavity probably have originally, in embryonic life, the prospective potency to differentiate into endometrial tissue. Normally, these potentialities are developed only in the portion which forms the lower part of the Müllerian duct. But such potentiality to form endometrial tissue by developmental error may persist and be reawakened in adult life by some unspecific stimulus, and thus give rise to focal development of endometrial tissue. Stimuli which have been thought to bring about such abnormal differentiation include inflammation (Meyer) and hormonal imbalance. Other evidences of hormonal disturbance, such as endometrial hyperplasia and endometrial polyps, frequently accompany endometriosis. The control of the ectopic endometrium by ovarian hormones is shown by the involution which may occur after menopause or castration. The rare cases of endometriosis involving extremities are explainable by the fact that in the fifth or sixth week of fetal life there is close proximity of the mesenchymal cells which will form the extremities and the celomic tissue (Gruenwald), so that a few celomatous cells with the potentiality of differentiating into endometrial tissue could by error be carried into the extremities. It is probable also that the endometrial inclusions in uterine adenomyomas have a local origin, as they cannot be traced back to the lining of the uterine cavity nor to the serosa.

Endometriosis Interstitialis.—While in the uterine endometrium there occurs considerable variation in the quantitative relations of the glands and cytogenic stroma, still greater variation is observed in ectopic endometrium. Usually in ectopic endometrium the glandular component is predominant, the stroma being small in amount or absent. Particularly on a surface (e.g., that of ovary) islands of endometrium tend to have little or no stromal tissue, and also are more likely to undergo cystic dilatation.

The occurrence of ectopic masses of cytogenic stroma without accompanying glands also has been described (Goodall, 1940) and termed endometriosis interstitialis. It is limited to the uterus and broad ligament. Invasion and spread of the stromal tissue appears to be by lymphatic channels and spaces; on the transverse cut surface of an involved broad ligament it may appear as yellowish projections which can be pulled out by forceps as smooth, elastic wormlike casts. The proliferation and invasion of the cytogenic stroma does not have the destruc-

tive action of cancerous invasion, and distant metastases do not occur. However, secondary malignant change in the tissues has been observed in a few cases.

Hyperplasia of the Endometrium

Endometrial hyperplasia is an important pathologic condition because of its high incidence and associated bleeding. Conceptions vary as to what should be included under this diagnosis, and there is no agreement as to the essential changes. The endometrium may be thickened up to 8 mm. or even more. The thickening may be due to increase in number of glands (glandular hyperplasia) or to predominant increase of stroma with relatively fewer glands (stromal hyperplasia). In the glandular hyperplasia, the excessive glands are irregularly distributed and run in various directions rather than parallel to one another.

In glandular hyperplasia, the glands may be secretory, but more commonly are of the proliferative type. In the hyperplasias in which the glands are tortuous and actively secreting, there often is an associated corpus luteum cyst which produces an excess or a prolonged concentration of progesterone. A valuable histologic criterion of this type of hyperplasia is a secretory activity of the normally inactive basal portion of the endometrium and the abolition of the partition of the endometrium into basal, spongy, and compact layers.

Glandular hyperplasia more often shows to an abnormally high degree the endometrial characteristics of the proliferative phase of the cycle. This change has been considered due to excessive or prolonged stimulation by estrogenic hormone, and may be associated with single or multiple follicular cysts of the ovary. Such cysts have been assumed to be the source of the excess estrogen, although hormone assays of the cyst contents have yielded contradictory results. Prolonged administration of estrogenic hormones to castrated women and to experimental animals has resulted in a similar glandular hyperplasia of the endometrium.

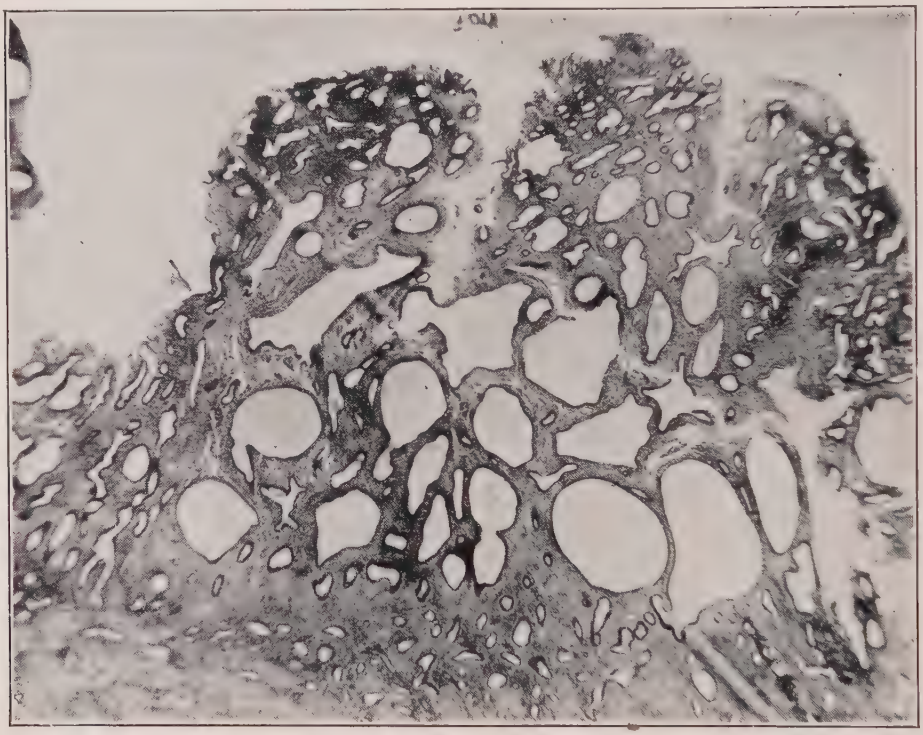

Fig. 928.—Hyperplasia of the endometrium. "Swiss cheese type." (From Crossen and Crossen, Diseases of Women, The C. V. Mosby Co.)

Characteristic of a special type of endometrial hyperplasia is a dilatation of glands into small cysts containing a serous fluid. This variation in the size of the glands with cystic dilatation gives a section an appearance reminiscent of Swiss cheese, and hence the term "Swiss cheese endometrium." The cystic glandular change is particularly frequent in hyperplasias occurring near or shortly following the menopause. Sometimes only a portion of a gland,

particularly the basal part, shows the cystic distention. A similar cystic change often occurs in remaining glands in the atrophic senile endometrium. The cystic dilatation may be a manifestation of a regressive or degenerative factor, rather than due solely to hormonal imbalance or excessive hormonal stimulation.

Most consideration has been given to the presence of excessive hormone stimulating the endometrium as a cause of hyperplasia. This has received support from studies which have shown excess of ovarian hormones in cases of hyperplasia, and from the reproduction of hyperplasia by administration of excess hormone. However, in some cases hormonal abnormality is not demonstrable, and endometrial involvement is focal or patchy rather than diffuse. Such cases may possibly be explained by an abnormal responsiveness of endometrium, either locally or diffusely, to normal hormonal stimulation.

Endometrial Polyps

Localized and irregular areas of thickening of the endometrium are common with endometrial hyperplasia. This polypoid endometrial hyperplasia differs from true polyps in that it consists only of a thickened mucosa, and lacks a connective tissue core containing blood vessels.

The endometrium composing the polyp may be of hyperplastic or of normal appearance. In the latter case the endometrium has the functional inactivity characteristic of the basal layer, and only uncommonly does it undergo cyclic changes. As the polyp grows it tends to fill the uterine cavity and become molded to its shape, forming first a cylindric and later a peculiar triangular or heart-shaped mass with a short pedicle. The presence of uterine submucous myomas distorting the cavity may also result in distortion of the polyps. Pressure on veins draining the polyp, or kinking of the pedicle frequently results in stasis and passive congestion of the polyp, followed by diapedesis of blood and frequently hemorrhage from rupture of small vessels near the tip. Softening and dark red discoloration, particularly near the tip of the polyp, result from the congestive changes with degeneration and necrosis.

Endometrial polyps, like the hyperplastic endometrium with which they are often associated, may be an effect of hyperestrinism. Cancerous change occasionally occurs in and may be limited to the endometrium of a polyp. It occasionally happens that such malignant tissue of a polyp is removed completely by curettage, and on subsequent removal and examination of the uterus, no remaining carcinomatous tissue can be found.

Metaplasia of the Endometrium

Glandular or surface epithelium of the endometrium may undergo changes of either tubal or squamous character. Epithelium of tubal type is most often found near the tubal ostia or in the fundus. A squamous change may be found as small nodes of cells bulging into the lumen or more frequently outward from the walls of glands. Squamous metaplasia is found mainly in the reproductive age, but has no constant relationship to pregnancy, hormonal imbalance, or inflammation. The metaplastic change is not malignant, nor does it appear to predispose to cancerous change, though it may follow the development of endometrial carcinoma.

Endometritis

Endometritis most often develops from infected parturition or abortion, complicates carcinomas of the cervix, or is a secondary infection extending from neighboring organs. The normal endometrium is rather resistant to bacterial invaders, but infection is favored by the presence of necrotic tissue, such as retained placental or decidual remnants or degenerated polyps. The inflamed endometrium is reddened from congestion and thickened by edema and congestion.

In mild cases of endometritis the microscopic diagnosis is made more difficult by the fact that a few neutrophiles, lymphocytes, and plasma cells may be present in a normal endometrium shortly before or after menstruation. Also, the normal decidua regularly presents some infiltration by leukocytes. The presence of plasma cells in any considerable number favors the diagnosis of endometritis.

Gonorrheal inflammation of the endometrium occurs in the spread of the infection from the cervix to the fallopian tubes. The inflammatory infiltration at first is composed mainly of neutrophilic leukocytes, but, later, after about three weeks, lymphocytes and then plasma cells predominate. The gonococcal infection rarely becomes chronic in the endometrium.

Tuberculous endometritis most often is an extension from a tuberculosis of a fallopian tube, but also may be of hematogenous origin from a more distant focus. The tuberculous foci of the endometrium begin in the stroma, and show the histologic features of tubercles elsewhere, although caseation is usually absent or slight. Adjacent glands show piling up of the epithelium. During the reproductive period the endometrial tubercles become cast off during menstruation before there is opportunity to become very large.

Carcinoma of the Endometrium

Carcinoma of the endometrium occurs with only about one-tenth the frequency of squamous carcinoma of the cervix, but is ten times as frequent as adenocarcinoma of the cervix. It occurs at an average age of about 55 years, ten to fifteen years later than the average age of cervical carcinoma.

Endometrial carcinoma appears to originate in either of two ways. It may begin as a diffuse malignant transformation of the endometrium, possibly multicentric in its beginnings. Other cases begin in a local area and by proliferation form a localized tumor mass before involving other more distant areas of the endometrium. They form soft irregular

masses originating at or near the fundus, usually quite definitely demarcated, projecting into uterine cavity and over the surface of adjacent endometrium. A proliferative mass of tumor projecting into the uterine cavity almost always develops before invasion of the myometrium occurs. The soft tumor mass which projects into and sometimes distends the uterine cavity shows an irregular surface with pale areas of ischemic necrosis. Advanced endometrial carcinoma spreads beyond and abolishes the demarcation line of the internal os, rather than stopping there abruptly as in the case of endometrial hyperplasia.

and the broad ligament contribute to this slower spread. After reaching the fundal serosa, endometrial carcinoma rarely gives origin to peritoneal carcinomatosis. Invasion of the bladder occurs particularly in carcinomas which penetrate the lower anterior wall of the uterus. Early stages of invasion of the muscular wall of the bladder, indicating inoperability, may give rise to a bullous edema of the mucosa of the bladder evident on cystoscopic examination. The rectum becomes invaded usually only in late stages. Lumbar lymph nodes near the lower end of the aorta become involved in tumors originating in the upper part of the uterus. Hypogastric nodes near the bifurcation of the iliac arteries less commonly become involved first in cases in which the carcinoma extends through lower parts of the myometrium. In rare cases of endometrial carcinoma small masses of tumor cells are found within the lumen of a fallopian tube.

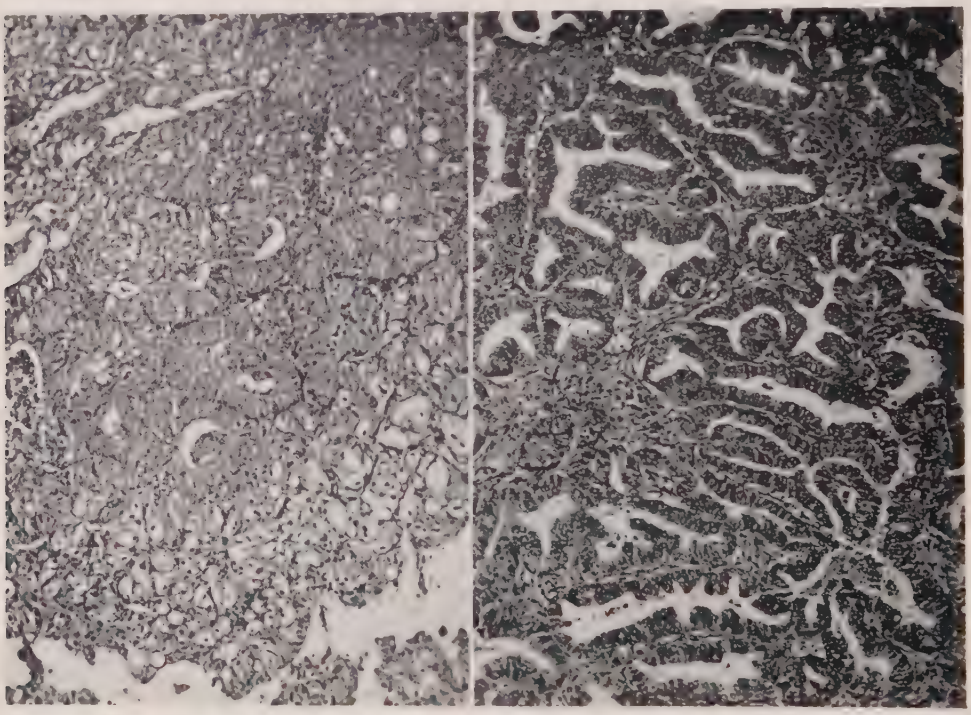

Fig. 929.—Carcinoma of the endometrium.

Clinical evidence suggests that the phase of purely exophytic growth toward the uterine cavity may last from a few weeks up to two or three years before invasive growth into the myometrium begins. Invasive growth into the myometrium is very slow, and the uterine cavity may be distended by soft, partially necrotic carcinomatous tissue while the myometrium may be invaded only to a depth of 1 or 2 millimeters.

Several months to a few years may pass before the invading carcinoma reaches the serosal surface of the myometrium. The progress tends to be slower than in the case of cervical carcinoma. The smaller vessels and perivascular lymphatic spaces in the fundus as compared to the cervical region

The microscopic structure of endometrial carcinoma varies from highly differentiated to undifferentiated forms, and a tumor which begins in well-differentiated form may become undifferentiated and anaplastic in late stages. In the well-differentiated form the tumor cells are columnar and arranged in well-formed glandular structures, but have large and hyperchromatic nuclei. Some of the neighboring glandular structures border on each other without any separation by stromal

tissue of epithelial cells of adjacent glands (back-to-back position). In the undifferentiated or anaplastic form the tumor cells are rounded, polyhedral or polymorphous, and their hyperchromatic nuclei are deformed and variable in size. The tumor cells may grow in irregular or solid masses, with only poor attempts at gland formation. Such glandular structures as may be formed may be simply a retained tendency to form a lumen lined by epithelial cells even without any participation by stroma (intraepithelial pseudoglands).

Etiology.—No etiological relationship of endometrial carcinoma has been established with any type of endometritis. Experimental hyperestrinism in animals and artificial hyperestrinism in women have not resulted in endometrial carcinomas. Nevertheless, a sequence of hyperestrinism, endometrial hyperplasia, and endometrial carcinoma seems to be followed in some cases, but certainly not in all. The relationship of endometrial hyperplasia to the development of carcinoma has been reported as frequent by some investigators and rare by others. The discrepancy probably arises from different criteria used in interpreting endometrial changes as hyperplasia. In those cases in which carcinoma followed hyperplasia, it was not the functional hyperplasia of the reproductive age, but the menopausal or postmenopausal type usually associated with a late menopause and absence of the normal postmenopausal involution. The high incidence of a late menopause in cases of postmenopausal endometrial carcinoma is one of the few well-established facts pointing to endocrine disturbance as a contributing factor in cancer of the endometrium.

Sarcoma of the Uterus

Sarcomas constitute less than 5 per cent of malignancies of the uterus. The age of highest incidence is 45 to 50 years. More cases occur before than after the menopause, but with a peak incidence in the climacteric period. As about two-thirds of all uterine sarcomas develop from myomas, it is consistent that the relatively high incidence of sarcoma should be about the menopausal age, a period in which myomas reach their maximum growth and development. Little is known about any causative role played by trauma, heredity, endocrine disturbance, or multiparity in the causation of uterine sarcoma.

Sarcoma of the uterus may originate from the muscle or connective tissue of the uterine wall, from the muscle or connective tissue of uterine myomas, from the stroma of the endometrium or from stroma of the cervical mucosa. In advanced cases the origin may be difficult to determine. Sarcomas originating from the endometrium tend to have a more diffuse type of proliferation, whereas sarcomas developing from myomas or from myometrium tend to produce circumscribed or demarcated homogeneous tumor masses. Sarcomas originate about four times as frequently from the body as from the cervix, more frequently from the uterine wall than from the mucosa, and more frequently from myomas than from myometrium. Those arising from myomas are usually from the small cellular myomas rather than from the large myomas which have exhausted most of their proliferative activity. Position of the myoma seems to have no influence. Rarely there appears to be multicentric origin from more than one myoma. The incidence of sarcomatous change in uterine myomas is probably less than 1 per cent, although higher figures have been given in some statistical series. The actual cellular origin is probably from undifferentiated mesenchymatous cells which are capable of developing into either smooth muscle cells or fibroblasts, and which normally contribute to the hypertrophy of the uterus during pregnancy, rather than from the differentiated cellular elements of a myoma or of myometrium.

The sarcomatous tissue usually appears as soft masses of whitish or pale pink color, and without distinct structural markings. Reddish areas of necrosis and hemorrhage may be present; such areas may undergo liquefaction forming irregular cavities containing semifluid brownish amorphous material. Myomatous tissue which has undergone sarcomatous change appears soft, white, and homogeneous, in contrast to the firm, striated or lobulated, better-vascularized tissue of a myoma.

Microscopically, sarcoma of the uterus may consist predominantly of undifferentiated small round cells (26 per cent), of more differentiated spindle cells (42 per cent), or multinucleated giant cells or cells with giant nuclei, mixed with round or spindle cells (32 per cent). The three cell types may be mixed, or different areas of the same tumor may show predominance of one or another cell type. Metastases often show a cell type different from the primary growth. Sarcomas of the round cell type are least frequent, of the highest malignancy, and arise mainly from myometrium or from myomas. Sarcomas developing from the stroma of endometrium or cervix often are of spindle cell type, and appear to be less malignant than the round cell sarcomas. In some spindle cell sarcomas transition to smooth muscle fibers

may be observed. Necrosis appears to result from failure of the blood supply to keep pace with the tumor growth. Directly around blood vessels the tumor cells may be preserved.

Microscopic differentiation of a cellular myoma and a spindle cell sarcoma may be difficult. Evidence favoring a sarcoma includes absence of distinct septa and of vessels of larger caliber, and homogeneous masses of immature cells, the nuclei of which appear polymorphous in size and staining. Transversely cut muscle bundles of a myoma may simulate round cells of a sarcoma. The course of the blood vessels may be helpful in this distinction, as they tend to run parallel with muscle bundles in a myoma, but show no relation to arrangement of cells in a sarcoma.

Mixed tumors arise from the cervix with three times the frequency. They occur mainly in children during the first few years of life, and form soft, arborescent masses which fill and distend the vagina and soon appear in the vulva. The grapelike gross appearance has given rise to the term "sarcoma botryoides." This variety is always highly malignant. Spread occurs by local invasion, hematogenous deposition in lungs and liver, and lymphatic extension to regional lymph nodes.

The origin of the uterine mixed tumors has been supposed to be from undifferentiated elements of the Müllerian duct. However, the constant presence of striated muscle cells suggests a greater probability of origin from primitive displaced cells of the myotomes, capable of forming striated muscle as well as cartilage and bone.

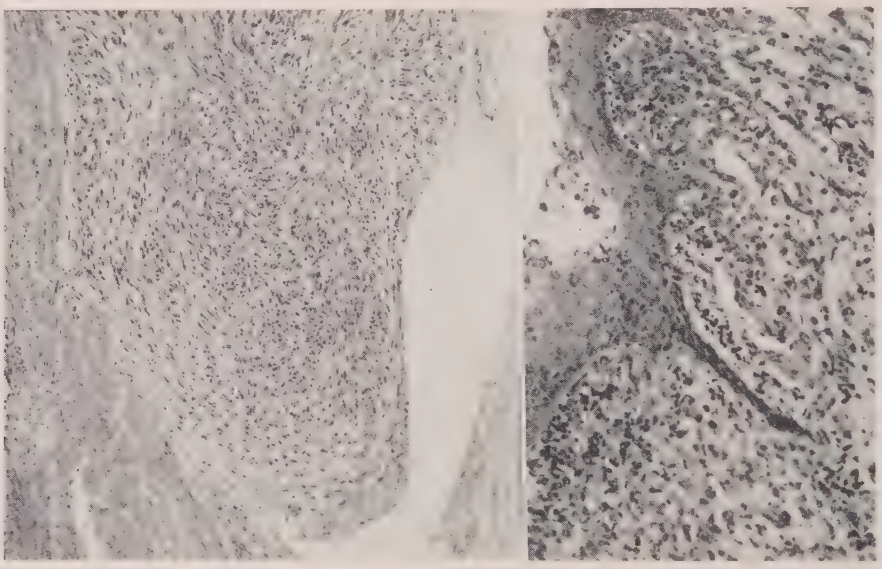

Fig. 930. Fig. 931.

Fig. 930.—Sarcoma of the uterus, originating from the myometrium.
Fig. 931.—Sarcoma botryoides, section from the free surface appearing in the vulva.

Metastatic spread of uterine sarcoma is mainly by the blood stream rather than by lymphatics, and the lung is the common site of secondary growths.

Mesodermal Mixed Tumors of the Uterus

Rare tumors which develop from the posterior part of the fundus or the cervix of the uterus consist of a variety of mesodermal tissues. They are composed of an undifferentiated cellular mesenchyma which surrounds cartilage, bone, fat tissue, striated and smooth muscle, etc.

The mixed mesodermal tumors arising in the fundal region develop from the submucous areas and form broad-based polypoid masses or a single pedunculated polyp. They occur mainly in adult women after the menopause, and may be of low malignancy. Usually, however, they are highly malignant.

Myoma of the Uterus

(Fibroleiomyoma, Fibroid, or Fibromyoma)

This tumor is known under various names. Clinicians frequently term this neoplasm "fibroid" which would indicate that the new growth bears a similarity to a fibroma. Similarity to a fibroma is not present in all of these new growths, and while "fibroid" has the sanction of usage, it expresses only a similarity of some of these tumors without definitely identifying the exact nature or origin of the entire group. Pathologists commonly use the term fibromyoma or leiomyoma.

If the word fibromyoma is employed it implies a tumor composed of two distinct types of tissue, a combination of a fibroma and a myoma and therefore, a mixed tumor. This is not the case, however, since the tumor involves only a neoplastic proliferation of muscle cells. It is true that fibrous tissue forms the septa and a fine network of fibers encloses and connects the individual muscle cells in a manner similar to that seen in normal unstriated muscle. There is never any primary proliferation of fibrous tissue which would resemble a true fibroma. An increase in connective tissue is encountered particularly in large and old tumors as the result of regressive changes in the muscle elements of the tumor. The degenerated or even necrotic muscle cells are replaced by a compensatory overgrowth of the connective tissue stroma. The only descriptive and accurate name for these tumors is leiomyoma, which indicates that the tumor originated from smooth muscle cells. If one is certain that no confusion with the rhabdomyoma is possible, the abbreviated term myoma is permissible.

The myoma is the most frequent tumor of the uterus, and also develops from the uterine ligaments. The fact that identical tumors originate from the uterus and its ligaments is strong proof that the ligaments are actually a part of the myometrium differing only in function in that they anchor the uterus to the pelvic bones. Anatomically there is no sharp demarcation between the muscle bundles of the ligaments and the uterus.

Gross Appearance.—The myoma grossly presents usually a globe-shaped or egg-shaped tumor. It has a smooth or bosselated surface. It grows by an increase of its own cellular components but never invades the myometrium, although it may markedly compress it. It varies in size from a pinhead to a large cantaloupe. If no degenerative changes occur within the tumor, it remains firm, being almost woody in consistency. This woody consistency generally appears as the tumor reaches a few centimeters in diameter. Smaller tumors are as a rule softer and more fleshy in appearance and become firmer when they increase in size and age.

The structural arrangement of the myometrium which facilitates function is not present in the myoma. In the myoma the muscle cells and fibers are rigidly bound together by a dense framework of fibrous tissue which prevents contraction of muscle bundles.

Since myomas contain relatively more of the firm white connective tissue and less of the soft pink muscular tissue than the surrounding muscle substance, they appear as pale, firm, ball-like foreign bodies in a background of softer reddish-pink myometrium.

Location.—Myomas may be classified into four groups according to location: (1) intramural, (2) subserous, (3) submucous, (4) ligamentary.

The intramural myoma develops within the myometrium and remains in this location during its growth period. If it originates near the external surface of the uterus, it may compress and thin the overlying peripheral myometrium and appear as a bulge on the surface of the uterus covered only by a thin layer of myometrium. In time it may extrude between the muscle fibers and then be covered only by the serosal coat of the uterus. If this change in position takes place, the tumor would be classified as a primary intramural and secondary subserous myoma.

Similar changes in position may be seen where an intramural myoma originating close to the endometrium protrudes into the uterine cavity. Since there is no well-defined layer of submucous myometrium comparable to the subserous myometrium, most of the tumors which project into the uterine cavity as submucous fibroids are covered only by endometrium. Some observers are of the opinion that all submucous myomas are primarily intramural and secondarily submucous. The ligamentary tumors originate from the ligaments proper or extend from a subserous position into the uterosacral or broad ligaments.

In a high percentage of cases myomas are multiple and combinations of different locations are not rare. Usually most of them are intramural.

Development and Encapsulation.—The developing myoma is represented in its earliest phase by a small group of cells within the myometrium which resemble myoblasts. The nuclei of these cells are oval and their homogeneous, red-staining cytoplasm is relatively scant in comparison with the size of the deeply

stained nucleus. Such groups of cells usually are not sharply demarcated from the contiguous myometrium.

When the cell group grows larger, one can distinguish at its outer border a ringlike zone of loose connective tissue separating the myoma from the normal myometrium. The zone of loose connective tissue will form the capsule and permits enucleation of even small myomas.

This capsule is of functional importance as it isolates the inert myomatous tissue from the actively contracting myometrium. Were it not for this intervening capsule, antagonism would result between the inert mass of the myoma and the active muscles of the myometrium. Each wave of contraction would be greatly weakened and energy wasted on each attempt to set in motion the passive myoma. Early observers called the peripheral loose fibrous zone a "capsule," although it is not strictly comparable to the connective tissue membrane which envelops the surface of tumors such as the dysgerminoma or the granulosa cell tumor. However, since the term has the sanction of usage it is still employed.

Another function of this so-called capsule is to provide passage and space for the nutrient vessels of the tumor. In the smaller myomas when the capsule is not yet fully developed, the larger arteries and veins penetrate the surface and enter the tumor at right angles in a radial direction. When the capsule becomes more pronounced, the large vessels take a course in the capsule and parallel to the surface of the tumor. From these large vessels small branches enter the tumor in a radial direction. This pattern of blood supply results in an adequate nourishment of the superficial zone of the tumor, while the central parts are poorly supplied. As a consequence, in rapidly growing tumors degenerative and necrotic changes are more prone to occur in the central parts.

Clinical Symptoms.—The clinical symptoms provoked by myomas are of variegated character. A sensation of pressure in the pelvis is usually induced only by large myomas. The irregular bleeding often present in the myomas is of twofold origin. The metrorrhagia of the first group may be provoked by the same hormonal disturbance which started the development of the myoma. In the second group the metrorrhagia is directly traceable to the myoma. In these instances a projecting submucous myoma may impinge upon the opposite wall of the uterus. This results in ulceration of the endometrium and capsule on top of the myoma. Erosion of the capsular vessels gives rise to various degrees of hemorrhage which are not related to the menstrual period. This type of hemorrhage also originates commonly from submucous myomas after the menopause.

Intramural myomas, particularly if multiple, may interfere with the normal slow contractions of the uterus at the end of normal menstruation which reduce the myometrial hyperemia and empty the uterine cavity of blood. Subserous myomas generally produce no metrorrhagias unless they are of a size sufficient to interfere with the myometrial contractions.

Degenerative Changes in Myomas.—Degeneration occurs frequently in myomas. Almost all large myomas exhibit some degenerative changes. In general, these changes are of two types. In one type the myoma becomes increasingly firmer as the result of atrophy of muscle bundles with compensatory replacement and overgrowth of the fibrous tissue component. Ultimately the fibrous tissue undergoes hyalinization and eventually calcification. The final picture of this process is a stonelike myoma which on microscopic examination reveals a hyalinized stroma devoid of living cells in which diffuse amorphous deposits of calcium can be seen. The hyaline and calcifying changes are seen more frequently in myomas which originate from the fundus or the upper part of the body of the uterus.

The second type of degenerative change is more frequently seen in myomas which arise from the lower part of the body or from the cervix. This change is characterized by a decrease in consistency caused by edema and liquefaction of the central part of the tumor.

Microscopically these tumors disclose a reduction in muscle fibers with marked swelling and edema of the interstitial tissue. In some instances irregular cystic spaces separated by pale staining septa and filled with a thin serous fluid can be seen. These cystic changes should not be confused with that seen in lymphangiectatic myomas. In this latter group the cystic spaces are sharply demarcated and constitute actual lymph vessels or spaces lined by flattened endothelium. The cystic spaces resulting from edema or liquefaction are of irregular shape and show no lining cells.

Edema and liquefaction with cystic change are frequent in myomas of the sacrouterine and the broad ligaments. Because of their soft consistency such myomas may be mistaken for ovarian cystomas. This error can be avoided if it is recalled that ovarian cystomas are generally freely movable because they are attached to the ovarian ligament which forms their pedicle. Ovarian cystomas commonly grow in a cephalad direction so that they rest mobile within the free peritoneal cavity and are separated from the uterus. The cystic myomas of the ligaments, with exception of the round ligament, are immobile, fixed to the floor of the pelvis and closely attached to the wall of the uterus.

An interesting subgroup of myomas is represented by the so-called "red myomas." The term has been coined to describe the gross appearance of these tumors. Histologically the red myoma exhibits no constant picture. Most myomas, as well as the normal myometrium, exhibit a pale pink or red color from the muscle fibers, and a whitish tint which is imparted by the fibrous tissue. In the undegenerated myoma the muscular and the fibrous tissue are mixed as to produce a light pink color. If the muscle tissue predominates as is often the case in young rapidly proliferating myomas, the pink color becomes more intense so that the tumor becomes almost red. In other instances the red color results from an increased number of vessels which microscopically may simulate a venous hemangioma. Myomas which are extremely vascular are subject to hemorrhages

within their parenchyma which contribute further to the red discoloration.

In the postmenopausal period the myoma undergoes involutionary changes. Microscopically, the individual muscle cells show a typical regressive change whereby the cytoplasm is markedly reduced and the nucleus shows shrinkage. This marked diminution in the cytoplasm of the muscle cells and the relatively moderate shrinkage of the nuclei imparts to the myomatous tissue a cellular appearance which, due to the closely crowded dark nuclei, often resembles a young rapidly proliferating myoma or even a sarcoma. Errors of this kind can be avoided if careful attention is paid to the stroma of the tumor. In the young myoma and sarcoma, the stroma is scanty, whereas in the postmenopausal involuting myoma broad prominent hyalinizing septa are present almost constantly.

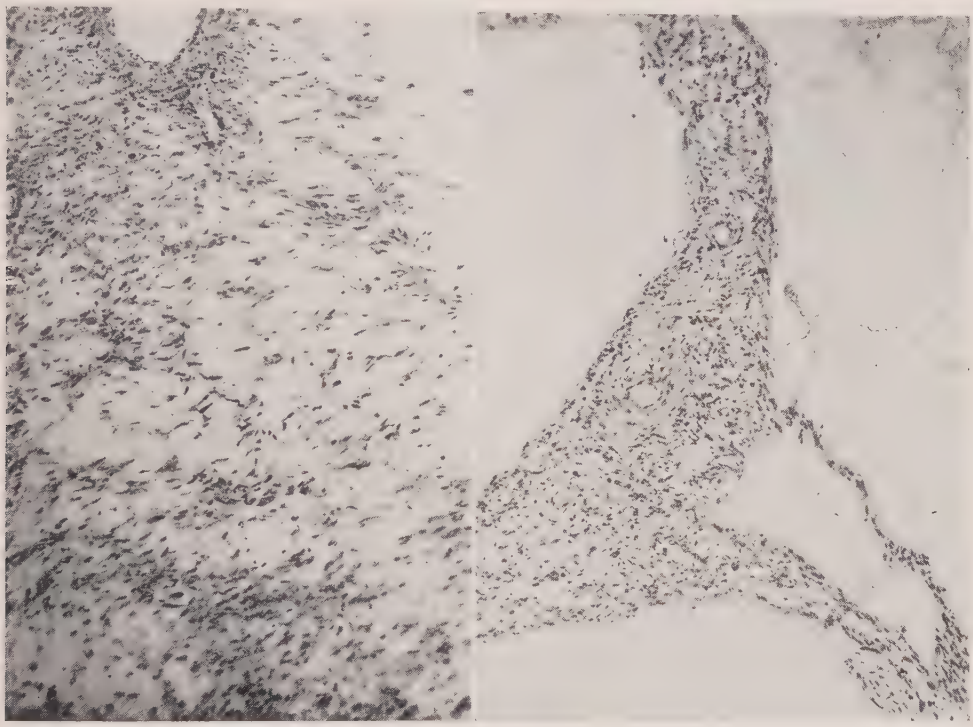

Fig. 932.—Soft myomas of the uterus. Softness from a large fluid content due to interstitial edema (left) and lymphangiectatic cavities (right).

Etiology.—The etiology of the myoma poses two problems: first, the identity of the tissue giving rise to the tumor, and, second, the nature of the extrauterine stimulus which provokes the growth response. The first problem is best solved by examination of very young myomas. These early tumors appear to start as a group of immature muscle cells of myoblastic character located usually in the middle stratum of the myometrium. Frequently, the cells are close to or even attached to an artery. It is logical to presume that a tissue which is capable of undergoing repeated cycles of enormous hyperplasia and hypertrophy, as seen in the myometrium during pregnancy, possesses a reserve of cells of low differentiation capable of more rapid proliferation than the common mature myometrial cells. Some observations indicate that these undifferentiated reserve cells of myoblastic character can be seen under favorable circumstances located at regular intervals within or along the adventitia of medium-sized arteries. At times they multiply by amitotic division and form parallel rows of equidistant nuclei. These rows of nuclei exhibit a so-called "rhythmic or palisaded structure" as often present in sarcomas and in neurinomas. The palisades or rows of nuclei can be seen under favorable circumstances in very young myomas. Ordinarily the pressure of the surrounding myometrial muscle bundles disrupts and distorts the original rhythmic nuclear pattern of the young myomas.

The nature of the extrauterine stimulus which provokes the myoblastic reserve cells to grow has been investigated by numerous observers using varied approaches to the problem. It has been held for several decades that the first appearance and growth of a myoma is limited to the childbearing age. The Swiss obstetrician, Hegar, was one of the first to enunciate that myomas never develop before puberty or after the menopause. He pointed out that myomas present during childbearing age do not enlarge after the menopause. This concept, which has been confirmed by clinical statistics, is known as Hegar's Law. Examination of the ovaries of

women with myomas disclosed, frequently, hyperactivity, for instance by follicular cysts. Strong presumptive evidence of abnormal ovarian activity is seen also in the fact that women with myomas often reach the menopause two to ten years later than normal women. The relationship of ovarian function to the myoma has resulted in the therapeutic administration of x-rays, particularly for multiple intramural tumor in preclimacteric and climacteric women.

Fig. 933.—Adenomyoma of the uterus. The submucous and intramural tumor blends with the myometrium without a capsular demarcation. The cervix shows retention cysts.

After x-ray castration followed by an artificial menopause the myomas may shrink in size, duplicating the changes seen after physiologic menopause. This therapeutic approach is restricted, however, by the fact that in postclimacteric women the ovaries are already functionless, and that in submucous myomas, while there is some shrinkage of the tumor, the denuded capsular surface with the eroded veins persists, so that the hemorrhage continues in spite of the x-ray treatment.

Attempts to prove the presence of excessive quantities of estrogen in the blood or the urine of women with myomas have failed in most cases. Biochemical examination of myomatous tissue has indicated its estrogen content to be negligible. This finding, however, must be accepted with caution since normal myometrial tissue, which is known to react to estrogen, is likewise almost free of the hormone.

That constitution and heredity may play a part in manifest by the fact that Negro women exhibit myomas more frequently than white women, and further, that in Negro women there is a definite tendency for the myomas to be larger, multiple, and more numerous than in white women.

Pyometra

If obliteration or occlusion of all three uterine outlets, namely, the oviducts and cervix, should occur, and the uterine cavity is filled with retained purulent material, the resulting lesion is termed pyometra. It is important to distinguish clearly pyometra which designates purulent fluid within a closed uterine cavity and purulent endometritis where there is purulent exudate within the uterine cavity which is freely discharged through a patent cervical canal.

The complete closure of the intramural portion of the oviduct as it traverses the myometrium is particularly prone to occur because the lumen is narrow and is reduced by plump thick triangular mucosal folds which are closely approximated. Complete occlusion of both oviducts does not result in pyometra unless there is also coincident complete obliteration of the cervical canal, and complete cervical closure is relatively rare.

Congenital atresia of the cervical canal, partial or complete congenital atresia of the vagina, and imperforate hymen may all lead to retention of blood within the uterine cavity, which is termed hematometra. Similar collections of blood within the vagina are indicated as hematocolpos. Both of these effects may be seen in young girls at the time of the expected first menstruations but are rarely seen in women past puberty.

Most cases of pyometra are seen in adult women and are the result of occlusion of the cervical canal by squamous or glandular carcinoma or by shrinkage following radium therapy of cervical carcinoma. In the postmenopausal period pyometra may be the aftermath of senile fibrosis of the cervix. This fibrotic change is likely to occur in the isthmus or in the cervical canal if through pressure the senile endometrium or the lining of the endocervix undergoes complete atrophy and is replaced by granulation tissue. Subsequently, the opposing layers of granulation tissue fuse and completely obliterate the cervical canal.

DISORDERS OF PREGNANCY AND THE PLACENTA

Decidual Changes in Pregnancy

When pregnancy occurs, the glands and cytogenic stroma of the endometrium undergo changes which are a continuation

and completion of endometrial alterations which occur normally during the intermenstrual cycle. Endometrial glands become dilated, with marked increase in transverse diameter, and their epithelial lining cells proliferate and pile up as intraglandular projections of epithelial cells without a stromal core. Also the stromal cytogenic cells become enlarged, the nucleus showing a lesser relative degree of enlargement than the cytoplasm. The nuclei are pale, ovoid or round, and

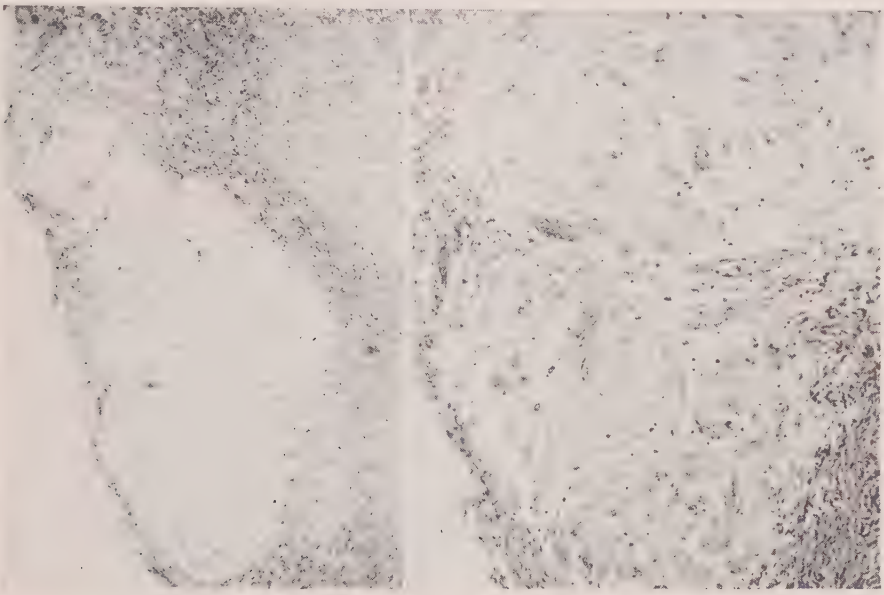

Fig. 934.—Node of decidua in the ovary of an adult woman in the seventh month of pregnancy.

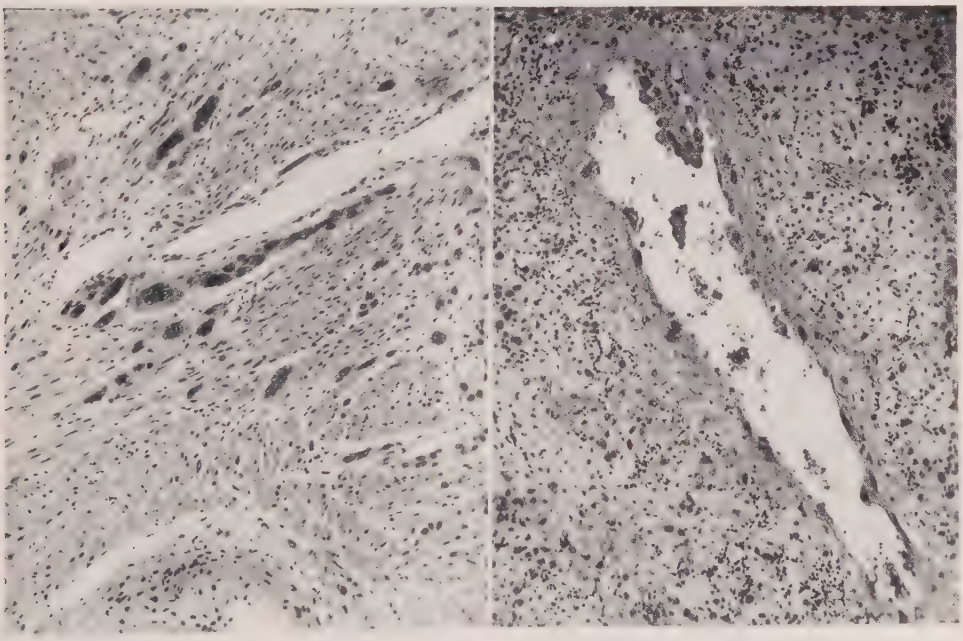

Fig. 935.—Chorionic invasion. Left: Chorionic cells in inner layer of myometrium in the third month of pregnancy. Right: Decidual blood vessels showing desquamation of swollen lining endothelial cells into lumen, simulating chorionic cells.

appear relatively small because of the marked increase in the cytoplasm. The cells assume a spindle shape, and are in close contact so that they have an epithelium-like appearance. The term decidua is applied to the altered endometrium during pregnancy. Decidual changes involve the entire endometrial lining, and are more pronounced on the wall where the ovum embeds itself, but direct mechanical effect of the embedded ovum and its proliferating chorion are not the cause of the decidual changes.

Ectopic decidual changes may develop outside the uterine cavity in the presence of a normal intrauterine pregnancy. Such changes are very frequent in certain sites, such as the albuginea of the ovary, the subperitoneal tissue of the pouch of Douglas, and beneath the serosa of the posterior wall of the uterus. More unusual locations are the appendix, lymph nodes, inferior aspect of diaphragm, omentum, vagina, in granulation tissue of cervical erosions, and in stroma of inflamed cervical polyps. Peritoneal nodes of ectopic decidua appear as small, flat or slightly elevated, gray patches with a shiny surface, and 1 to 5 mm. in diameter. Cells showing decidual change are sharply demarcated from adjacent cells, without transitional involvement.

In ectopic pregnancy, the uterine endometrium undergoes the same decidual changes as in intrauterine pregnancy. When the ectopic fetal placenta separates, the intrauterine decidua is discharged as a triangular, mushy, edematous sac of necrobiotic tissue.

Chorial Invasion

Except in the earliest phases of the developing ovum, the borderline between chorion and decidua is even and distinct (Nitabuch's fibrin). However, certain invading chorial cells with a high degree of motility migrate to the subjacent decidua. Here they grow larger, become round, ovoid or irregular in shape and acquire multiple, hyperchromatic irregular nuclei. These giant chorial cells may appear singly or in great number in some areas of the decidua. As they reach deeper layers of the decidua or the inner part of the myometrium, they shrink but still are recognizable by their very dark irregular nuclei. These chorionic cells may penetrate maternal blood vessels, and be carried in the blood stream to the capillaries of the lungs. After delivery or abortion these chorionic cells disappear within one or two weeks. Beneath retained remnants of placenta, chorionic cells may remain viable for several months following delivery of an intrauterine pregnancy. If chorionic cells without overlying placental remnants are found in a curetting made more than two weeks after delivery or abortion, chorionic epithelioma should be suspected.

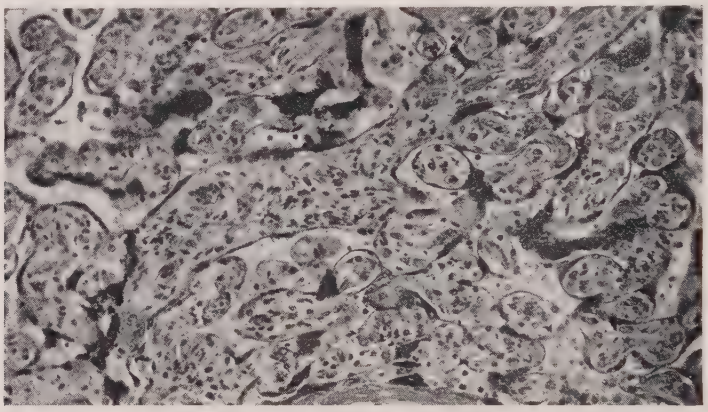

Fig. 936.—Syphilitic placenta (full term). The villi present a dense stroma, the chorionic lining is degenerated, and the intervillous space is reduced.

Placental Infarcts

If placental villi lose their chorionic lining, the maternal blood in contact with the denuded stroma of the villi undergoes clotting. Such denudation occurs when the chorionic lining becomes necrotic and is cast off as a result of regressive changes or kinking or twisting of some villi. Such areas of clotting may grow larger by apposition and formation of new clots at a free surface. Lysis of red cells occurs, leaving masses of fibrin which undergo condensation and hyalinization. Such areas appear as firm white nodules in the otherwise dark red, soft placental tissue, and are called placental infarcts. They tend to be excessive in size and number when toxemias of pregnancy or renal disturbances are present. Microscopically, they appear as dense, eosinophilic amorphous areas in which structural outlines of necrotic villi may be discernible.

Estimation of Age of Placental Tissue

An approximate estimate of the duration of a pregnancy terminated by abortion may sometimes be made from placental remnants obtained

by curettage. Trophoblastic masses without formation of villi point to the previllous early stage before the end of the second week. Villi with loose connective tissue cores which contain no vessels or only very small narrow vessels are found earlier than the tenth week. When vessels of the villi contain nucleated red blood cells only, the placenta is younger than four months. After the fifth month, usually only anuclear red cells are found. An intact Langhans layer beneath the syncytium points to an age of the placenta of less than six months. After the sixth month, Langhans cells increasingly disappear, and at full term only remnants or occasional single Langhans cells are present.

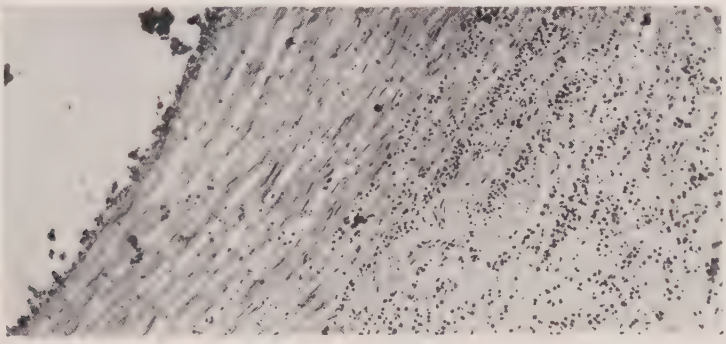

Fig. 937.—Umbilical cord, congenital syphilis, showing lymphocytic infiltration in and around the wall of the vein.

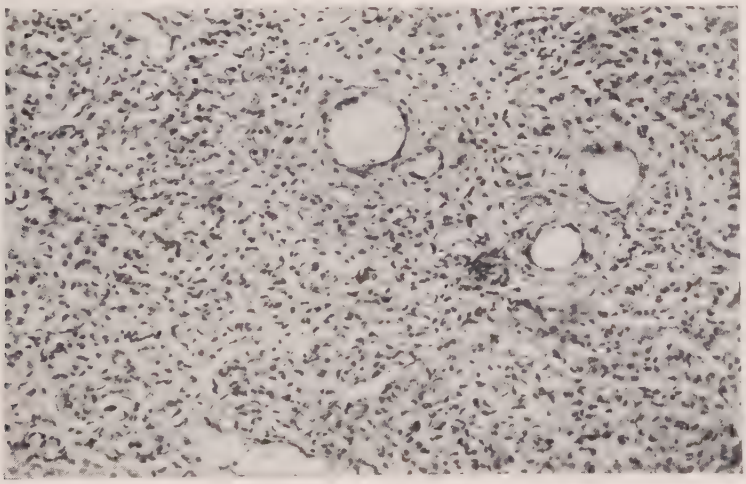

Fig. 938.—Chorioangioma in an otherwise normal full-term placenta. The small endothelium-lined cavities, through which fetal blood circulates, are set in a fibrous stroma.

Syphilis of the Placenta

The syphilitic placenta is characterized by fibroplastic thickening of the villi, which causes the placenta to appear thicker, heavier, and more massive than the normal.

Microscopically there is a marked increase of the stroma of the villi. The blood vessels, particularly in the latter third of pregnancy, show proliferative changes of the intima comparable to a chronic obliterative endarteritis. Inflammatory infiltration may be present in the umbilical cord, particularly around the vein and more marked near the placental than at the fetal end. This finding is not specific for syphilis.

Tumors of the Placenta

Benign tumors of the placenta are exceedingly rare, though cases of fibroma, myxoma, osteoma, etc., have been reported. **Chorioangioma** is a vascular nodule 2 or 3 cm. in diameter, which originates from the chorion and projects over the maternal surface of the placenta at or near term. It represents one villus markedly enlarged in width by a hemangioma-like proliferation of its capillaries. The small vessels have a typical endothelial lining and are separated by loose stroma. It is debatable whether the condition should be classed as a neoplasm or as a malformation with a limited capacity of proliferation.

Hydatidiform Mole

The hydatidiform mole is the result of degenerative changes in the placental villus. This process of transformation exhibits three typical steps:

1. No vessels are formed within the villi, or they are formed but disappear again so that microscopic examination reveals either no vessel at all or only shadows of collapsed vessels.

2. Edema appears in the stroma of the villus and may progress to such an extent that the central portion actually is liquefied, as the result of retention of thin watery fluid. This marked edema produces an enormous bulbous enlargement of the terminal portion of the villus, which may exceed 10 mm. in diameter, in contrast to the tip of the normal villus which cannot be discerned with the naked eye. It is this enormous dilatation which changes the villi into grossly evident thin-skinned, grapelike bodies, varying in size from that of a pinhead to that of a small cherry.

3. The chorionic surface epithelium proliferates and forms solid budlike projections composed only of syncytium. At times a layer of Langhans cells may be identified subjacent to the syncytial bud, but more frequently the Langhans cells are absent. In the cytoplasm of this proliferating syncytial projection, ovoid cystic vacuoles filled with a clear translucent fluid appear. Vacuoles of varying size

Fig. 939.—Hydatidiform mole. Note the projecting grapelike vesicles which compose the mass. (From Anderson, Synopsis of Pathology, courtesy Dr. H. C. Schmeisser.)

resemble those found in the chorionic trophoblast during the previllus stage of the ovum.

Two theories have been generally invoked to explain these changes. In 1895 Marchand advanced the thought that the hydatid mole was a benign neoplasm and emphasized the proliferation of the chorionic epithelium which he felt was the result of stromal edema. It was his belief that the hydatid mole was a benign chorionic tumor bearing the same relationship to its malignant counterpart, the chorioepithelioma, that a fibroma does to a sarcoma.

The second interpretation focuses attention on the avascularity of the villus which is almost constant in typical cases of hydatidiform mole. Careful observation has shown that the earliest transition of the villi into a hydatidiform mole occurs at the time when under normal circumstances the intrinsic vascularization of the placenta is completed, and the vascular system of the placenta is supplied by the heart itself as the central pump. This phase of placental circulation occurs commonly three weeks after the previous ovulation or five weeks after the last menstrual period prior to pregnancy. If malformation or early death of the fetus occurs, placental vessels fail to develop or, if developed to some degree at that time, these vessels collapse and disappear. These vessels have for their chief function the transportation to the growing fetus of nutriment absorbed by the chorionic epithelium. If through absence of placental vessels this transfer of nutrient material is impossible, the nourishing fluid is retained and accumulates within the stroma resulting in edema of the stroma and proliferation of the chorionic lining due to nutrient protein and salts dissolved in the fluid. If this process due to absence of placental circulation involves all of the villi, a hydatidiform mole results.

Ordinarily, early malformation or fetal death is followed by a simple abortion with discharge of the placenta. In occasional instances, however, the placenta is retained and undergoes transformation into a hydatidiform mole. The retention of the placenta in these cases is attributed to an unusually resistant and active chorionic epithelium, which refuses to be dislodged after death of the fetus. This mechanism would indicate that the hydatidiform mole is the result of a specific degenerative change and is not a benign neoplasm. Hydatidiform degeneration can be found in several villi in about 50 per cent of the placentas in abortions with pathologic ova. Even in normal placentas during the last three to four months of pregnancy, an occasional single villus showing hydatidiform degeneration can be seen. A typical hydatidiform mole is extremely rare in association with an ectopic pregnancy. However, hydatidiform transformation of some villi can be found in a high percentage of tubal ectopic pregnancies, although rarely reaching a size comparable to the uterine mole.

The factors which determine whether a placenta will be expelled, or will be retained as the result of the high vitality of the chorionic epithelium and give rise to a hydatidiform mole, are not known. Some feel that this quality is an intrinsic congenital character of the placenta, whereas others feel the anterior lobe of the pituitary secretes excessive quantities of hormone which stimulate and activate the chorionic cells of the normal placenta. That the chorionic epithelium in hydatidiform mole has increased inherent vitality is further borne out by observing its secretory power. The Aschheim-Zondek and Friedman tests are based upon an excessive production of luteinizing hormone during pregnancy which appears in the blood and is excreted in the urine. In hydatidiform moles the excess of hormone is reflected by positive tests even when the urine is diluted twenty to forty times before injection into test animals.

The excess of luteinizing hormone in hydatidiform mole reacts upon the ovaries of the patient, accentuating the effect of the hormone on the theca of growing follicles and of corpora atretica. This hyperluteinization and proliferation may progress to such an extent that the corpora atretica enlarge to the size of small chestnuts and are then known as lutein cysts. The central cavity of such cysts is often filled with dark blood clots.

The evidence that the lutein cysts which sometimes enlarge the ovary to the size of a fist are the result of the hydatidiform mole rather than its cause, is furnished by the fact that surgical removal or spontaneous expulsion of the mole is followed within several months by regression of the cysts with the ovary again returning to its normal dimensions.

The positive pregnancy tests with highly diluted urine and lutein cysts of the ovary are also found in malignant choriocarcinomas, indicating great and unusual functional activity of the chorionic epithelium in both lesions. However, these findings of hyperfunction of the chorionic epithelium cannot be construed as direct evidence of a neoplasm since they are only marks of increased hormonal secretion comparable to the increased secretion coincident with the simple hypertrophy of any ductless gland.

The incidence of hydatidiform mole is one in about two thousand pregnancies. It may occur at any age during the childbearing period. One-fifth of the cases are in primiparous women, while four-fifths are in multiparous women.

In abortions associated with pathologic ova early changes of the hydatidiform mole character are frequent, whereas in those associated with normal ova these changes were present in only about 12 per cent, according to Hertig and Edmonds.

About 8 per cent of all moles give rise to subsequent chorioepitheliomas. The further observation that 40 per cent, or more than one-third, of all chorioepitheliomas take origin from previous hydatidiform moles emphasizes the necessity of radical treatment and careful prolonged postoperative supervision in all cases of mole microscopically suspicious for malignant changes.

Choriocarcinoma

Choriocarcinoma is a relatively rare malignant tumor which may develop from hydatidiform mole, or after abortion, miscarriage, or a full-term pregnancy. The time between delivery or abortion and the first clinical signs varies from a few weeks up to several years.

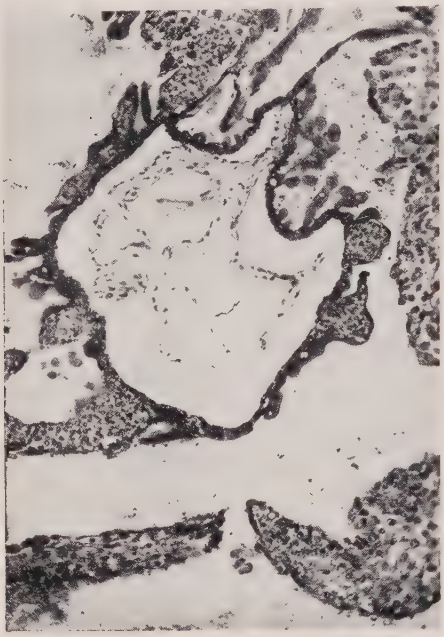

Fig. 940.—Choriocarcinoma developing from a hydatidiform mole. The villus shown has advanced shrinkage of its edematous stroma and proliferation of the chorionic lining.

Choriocarcinoma developing from placental remnants appears as a soft, amorphous hemorrhagic or cystic nodule which first extends into the uterine wall, and in a later stage projects into the cavity. If it originates from chorionic wandering cells within endometrium or myometrium, it appears as a poorly demarcated area of soft hemorrhagic, mushy tissue. Metastases also tend to undergo necrosis and to be hemorrhagic.

Uterine choriocarcinomas originate either from malignant proliferation of the chorionic lining of villi or from chorionic cells which have invaded endometrium or myometrium as occurs in early phases of pregnancy. The tumor tissue consists of two components, (1) pale, polyhedral cells with large vesicular central nuclei and clear or pale cytoplasm (Langhans type), and (2) giant cells with dark-staining cytoplasm, no boundaries between individual cells, and multiple, small oval, dark nuclei, corresponding to the syncytial lining of the villi. The syncytial type of cell occurs as in the development of the normal placenta wherever the chorionic cells of the Langhans type have access to blood.

Metastasis occurs very readily by the blood stream, and may occur early in the course of the tumor. The lung is the common site of metastasis, but the brain and liver are also frequently involved. Almost any tissue may be the site of metastasis in some cases.

Diagnosis of choriocarcinoma may be made by examination of curettings when they have caused hemorrhage early in their course. Those cases which begin in the myometrium may not be revealed by curettage in early stages. The presence of chorionic cells later than two weeks after abortion or delivery should cause suspicion of choriocarcinoma. However, beneath a placental polyp chorionic elements may remain alive for several weeks or months without malignant change. Endocrine tests also assist in diagnosis. Proliferating chorionic cells of a hydatidiform mole or choriocarcinoma produce

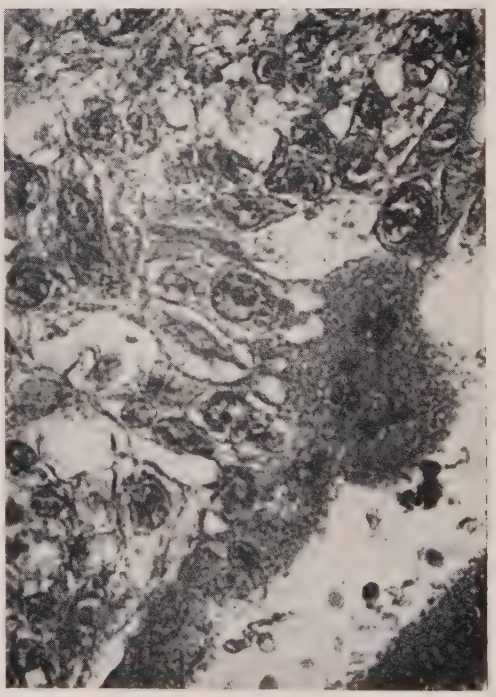

Fig. 941.—Choriocarcinoma. The darker granular cytoplasm of the syncytial cells is seen on the right, and the clear cytoplasm of the Langhans cells on the left.

gonadotropic hormones in much larger quantities than present in normal pregnancies. The Friedman and the Ascheim-Zondek tests for pregnancy are positive in urine dilutions of 1:50 up to 1:100, 1:200, or even higher. Normally, the tests become negative ten days to two weeks after delivery or abortion. Tests which remain or become positive after this time, particularly with increasing dilutions, justify suspicion of choriocarcinoma. If the test remains positive, and particularly with increasing dilutions, after removal of the uterus, metastases may be suspected.

In addition to an origin from the uterus in relation to a pregnancy, choriocarcinoma may originate from the gonads, particularly testicle and less often, ovary. It may be combined with a teratoma or originate as a pure choriocarcinoma. Extragenital choriocarcinomas, originating from lung, liver, etc., also have been observed. Ovarian chorioepithelioma occurs more commonly before puberty than in adult life, and may cause changes of precocious puberty. Excessive gonadotropic hormone production occurs with ovarian and testicular as well as uterine chorioepitheliomas.

Syncytial Endometritis

A particularly marked invasion of myometrium by chorionic cells during pregnancy has been called syncytial endometritis. In very marked cases it has been termed syncytioma. The condition is benign. The terms used are misnomers, as the condition is neither inflammatory nor neoplastic, but simply an exaggeration of the common invasion and growth in the myometrium.

Toxemia of Pregnancy

The etiology of the toxemia of pregnancy (*eclampsia*, pre-eclampsia) is still uncertain. The main theories are that it is (1) a form of hypertensive cardiovascular renal disease, modified and colored by the metabolic disturbances of pregnancy, (2) an endocrine dysfunction, in which the pituitary plays the main part, (3) due to a toxic material absorbed from the placenta, particularly from areas of infarction. Whatever the exciting causes, changes in structure and function of the kidneys are constantly present.

Lesions are found in the kidneys, liver, placenta, and sometimes in other organs. The changes in the kidney have been described (see page 590). Narrowing of capillary loops of glomerular tufts, mainly by thickening of the basement membranes, and degenerative changes in convoluted tubules are the usual findings.

The liver may show gross lesions which, while not constantly found, are so characteristic as to be diagnostic (see page 813). Irregular large and small areas of hemorrhage may be evident on both the capsular and cut surfaces. Areas of hemorrhagic or anemic necrosis are common. Microscopically, there are hemorrhages and necroses of hepatic cells. These lesions are particularly frequent in periportal areas, although any part of the liver lobule may be involved.

Necrotic and hemorrhagic areas similar to those of the liver are occasionally found in other tissues, such as adrenal cortex. Areas of infarction very often occur in the placenta. The pituitary has been described as having increased numbers of basophiles, which may show hyaline degenerative changes. Basophilic invasion of the posterior lobe of the pituitary probably has no significance as far as eclampsia is concerned.

VAGINA

Embryologic Development.—The vagina, like the uterus and the fallopian tube, is derived primarily from the Müllerian ducts, but the central epithelial strand of the primitive vagina becomes replaced by epithelium from the lining of the urogenital sinus. The stratified squamous epithelium of the vagina and vaginal portion of the uterus is derived from the urogenital sinus, and hence is of entodermal origin.

Cyclical Changes.—The stratified squamous epithelium of the vagina is modified and controlled by ovarian sex hormones. The epithelium shows three stages during life, corresponding to phases in sexual functions. Before puberty the epithelium is thin and immature. During the reproductive period of life it matures and becomes thicker. After the menopause it undergoes marked involution, due mainly to the reduction or withdrawal of sex hormones, and not just the changes of advanced age.

During the reproductive phase of life the vaginal epithelium undergoes cyclic changes corresponding to the intermenstrual changes of the ovaries and uterus. During pregnancy, the large quantities of sex hormones present bring about proliferative thickening.

Vaginal smears of rodents can be readily used to indicate the hormonic status of the animal. In the human being, however, the changes being much less distinct, careful preparation and ample experience are necessary for the proper interpretation of vaginal smears. Size, shape, and glycogen content of the cells can be used to indicate higher or lower degrees of maturity of the vaginal epithelial cells, reflecting respectively large or small amounts of estrogenic hormones. Papanicolaou has developed special techniques for vaginal smears. The presence of estrogenic hormone is judged by high maturity of the cells, as manifested by storage of glycogen or keratinized material in their walls. Progesterone counteracts this influence, produces desquamation faster than proliferation, and the desquamated cells have less keratinization of their walls, and their nuclei are vesicular rather than shrunken. Large quantities of mucin, numerous leukocytes, and a greater density of bacterial flora also point to a progesterone influence, due to its stimulation of cervical secretion. Failure of change from one type of smear to the other in the middle of the menstrual cycle thus indicates failure of ovulation and subsequent corpus luteum formation, and justifies the conclusion that an anovulatory cycle is taking place.

Trichomonas Infections of the Vagina.—*Trichomonas vaginalis* is a protozoan parasite a little smaller in size than desquamated epithelial cells. It is highly motile, possessing an undulating membrane and four flagellae. Its pathogenic importance is still debatable. It is

present in many normal vaginas, without any evidence of vaginitis. On the other hand, a particular type of vaginitis characterized by a diffuse scattering of demarcated small red spots over the surface of the vagina has been found associated with the presence of many trichomonas.

Vaginitis.—The thin immature epithelium of prepubertal ages and the thin involuted epithelium of postclimacteric years are more susceptible to bacterial infections than the thick mature epithelium of the reproductive period. Gonococcal infection produces the most common vaginitis of childhood, but the adult vaginal epithelium is very resistant to infection by this organism. In gonorrheal vaginitis there is a swollen, velvety, deep red mucosa, which microscopically shows nonspecific inflammatory changes with marked hyperemia, edema, and leukocytic infiltration. Gonococci can be demonstrated in epithelial and subepithelial layers. Administration of estrogenic hormones, which brings about thickening and maturation of the epithelium, has been shown to be more effective than the application of antiseptic douches to the vaginal surface. Local application of the hormones by vaginal suppositories appears to be more efficient than oral or parenteral administration. The mechanism of action is probably by promoting production of epithelial glycogen, which, on being broken down to lactic acid, produces a vaginal reaction unfavorable for the organism. The rarer postclimacteric gonorrheal vaginitis similarly responds favorably to estrogenic therapy.

Other organisms causing vaginitis include some yeasts, such as Monilia. Vaginitis due to such a fungus infection shows a soft, mushy, whitish mucosal surface, and the vaginal lumen contains a thick dryish discharge which consists of many desquamated epithelial cells mixed with mycelia of the fungus. The fungus sometimes can be found among the flora of a normal vagina, and changes in the medium, such as during pregnancy or with diabetes mellitus, apparently promote pathogenicity or allow invasion by this organism.

Benign Tumors.—Benign tumors of the vagina are rare and most are of mesodermal origin, such as fibromas, lipomas, and myomas.

Malignant Tumors.—Malignant tumors of the vagina are uncommon, carcinoma being the most important. Squamous cell carcinoma arises from the lining epithelium, and may grow outward in papillomatous fashion or may extend by infiltrative downgrowth and become secondarily ulcerative.

VULVA

Infantilism (Genital Hypoplasia).—Full development of female sex organs and characters may fail to be achieved due to insufficient stimulation by or response to sexual hormones. The hormonal deficiency may be due to either pituitary or ovarian deficiency, or both. Infantilism may be manifested by deficient development of secondary sexual characteristics and hypoplasia of the genital organs, or may be limited to the latter. In such cases the findings may include thin small labia, a small scarcely projecting clitoris, a greater depth of the vestibule, and a masculine distribution of pubic hair with extension upward toward the umbilicus. The perineum may be short and concave, and in the midline or in its upper part may be covered by an extension of the mucosa of the vulva.

Kraurosis.—Following the menopause the tissues of the vulva undergo a physiologic involution. The labia shrink, the clitoris becomes flattened, and the epithelium of the mucosa and skin becomes thin, pale, and either smooth or wrinkled. The stroma under the epithelium also undergoes shrinkage and fibrosis. An excessive degree of such involutionary changes is known as kraurosis. While withdrawal of estrogenic hormones following the menopause is the underlying basis, some other local factor must be present in addition. Kraurosis rarely follows the artificial menopause produced by operative removal of the ovaries. Rare examples of kraurosis have occurred before the menopause, or have been unilateral.

Leukoplakia is a term used for slightly-elevated, demarcated white patches which occur on mucosal surfaces. The underlying microscopic changes in such vulval areas varies greatly in different cases. It may be a sharply demarcated area of thickening and excessive keratinization of the epithelium, with chronic inflammation of the underlying stroma. In other cases the leukoplakic area shows thinning of the epithelium with shrinkage, fibrosis, and decreased vascularization of the underlying stroma, the changed area merging by gradual transition into adjacent normal tissue. Occasionally the leukoplakic area shows a localized malignant change of the surface epithelium without invasive downgrowth, a change comparable to the so-called "carcinoma-in-situ" or Bowen's disease of the skin. Thus the whiteness of the plaque seen clinically may be due either to thickening and hyperkeratosis of the epithelium, to thinning of the epithelium allowing a fibrotic and devascularized underlying stroma to shine through, or to carcinomatous change.

Leukoplakic vulvitis has been described by some as a process occurring in hypertrophic and atrophic stages, the latter stage differing from true kraurosis in that it is secondary to an inflammatory process rather than being a primary shrinkage. Some have looked upon leukoplakic vulvitis and kraurosis as different stages of the same process (a "chronic dermatitis of the vulva"). Others have made distinctions according to the areas affected, kraurosis being limited to the mucosa within the boundaries of the labia minora, and leukoplakic vulvitis affecting the skin around the vulva. Generally, gross inspection does not determine to which of these groups a leukoplakia belongs. The possibility of cancerous change necessitates biopsy in each case of leukoplakia of the vulva.

The etiology of the hypertrophic changes is not known. The atrophic changes, particularly if primary, are usually considered to be due to reduction of ovarian hormones. Administration of female sex hormones, locally as well as orally or parenterally, has been a successful therapeutic procedure.

An important relationship to malignant change is indicated by the fact that about 50 per cent of carcinomas of the vulva are preceded by chronic atrophic vulvitis.

Infection.—Gonorrheal infection in Skene's ducts and sometimes in Bartholin glands, may be obscured by secondary infection with other organisms. The secondary infection may produce abscesses of Bartholin glands which may perforate on a labial surface. Retention cysts of Bartholin glands result from inflammatory occlusion of ducts. Such cysts may increase in size up to a diameter of 6 cm. or more, the overlying skin and mucosa becoming stretched and thinned. The cyst cavity contains a clear serous or slightly mucinous fluid, and is lined by a flattened or atrophic epithelium. Islands of normal glandular tissue can almost always be found in the connective tissue of the walls of such cysts.

Carcinoma of the Vulva.—Carcinomas of the vulva are mainly squamous cell carcinomas arising from surface epithelium but rarely may be a basal cell carcinoma, or adenocarcinoma may develop from sweat glands, sebaceous glands, Bartholin glands, Skene's ducts, or accessory mammary tissue.

Squamous cell carcinoma of the vulva may be either a projecting warty growth or an ulcerative lesion. Microscopically it usually shows good differentiation, with formation of many keratin pearls. However, it spreads in early stages to adjacent inguinal lymph nodes, and so is highly malignant. More radical surgical excision and irradiation are necessary for successful treatment than in the case of squamous cell carcinomas elsewhere having comparable microscopic differentiation.

Basal cell carcinomas of the vulva are much less common than the squamous cell tumors.

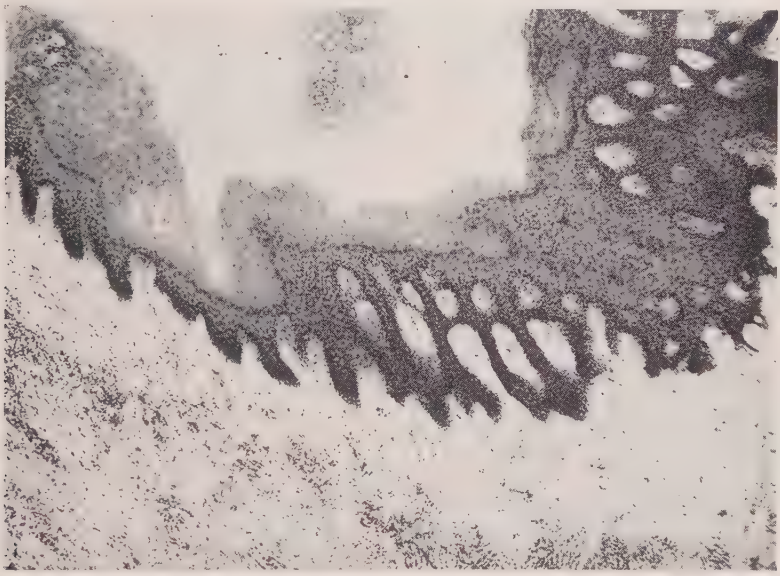

Fig. 942.—Chronic atrophic dermatitis of the vulva (kraurosis). Hypertrophic stage showing elongated papillae, thickening of the squamous stratified epithelium, edema and inflammatory infiltration of the subepithelial stroma. (Courtesy Dr. E. Davis, University of Chicago.)

Benign Tumors of the Vulva.—Various benign tumors occasionally involve the vulva, such as fibromas, lipomas, neurofibromas, leiomyomas, hemangiomas, etc. *Hydradenoma* is a distinctive variety of benign neoplasm of the vulva originating from apocrine sweat gland tissue. It is a circumscribed nodular tumor, varying up to 2 or 3 cm. in diameter. The overlying epithelium is slightly elevated and occasionally becomes ulcerated. Microscopically it shows a dense papillomatous structure consisting of thin, moderately vascularized connective tissue septa covered by nonciliated columnar cells. Sometimes certain areas show cuboidal or rounded cells beneath the columnar cells. Hydradenomas are almost always benign, and only rare cases have undergone secondary malignant transformation.

Like basal cell carcinomas of the skin elsewhere, they are slowly growing ulcerative lesions which rarely metastasize and are of low malignancy.

The uncommon adenocarcinomas of the vulva appear to be most often the result of a malignant change in a hydradenoma. They grow slowly, have little tendency to metastasize, except in late stages, and are usually successfully treated by simple excision.

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Chapter 40

THE BREAST

JOSEPH F. KUZMA

Development and Structure

General Anatomy of the Mammary Gland.—The adult female breast is a modified compound alveolar secretory gland derived from the skin. It is composed of approximately twenty irregular lobes radiating from the central nipple area. Each lobe has an excretory duct with a local dilatation of the duct beneath the nipple known as the sinus lactiferous. The ducts do not anastomose although two or more may have a common opening at the nipple. Multiple duct branching (lobes) ending in clusters of epithelial cells (lobules) constitute the parenchyma. Large ducts at the nipple are lined by stratified squamous epithelium which gradually merges with the columnar cells of the smaller ducts. The peripheral portions have low columnar cells, frequently of two layers, which blend into the cuboidal cells of the lobules. Just within the basement membrane fibrillar elongated cells derived from epithelium (myoepithelial cells) may be seen.[4] Outside of the basement membrane some elastic fibers course along the larger ducts. The histologic picture of the mammary gland depends to a great extent on the functional state. The bulk of the stroma is a dense eosinophilic collagenous substance punctuated by the ducts and lobules and marked by variable islands of fat. In certain places there is a modification of the stromal connective tissue in the nature of long strands that extend from the breast proper to the corium. These are called *retinacula mammae,* of which the cephalic ones are known as the suspensory ligament of Cooper. The stroma immediately supporting the lobules of the breast is known as the intralobular connective tissue, which is continuous with the periductal tissue. The periductal and intralobular tissue varies with the functional state and may be considered as a part of the "parenchyma." It is loose reticular or myxomatous in appearance and is sharply defined from the more dense interlobar substance. Except during pregnancy and lactation the bulk of the breast is made up of connective tissue.

Embryology.—As in all mammals, the human breast develops in a primitive epidermal thickening known as the milk line, which extends bilaterally on the ventral surface between the upper and lower limb attachments. In the human embryo the milk line appears at about the sixth week. This primitive line then gradually atrophies but at the ninth week the site of the permanent mammae can be recognized by the persistence of the epithelial thickening. The primitive nipple buds are formed at this time. By the sixth month of development some fifteen to twenty solid epithelial cords extend into the corium from the basal layer of the primitive nipple. By the ninth month these branching cords have developed a lumen and may have two or three layers of cells.

Congenital Anomalies of the Breast.—The commonest anomaly of breast development is the growth of supernumerary breast parts. Frequently, this is merely the presence of accessory nipples (polythelia) along the milk line. In the white population the greater number of these are said to appear below the normal breast and are somewhat more common in the male than in the female. Less common but more important from the clinical standpoint is the presence of accessory breast tissue (polymastia) in the axilla. Frequently this is not associated with the presence of a nipple and areola and may not be recognized until painful swelling and tenderness develop with the advent of pregnancy. Likewise, the possibility of development of cancer in an axillary ectopic breast is ever present. *Amastia* results from the disappearance of the entire mammary line including the usually defined bud of epithelial proliferation in the thoracic area.

The Neonatal Mammary Gland.—At birth the breast consists of moderately branched extremely dilated ducts containing pinkish secretion material. The breasts of both sexes show similar change. The influence of the maternal hormones promotes epithelial proliferation so that the terminal portions of the ducts have columnar epithelium with secretory buds. Whatever secretion is developed is derived from the duct epithelium, as the phase of lobular development has not yet been accomplished. The periductal tissue is quite vascular at this time. Approximately two weeks after birth the columnar cells recede in height, become vacuolated, and are cast off. The adjacent connective tissue then fills the areas occupied by the dilated ducts. In 60 per cent of infants clinical examination reveals enlargement, induration, and congestion. These findings may be confused with true inflammation which is much less common.

The Mammary Gland of Adolescence.—Before the onset of menstruation there is a gradual development and physical enlargement of the breast. This generally takes place over the course of three to five years. Enlargement in the mass of the breast is brought about by proliferation of all its components. Proliferation of periductal stroma keeps pace with growth of the ducts. The intervening connective tissue increases in proportion. The ducts themselves elongate and divide. Their terminal branches where growth is greatest dilate and form bunches of cystlike structures. Microscopically at this time the dilated ducts show proliferation of the epithelium in the form of

pseudostratification and clump formation. Such clumps are particularly prominent about the ends of the smaller branched ducts and indicate the sites of future acinar development. As the growth proceeds, the solid clumps of cells (of ductules) undergo central autolysis and thereby become epithelium-lined channels. However, not all portions of the breast develop simultaneously or to the same degree. Elaboration of estrogenic hormone by the ovary is responsible for this phase of development.[2]

The Mammary Gland of Sexual Maturity.—That the breast is under the influence of the sexual cycle can no longer be doubted. This was first described by Rosenburg[7] in 1922; however, later detailed study by large section technique of the breasts has expelled the doubts fostered by many authors after Rosenburg's reports.[24] Moderate volume changes of the normal nonpregnant breast during the sexual cycle is attested to by many patients. There is also subjective sensation of "fullness" and tenderness. This is confirmed by the enlargement of the superficial veins and the difficulty of adequately palpating the breast parenchyma at this time of the sexual cycle. The cellular activity of the breast is somewhat parallel to that of the endometrium, but as in the ovary only some follicles are affected so in the breast only a proportion of the lobules undergo cyclic changes. During the phase of menstruation breast epithelium shows shrinkage of the duct branches with desquamation and atrophy of the epithelial cells. The cells which remain are relatively small, low columnar, and have deeply staining nuclei. They are very closely associated with the more deeply situated undifferentiated basal cells. In the relatively dense periductal connective tissue small, round cells may be prominent. Several days after cessation of menstruation the proliferative phase becomes evident. This is characterized by the expansion of the duct system, increase in the size and number of the epithelial cells and the development of a soft, edematous, pale-staining, relatively acellular periductal connective tissue. Shortly thereafter, the multiple branchings of the ducts continue, under the influence of luteal hormone, to the point of definable lobule formations of crowded epithelial cells; however, this is not uniform. The premenstrual hyperplasia of columnar cells is accompanied by an abortive "secretory" activity. The relationship between the periductal tissue and the epithelium is, therefore, converse. During the epithelial proliferation phase the surrounding periductal tissue softens, develops a mucoid character and becomes considerably decreased in bulk. When secretion takes place into the ducts, the distention may further obscure the periductal connective tissue. With the advent of epithelial involution the connective tissue proliferates and replaces the area occupied by the large duct or lobule. At this time it is moderately cellular. Cyclical changes are not seen in amenorrhea associated with castration or chronic illness such as tuberculosis or diabetes.

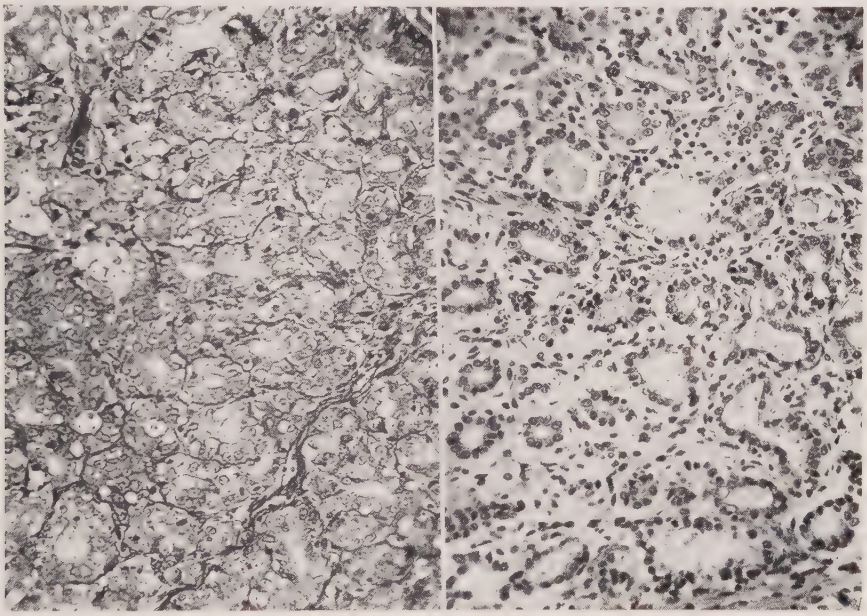


Fig. 943. Fig. 944.

Fig. 943.—Breast at term of pregnancy.

Fig. 944.—Breast showing involution nineteen days post partum (patient aged 22 years, never nursed). (Courtesy Dr. H. Ingleby.)

The Mammary Gland in Pregnancy and Lactation.—The earliest change detected externally is the moderate increase in firmness of the

breast associated with enlargement of the superficial veins and the gradually developing pigmentation of the areola and nipple. The first three months of pregnancy are characterized by cellular proliferation. This is particularly marked at the blind ends of the branched ducts and in the sites of lobular development. The lobules increase in size and the ducts become moderately dilated. As the epithelial tissue becomes more and more prominent, the periductal tissue softens and has a less intense staining character. Eventually the lobular proliferation is characterized by forms of acini with their acinar ducts accompanied by a delicate vascular connective tissue bed. It has been pointed out that the centralmost parts of breast beneath the nipple develop blind duct pouches that may act as reservoirs.[8] At term of pregnancy, superficial epithelial cells of the breast have differentiated into a fat-containing colostrum cell. Such cells are shed in variable amounts and constitute what is known as the initial secretion of the breast (colostrum). Shortly after delivery the basal cells lining the dilated acini become the secretory epithelium with pale cytoplasm and various globules. This lactation cytologic change is accompanied by immense increase in the secretory lobules. Acinar differentiation and secretory function are promoted by luteal hormones, pregnancy placental hormones, and the lactogenic stimulus of the pituitary.

In the phase of involution following lactation the collapse of the dilated secretory lobules and ducts may be followed by failure of adequate connective tissue growth, producing thereby a breast of a flattened contour and flabby consistency. The irregularity of involution, persistency of dilated ducts and the periductal and perilobular lymphocytic infiltration may constitute chronic cystic mastitis—lobular hyperplasia. However, it is generally accepted that mastodynia disappears and cystic disease of the breast improves after lactation. This may be due to luteal hormone influence. Tumor formations are adversely influenced by pregnancy and lactation. Fibroadenomas grow rapidly and may increase remarkably. Carcinoma of the breast is noted a bit more frequently after abnormal lactation and if present during pregnancy it is so stimulated in growth that prognosis becomes hopeless.[2]

The Senile Breast.—After menopause the striking change is the atrophy of the acini and lobules with gradual epithelial involution progressing toward the nipple from the periphery. The duct system may thereby be shortened so that the peripheral portions are accompanied by elastic tissue which generally does not extend to the lobular areas of the functional breast. The involution is frequently irregular and quite commonly accompanied by dilated ducts lined by small deeply stained epithelial cells. Eventually the stroma also decreases in bulk by nature of sclerosis and loss of cellularity. The periductal tissue becomes hyalinized.

Hypertrophy of the Breast

Hypertrophy of one or both breasts may take place at any time and is brought about by abnormal hormonal relationships. Before puberty, hypertrophy is usually bilateral and is frequently the physical evidence of estrogen-producing tumors. These include granulosa cell tumors of the ovary, chorioepithelioma of the ovary, adrenal gland (cortical cell tumors), and pituitary tumors. Such changes are reversible, as evidenced by the regression of the breast size following extirpation of the hormone-producing tumors. At the time of adolescence or shortly thereafter, irreversible hypertrophy of one or both breasts may take place (virginal hypertrophy). The breast may become extremely pendulous, the veins enlarged, and the nipple drawn into the pendulous mass. Prominent histologic change is the increase of the fibrous tissue and the attempted lobular formation. According to Geschickter[2] such an increase in the size of the breast rests in its inherent abnormal sensitivity to estrogenic hormones; sensitivity may not be bilaterally the same. In both the precocious hypertrophy and the true virginal hypertrophy the estrogenic activity is evidenced by duct epithelial hyperplasia and hypertrophy accompanied by irregular meager secretory activity. The development of acini depends upon luteal hormones and pituitary influence rather than on estrogens. The findings of follicular cysts of the ovary or a fibroadenoma in such a breast has been noted.

Hypertrophy of Male Breast (Gynecomastia).—The development and growth of the male breast parallel that of the female up to the time of adolescence. Even in this period of life there is an abortive attempt at breast growth and differentiation. Abnormal enlargement of the breast may take place at any period of life, most frequently in boyhood and in senility. Usually only one breast is involved with no appreciable difference of incidence in respect to left or right. In the majority the enlargement is evident as a buttonlike swelling beneath the areola; in unusual circumstances the breast enlarges and assumes proportions similar to that of the virginal female breast. The condition is best expressed in the words of Karsner,[10] "Gynecomastia is an enlargement of the mammary gland or glands of males due to proliferation of connective tissue, dense in the general stroma and often loosely arranged in periductal regions, together with variable degrees of multiplication, elongation, or branching of ducts, or of all three, without formation of true acini, accompanied by periductal or more widespread infiltration of lymphocytes, plasma cells, large mononuclear cells, and occasionally eosinophiles or neutrophilic polymorphonuclear cells, or both; secretion is frequently present in ducts, may be discharged spontaneously or manually expressed, but rarely if ever is it true colostrum or milk. This definition excludes pseudogynecomastia, due to the deposition of fat in the mammary regions, as well as suppurative or other essentially inflammatory processes, granulomatous lesions, and neoplasms, either benign or malignant."

Gynecomastia is about three times as common as carcinoma in the male breast. There is no relationship between carcinoma and gynecomastia. Rather remarkable enlargement of the male breast can be produced by the administra-

tion of stilbestrol. With such hormonal stimulation, however, the growth and differentiation potentialities are limited and never parallel those of the female breast. Hormonal imbalance with the actual or relative increase of estrogenic hormones is the practical consideration of the etiology of gynecomastia. True gynecomastia does not appear in eunuchs. Tumors of the testis, such as teratomata which may produce estrogen, are associated with hypertrophy of the male breast. Decreases in androgenic activity of the testis may have similar results. The gynecomastia seen in elderly men may be brought about by the declining androgenic hormones of that period of life. Likewise, in dietary deficiency and in cirrhosis of the liver the failure of proper de-estrogenation may at times be associated with hypertrophy of the breast. Pituitary adenomata which influence the thyroid, the adrenals, and the gonads are at times associated with gynecomastia. Although there is doubt that injury is a causative factor, it cannot be denied that it may provoke a more rapid increase in growth.

Fig. 945.—Gynecomastia showing the elongation and abortive budding of the ducts which are surrounded by a loose periductal stroma in which lymphocytes are evident.

Inflammations of the Breast

Acute Mastitis.—Acute bacterial-induced mastitis is practically limited to the period of lactation, in most cases the first three weeks of nursing. It occurs in less than 1 per cent of lactating women, but approximately one-half of the cases are primiparas. The causative agent, generally *Staphylococcus aureus*—less commonly streptococcus—invades the breast through fissures of the nipples and the exposed lymphatics or by way of the milk ducts. Breast engorgement following irregularity of nursing incident to cracked nipples enhances the possibility of bacterial invasion. The painful, swollen, indurated, reddened, and hot breast may be exquisitely tender. Changes are either diffuse or focal. With the advent of suppuration, localization and softening become apparent. Abscesses have classical locations, namely, subareolar, parenchymal, or stromal and retromammary. Early cases of puerperal mastitis can easily be confused with acute inflammatory carcinoma, or vice versa. In the later stages repair and fixation to the skin may likewise be erroneously interpreted. The axillary nodes are frequently enlarged and generally are tender. Gross findings of suppuration or abscess formation and microscopic changes of acute inflammation are in no wise peculiar in this organ. Rarely, however, a late-appearing subacute or a relapsing puerperal mastitis may closely resemble plasma cell mastitis or tuberculosis.

Plasma Cell Mastitis.—The uncommon entity known as plasma cell mastitis (pseudotuberculosis) occurs after pregnancy (multiple) in women

of about 40 years. A history of difficult nursing (inverted nipples, cracked nipples, death of infant) is elicited in 50 per cent of the cases.[12] Stasis and inspissation of secretions initiate this inflammatory disease. It is chemical in nature rather than bacterial and actually constitutes a type of foreign body reaction as evidenced by eosinophiles, foam cells, giant cells, colostrum cells, and fatty acid crystals. The lesion is one of induration beneath a quadrant of the areola associated with a lump formation and distortion of the nipple. It may be accompanied by pain and tenderness of variable degree or by a cloudy discharge from the nipple. At times it is multicentric in origin. The ducts may be palpably thickened and the axillary nodes enlarged. The diseased area presents a level cut surface of grayish mottled character punctuated by distorted ducts, expressed secretions, and minute areas of necrosis. Microscopic appearance is at times very similar to tuberculosis. Epithelioid cells and giant cells may be clustered in a tubercle-like arrangement; however, polymorphonuclear cells are quite common and foam cells are prominent. The most characteristic findings are the absence of the caseation, the absence of tubercle bacilli, and the predominant plasma cells. The grouping of giant cells and foam cells about lipoid crystals is a prominent feature and may resemble fat necrosis. Parenchymal destruction followed by repair and granulation tissue follows the more diffuse inflammation with necrosis. Variable amounts of connective tissue in the phase of regeneration and repair increase the hardness of the area and cause retraction of the nipple. Clinically and grossly, therefore, there may be striking resemblance to mammary carcinoma. However, the poorly defined diffuse induration without chalk streaks or cicatrization but with minute cysts of fatty material makes possible the differential diagnosis of plasma cell matitis from carcinoma in most cases.

Chronic Mastitis.—Chronic matsitis, with the exception of the chronic puerperal mastitis, is a granulomatous inflammation. In most instances it is secondary to a systemic disease.

TUBERCULOSIS.—Tuberculosis of the breast occurs mainly in young women and is extremely rare. Portal of entry is retrograde through the lymphatics, or by direct extension from tuberculous osteomyelitis of the ribs. It is, therefore, usually secondary to tuberculous cervical lymphadenitis or to pulmonary tuberculosis.

SYPHILIS.—All forms of syphilis, including the chancre of the nipple, syphilitic mastitis of the secondary stage, and gummata, are very rare. The gross appearance may be confused with Paget's disease in the primary stage, or with acute diffuse mastitis in the tertiary stage.

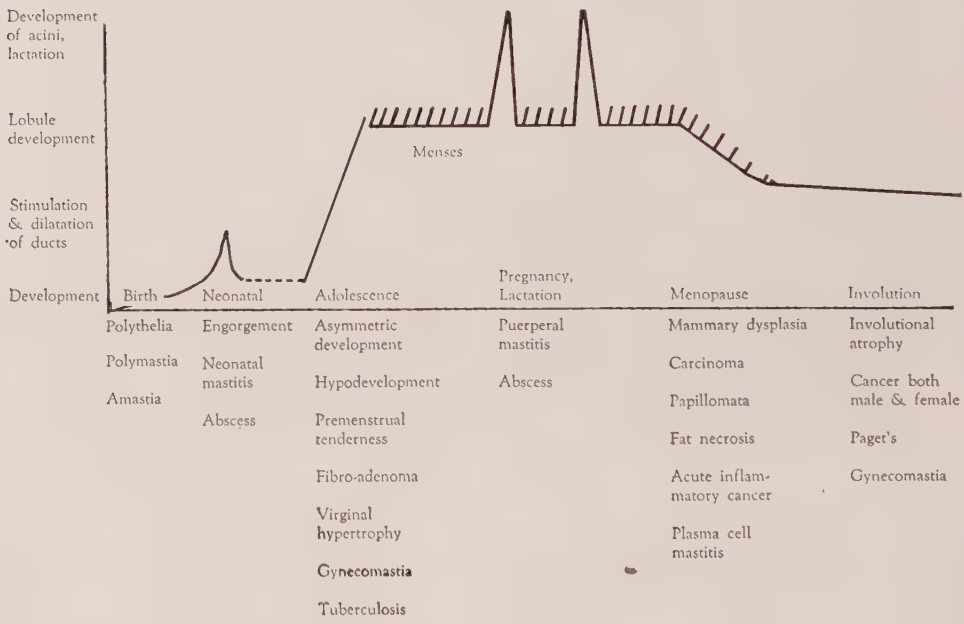
BLASTOMYCOSIS.—Blastomycosis is always secondary to systemic mycotic infections, particularly that of the lungs. Its extension is frequently through sinuses of the chest wall or blastomycotic osteomyelitis of the ribs.

ACTINOMYCOSIS.—Actinomycosis very closely resembles tuberculosis. It is characterized by diffuse induration with cutaneous sinuses. It is generally secondary to pulmonary actinomycosis.

Fat Necrosis.—A peculiar and unusual breast "tumor" is occasionally encountered in fat, pendulous breasts following injury. A history

TABLE XVI

DISEASES OF THE BREAST ACCORDING TO AGE



of physical violence to the breast, however, is elicited in less than one-half of the women with this condition. Indeed, fat necrosis may be associated with a suppurative disease of the breast, with carcinoma, with ischemia produced by pressure, and with "biopsy" breast surgery.[15] Symptoms may be present for months or years.

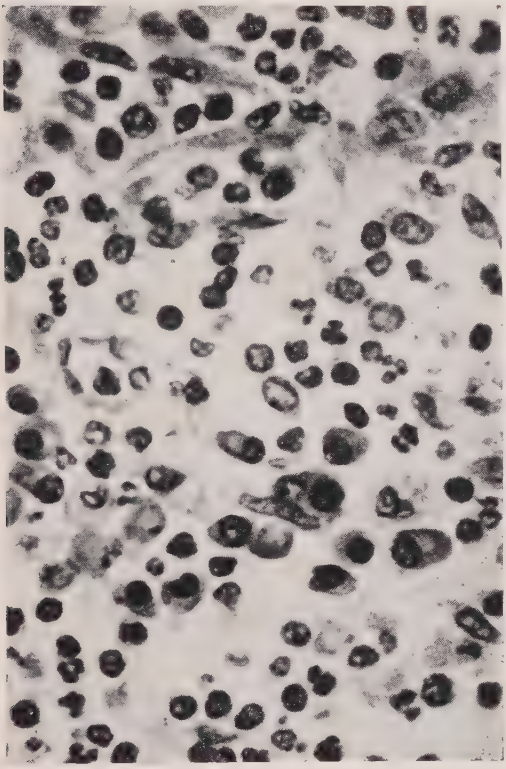


Fig. 946.—Plasma cell mastitis. There is a mixed cellular complement with outstanding plasma cells.

Clinical characteristics of a hard, somewhat fixed lump in the absence of discoloration of the skin easily may be misinterpreted as that of a malignant tumor. In the early stages the lesion appears as a well-defined, firm, solid, homogeneous, lardaceous substance. As necrosis progresses, it may change to a light yellow, orange, brown or brownish-red color, depending upon presence or absence of hemorrhage. Cyst formation, hemorrhage, calcification, stellate scarring, and fixation are almost constant in the old lesion. Histologic architecture of acute inflammation in the adipose tissue may be more striking than "fat necrosis." Polymorphonuclear cells, plasma cells, lympocytes, and monocytes are constant. The monocytes may be of epithelioid or foam type but generally form foreign body giant cells. Early stages of the disease present opaque fat cells (fat saponification), and later there is found true necrosis with the presence of cholesterol crystals (sharp, angular clefts) and calcification. Ultimately, regeneration and repair produce stellate scarring and fixation to the skin which may lead to an erroneous clinical diagnosis of carcinoma.

Mammary Dysplasia

Under this heading one must present a historically heterogeneous, challenging group of conditions composed of lesions fundamentally so similar that it becomes advantageous (if not imperative) to consider them under a single, descriptive, defining term. The many points of similarity in development, clinical expression, and histology greatly outweigh those of dissimilarity. It has taken the time from Brodie, 1846, and Reclus, 1883, to evolve the present-day concept of a single disease in various forms, cloaked in as many or more names—maladie cystique (Reclus), mastopathia cystica (Aschoff), fibrocystic disease, cystic hyperplasia, chronic cystic mastitis or Schimmelbusch's disease, mazoplasia, cystiphorous desquamative epithelial hyperplasia (Cheatle, Cutler), fibroadenomatosis cystica (Semb) and mammary dysplasia (Geschickter). Present feeling is that the confusing no-

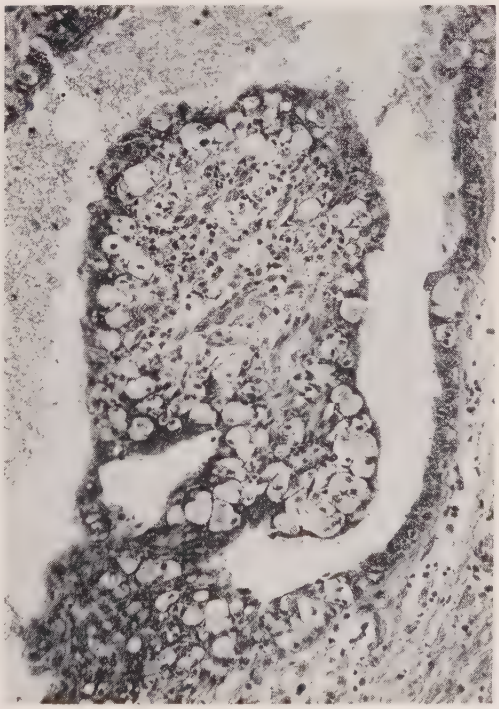


Fig. 947.—Plasma cell mastitis, showing colostrum corpuscles. (From Ingleby, Ann. Surg. **109**: 1939.)

menclature had birth in the arbritrarily selected criteria of lesions without cognizance of one essential disorder in somewhat different qualitative and quantitative phases.

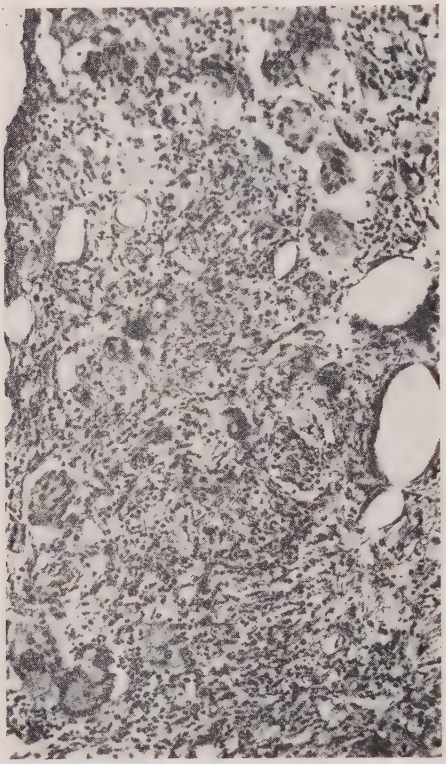


Fig. 948.—Fat necrosis. This lesion is rather old, showing numerous multinucleated giant cells, spaces occupied by lipoids, moderate fibrosis, and numerous small round cells.

Mammary dysplasia is essentially an abnormal interplay of parenchyma and stroma, developed and expressed by failure of reciprocal proliferation and involution. The paramount change centers about the breast lobule of sexual maturity. The condition, therefore, is not very active in postmenopausal life nor is it a disease of the male breast. It is, moreover, neither inflammatory nor neoplastic, and the irrevocable term of chronic cystic mastitis is not generic. Anatomic changes of this condition are the reflection of ovarian hormonal imbalance (namely corpus luteum deficiency with relative or absolute hyperestrinism) acting upon the susceptible breast over a long period of time.[21, 23] In the few cases investigated, pregnandiol levels were found to be lower than normal (11.6 mg. per premenstrual cycle as compared with a normal of 30 mg.).[2, 17]

Basically the condition is a lumpiness of the mammary gland. It is found in women chiefly in the last decade of reproductive life, but although developing in this period, it may not have prominent symptoms or be recognized until after the menopause. It is commonly bilateral and associated with premenstrual pain. The upper outer quadrant of the breast is chiefly involved. The hormonal irregularity is also evident in sterility or irregular menstruation. Failure of pregnancy and lactation or disturbances attending these physiologic processes predispose to mammary dysplasia, while normal pregnancy and lactation are the best therapies. Many cases apparently subside spontaneously.

Writers frequently refer to the relation of chronic cystic mastitis to mammary carcinoma. Warren found mammary carcinoma 4.5 times more frequently in a group with chronic cystic mastitis, irrespective of age, than in the normal population.[22]

The appearance of the lesion depends to a great extent upon the relationships between, and the degree of:

A. Canalicular development, growth, dilatation, and cyst formation.

B. Epithelial cell proliferation, wandering or involution.

TABLE XVII

	MAZOPLASIA (LEAST CHANGE)	ADENOSIS	CYSTIC MASTITIS (GREATEST CHANGE)
Epithelium	Normal?	Hyperplastic	Atrophic or "apocrine" change
Stroma	Slightly increased	Intralobular increase	Sclerotic
Lobules	Slightly irregular	Large, irregular, very cellular	Atrophic, irregular, cystic
Cysts	Microscopic	Variable	Large, macroscopic
Area	Diffuse area involved	Periphery of breast	Mid-zone
Inflammation	None	Generally little	Prominent

C. Stromal reaction—lobular infiltration or sclerosis.

D. Inflammatory cell infiltration.

Upon this basis three forms (phases) of mammary dysplasia are recognized. Commonly one or the other form predominates in any one patient but transitions do occur.[2, 21]

Mazoplasia (Mastodynia, the Early Phase With Minimal Change).—*Gross appearance:* The mammary gland is involved by a periodic swelling and diffuse granularity of the affected area. One-fourth of the cases may develop adenosis. Cutting is somewhat difficult and section so made presents a white, poorly demar-

Fig. 949.

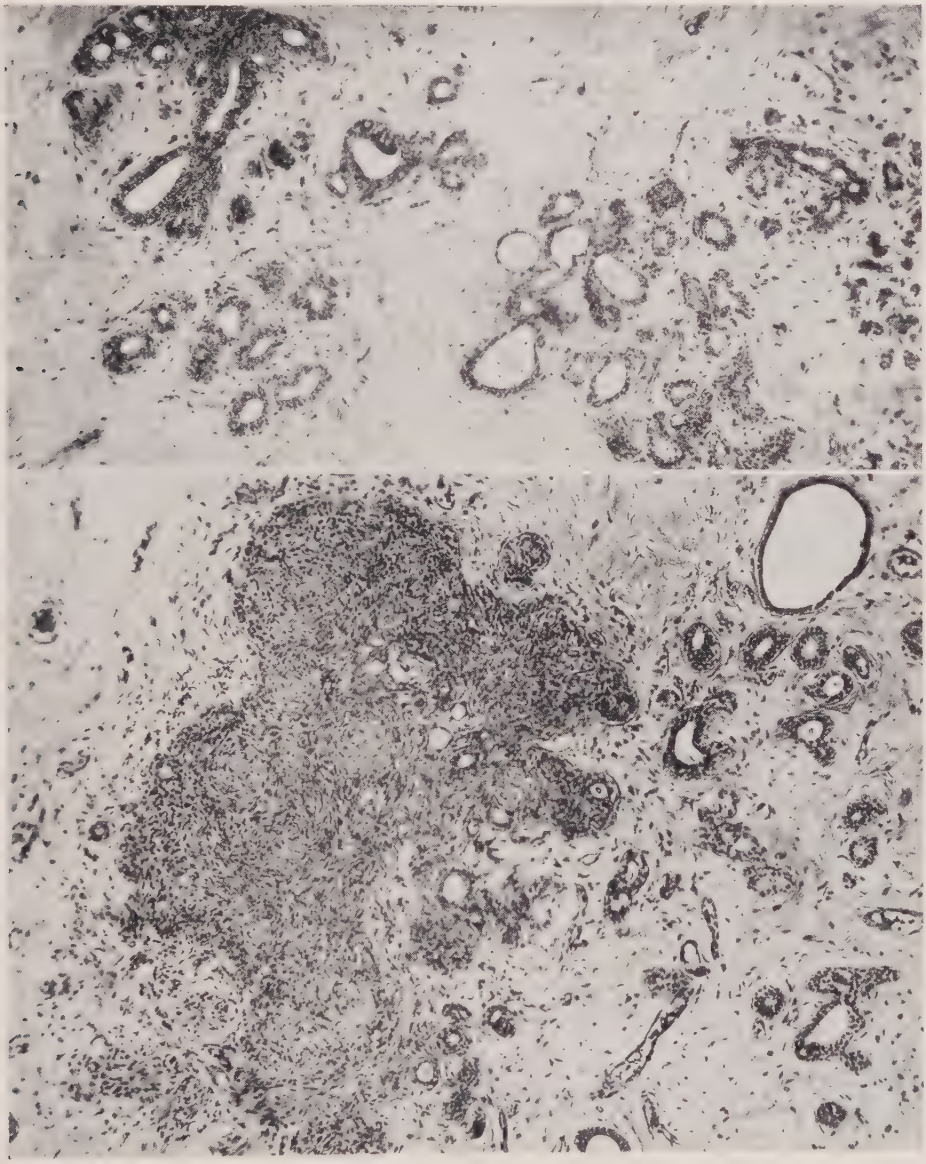


Fig. 950.

Fig. 949.—Mazoplasia. The lobular structures are distorted by growth of connective tissue without distinction between lobular and general connective tissue. (Courtesy Dr. H. Ingleby.)

Fig. 950.—Adenosis. Note the lobular distortion, increase of connective tissue, and profuse epithelial spilling. Silver stains, however, show intact basement membrane surrounding the clusters of epithelial cells. (Courtesy Dr. H. Ingleby.)

cated, dense, irregular, stiff, and tough substance marked by minute pinkish dots of the parenchyma. *Microscopic appearance:* The essential change is a moderate thickening and increase of the lobular stroma and its fusion with the general connective tissue. The ducts are microscopically dilated and the lobules are variable in size and irregular in outline. The epithelium may be nearly normal or multilayered, secretory or vacuolated, flat or desquamating—more commonly all phases may be encountered in the perusal of large sections. However, the deviations from normal are usually not very pronounced.

speckled, shotlike areas containing yellowish, grumous plugs closely associated with the cysts. *Microscopic appearance:* Diffuse fibrosis with loss of distinction between intralobular and periductal connective tissue and the general stroma is characteristic. Many ductules are dilated and contain clear or cloudy fluid. The epithelium is usually hyperplastic and lines the proliferating ductules with several layers of cells, at times forming minute papillomata or "spilling" out of its confines to cause considerable disorganization of the lobules. Separation and disorganization of the lobules by advanced intralobular fibrosis accompanied by epi-

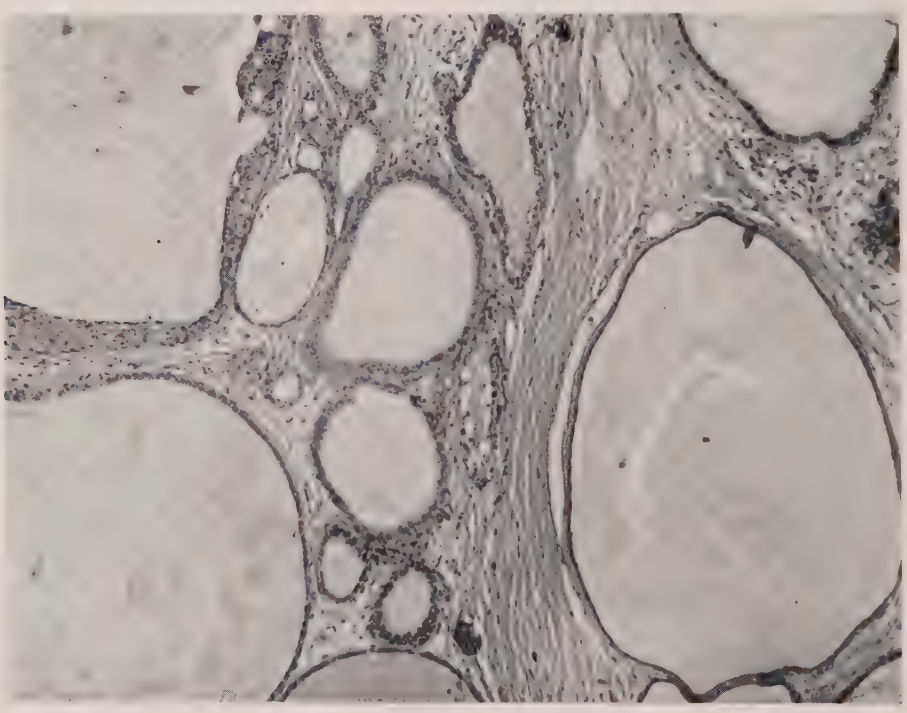


Fig. 951.—Marked cystic change showing both atrophic epithelium and the piled-up hyperplastic epithelium of other cysts. The stroma is sclerotic and contains lymphocytes. (Courtesy Dr. H. Ingleby.)

Adenosis.—*Gross appearance:* The breast is rather small and fibrous in character. It has an easily palpable exaggerated parenchyma with sharp peripheral boundaries. The nodularity to palpation, which is quite characteristic, is mostly peripheral. The gland cuts with difficulty. Involved areas resemble mazoplasia but have two differences: (a) minute pinhead- to pea-sized clear cysts; (b) small, rubbery-hard, finely granular,

thelial proliferation resembling glandular growth and invasion has been termed *sclerosing adenomatosis* or fibrosing adenoma. Such a lobule presents a filigree pattern and is frequently associated with myoepithelial hyperplasia.

Cystic Disease.—*Gross appearance:* The breast is likely to be a little more fatty than in the two previous conditions. It presents a round, smooth, tense movable mass averaging 3 to 4 cm. in diameter,

which transiluminates and may be fluctuant. The area is closer to the center of the breast than is adenosis. Sections show an exaggerated pattern of adenosis; cysts are variable, multiple, and large, and protrude into the stromal fat. They are somewhat translucent, causing the light brownish contents to appear bluish through the cyst wall (blue dome cyst). The shotty areas are also larger, harder, and more yellowish. On pressure in some cases abundant pasty material can be expressed in the form of ribbons. *Microscopic appearance:* The irregular lobules are small,

Fig. 952.

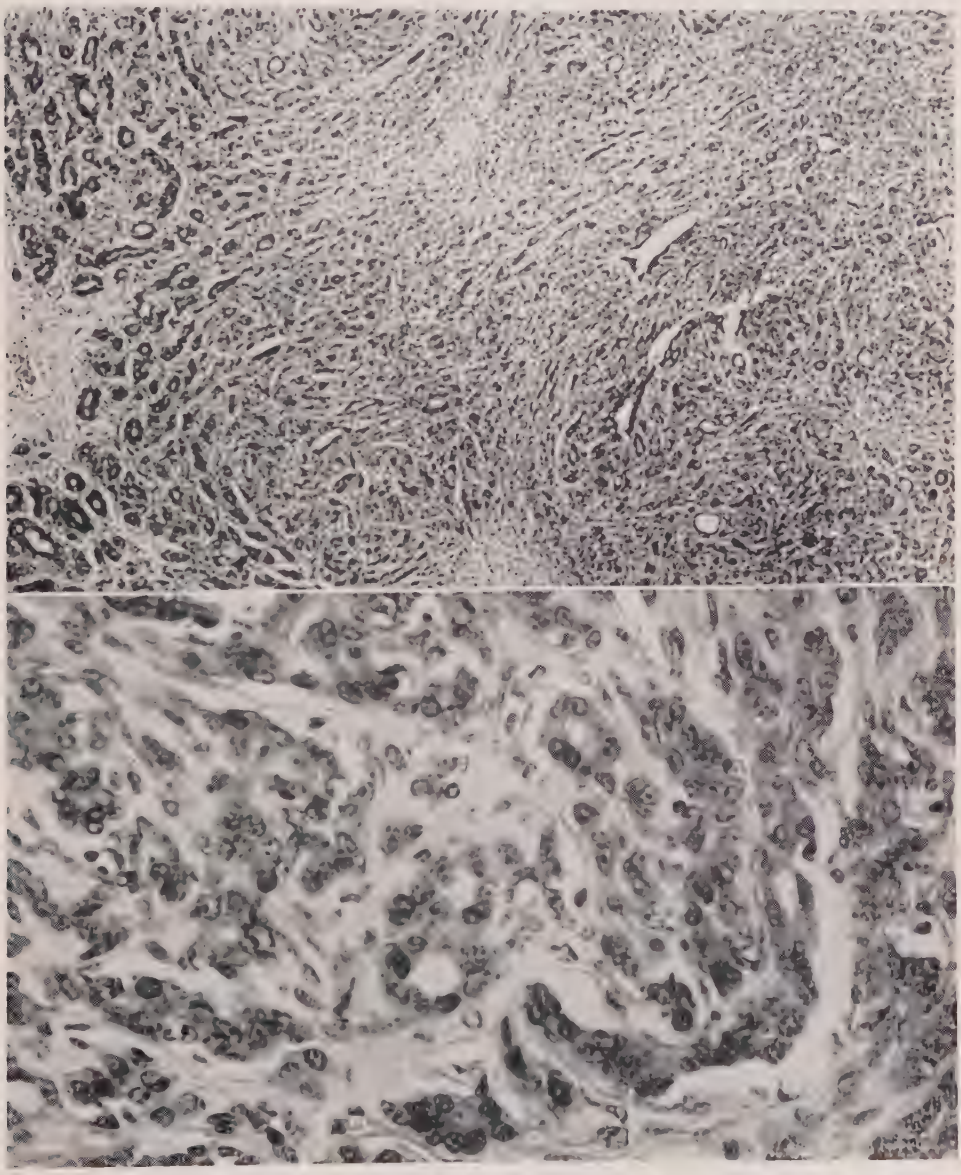


Fig. 953.

Fig. 952.—Sclerosing adenomatosis in which four lobules of the breast are represented in a pattern of delicate filigree architecture.

Fig. 953.—High-power magnification of the central portion of one of the lobules of sclerosing adenomatosis. The admixture of fibrous stroma with disorganized glands closely mimics the pattern of infiltrating adenocarcinoma.

acini are few, and ductules are dilated and filled with amorphous granular material. Larger cysts have atrophic, flattened, or absent epithelium accompanied by a very dense, sclerotic, outlining stroma. Epithelial involution is the keynote, to which, however, there are two exceptions: (a) the occasionally persistent focus of hyperplasia or papilloma formation and (b) the hyperplasia of apocrine-like glands. This latter finding is a prominent feature although similar glands may be found in many otherwise normal breasts or associated with fibroadenoma, papilloma, or sclerosing adenomatosis. The glands are variable and large. The lining acidophilic epithelium is very tall and commonly presents plump papillary projections. Nuclei are nearly basilar in position and are round and light staining. Knobby free margins of the tall cells as so often seen make the identification easy (gasoline pump cells). Lymphocytic or mononuclear infiltrations around ducts, smaller cysts, and in the lobules are both prominent and constant. In some instances myoepithelial proliferation adds to the epithelial hyperplasia.

Miscellaneous Cystic Disorders.—A galactocele or milk cyst develops in young females during lactation. The contents are truly milky or inspissated. It develops presumably because of duct obstruction. The cyst wall may show areas of necrosis, round cell infiltration, and condensation of the adjacent stroma. It is a rare occurrence. **Dilated ducts** or ductile ectasia occurs at or after the menopause and consists of visible or palpable dilated ducts filled with a puttylike material beneath the nipple. Ducts show desquamating secretory epithelium with lymphocytes and monocytes in the duct walls. The inflammatory reaction is in response to chemical irritation of decomposition. The condition is the result of irregular proliferation and secretion in women of 50 or over.

Benign Tumors of the Breast

Fibroadenoma.—Fibroadenoma is a slowly growing, estrogen-induced, benign tumor occurring in females, most often before the age of thirty.[26, 27] Virtually it begins as mammary dysplasia and frequently it is associated with minute cysts. The sharp limits of the focus involved, the actual new growth of tissue, and the irreversible nature constitute the reasons for considering it a neoplasm. The reason why a focal area should be affected by hormonal imbalance (hyperestrinism or hypersensitivity to estrin) has not been explained. Menopause usually results in cessation of the growth of the tumor while

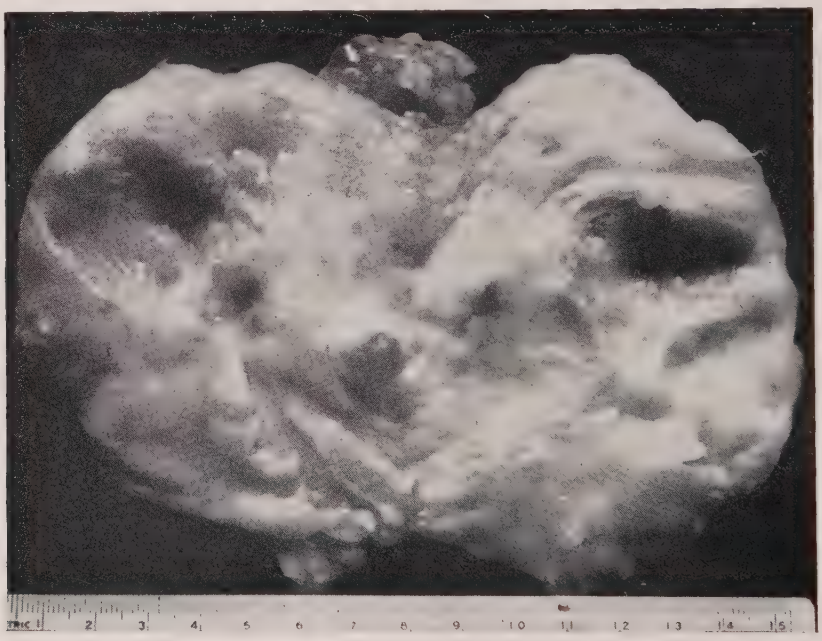


Fig. 954.—Cystic disease of the breast. The larger cyst is bisected and shows a glistening smooth lining. In the center is a smaller bulging cyst.

pregnancy and lactation cause it to grow readily.[29] Rarely it continues in its growth and eventually produces a huge mass that may metastasize as a sarcoma.

The condition is usually solitary but occasionally multiple, bilateral, or recurring. The skin overlying the tumor and the axillary nodes shows no change. The tumor is movable, solid, rubbery in consistency, and smooth or lobulated. Its average size is about 3.5 cm. It does not transilluminate.

The *gross appearance* is distinctly different from that of any other mammary

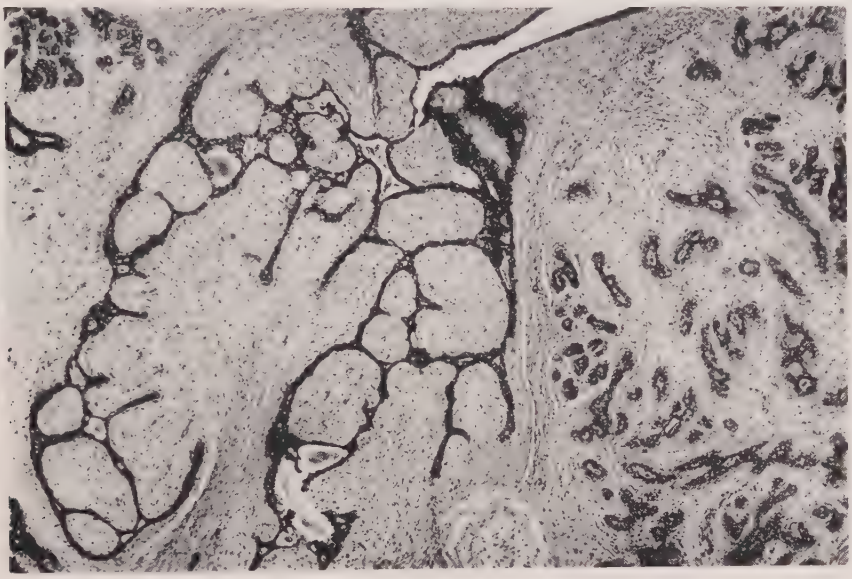


Fig. 955.—Fibroadenoma showing intracanalicular formation in the left side of the photograph and a pericanalicular arrangement in the lobule of the right side of the photograph.

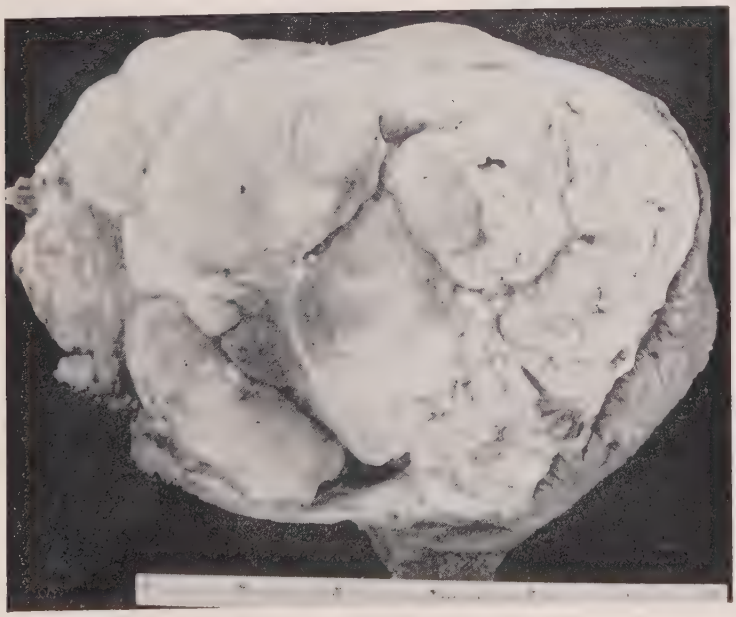


Fig. 956.—Giant intracanalicular fibromyxoma showing lobulated smooth glistening masses occupying most of the breast. The left one-third of the breast shows the pattern of the long-standing benign fibroadenoma.

tumor. Its encapsulation, partial or complete, and rubbery consistency allow sectioning only if the tumor is firmly held, or else it will slip and roll away from the knife. A sharp distinct edge outlines the decidedly elevated, flat, or slightly convex cut (or sectioned) surface. Firmer lesions are grayish-white; softer ones are pink. Either form, however, is grossly homogeneous. The surface made by section may present a fine granularity or a delicately fissured geographic pattern. Old lesions are hyalinized and may be calcified. The varied pattern of microscopic response to the hormonal imbalance has given rise to many unnecessary names. Three histologic variations are acceptable depending probably upon the rate of growth of the connective tissue rather than on its origin.[27] Names applied are based on the predominance of either connective tissue or glands and their relationships, as no fibroadenoma is a pure histologic type.

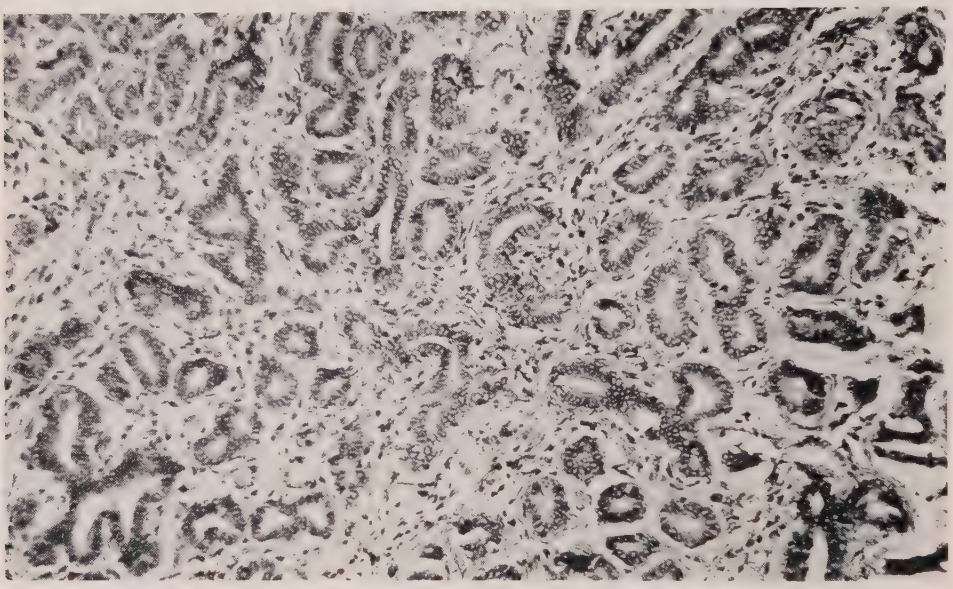


Fig. 957.—Adenoma of the breast. This shows a highly glandular breast substance in which there is some suggestion of branching duct development. The stromal reaction is inconspicuous in comparison with the marked gland proliferation.

Intracanalicular Fibroadenoma (Intracanalicular Myxoma).—The connective tissue is exceedingly active and proliferating. Large polypoid masses growing into the parenchymal channels, thereby becoming covered by epithelium, produce a mosaic of distorted myxomatous discs. The epithelium is intimately applied to these projections and is continuous with that of the duct. It is atrophic at points of physical contact, and heaped up or multilayered in dilated segments of the elongated tortuous ductules. Huge formations of this type, 10 cm. or greater in diameter, are known as *giant intracanalicular myxoma* or *cystosarcoma phyllodes.* They are usually benign but have in a few instances recurred and metastasized as fibrosarcomas, both to the axilla and distally.[30]

Pericanalicular Fibroadenoma.—This tumor has a denser stroma. Both epithelium and stroma in proliferation make up the tumor. The ductules and lobules are hyperplastic and distorted by connective tissue growth. More typical, however, are sweeping encircling bands of dense connective tissue about the ductules and glands.

Adenoma.—Adenoma differs from the others in its remarkable epithelial proliferation of mature irregular closely packed glands outlined by tall, partly secreting epithelium. It may be so cellular as to recall the histology of adenocarcinoma; however, there is usually a neighboring connective tissue hyperplasia and lobular dis-

tortion or a close resemblance to fetal breast tissue ("fetal adenoma").

Papilloma.—Intraductal or intracystic papilloma is a pedunculated raspberry-like mass attached to the wall of a dilated duct or a cyst located within the boundary of the areola. Papillary hyperplasia in lobules is understandable and not uncommon (adenosis). Papillomatous growths developing in the large ducts are an enigma. They occur predominantly in parous women at or shortly before the menopause. The lesion may not be palpable but there may be spontaneous or induced bleeding from the nipple in more than one-half of the cases. Multiple

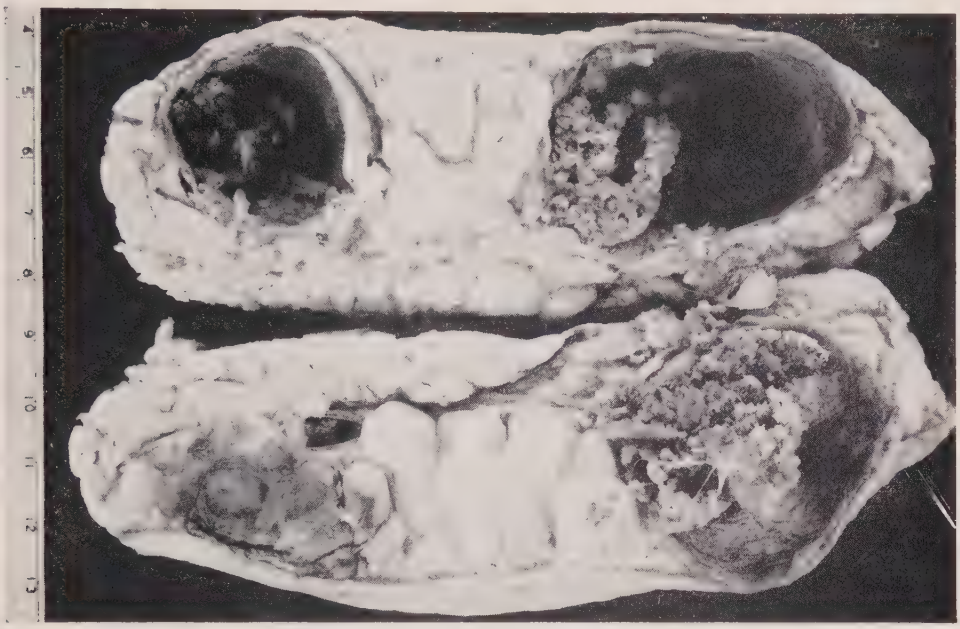


Fig. 958.—Gross specimen of breast showing intracystic papilloma. (Courtesy Dr. S. B. Pessin.)

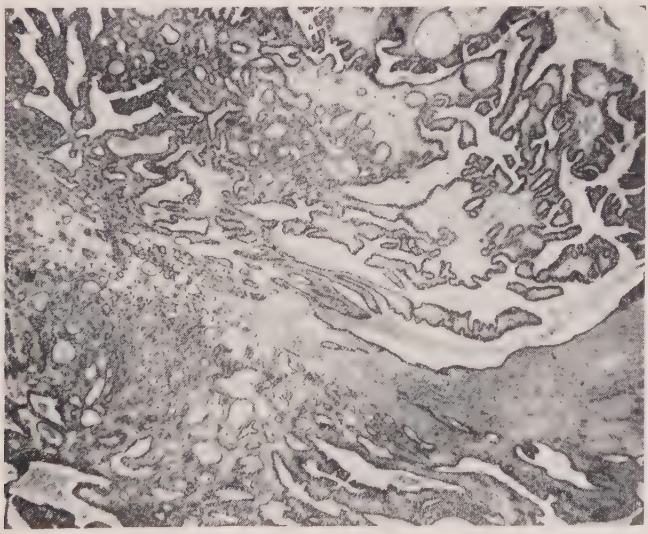


Fig. 959.—Intraductal papilloma near nipple, present five years in a woman 71 years of age.

papillomata are common. A very small percentage of these become papillary adenocarcinomas.

The papilloma appears as a firm, granular or raspberry-type of nodule, filling a duct or forming a small nipplelike projection on the wall of the cyst. Its point of attachment to the wall is narrow. Those less than 1 cm. in diameter are pale and glistening like cartilage. Larger ones are pink and deeply but delicately fissured on the surface. The villous or arborescent character is emphasized by the ease with which small particles may be broken off. A cloudy sanguineous fluid may fill the duct. Large tense cysts containing papillomata are frequently distended with bloody fluid. The microscopic structure is usually a delicate branching villous pattern of narrow vascularized connective tissue stalks covered by a single layer of cuboidal epithelium. Epithelial cell height, thickness, and organization depend to a great degree upon mechanical influences. The epithelial cells are atrophic in the old lesions with broad hyalinized stalks, and hyperplastic in those of delicate architecture. Hyperplasia, even with disorganization and the presence of mitoses, is generally considered benign unless there is demonstrable invasion through or loss of the basement membrane. The histologic pattern described is the conventional example of intracystic papilloma (pseudoglandular type). However, variations may be extreme.[33] In ascending order of potential malignancy these are: (a) fibropapilloma, wide fibrous core with atrophic epithelium; (b) pseudoglandular; (c) pseudoglandular with piled-up cells resembling urinary epithelium (transitional type); (d) true glandular type, acinar-like epithelium; and (e) papillary carcinoma, invasion demonstrable.

Malignant Tumors of the Breast

Incidence.—Mammary carcinoma may affect either breast, accessory breast tissue, or the male gland. It constitutes 11 per cent of all cancers and ranks second only to cancer of the gastrointestinal tract and uterus.[2] In the practice of surgical pathology, benign and malignant tumors occur with nearly equal frequency. Most cancers are discovered shortly before, during or just after the menopause. The older the patient, the more probable it is that a single lump in the breast is a carcinoma.

Predisposition.—A prolonged reproductive life span with menopause coming after 50 years is an unfavorable circumstance.[37] The action of estrogens for long periods of time is predisposing to the development of malignancy. A history of few pregnancies with irregularity of lactation is commonly elicited. Carcinoma is less common after castration in early life. Mammary carcinoma is 4.5 times as frequent in women with pre-existent breast lesions such as chronic mastitis and chronic cystic mastitis.[22] The role of heredity in the development of cancer is not understood although a number of recorded instances show development of breast cancer in siblings and successive generations. The experimental work in reference to heredity and to the "milk factor" is not directly applicable to human beings. The part played by trauma in the development of mammary tumors is negligible. This is borne out by the infrequency of breast carcinoma compared to the frequency of injury and the lack of relationship between the size of the tumor and the time factor following injury. Most tumors are much too large when noticed to have been initiated by a dated physical violence; however, it must be conceded that degeneration and hemorrhage may occur in a tumor as result of injury and that its rate of growth may be accelerated.

Etiology.—The cause of mammary cancer is not completely known. The highly specialized biologically active mammary tissue under the influences of hormones (especially estrogen) undergoes periodic hyperplasia and involution. Imbalances lead to mammary dysplasia or to accentuated repair and hyperplasia which eventually cross the threshold of neoplasia. This is more than speculation since estrogens act principally upon the ducts and ductules from whence most carcinomas arise. Geschickter[2] states, "All of the estrogens of sufficient potency for clinical use will produce mammary cancer in the rat regardless of chemical composition or physiologic potency. . . ."

"To date, from a toxicologic standpoint, the most important finding with respect to the estrogens is the production of mammary cancer by prolonged administration. In the clinical administration of the estrogens this toxicologic property has not yet been verified but must be considered when compounds of high potency with prolonged activity are administered. The species difference remains an unknown factor."[2]

Pathologic Anatomy.—Malignant tumors arise most frequently in the upper outer quadrant of the breast. The central area is next in frequency and then the upper inner quadrant followed by the lower inner quadrant.[2] The lesions arising far out in the periphery of the breast metastasize to regional nodes earlier than those which arise in the central portion of the breast, but lesions

of the inner quadrants have a less favorable prognosis because of mediastinal metastasis.[38] In the elderly individual cancer is likely to be of a hard fibrous character. In the small atrophic breast duct carcinoma of comedo variety is seen. In the atrophic but fatty breast early metastasis may arise from a very small focus of carcinoma. Young women, particularly with pregnancy, are likely to have a highly anaplastic, rapidly growing malignancy.

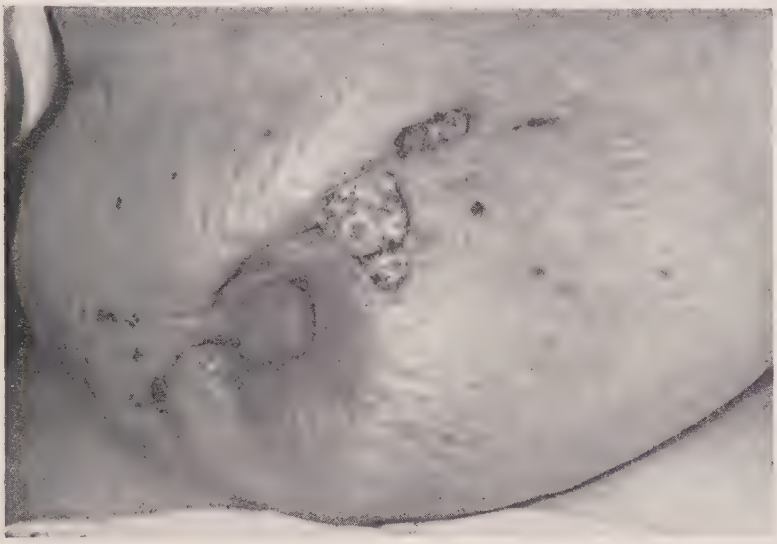


Fig. 960.—Infiltrating adenocarcinoma producing retraction of the nipple, marked dimpling of the skin, and invasion of the skin surface.

There are two important gross types of breast carcinomas: (a) The classical example is that of a single, hard, poorly movable, nonelastic, easily cut nodule. Sections have a dry, gritty, opaque surface marked by radiating, translucent lines of connective tissue accompanied by small yellowish or opaque grayish dots and streaks. The central portion of the tumor is slightly concave and the margins extend into the stroma between which the fat lobules may protrude above the level of the tumor; therefore, the border may be scalloped. The concave surface, the chalky streaks, the pouting fat tissue, and the blending of the tumor with the stroma in a radiating fashion are the paramount characteristics. The lesion may be firm enough to grate on cutting, and if one cuts thin slices of the tumor these maintain an extremely sharp edge and a level surface. The tissue appears extremely turgid and is not elastic or flexible. The infiltration of the connective tissue produces a contraction of the dermal papillae and of Cooper's ligaments, thereby developing the "orange peel" appearance of the skin. Periductal invasion causes retraction of the nipple. Intimate fixation to breast stroma and sometimes to the underlying fascia makes the tumor limited in movement. (b) The other gross type is that of an opaque, white or pink, soft-textured, highly cellular tissue which uniformly bulges above the cut surface and has an encephaloid character. This is particularly likely to be accompanied by cyst formation and hemorrhage. Either of these two types is characteristic enough to enable one to make a correct gross diagnosis in the majority of instances. (See Fig. 309, page 425.)

More than 90 per cent of the malignant mammary gland tumors arise from the epithelium of the duct system, either the large or the small channels; acinar carcinomas and sarcomas comprise the remainder. Basic features of adenocarcinoma may be found in virtually any mammary carcinoma, although one or another modification of histologic architecture (scirrhous, comedo, papillary, medullary) may predominate, and several

varieties may occur in one tumor. The site of origin and the histologic potentialities of the cell determine to some extent the pattern of the malignancy. The larger ducts frequently produce a papillary carcinoma. Intermediate ducts produce comedo carcinoma and Paget's disease, while the lobules are the seat of true infiltrating adenocarcinoma. Fully differentiated cells such as those of the premenstrual hyperplasia and those of lactation acini do not divide and in all probability do not give rise to cancer.

Prognosis.—In dealing with mammary cancer there is no "good prognosis"; most are necessarily gradations of "bad prognosis." This must be borne in mind if it is true that three-fourths of the patients sooner or later have recurrences and metastasis.[48] Two-thirds survive five years if no axillary nodes are involved at the time of radical surgery. Cancer developing under the age of 40 is the expression of very intense estrogenic activity and high susceptibility of breast tissue and therefore is associated with poor prognosis. Likewise, pregnancy exerts an unfavorable influence on the growth of a malignancy. Prognosis becomes less and less favorable with longer duration of symptoms, larger size of the lesion, and involvement of axillary lymph nodes. (See Fig. 335, page 445.)

Surgical Orientation.—Practically any benign lesion (fat necrosis, plasma cell mastitis, tuberculosis, abscess of the breast, and mammary dysplasia) may have one or more or all of the accepted clinical criteria of mammary cancer including axillary node enlargement. Likewise, a mammary cancer may be insidious in its onset and have none or only equivocal clinical signs of malignancy. This, of course, is the unfortunate truth of the early carcinoma and too frequently a physician will "watch" a lesion only to see the diagnosis blossom in the convincing form of metastases. It is exceedingly foolish to be governed by "statistics" in the care of mammary tumors; such is hindsight and poor at that. A given individual with a breast lump is 100 per cent one way or the other and too frequently only a biopsy can tell whether the lesion is benign or malignant. It is of paramount importance to remember that a lump in the breast is never normal, has no business being there, and has a 50 per cent chance of being a cancer. In postmenopausal women a single nodule in the breast is almost certainly a carcinoma.

Biopsy.—Biopsy should be synonymous with total, skillful removal of the tumor except in the very large or obviously malignant lesion wherein a radical mastectomy should be the primary and definitive surgery. The true biopsy or cutting into a tumor should be done after its removal, preferably by a competent pathologist who may find it desirable to do a frozen "quick" section for histologic study. Total removal is preferable to cutting into in situ for two reasons. First, if the tumor is benign, the operation is completed. Second, if the lesion is malignant, one has avoided the theoretical, if not practical, objection to opening vessels and contaminating the wound with tumor cells. Further more, if the tumor is removed, there will be no massaging of tumor cells into the lymphatics during the ensuing radical mastectomy. Some surgeons prefer to do radical mastectomies by first performing the axillary part of the operation in order to prevent tumor cells, expressed by manipulation, from escaping through the axillary filters into the general circulation.

Grading.—The grading of breast tumors at the time of the operation is not desirable in the infiltrating lesions. If a diagnosis of malignancy is made, that should be sufficient and the accepted treatment for cancer of the breast should be instituted. Not infrequently the surgeon will be adversely influenced by a "tumor grade." He may be tempted to do incomplete radical mastectomy in view of a tumor of low grade or he may suffer a false despair in the face of a high grade lesion. All radical breast surgery should be complete and thorough irrespective of the grade.

Metastasis.—The principal route of metastasis is lymphatic, notably that of the axilla, since the majority of lesions are found in the upper outer quadrant of the breast. Of the general group of carcinomas at the time of operation 60 per cent have axillary metastasis. In instances of bilateral simultaneous mammary cancers 71 per cent have axillary involvement. The lesions which are diagnosed as grade IV are associated with 84 per cent axillary metastasis.[48] Other lymphatic routes involve the lower cervical chain, the supra- and infraclavicular lymph nodes, the intercostal, retrosternal, and mediastinal routes particularly from the medial and lower quadrants of the breast. There is also an epigastric pathway which may lead directly to the mediastinal or abdominal nodes. Intramammary secondary foci are not too uncommon, and extension across the midline to the opposite breast occurs occasionally. The skin may be involved by way of the periductal lymphatics, lymphatics of Cooper's ligament. or by direct continuity. Multiple nodular cutaneous metastasis of the chest

wall is known as cancer *en cuirasse*. Visceral metastases are most prominent in the lungs and pleura, occurring in over one-half of the cases. Liver, bone, brain, adrenal, and spleen follow in order of frequency. Dissemination of tumor cells to the spine and brain may be explained by recently described vertebral vascular communications which favor retrograde spread.[35] It is peculiar that both cutaneous and osseous metastases are very unusual distal to the elbows and knees.

Classification of Mammary Cancer

Mammary tumors may be classified according to gross characteristics (scirrhous, colloid, medullary), histologic characteristic (adenocarcinoma, carcinoma simplex, sarcoma), histogenesis (duct, lobule, acini), or by activity (infiltrating, noninfiltrating). It is obvious, therefore, that a classification can readily become both confusing and unwieldly, and the proposal of a generally acceptable one is a distinct challenge. Terms denoting histology are based on the predominant architecture and not on purity of the lesion. It must be cautioned, therefore, that many patterns may be seen in any one carcinoma. A working classification may well combine the various features which make a tumor histologically, clinically, or otherwise distinct. The following orientation scheme, to which benign tumors have been added, is modified from Foote and Stewart.[40]

Table XVIII

Tumors of Mammary Gland

Benign
- I. Epithelial
  - A. Papillomata
- II. Mixed epithelial and mesodermal
  - A. Fibroadenoma
    - 1. Intracanalicular
    - 2. Pericanalicular
    - 3. Adenoma
- III. Mesodermal—Breast tumors only by geography and in no way distinctive in the mammary gland; viz., lipoma, angioma, fibroma, myoma, chondroma, osteoma

Malignant
- I. Mammary ducts
  - A. Noninfiltrating tumors
    - 1. Papillary carcinoma
    - 2. Comedo carcinoma
  - B. Infiltrating tumors (adenocarcinoma)
    - 1. Paget's disease
    - 2. Papillary carcinoma
    - 3. Comedo carcinoma
    - 4. Adenocarcinoma with productive fibrosis (scirrhous, simplex)
    - 5. Medullary carcinoma
    - 6. Colloid carcinoma
- II. Mammary lobules
  - A. Noninfiltrating—"in situ"
  - B. Infiltrating—lobular adenocarcinoma
- III. Epithelial or mesodermal origins such as tumors of the skin, skin appendages, and supporting tissues of breast. These are the same as found elsewhere in body—dermoid cyst, sweat gland tumors, basal or squamous cell carcinoma of skin, liposarcoma, etc.

Adenocarcinoma.—Approximately three-fourths of mammary carcinomas are associated with desmoplasia and have generally been called scirrhous carcinoma. The average age of occurrence is about 50 years, duration of symptoms ordinarily is less than a year, and the lesion averages 2 to 3 cm. in diameter. Almost two-thirds of such patients have axillary gland metastasis at the time of removal. The classical signs of mammary cancer generally refer to this particular form in which there is an extremely hard, fixed, infiltrating nodule with a slightly concave cut surface marked by grayish and yellowish streaking. Its early infiltration produces fixation, dimpling of the skin, retraction of the nipple, and axillary metastasis. When the tumor is larger, there is almost constant axillary gland involvement. The histologic character is that of a very prominent central hyalinized fibrosis associated with minute angular cleftlike spaces containing few closely packed epithelial cells. These may form minute columns or threadlike groups. The proportion of cells to stroma, however, varies considerably. When the cells are found in larger groups or broad columns, the tumor is known as *carcinoma simplex*. The cells are moderate in size, are generally deeply stained, and the distinction between cytoplasm and nuclei is frequently obscure. In the instances where cells are more numerous, differentiation is good and alveolar arrangement may be evident. Periductal and perivascular infiltration is most common. Invasion of fat lobules has features of fat necrosis. Grading of such a tumor is diffi-

cult since it may range from an extremely fibrous tumor to the more cellular simplex carcinoma. The size of the lesion, duration of symptoms, and presence or absence of metastasis to axillary nodes are much better criteria for prognosis.

Medullary Carcinoma.—Approximately 15 to 20 per cent of the malignant tumors belong to the group called medullary carcinoma.[40] Cancer cyst and neomammary cancer are other terms used.[2] It is characterized by a deeply situated, midzonal, circumscribed movable mass. The skin may be stretched over the bulging mass but it does not show dimpling and is generally free of ulceration. The gross lesion appears as a soft, partially cystic or hemorrhagic, bulky, somewhat opaque white tumor. It frequently resembles lymphoid tissue or has encephaloid characteristics. It is generally spherical and in two-thirds of the cases is larger than 5 cm. in diameter. Such a tumor generally grows slowly but may rapidly enlarge because of hemorrhage or necrosis. Prognosis is better than in adenocarcinoma. The microscopic picture is that of a highly cellular tumor composed of large, oval or polygonal cells with slightly basophilic cytoplasm and vesicular nuclei with prominent nucleoli. The size and polarity of such cells are quite variable and mitoses are common. Minute foci of keratin may be present. Various round or oval masses and thick papillary-like stalks of epithelial cells are common. Usually a generous lymphocyte infiltration accompanies the epithelial cells and forms an important histologic characteristic.

Comedo Carcinoma.—This tumor, comprising somewhat less than 10 per cent of the mammary carcinomas, is so named from the physical characteristics of plugs of pasty material expressible from the surface of the tumor. It is a slowly growing tumor which may have a course extending over years. It averages 5 cm. in diameter, is rather soft, and only 15 per cent of the cases have involved axillary nodes. Three-fourths of the patients survive a five-year period with radical mastectomy. A central location of the tumor is associated with cloudy nipple discharge in approximately one-third of the cases. Skin ulceration and retraction of the nipple are very late findings. It occurs particularly in women after the menopause, and is more frequently associated with chronic cystic mastitis than other carcinomas.[2] It arises from the small or intermediate ducts, and in its

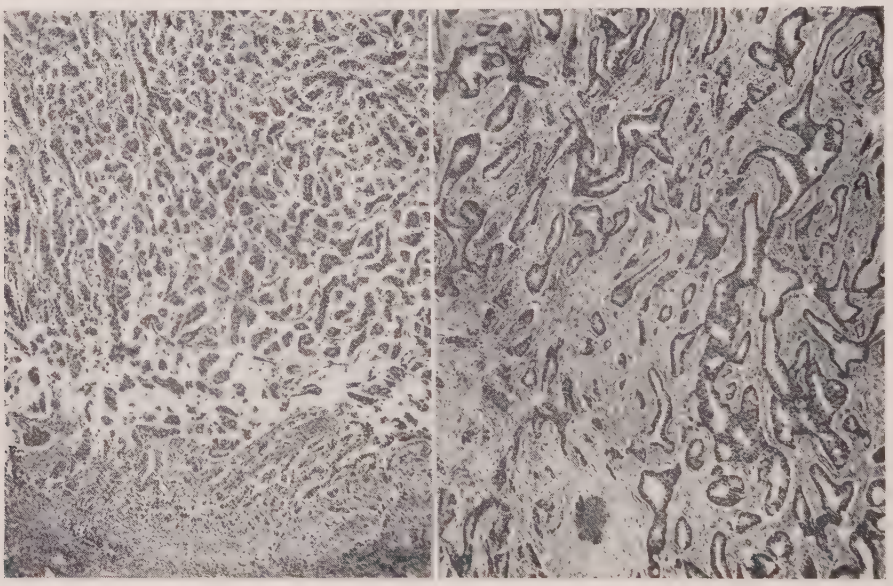


Fig. 961.—Two fields from the same microscopic section of early breast carcinoma in a middle-aged woman, to show different appearances present in the same tumor. (Courtesy Dr. H. Ingleby.)

growth the ducts of a given portion of the breast become filled with plugs of tumor cells. The tumor is usually somewhat circumscribed, quite firm in consistency, and grayish in color. It has an infiltrating gross appearance, but it is not as hard as the scirrhous carcinoma. The tumor areas present grayish dots, from which ribbonlike plugs of yellowish-gray pasty material or solid tumor plugs are extruded upon pressure. Adjacent breast substance is generally atrophic but

Fig. 962.

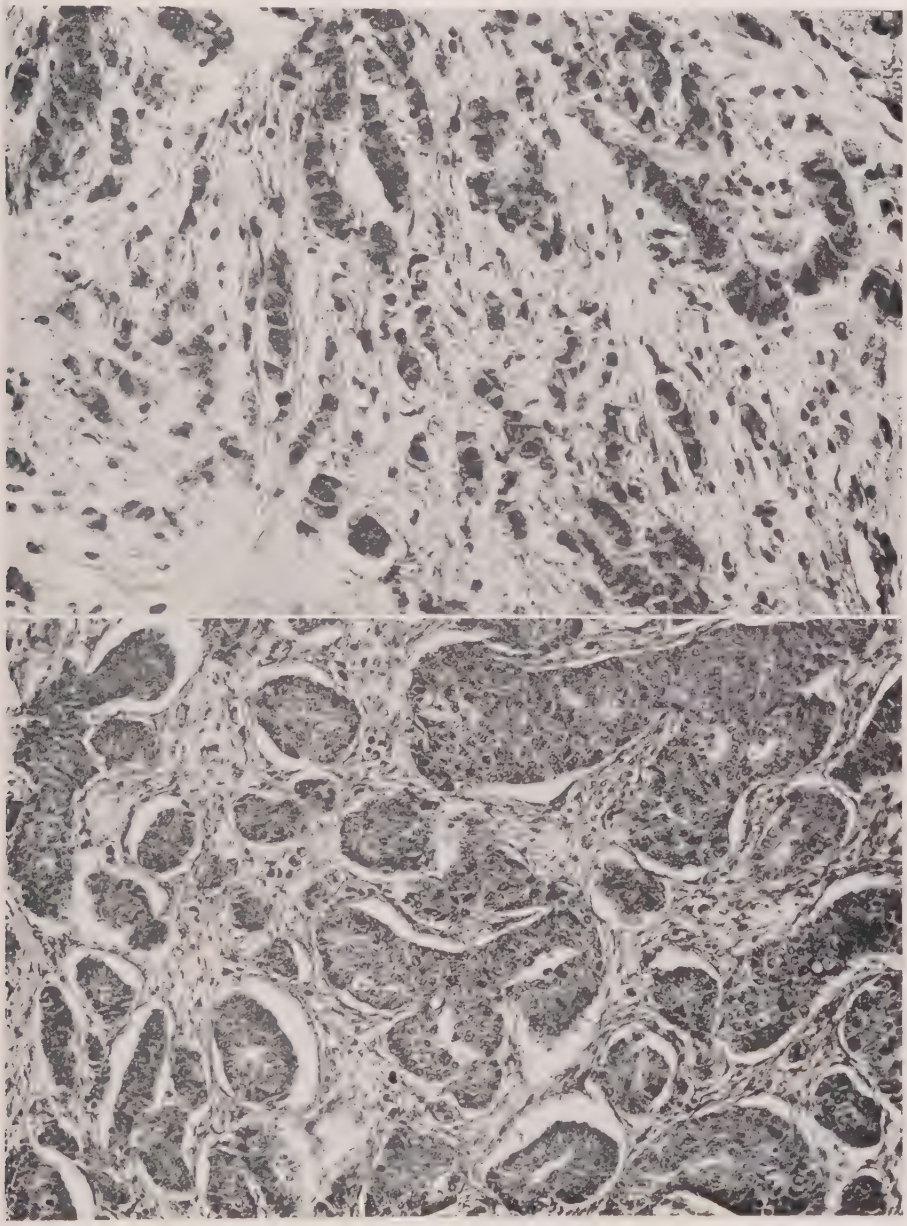


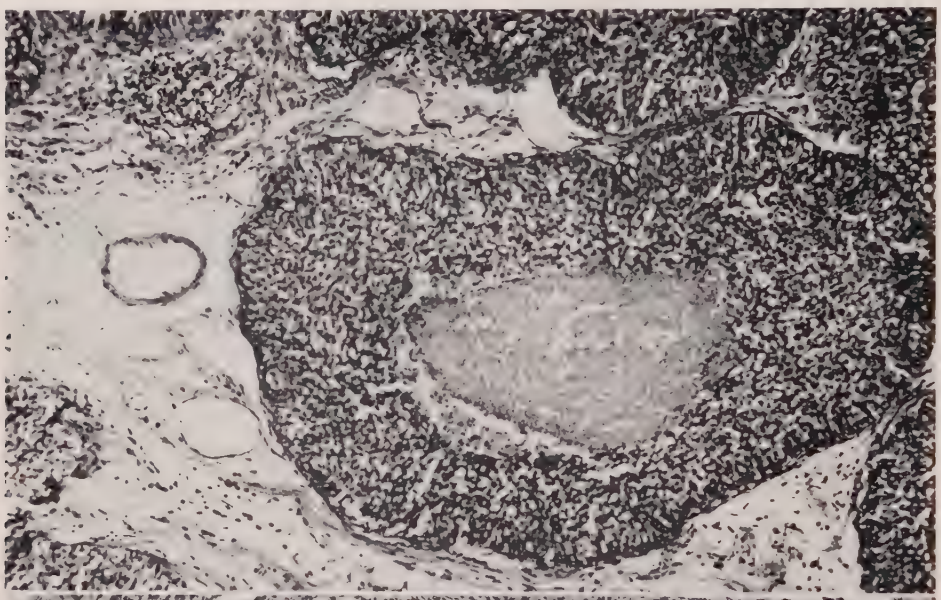
Fig. 963.

Fig. 962.—Scirrhous carcinoma. Note the dense hyalinized stroma with the narrow elongated columns of epithelial cells.

Fig. 963.—Large clusters and cords of epithelial cells in dense stroma forming the pattern of carcinoma simplex.

may be marked by the presence of large lobules such as are seen in adenosis. Microscopic characteristics are those of many cores of highly cellular epithelial tissue generally containing a central granular amorphous eosinophilic necrosis. The larger the area the more prominent is the necrosis. The pattern frequently follows that of the duct system. Occasionally there is liquefaction of some of the cells in the epithelial layer giving an appearance of accessory acinar formation. Such,

Fig. 964.



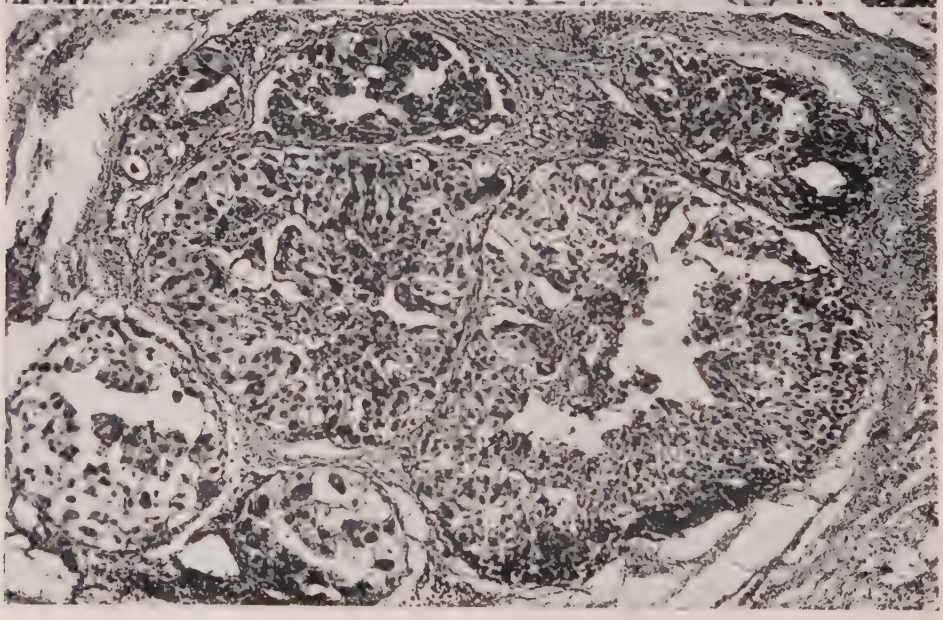


Fig. 965.

Fig. 964.—Comedo carcinoma. The large ductlike structure is formed by small deeply stained cells and has a central amorphous mass of debris.

Fig. 965.—Duct carcinoma. The cells in this tumor are larger, more pleomorphic and papillary in character than those of the comedo carcinoma; however, there is some central necrosis.

however, are not vascularized. The cells are generally small, dark, and have dense nuclei. Cells nearer the center may be larger and less intensely stained. Hyperchromatism, mitoses, and loss of polarity are quite prominent. Smaller cell groups, generally solid, may be found in the periductal tissue and invading the stroma. In its invasion it very commonly mimics other histologic patterns such as gland formation, papillary structures, and productive fibrosis. Occasionally the cellular growth is confined to the duct system. It is then known as a noninfiltrating variety and is adequately treated by simple mastectomy[40]; however, one must be certain of the absence of infiltration.

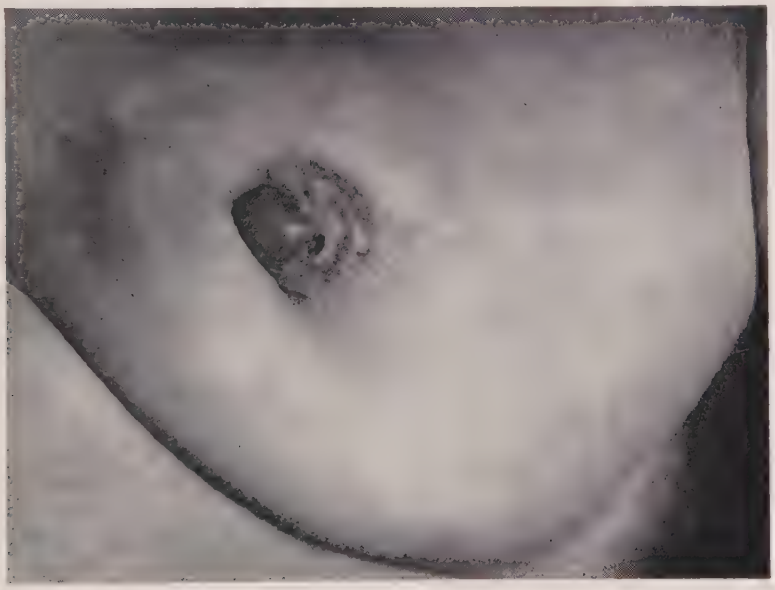


Fig. 966.—Paget's disease of the nipple. The nipple is retracted, and surrounding its base there is a scaling dermatitis associated with a thickening and induration of the periphery of the areola.

Duct Carcinoma.—This tumor is quite similar to comedo carcinoma but it ordinarily lacks the central necrosis of the tumor cell discs. It is more rapid in its progress, with a brief period of symptoms, and is more commonly associated with pain or discharge from the nipple and involvement of axillary nodes.[2] It arises from the central ducts. The gross appearance is similar to that of comedo carcinoma, but small tumor cell masses may be expressed rather than ribbons of pasty material. The microscopic picture is that of a profuse growth of the duct epithelium, forming large clear cells with large nuclei, prominent nucleoli, and frequent mitoses. Minute papillary-like projections and accessory acinar formation are more prominent than in comedo carcinoma. Pleomorphism is noteworthy. In some instances clear areas within the tumor-filled ducts are evident, but eosinophilic necrosis is not striking in the typical case. Comedo carcinoma and duct carcinoma are both of ductal origin and may be considered one tumor. However, because of significant difference in prognosis, an attempt should be made to separate the two lesions. Comedo carcinoma is differentiated from duct carcinoma by its smaller, more uniform, and more deeply stained cells and the eosinophilic, packed debris in the center of cell masses.

Paget's Disease of the Breast.—Paget's disease is a chronic eczematoid thelitis associated with a central duct carcinoma. It has a course of long duration which begins with subjective symptoms of burning, itching, or soreness of the nipple, followed by physical findings of hyperemia and enlargement. This change extends to the areola and is accompanied

by fissuring, weeping or oozing, crust formation, and eventually ulceration and destruction of the nipple. Occasionally the nipple changes are preceded by a definable lump in the breast. It comprises approximately 5 per cent of mammary carcinomas and occurs in an older age group of women than the usual carcinoma. Approximately one-third of the cases have axillary node metastasis, but if the lesion is limited to the nipple, prognosis is very good. Gross examination of the tissue beneath the nipple area shows dilated thick ducts containing grumous pasty material. Some ducts may also be identified as being filled with cell masses, fixed and indurated. The periductal infiltration produces a fairly well-defined tumor not different from that described above, although it may be very small. The nipple and cutaneous manifestations of the disease are characterized by the presence of very large, pale, vacuolated cells (Paget cells) in the rete pegs of the epithelium. These may show large hyperchromatic nuclei, and mitoses. The epidermis, therefore, has a "moth-eaten" histologic appearance. Question still exists whether Paget cells represent an epidermoid carcinoma of the nipple arising in situ, whether they represent an intraepithelial metastasis from the constantly present underlying duct carcinoma or whether they are just "peculiar cells"

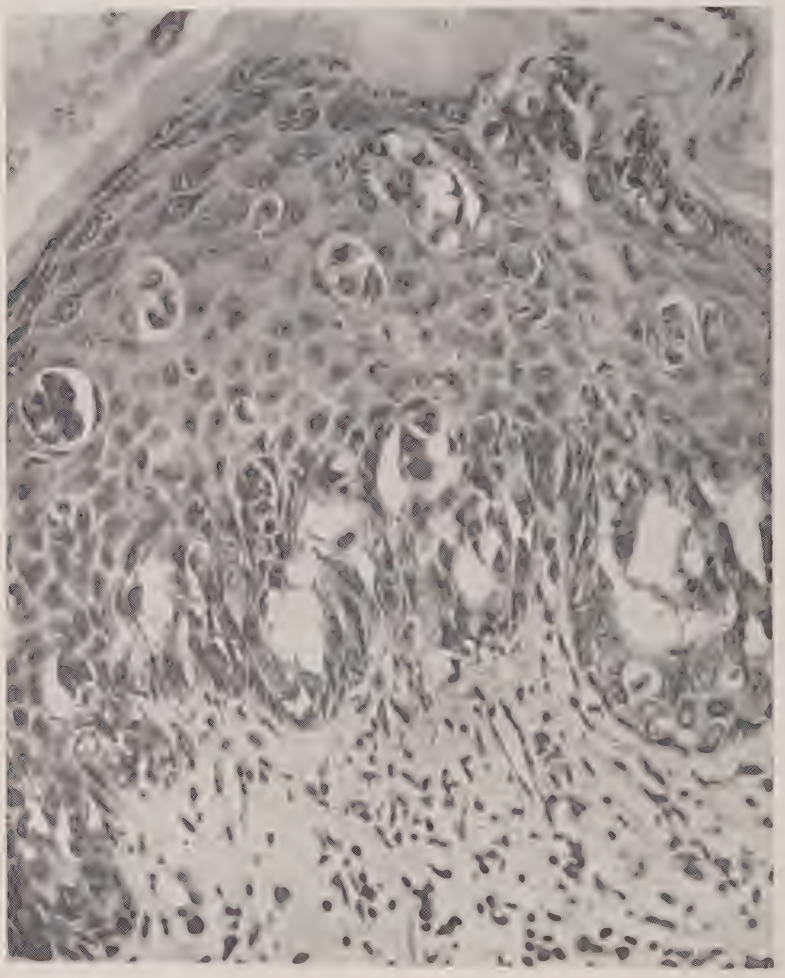


Fig. 967.—Paget's disease of the nipple. The epithelium shows a surface hyperkeratosis and a very marked disorganization of its basal portions, numerous vacuoles, and many large extremely pale cells. Note the mitotic figure.

found in some cases of duct carcinoma.[1, 40, 43, 44] It is probably correct that Paget's disease is not a primary tumor of the squamous epithelium of the nipple since in its metastasis it does not have epidermoid characteristics. Paget cells arise in situ but are probably related to the cells of the nipple bud and therefore differentiate into duct epithelium rather than squamous epithelium.[2] The second and third suppositions also cannot be proved since Paget cells are infrequently found in proportion to the number of cases of duct carcinoma. In the instances of extramammary Paget's disease the origin from sweat gland ducts cannot be ruled out.

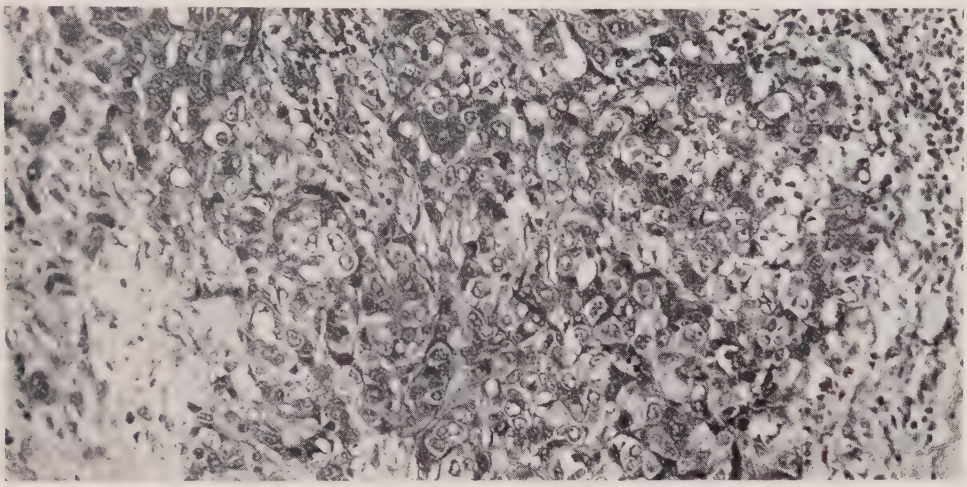


Fig. 968.—Paget's disease metastasis to axillary lymph node. The cells are large, clear, and maintain the histologic features of the nipple skin changes.

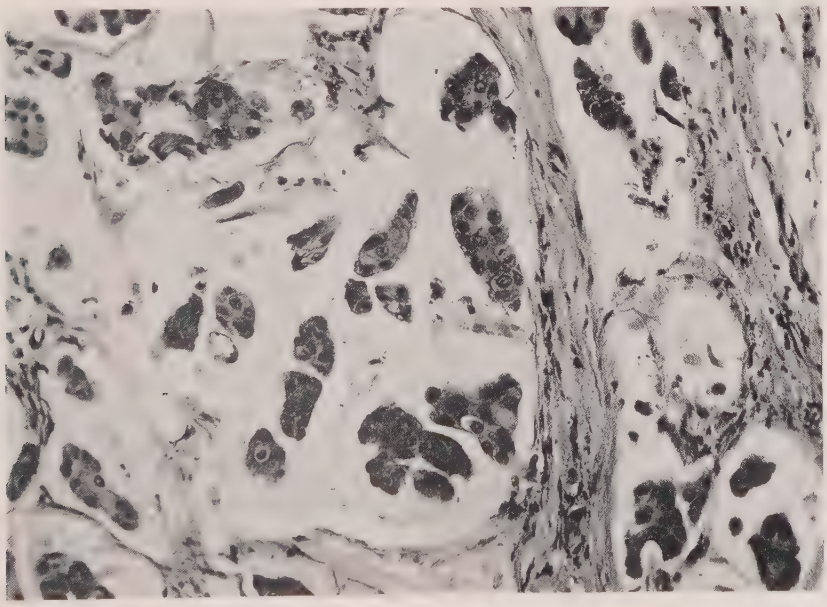


Fig. 969.—Mucoid adenocarcinoma showing compressed clusters of tumor cells with abundant extracellular mucinous material.

Papillary Adenocarcinoma.—This centrally located tumor frequently has its origin in the intraductual or intracystic

papilloma. It grows slowly and frequently is 5 cm. or more in diameter. It occurs mainly in the 35- to 40-year age group. It is commonly associated with discharge from the nipple and the presence of a large, soft, bulky nodule. With central hemorrhage or cyst formation it may be fluctuant. In the late stages it loses its movable characteristics and ulcerates through the skin. Axillary node involvement is quite late and not prominent. The microscopic architecture is papillary in type showing a communicating dendritic pattern. The cells are variable, in some instances forming large sheets and in other instances forming single cell layers. Lymphoid cells about the borders are not unusual. Histologic invasion is evident at the attachment of the papillary mass and is characterized by cells of moderate hyperchromatism, lack of polarity, and frequent mitoses. Even in the more delicate papillary pattern vascular stalks are uncommon. The benign papilloma is commonly misdiagnosed as papillary adenocarcinoma. The gland arrangement of the small, oval or columnar cells on vascular stalks, absence of lymphocytic reaction, and maintenance of cellular polarity are generally sufficient characteristics for the differentiation of the benign lesion.

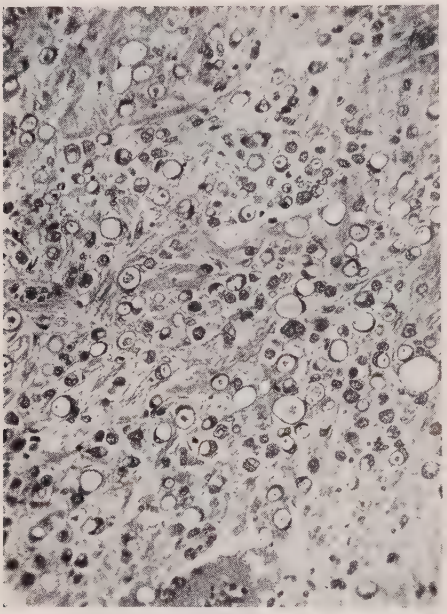


Fig. 970.—Mucoid carcinoma. Early stage. Note signet-ring cells.

Mucoid Carcinoma.—This adenocarcinoma is also known by the name of colloid or gelatinous carcinoma. It is not a common lesion. This tumor grows rather slowly and is associated with late metastasis and lack of nipple retraction. Grossly the tumor is fairly well demarcated but not encapsulated. It produces a spherical mass of moderately firm character with a translucent, moist, gelatinous or slimy surface marked by a delicately interlacing pattern of more solid opaque tissue. Its gross characteristics frequently closely resemble those of mixed tumor of the parotid gland. On cutting, strings of mucoid material may adhere to the knife. It is very slippery and small particles of mucoid material can easily be removed from the tumor by scraping. The bulging droplets of slimy material are most pronounced

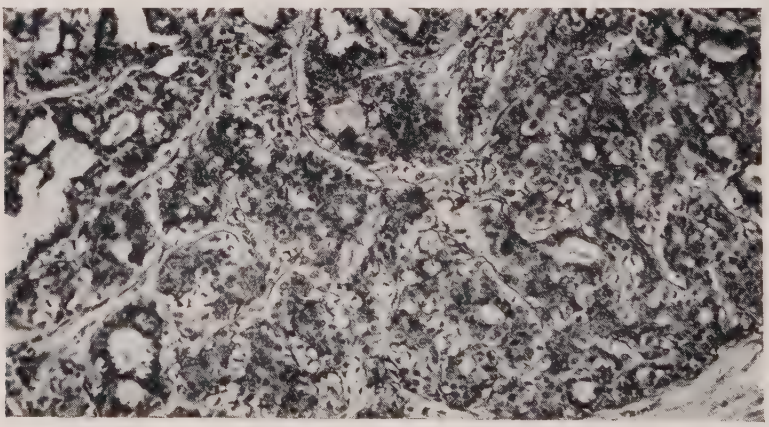


Fig. 971.—Lobular carcinoma in situ. Note the sharp demarcation from the stroma and the exaggerated pattern of the usual well-developed lobule. The lesion is highly cellular and frequent mitoses can be seen.

after formalin fixation. The typical microscopic picture is that of a multilocular cystlike formation. The spaces contain a light grayish-blue-staining amorphous material. At some point around the periphery of these spaces small clusters of deeply stained epithelial cells may be evident. They generally are poor in detail, apparently because of mechanical pressure. The paucity of cells in the large mucoid areas is an expression of restraint of growth. It follows the extracellular production of the mucoid material. Since metastases also possess the mucoid characteristics, the origin of the mucoid material must be the epithelial cell and not the stroma as suggested by Ewing.[3] Between such cystic spaces the breast stroma and parenchyma may be infiltrated by columns and nests of deeply stained epithelial cells. These have round solid nuclei, eccentrically placed, resembling papilloma cells. The cytoplasm contains a single small or large vacuole. Signet-ring forms are produced by large amounts of intracellular mucoid substance. When the predominant picture consists of large mucoid spaces with few cells, the tumor is usually slow in its growth and metastasizes very late; however, the presence of cellular areas in which the cells are signet ring (intracellular mucus) always makes such tumors unpredictable.

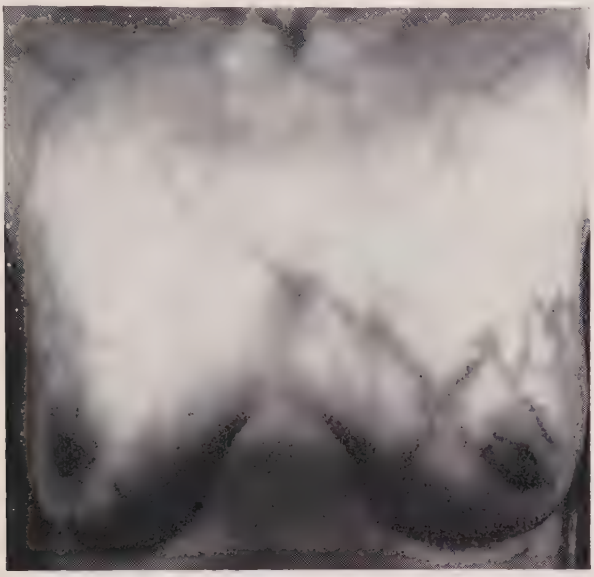


Fig. 972.—Disturbance in vascular pattern of left breast in the presence of a tumor; infrared photography. (Courtesy Mr. L. C. Massopust.[52])

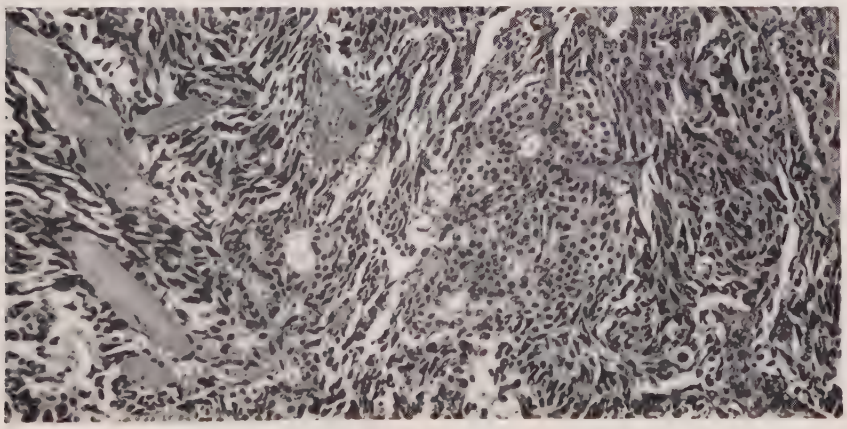


Fig. 973.—So-called carcinosarcoma of the breast. Infiltrating carcinoma of the breast having features of sarcoma. In the center some of the larger, paler cells show minute gland formation.

Acute Inflammatory Carcinoma.—This is a condition occurring in the obese pendulous breasts of young women, especially during lacta-

tion (50 per cent). It comprises 1 per cent of mammary carcinomas and is a special tumor only by virtue of clinical findings. It very closely resembles an acute inflammation of the breast and has been called erysipeloid carcinoma or carcinomatous mastitis. It is generally associated with outstanding signs and symptoms of inflammation both local and generalized. It is sudden in onset, showing a rapidly developing discoloration and induration of the breast. It develops an intense reddish-purple hue which may extend onto the chest wall or to the opposite breast. The skin is hot and dry and frequently shows a diffuse scaling. It has a particularly indurated feel. The crusted nipple is generally retracted so as to be barely visible. Frequently the breast substance presents no definable tumor but a diffuse brawny induration.

Sarcoma.—Sarcoma occurs at the average age of 40 and is generally preceded by a slowly growing fibroadenoma.[46, 51] A sudden enlargement of a pre-existent tumor, without physical characteristics of a carcinoma and in the absence of axillary node involvement, is a significant clinical finding. It is a large lesion, 5 cm. or more in diameter, and proportionately firmer in consistency than a carcinoma of similar size. Lung metastases usually occur before there is axillary involvement. Grossly the tumor is fairly well circumscribed, fleshy, occasionally cystic, and presents various interlacing reticular patterns. Whorls of connective tissue with variable pleomorphism, mitoses, and loose myxomatous connective tissue are the usual histologic features. If the epithelial elements partake in the tumor formation, it is then known as an adenosarcoma.

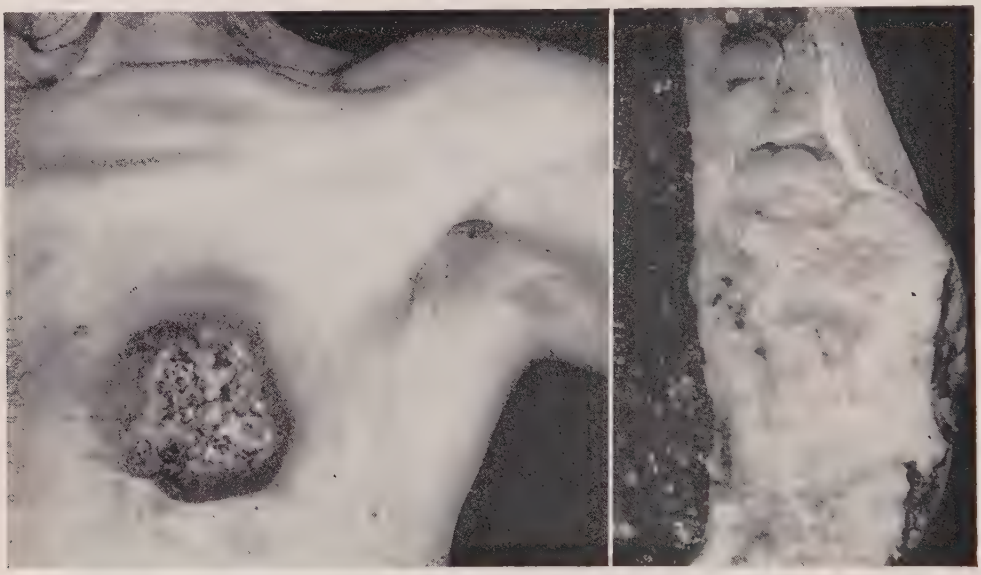


Fig. 974.—Carcinoma of the male breast showing ulceration and induration. The gross specimen reveals attachment to the pectoral muscle and invasion of the skin.

On gross examination of such a breast a very thick edematous skin and breast stroma is readily identified. In many instances the fat and stroma are poorly demarcated and there is diffuse induration of all structures. In rare instances a large, centrally situated, poorly defined mass can be identified and this generally has the characteristics of an infiltrating adenocarcinoma. Histologic characteristics are not specific but infiltration of the subepidermal lymphatics and vessels is the identifying feature. This apparently represents retrograde lymphatic metastasis from blockage of the deeply situated lymph channels.[50] Similar minute clusters of neoplastic cells infiltrate throughout the breast substance. One-half of the cases develop widespread skin metastasis and more than three-fourths of the cases have axillary metastasis when seen.

Lobular and Acinar Carcinoma.—Lobular and acinar carcinomas of localized character closely resemble normal histologic architecture and are not common.[45]

Lesions which resemble this have been called carcinosarcomas but such metastasize as a carcinoma and therefore the term is not a good one. The deeply stained elongated cells of the "sarcoma" feature, although anaplastic, resemble the cells of comedo carcinoma. *Lymphosarcomas* may occasionally arise in the breast. They are extremely malignant but otherwise similar to lymphosarcoma elsewhere.

Carcinoma of the Male Breast.—Carcinoma is an uncommon lesion in the male breast and occurs in an older age group than carcinomas of the female breast. Pain and axillary node involvement are present in one-half the cases and ulceration of the skin occurs in one-third of the cases. Since the breast substance in the male is smaller, infiltration, fixation, ulceration, and other signs of carcinoma of the female breast are greatly accentuated. Prognosis, therefore, is very poor. Grossly the tumor is diffusely infiltrating and is intimately attached to the skin and to the pectoral fascia. Ordinarily there is no breast substance identifiable,

The tumor substance is opaque, white, frequently marked by small cysts and minute areas of hemorrhage or necrosis. Such tumors arise from the tubules of the male mammary gland, 50 per cent of them having the usual adenocarcinomatous picture. Other variations represent the scirrhous, duct, papillary, or squamous cell forms.

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Chapter 41

THE SKIN

ARTHUR C. ALLEN

Introduction

The generally held impression that dermatoses lack differential histologic characteristics does not reflect the sizable group of cutaneous diseases which has a significant morphologic individuality. In many instances, the distinguishing features are so clear-cut that a diagnosis may be offered on examination merely of the histologic slide; in other cases, a small range of diagnoses may be suggested by the section; in the remainder, the microscopic changes give no diagnostic help in the absence of a clinical history. Although the size of the last group will obviously be determined by the experience of the examiner, the percentage of cases that falls into it can be made sufficiently low as to merit the interest of the general pathologist who has tended to regard the subject with diffidence. One of the major difficulties in the learning of dermatopathology is that the changes are usually not of the "all or none" or *qualitatively* distinct variety, but are often a matter of *quantitative* differences. The proper judgment of these differences depends on a knowledge of the normal histologic range of the structures of the skin as well as on an ability to add up and interpret a whole series of quantitative changes in these structures.

The Structure of Normal Skin

It is obvious that the skin normally varies in color, elasticity, thickness, blood supply, and texture, depending on anatomical location, age, state of nutrition, endocrinological status, and race of the individual. With the unaided eye, fine (Blaschko's) ridges are noted over the skin generally, and coarse folds, allowing for movement, are present, particularly over the joints. Between the ridges are *sulci of Heidenhain.* The ridges are further marked by delicate crisscross triangular or polygonal lines. The ostia of sweat glands, the pores, open onto the ridges. The hair, of course, varies, too, in texture, length, density, contour, and color, depending on age, race, sex, etc. The smooth, hairless skin, or the skin with fine lanugo hairs, is known as *glabrous* skin. The epidermis varies over most of the body from 0.07 to 0.12 mm. and from 0.8 to 1.4 mm. or more on the palms and soles. The cutis has a corresponding range of thickness. The junction of the cutis and the subcutis or subcuticular fat is usually indistinct, except in certain regions such as the forehead, ear, perineum, and scrotum.

Fig. 975 represents a diagram of normal skin. It is important to bear in mind that the skin varies in different parts of the body. For example, sebaceous glands are particularly prominent about the face, especially in the region of the nose, so that diagnoses of hyperplasia or adenoma of sebaceous glands should take this feature into account. The epidermis is normally thin and the rete pegs relatively inconspicuous over the tibia, the breast, and the flexor surfaces of forearms; this variant should not therefore be mistaken for atrophy. Similarly, the thickness of dermis over the lower legs, for example, is normally much less than that of many other portions of the body, so that the possibility of confusion with atrophy, as of scleroderma, must be remembered. The elastic tissue of the dermis shows such a large range in its quantity as well as in the degree of fraying and splintering of the fibers even in normal tissues, that considerable caution must be used in concluding that abnormalities of elastic tissue are present. In some portions of the body, as in the skin of the ear, the downy vellus hairs are seen in cross-section scattered through the dermis, and may be misinterpreted as neoplasms of hair follicles. Finally, the normally thick stratum corneum of the sole of the foot may prompt the diagnosis of keratoderma. These are a few of the examples of the variation in cutaneous histology, an accurate evaluation of which is clearly essential for an appraisal of some of the qualitatively similar pathologic changes.

Epidermis.—The epidermis is composed of the following layers: (1) basal cell layer (stratum germinativum), (2) prickle cell layers (stratum spinosum, rete mucosum, rete malpighii), (3) granular layers (stratum granulosum), (4) stratum lucidum, and (5) cornified layer (stratum corneum). The basal cell layer is one cell thick and forms the junction between epidermis and dermis. The nuclei are relatively hyperchromatic, arranged perpendicular to the epidermal "basement membrane," and normally contain a few mitoses as evidence of the activity of a layer which serves in part as the progenitor of the remainder of the epidermis. Contrary to general teaching, the presence of mitotic figures in the normal stratum spinosum indicates that these cells, too, give rise to prickle cells.[14] Interspersed in the basal layer are cells with a clear zone separating and often compressing most of the cytoplasm and nucleus

away from the cell wall (the so-called "cellule claire"). The cytoplasm may or may not contain melanin but these cells are dopa positive and, accordingly, are melanoblasts. Not all melanoblasts of the basal layer are "clear cells." For a long time, it has been accepted, on specious evidence, that these cells were really nerve endings that had migrated from the basal layer of the normal epidermis of dark-skinned races, or in the epidermis of irradiated individuals, in Addison's disease, in acanthosis nigricans, and many other conditions is, of itself, a strong argument against their neurogenesis. This process of conversion of basal cells into melanoblasts normally takes place continuously and may be retarded (as in vitiligo) or accelerated (as in sunburn). It seems hardly likely that the numbers of epidermal nerve endings would be appreciably increased in colored races or in a very short time after irradiation. For this and other reasons, which will be discussed in the sections dealing with

Fig. 975.—Structure of skin. Section through palm showing various layers of epidermis. *C*, The corium; *BV*, a blood vessel; *N*, the cross section of a nerve; *FC*, fat cells; *SG*, sweat glands; *MTC*, Meissner tactile corpuscle; and *PC*, a lamellated Vater-Pacini corpuscle. (From McCarthy: Histopathology of Skin Diseases, The C. V. Mosby Co.)

neural crest, had become incorporated in the epidermis, and later became the source of some pigmented nevi. There are many reasons for disbelieving their neural nature. It might be mentioned here that the mere fact that these melanoblasts occur in greater numbers in the

nevi and melanocarcinomas, these cells are regarded as basal cells which normally and continuously are altered to form melanoblasts,[115] and that this process of modification varies in speed and extent with different age groups, races, and stimuli.[115a, 115b, 122]

The prickle cells are several layers thick, the number varying in different parts of the body. The cells are joined by cytoplasmic bridges (spines, prickles) which serve as the most easily recognizable identification of such cells, both in squamous cell neoplasms and in metaplastic processes. Glycogen is usually present in the stratum spinosum. The stratum granulosum averages about two layers thick and is composed of cells with blue, round cytoplasmic granules of keratohyalin. These granules are now thought to be a nuclear product related to desoxyribose nucleic acid. The stratum lucidum, which is practically confined to the palms and soles, is a clear, homogeneous, acidophilic, anuclear, thin layer of "eleidin." The stratum corneum, also normally without nuclei, is made up of various thicknesses of keratin. Fat globules may be present in the two uppermost layers. There is convincing histologic evidence to indicate that a true epidermal basement membrane does not exist. Basement membranes in other locations, such as those about sweat glands, renal tubules, etc., are argyrophilic. No such epidermal basement membrane is demonstrable with silver stains although an illusion of one is occasionally created by argyrophilic granules of melanin aligned in the basal layer. On the other hand, stains with the periodic acid Schiff reagent do reveal what appear to be interrupted segments of a basement membrane. This simulation is probably caused by the presence of polysaccharides which have been irregularly concentrated by the varying densities of the subepidermal collagen, especially with edema of the upper cutis. In this connection, one other fact should be mentioned. Basal cells do have intercellular bridges or prickles which bind them to the overlying cells of the stratum spinosum, and, in their upper portion, to each other; to the corium, they are attached not by a basement membrane but by cytoplasmic processes Herxheimer fibers which interdigitate with underlying collagenous fibrils from the cutis.

Dermis.—The dermis or corium is divided into the superficial pars papillaris and the deeper pars reticularis. The papillae of the dermis alternate with projections of epidermis called rete pegs. The length of the papillae, the thickness of the overlying epidermal plate, the vascularity, the edema, the direction and consistency of the collagenous fibers of the papillae are all of diagnostic value. In the papillary portion the fibers of collagen tend to run vertically; in the deeper part, the fibers are rather loosely dispersed in a horizontal direction. Accuracy in evaluating changes in the consistency, tinctorial qualities, and cellularity of the collagen of the dermis will furnish the basis for many diagnoses.

The cutaneous *appendages* include the sweat glands, sebaceous glands, hair follicles arrectores pilorum, and nails. The sweat glands are coiled glands of two varieties: (1) eccrine and (2) apocrine. The eccrine glands are universally distributed in the skin and are made up of several coils of tubular glands lying deep in the dermis. These glands empty their secretion into a tubule traversing the dermis and epidermis, opening into the fine ridges of the skin as pores. The coils are lined by two layers of cells: (1) cuboidal epithelium with an eosinophilic inner border, and (2) flattened, so-called myoepithelial or "basket" cells resting on an argyrophilic basement membrane. The ducts are lined also by two layers of epithelial cells but the myoepithelium is absent. The inner lining of the ducts of sweat glands is keratinized in their course through the epidermis, and, indeed, some of the neoplasms of sweat glands show evidence of squamous cell metaplasia. In any case, the inner hyaline membrane of the ducts often serves as a clue to the genesis of these neoplasms. The apocrine glands occur in the axilla, groin, nipple, umbilicus, anus, and genital region. The glands are several times larger than the eccrine, and are lined generally by a single layer of tall columnar cells with acidophilic cytoplasm the luminal border of which is often frayed as if by droplets of secretion. The ducts of these glands which become functionally developed near the time of puberty are usually intimately connected with the hair follicles. The *sebaceous or holocrine glands* are racemose structures that serve mainly as appendages to the hair follicles to which they are attached. Each alveolus is rimmed by a basement membrane surrounding one or two layers of squamous cells, internal to which are the characteristic sebaceous cells with small round nuclei and abundant, finely latticed, fatty cytoplasm. The sebaceous cells are pushed toward the duct wherein they finally rupture and release their fatty contents in the hair follicle. Modifications of sebaceous glands occur in eyelids and ears, in the areolae of the nipple, and in the male and female genitalia (glandulae odoriferae); in these regions they are unconnected with hairs or hair follicles. The *hair* consists of a shaft which at its lower end enlarges into a bulb. The bulb embraces an invaginating dermal papilla through which the hair receives its blood supply. The intracutaneous portion of the hair shaft and the bulb are enclosed in a hair follicle. The hair shaft is made up of a cuticle, a sheath, and a more or less pigmented cortex and medulla, the latter being absent in lanugo hairs. The *arrectores pilorum* are bands of smooth muscle originating in or near the papillary layer of the dermis and inserting at several points into the outer layer of adjacent hair follicles just above their papillae. The direction of the muscle is at an angle to the hairs so that their contraction ("goose-flesh") causes the hairs to be erected; at the same time, the superficial vessels are constricted to avoid cooling and sebaceous secretion is expelled by the pressure of the contracting arrectores pilorum.

Glycogen is present not only in hair (internal sheath and cuticle of cortex and medulla) but also in the sweat glands (and some sweat gland adenomas, Fig. 1050) and in the peripheral cells of sebaceous glands. Fat, too, may be found in sweat glands. The *nails* are dense,

semitransparent, compactly layered modifications of the stratum corneum. The proximal visible portion of the nail is known as the *body* and is colored an opaque white to whitish pink (*lunula*) just anterior to its covered portion or *root*. The three attached edges of the nail rest in grooves over which are extensions of skin called *nail folds*. The transparent crescentic membrane covering the posterior segment of the lunula is the *eponychium*. The epidermis surrounding the nail borders is the *perionychium*, and the epidermis underlying the nail is the *hyponychium*. The *nail matrix* is the posterior nail fold continuous with the eponychium. The *nail plate* or true nail rests on the *nail bed*. Normally, fine longitudinal lines traverse the nail plate and fit into corresponding grooves of the nail bed. These lines become more pronounced with age. Regeneration of a lost fingernail takes from 100 to 160 days and about three times as long for toenails. The changes which occur in the nail plate furnish important clues in the diagnosis of disease. These changes include fine pitting of the surface, transverse whitish Beau lines, various other discolorations, brittleness, dysplasias, thickenings, and spontaneous loss of the nails. General debilitation, psoriasis, Atabrine toxicity, fungi, congenital changes, idiopathic pigmentary disturbances, endocrine deficiencies, malnutrition, chemical irritation, and neoplasia are some of the conditions which may produce characteristic changes in the nails.

The *blood* and *lymphatic vessels* of the skin are arranged in plexuses. The arterial vessels are derived from the subcutaneous arteries which give off plexuses to the papillary layer as well as to the reticular layer and the various appendages. It has been suggested that the selective localization of infiltrate to various components of the dermis is related to the pattern of these plexuses. In the skin of certain regions of the body, particularly the fingers, there are normally arteriovenous shunts or glomera which serve to regulate blood flow and surface temperature. The glomus is composed of an afferent arteriole, a shunt called the Sucquet-Hoyer canal, and an efferent vein. The canal is lined by layers of rounded glomus cells which have a contractile function. The veins also form plexuses in the papillary, subpapillary, and deep reticular layers, as well as about the appendages. The lymphatic plexuses are localized principally in the papillae and at the junction of dermis and subcutaneous tissue. The deeper lymphatic vessels have valves. The *nerves* of the skin are preponderantly medullated; a few are nonmedullated and lead to the blood vessels, smooth muscles, epidermis, hair follicles and glands. The specialized nerve endings include the corpuscles of *Vater-Pacini* which are found in the deep layers of the skin and subcutaneous tissue, mucous membranes, and in the conjunctiva and cornea; these structures are particularly numerous in the skin of the nipple and external genital organs. Other nerve endings are the *Meissner's corpuscles* of the papillae of the skin of palms, soles, and tips of fingers and toes, the end bulbs of *Krause*, which are smaller than but structurally similar to the Meissner corpuscles and are found in the external genitalia, the elongated, dermal, corpuscles of Ruffini, and the intraepidermal disc-like, tactile *Merkel-Ranvier* corpuscles which are identified with silver stains and are present in the epidermis and external root sheath of hairs. There is good reason to doubt, as do Maximow and Bloom,[16] that the nebulous Langerhans' cells are actually cells, nerve endings or "worn-out melanoblasts." No useful purpose can be served by retaining this ill-defined term which has for several decades been the source of much confusion and admittedly erroneous interpretations. The endings are presumably receptors for touch (Merkel-Ranvier and Meissner corpuscles), pressure (Pacinian corpuscles), heat (corpuscles of Ruffini), and cold (end bulbs of Krause).

Definitions

Clinical Terms.—

Macule—circumscribed, flat area of altered coloration of skin, evanescent or permanent, varying in size from pinhead to several centimeters, in color from red (erythema), brown (ephelis), and the various colors of blood pigment (petechiae and ecchymoses) to white (vitiligo), and in shape from circular, polygonal, linear to the polymorphous varieties of erythema multiforme.

Papule—circumscribed elevated area varying in size from pinhead to about 5 mm., in surface contour from flat, conical, pointed, circular to umbilicated; in color, from red yellow, white to violaceous; and in shape of base from round to more or less polygonal (e.g., the papules of lichen planus and psoriasis). The papule, as well as the macule, may provoke pruritis, burning sensation, anesthesia, and pain, or may cause no symptoms. Both macules and papules may be overlain by scales.

Nodule—an enlarged papule varying in size from about 0.5 cm. to 2 cm., usually deep-seated, involving the lower dermis and subcutaneous fat (e.g., the nodules of rheumatoid arthritis, leprosy).

Vesicle—circumscribed single or grouped elevations of the epidermis beneath which are collections containing serum, plasma, or blood. The surface may be flat, globoid, or umbilicated (e.g., smallpox, eczema).

Pustule—vesicles containing pus predominantly (e.g., impetigo).

Bulla (bleb)—similar to vesicles except that the bullae are larger, varying from 0.5 cm. to more than 8 cm. (e.g., pemphigus).

Scale—loosened, imperfectly cornified parakeratotic superficial layer of skin which is shed as fine, branny, dirty white, yellowish keratinous dust or large pearly white flakes. The distribution may be focal or universal, and is usually associated with inflammation of the skin (e.g., psoriasis, exfoliative dermatitis) but need not be (as in ichthyosis).

Crust—residue of dried serum, blood, pus, epithelial, keratinous, and bacterial debris. Crusts vary in color from yellow to green to dark brown depending on the admixture of the different ingredients; and in consistency from a thin superficial watery (as in impetigo) to a thick bulky,

loosely or firmly attached covering of a rupioid syphiloderm. Crusts follow the oozing of serum, blood, or pus in a disrupted, eroded, or ulcerated epidermis, as in eczema, impetigo, smallpox, abrasions, and other conditions.

Excoriation (erosion)—superficial erosion and ulceration produced mechanically, usually by the fingernails in scratching pruritic skin or in picking at various lesions as in "neurotic excoriations."

Fissure (rhagade)—linear, often crusted, tender, painful defect in continuity of the skin, occurring usually at mucocutaneous junctions at sites where there is normally considerable elasticity of the skin; e.g., about the anus, mouth, fingers, palms, soles, and in such diseases as syphilis, nonspecific anal fissures, keratoderma, intertrigo, and eczema.

Ulcer—defect of the skin, deeper than an erosion or excoriation, extending at least into the dermis. The edges of an ulcer may be ragged, punched-out in appearance, undermined or everted; the floor may be glazed or granular, puriform or hemorrhagic, shallow or deep; the outline of an ulcer may be circular, serpiginous, cresentic, ovoid or irregular. Ulcers may be painless or exquisitely sensitive. Ulcers heal generally by concentric scarring and epithelization (e.g., tropical, diphtheritic, and, varicose ulcers).

Lichenification—thickening of the skin with exaggeration of its normal markings so that the striae form a criss-cross pattern. Lichenification follows chronic irritation of pruritic skin.

Histologic Terms.—

Acanthosis—thickening through hyperplasia of the rete malpighii. Acanthosis may exist without hyperkeratosis. (Fig. 981.)

Hyperkeratosis—thickening of the keratinized layer, the stratum corneum. Hyperkeratosis is generally associated with a prominent stratum granulosum. (Fig. 1010.)

Parakeratosis—the persistence of nuclei in the stratum corneum, signifying the presence clinically of a loosely adherent scale (e.g., dandruff). Parakeratosis is characterized by the absence or marked diminution of the stratum granulosum, except in the stage of healing. (Fig. 981.)

Spongiosis—intercellular edema of the epidermis which, when marked, progresses to vesiculation (e.g., eczema). (Fig. 987.)

Ballooning degeneration—one of the diagnostic morphologic phenomena leading to vesiculation in virus diseases. It is characterized by the isolation of a cell from its neighbors, especially in the lower layers of the epidermis, the withdrawing of its prickles following intracytoplasmic edema and vacuolization, and the amitotic division of its nucleus so as to form a multinucleated giant cell (e.g., variola, but particularly herpes and varicella). (Fig. 988.)

Reticular colliquation—a characteristic of the cutaneous vesicles due to viruses, as is ballooning degeneration. The cytoplasm of several cells becomes edematous, granular, coalescent, partially disintegrated; the residual cytoplasm forms reticulated septa that separate multiloculated intraepidermal collections of fluid or vesicles; the nuclei become small, pyknotic or completely karyorrhectic. (Fig. 988.)

Dyskeratosis—abnormality of development or distinctive alteration of epidermal cells. Two types are distinguished:

1. Benign dyskeratosis; e.g., the molluscum bodies of molluscum contagiosum, represented by swollen brightly eosinophilic cells, mostly of the stratum granulosum, containing virus elementary bodies; or the *corps ronds* and *grains* of the stratum granulosum and stratum corneum, respectively, as noted in Darier's disease. In the case of molluscum contagiosum the dyskeratosis is apparently due to a virus; in Darier's disease, the change is probably the effect of vitamin A deficiency. (Fig. 976 and Plate IV.)

2. Malignant dyskeratosis; anaplastic changes such as hyperchromatism, changes in polarity, increase in mitotic figures and enlargement of nuclei and nucleoli so as to signify potential or actual development of carcinoma. (Fig. 1012.)

Pseudoepitheliomatous hyperplasia—marked acanthosis with extensive downgrowth of rete pegs such as may occur at the periphery of an ulcer, in bromodermas and following insect bites. Occasionally the exuberant epidermal hyperplasia is mistaken for carcinoma. (Fig. 1040.)

Liquefaction degeneration—obliteration of the line of demarcation of epidermis and dermis by edema of the basal cells and subepidermal dermis as well as by the presence of inflammatory cells at this junction (e.g., lichen planus and lupus erythematosus). (Fig. 993.)

Eponyms.—Eponyms are a part of the literature of the diseases of any organ and are especially common in dermatological parlance. There are obvious disadvantages to the use of an eponym instead of an objective descriptive name for a disease entity. On the other hand, to honor a pioneering observer by attaching his or her name to a symptom complex adds a degree of historical warmth and color that may compensate for the loss of immediate definition. Only a small fraction of the many existing eponyms are herein included. The generally familiar or the uncommonly used eponyms have been omitted.

Albright's syndrome—polyostotic fibrous dysplasia, cutaneous pigmentation (café-au-lait) and precocious puberty.

Bazin's disease—erythema induratum.

Behçet's triple symptom complex—iritis along with ulcers of mouth and scrotum.

Bockhart's impetigo—superficial staphylococcic folliculitis.

Brooke tumor—trichoepithelioma; epithelioma adenoides cysticum.

Buschke's disease—scleredema adultorum.

Carrión's disease—verruga peruana; Oroya fever.

Darier-Roussy sarcoid—subcutaneous sarcoid.

Duhring's disease—dermatitis herpetiformis.

Ehlers-Danlos syndrome—hyperelastosis cutis, dermatorrhexis, laxity of joints.

Fordyce's disease—heterotopic sebaceous glands of mucous membranes of lips and oral cavity.

Fox-Fordyce disease—chronic, pruritic papular eruption of axilla, groin, and genitalia.

Gougerot and Blum disease—pigmented purpuric lichenoid dermatitis, principally of lower extremities.

Habermann's disease—pityriasis lichenoides et varioliforma acuta.

Hailey-Hailey disease—chronic benign familial pemphigus (so-called bullous Darier's disease).

Hallopeau's acrodermatitis—acrodermatitis continua, dermatitis repens.

Haxthausen's disease—keratoderma climactericum.

Hebra's disease—pityriasis rubra.

Hopf's disease—acrokeratosis verruciformis, a hereditary condition characterized by flat verrucae.

Hutchinson's syndrome—a triad of stigmata of congenital syphilis: interstitial keratitis, peg-shaped, notched incisor teeth, and nerve deafness.

Kast's syndrome—the association of cutaneous hemangiomas with chondromas or dyschondroplasia.

Letterer-Siwe disease—malignant, usually nonlipid histiocytosis or "reticulosis" of skin and viscera of infants.

Lewandowsky's disease—rosacea-like tuberculid.

Maffucci's syndrome—cutaneous hemangiomas associated with dyschondroplasia and "spider" hands.

Majocchi's disease—purpura annularis telangiectodes with characteristic vascular changes in the skin.

Moeller's chronic superficial excoriations of the tongue.

Osler-Rendu-Parkes Weber syndrome—hereditary hemorrhagic telangiectasia.

Parkes Weber syndrome—hypertrophy of a limb due to congenital hemangiectasia.

Parkes Weber-Christian syndrome—relapsing, febrile, nodular panniculitis.

Pautrier-Woringer syndrome—dermatopathic lymphadenopathy.

Pringle's adenoma sebaceum—associated with tuberous sclerosis.

Reiter's syndrome—nonspecific urethritis, arthritis, conjunctivitis, and often dermatitis identical with keratoderma blennorrhagicum.

Riehl's melanosis of oral mucous membranes.

Romberg's disease—progressive hemiatrophy of the face, along the distribution of the fifth cranial nerve.

Schamberg's disease—progressive pigmentary purpuric dermatosis of lower extremities.

Senear-Usher syndrome—pemphigus erythematodes.

Sjögren's syndrome—keratoconjunctivitis sicca, xerostomia, rhinitis and laryngitis sicca, alopecia, and sclerodermatous changes.

Spiegler-Fendt sarcoid—a benign dense lymphocytic nodularity of the skin, clinically resembling sarcoid and histologically easily confused with lymphosarcoma or leukemia cutis.

Stevens-Johnson syndrome—a severe form of erythema multiforme characterized by fever, severe malaise, and erosions of the mucous membranes, conjunctiva, and genitalia.

Sturge-Parkes Weber syndrome—nevus flammeus (hemangioma), contralateral hemiparesis, epilepsy, mental retardation, cerebral calcification.

Sulzberger-Garbe disease—discoid, lichenoid, eczematoid dermatitis (probably neurodermatitis).

Sutton's disease—periadenitis mucosa necrotica recurrens; chronic aphthous stomatitis.

Vogt-Kóyanagi syndrome—bilateral uveitis, premature alopecia and graying of the hair, dysacusia, and symmetrical vitiligo, especially of the extremities.

Werner's syndrome—scleroderma, poikiloderma, bilateral cataracts, pluriglandular dysfunction, and premature graying of hair.

DERMATOSES

In order to set up what may possibly be a more workable and more orderly classification of the varieties of dermatoses than seems currently to exist for pathologists, the diseases of the skin have been divided primarily into histologic categories. While some overlapping of criteria is present, it is hoped that the basis for the classification is, in general, sufficiently clear-cut to be of practical value. The diseases listed are not only those which the pathologist is most likely to encounter but which, with minor exceptions, are diagnosable on histologic changes alone.

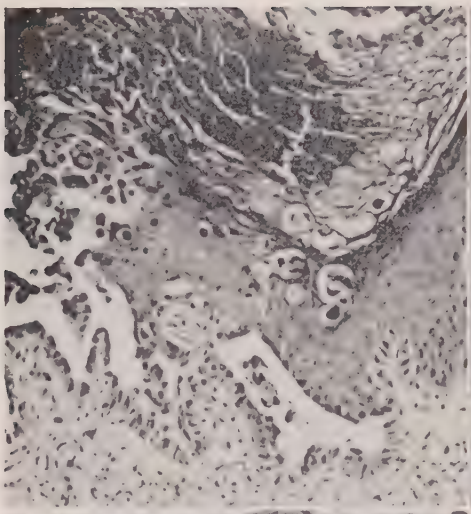
Diseases Principally of the Epidermis

Hyperplasias

Darier's Disease.—Clinically, Darier's disease (keratosis follicularis; psorospermosis) is recognized by the development early of small, uniform, firm, reddish-brown, greasy keratinous papules which subsequently become coalescent, papillomatous, crusted, and acquire an offensive odor. The lesions tend to be located about the face and neck and spread to the chest, limbs, and loins. The palms and nails may be involved. The disease occurs principally in the second and third decades. Its etiology has been attributed to vitamin A deficiency on the basis of low blood levels of vitamin A in some patients, the favorable though unreliable response to vitamin A administration, and the experimental association of some types of hyperkeratinization with vitamin A deficiency.

The histologic picture is so distinctive as to be pathognomonic and consists of (1) focal, truncated masses of keratin, usually partially parakeratinized, especially near the surface. These keratinous masses may be located over the ostia of hair follicles or over the interfollicular epidermis. For this reason, the term *keratosis follicularis* is inaccurate. (2) *Corps ronds,* or dyskeratotic cells, practically limited to the stratum granulosum, contain nuclei which are rounded and surrounded by a clear cytoplasmic halo. The keratohyaline granules that characterize the cells of the stratum granulosum are usually absent in the *corps ronds.* (3) The "grains" are cells basically similar to the *corps ronds* but occur in the lower portion of the overlying keratinous masses and consist of cells with perinuclear spaces in the parakeratotic foci. (4) The cleavage (suprabasalar) of the epidermis at the junction of the basal layer and the lowermost layer of the stratum spinosum forming a lacuna or small vesicle with a papillary base (Fig. 976). In addition, there may be a nondescript hyperemia and perivascular infiltrate by mononuclear cells in the upper corium. The lesions which may offer some difficulty in differentiation are the congenital keratosis follicularis and benign chronic familial pemphigus (bullous Darier's disease).

Fig. 976.



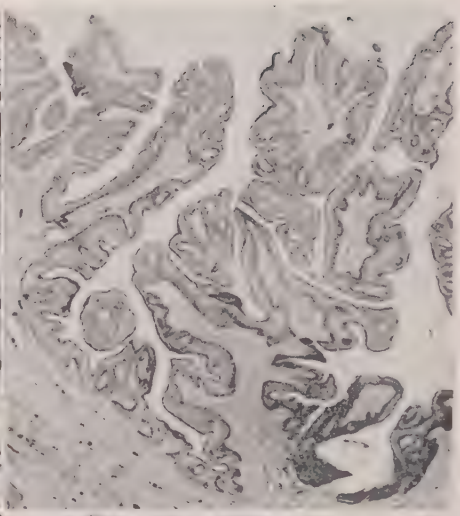
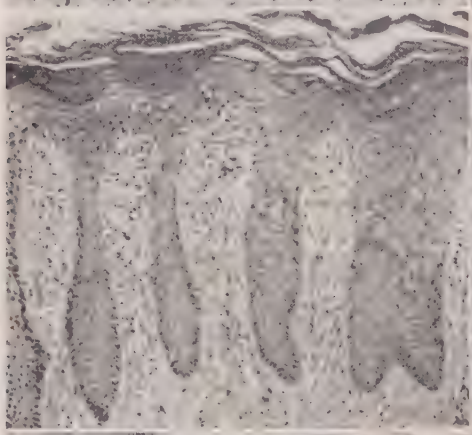


Fig. 977.

Fig. 978.



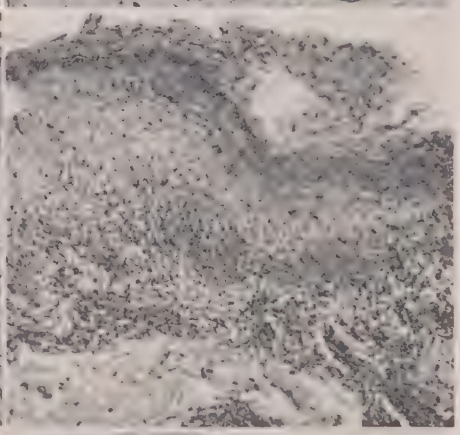


Fig. 979.

Fig. 980.

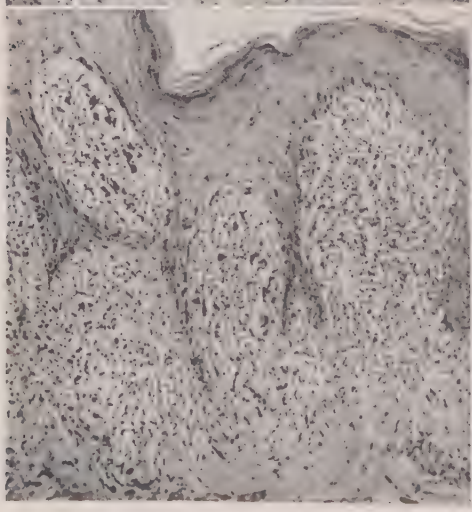


Fig. 981.

Figs. 976-981.—(*For legends see opposite page.*)

Congenital keratosis follicularis is histologically quite similar to Darier's disease although the lesions of the latter appear more regular, smaller, and often multiple even in the same section. The congenital lesion is likely to be single and has a predilection for the scalp. The benign chronic familial pemphigus shows a prominence of the suprabasalar cleavage but lacks an appreciable keratinous mass and rarely has *corps ronds* and grains. The relationship of this entity to Darier's disease is questioned (Fig. 986). *Verruca vulgaris, porokeratosis Mibelli, keratosis pilaris,* and *lichen spinulosus* offer some differential difficulties histologically by virtue of the presence of focal keratinous masses or projections but the other criteria of Darier's disease are absent in these lesions.

Acanthosis Nigricans.—Acanthosis nigricans appears as patches of gray-black, warty masses with a predilection for the axilla, the groin, the submammary region, the elbows and knees and occasionally oral mucous membranes. Two types are recognized, (1) juvenile and (2) adult. The distinction is based on age rather than any difference in appearance of the lesions. The adult type is prone to be associated with visceral cancer in about 50 per cent of cases, particularly in patients beyond the fourth decade. In about 65 per cent of cases, the associated cancer is a gastric adenocarcinoma; adenocarcinomas of other viscera, such as lung and occasionally uterus, may be found. This association in elderly people of acanthosis nigricans and abdominal cancer is a very real if poorly understood phenomenon and may be dependent in some instances on the encroachment on the sympathetic nerve chain by the cancer. The histologic picture of acanthosis nigricans is that of a papillary hyperkeratosis in most areas disproportionately greater than the underlying acanthosis (Fig. 977). The epidermis is thrown into folds by its excessive lateral growth and in sections often appears reticulated where rete pegs have joined. The basal layer is densely pigmented with fine argyrophilic melanin granules, and a few chromatophores lie in the upper corium. This folding of a hyperkeratotic epidermis in which the basal layer is diffusely darkened as an almost solid line of melanin is characteristic of acanthosis nigricans. There is no anaplasia of the epidermis even in those cases accompanied by abdominal neoplasms. The lesions histologically simulated by acanthosis nigricans are xeroderma pigmentosum, various forms of verrucae, including seborrheic keratosis (pigmented papilloma), the pseudoacanthosis nigricans associated with obesity, and, because of the basal pigmentation, Addison's disease and nevus unius lateralis.

It is of interest that the acanthosis nigricans associated with visceral cancers may regress when the cancer itself is under temporary control, only to become more conspicuous when the cancer recurs or metastases are seeded. It is of further interest that a scar in an area of acanthosis nigricans develops pigmentation at its borders whereas a cutaneous scar in Addison's disease is itself pigmented. The role of endocrines in both the benign and malignant types is suggested; occasionally, the benign or juvenile type is associated with Cushing's syndrome.[34]

Nevus unius lateralis is essentially a linearly distributed verruca usually along the pathway of a cutaneous nerve.

Molluscum Contagiosum.—Molluscum contagiosum is a mildly contagious autoinoculable disease of the skin, caused by a virus, and characterized by pinhead to pea-sized waxy, firm, buttonlike, often pruritic papules occurring on the face, trunk, and genital regions particularly. The lesions develop slowly over a period of weeks and may remain indefinitely without therapy. The disease appears especially in children and may occur in epidemic proportions in institutions (see Plate IV and discussion, page 331).

The histologic picture should be immediately recognizable. The connective tissue papillae between the lobules are compressed or altogether obliterated so that the downward projecting lobules appear as a bulbous downgrowth (see Plate IV). This lobulation of the epidermis is almost as suggestive of the diagnosis as is the pathognomonic feature, the molluscum bodies, and may serve to help differentiate this lesion from verrucae, particularly when the molluscum bodies happen to be inconspicuous. The molluscum bodies are clustered cells principally of the stratum granulosum, but also of the stratum spinosum, which are enlarged, as are virus-infected cells generally, and contain homogeneously smooth, brightly eosinophilic cytoplasm. The nucleus is inconspicuously flattened to one side of the cell, and keratohyaline granules tend to disappear. The cytoplasm, when studied with vital stains, appears actually to contain many elementary bodies (of Lipschutz) embedded in a mucoid matrix. These dyskeratotic cells are enclosed in an eosinophilic keratin-like cell membrane that resembles the cell membranes of plants. The molluscum bodies have been confused with the brightly eosinophilic cells of the stratum granulosum that are often prominent in verruca vulgaris. These latter cells are usually associated with vacuo-

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Fig. 976.—*Darier's disease* (keratosis follicularis) showing suprabasalar cleavage, corps ronds, grains, and marked parakeratosis. (All of the photomicrographs in this chapter are of sections stained with hematoxylin and eosin unless otherwise stated.)

Fig. 977.—*Acanthosis nigricans* with melanin pigmentation of the basal layer.

Fig. 978.—*Psoriasis* with conspicuous parakeratosis, elongated, clubbed pegs, thinned suprapapillary epidermis, and rigid vessels in the papillae.

Fig. 979.—*Parapsoriasis* with spotty parakeratosis, acanthosis, transepidermal migration of inflammatory cells and infiltrate immediately subepidermal.

Fig. 980.—*Lichen planus* with hyperkeratosis, acanthosis, pointed pegs, liquefaction degeneration, and a dense subepidermal inflammatory zone.

Fig. 981.—*Keratodermia blennorrhagicum* with prominent parakeratosis and acanthosis, clubbed rete pegs, and diffusely scattered leukocytes.

lization of the cells of the stratum granulosum and are not enlarged nor do they contain the characteristic homogeneous cytoplasm of the molluscum body. Regression of the lesions of molluscum contagiosum has followed several days after a short course of aureomycin or terramycin therapy.

Vesicles

The vesicles of various diseases may closely simulate each other clinically. Inasmuch as the prognostication, even as to fatality, may depend on the exact diagnosis, it is clearly important that the diagnostic histologic features be definitively evaluated. In general, three types of vesicles occur: (1) eczematous, (2) cleavage (e.g., dermatitis herpetiformis, pemphigus, epidermolysis bullosa, impetigo, burns), and (3) virus (e.g., smallpox, chicken pox, herpes, Kaposi's varicelliform eruption).

Eczema.—Eczema, which is derived from a verb meaning "to boil out," is in most instances the cutaneous response of a sensitive skin to an allergen. The response may begin as an erythema and evolve through the papular, vesicular, pustular, and exfoliative stages. Some cases of eczema remain in one of the phases, e.g., eczema rubrum, eczema squamosum, eczema papulosum, but in most cases the disease passes through the stage of vesiculation. From the histologic point of view, the vesicle of eczema, whatever the etiology, is basically the same whether the allergen is an external irritant, ingested food, or the product of superficial fungi as in the epidermophytid. Moreover, the histologic picture of the eczematous vesicle differs sharply from that of pemphigus, dermatitis herpetiformis, and the virus lesions of smallpox, chicken pox, and herpes. The vesicle of eczema begins as foci of spongiosis in the rete malpighii. The intercellular edema progresses so as to form microvesicles which coalesce with adjacent vesicles similarly formed. The walls of such vesicles are the compressed adjacent cells which are usually arranged as septa in the large blisters (Fig. 987). Similar histologic changes occur in the vesicles of pompholyx, dyshidrosis, acrodermatitis perstans, and other eruptions of unknown etiology which are localized principally to the hands, as well as in the vesicles of pustular bacteroids. The latter are usually sterile pustules of palms and soles and are assumed to be provoked by allergic reactions to bacterial products.

Dermatitis Herpetiformis (Duhring's disease).—The lesions of dermatitis herpetiformis are symmetrically distributed in groups in the scapular regions, on the buttocks, or on the extremities. The lesions may be erythematous macules or papules, but in most cases they are characterized by vesicles which may vary from those detectable only microscopically to large bullae. The disease may be accompanied by mild constitutional symptoms and signs. Itching, burning, and pricking sensations are almost always present. The disease is characterized by spontaneous remissions and relapses. The etiology of the disease is unknown. The iodide sensitivity test is no longer regarded as specific for dermatitis herpetiformis. The lesions respond remarkably and immediately to penicillin and sulfapyridine, but usually do not react satisfactorily to other sulfonamides. The patients must be kept on maintenance doses of these chemotherapeutic agents, failing which the eruption reappears.

The microscopic features of the vesicle of dermatitis herpetiformis consist of a collection of serum, fibrin, and a few neutrophilic and eosinophilic leukocytes which have cleaved and lifted the entire epidermis from the corium. The epidermis itself shows no other constant change. Of diagnostic importance is the change in the dermal base of the vesicle; that is, particularly, the flattened papillae which are edematous and infiltrated with cells of the same type that are found in the vesicle itself. The absence of eosinophilic leukocytes by no means precludes the diagnosis of dermatitis herpetiformis although those cells are often noted in considerable numbers. Occasionally, eosinophiles, both within the fluid of the vesicle and in the underlying dermis, occur in pemphigus, particularly in *pemphigus vegetans.* The fully developed lesion of dermatitis herpetiformis is rarely a diagnostic problem, but frequently a very early or, at least, a very small lesion is biopsied at a stage prior to appreciable vesiculation; the principal clue in these is the occurrence of small clusters of leukocytes immediately subepidermal, and associated with a suggestion of edema and leukocytic reaction in a small bit of the underlying dermis (Fig. 983). The accurate diagnosis of this particular vesicle is of critical importance because of the possibility of confusion with the fatal disease, pemphigus. The presence of eosinophilic leukocytes in the infiltrate is of considerable aid in the diagnosis of dermatitis herpetiformis but their presence is not as constant as is usually stated. Often the vesicles of the varieties of pemphigus and of epidermolysis bullosa are bland in the sense that they provoke little or no dermal reaction in contradistinction to those of dermatitis herpetiformis. However, there are sufficient exceptions to this rule so that the mere presence of inflammatory reaction does not preclude the possibility of pemphigus, although in epidermolysis bullosa such reaction is usually due to trauma or secondary infection and is rarely an intrinsic part of the disease. Furthermore, some of the vesicles of pemphigus and especially of epidermolysis bullosa occur not at the junction of the epidermis and dermis but between the stratum corneum and stratum granulosum or at some level of the rete malpighii. Similarly, the vesicle of impetigo contagiosum is formed between the stratum corneum and rete malpighii and so is easily distinguished from that of dermatitis herpetiformis; in addition, there is generally considerably more purulent exudate within the lesion of impetigo contagiosum. The vesicles of the virus lesions, that is, smallpox, chicken pox, and herpes simplex and zoster, are easily recognized by their distinctive inclusion bodies, reticular colliquation, and ballooning degeneration (see Definitions).

Pemphigus.—Pemphigus refers to a group of diseases, generally fatal and characterized by bullous lesions. The cause of the disease is unknown, but some indecisive evidence has been

accumulated which suggests a virus etiology. The disease involves both sexes equally, mainly between 40 and 70 years of age, and most frequently begins in the mucous membranes of the mouth or in the skin of the trunk. It is fatal in somewhat over 50 per cent of cases. The several varieties of pemphigus include pemphigus acutus, pemphigus vulgaris, pemphigus foliaceus, and pemphigus vegetans. These forms are entities primarily on the basis of the acuteness of the disease or the type of lesions accompanying the vesicles as, for example, the foul-smelling scales of pemphigus foliaceus and the fungoid, papillomatous masses of pemphigus vegetans. Pemphigus erythematodes (Senear-Usher syndrome) used to be regarded as a separate entity with a good prognosis. It is now believed that this condition is actually a variant of pemphigus in which the

Fig. 982.
Fig. 984.

Fig. 983.

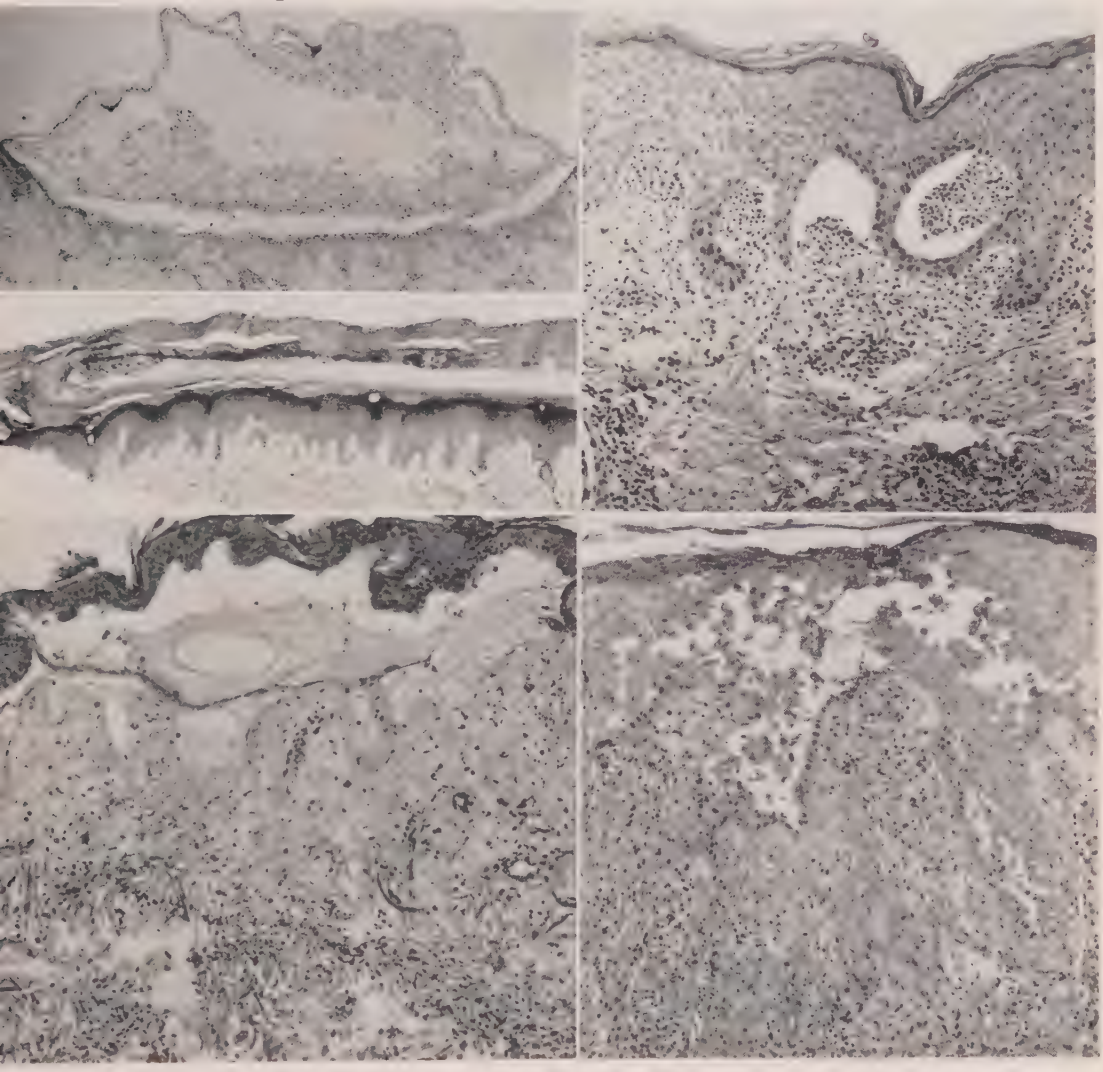


Fig. 985.

Fig. 986.

Fig. 982.—*Impetigo contagiosum.* A superficial cleavage vesicle with purulent exudate. (AFIP No. 99848.)

Fig. 983.—*Dermatitis herpetiformis* in its early stage, showing cleavage of epidermis from dermis by collections of leukocytes.

Fig. 984.—*Epidermolysis bullosa.* A cleavage vesicle in the stratum corneum, unlike the deeper, dystrophic form.

Fig. 985.—*Pemphigus vulgaris.* A cleavage vesicle between epidermis and dermis with relatively sparse dermal reaction.

Fig. 986.—*Benign chronic familial pemphigus* (Hailey-Hailey's disease) with suprabasalar cleavage and isolated clusters of epidermal cells within the vesicle.

erythematous stage may be prolonged.[23] The incidence of pemphigus vulgaris is about four times that of all the other varieties combined. Bullae are observed at some time in the course of pemphigus foliaceus and vegetans. The group name is applied also to benign chronic familial pemphigus, but there is reason to believe that this disease is quite distinct from the usually fatal varieties of pemphigus. The actual cause of death in pemphigus is not clear although the loss of abundant proteins in the bullous fluid is probably a significant factor. Recently, degenerative change in the cortices of the adrenal glands have been described, but these changes appear acute and would seem, at most, to be related to the terminal events. Fibrinoid degeneration in the arterioles of the testis has been noted by the author, but the significance of this alteration, which has been observed also in the typhus fevers, is not understood. Cases of cure, or at least remission, with convalescent serum therapy, or with penicillin, are on record. Of greater interest are the startling remissions, evident within a few hours, which may be depended upon to follow the administration of cortisone or ACTH even in moribund cases. However, relapse takes place if the therapy is stopped and it is doubtful if the ultimate prognosis is altered by these amazingly effective agents. The evaluation of therapeutic modalities must be tempered with the fact that spontaneous remissions take place in this disease, in the mild as well as severe cases.

The histologic picture of the cutaneous lesion of pemphigus is as follows:

1. The typical vesicle or bulla consists of a collection of serous fluid most often between the epidermis and dermis, but, occasionally, the split is in the midst of the rete malpighii. As a rule there is little or no reaction in the dermis, although, as stated previously, there are many exceptions in which the upper dermis or submucosa is crowded with polymorphonuclear leukocytes admixed with the various mononuclear cells; that is, lymphocytes, plasma cells, and histiocytes. Such a vesicle or bulla characterizes pemphigus acutus or vulgaris but may be a part of the picture of other varieties of pemphigus (Fig. 985).

2. In **pemphigus vegetans**, in addition to the bulla just described, there is an associated pathognomonic lesion consisting of marked acanthosis with prominent prolongation of the rete pegs, between which are brilliantly dense collections of eosinophilic leukocytes. The eosinophiles may migrate into the epidermis which may become ulcerated and the seat of intraepidermal microabscesses. The ulcerations, the intraepidermal abscesses, and the extensive acanthosis with winding reticulated pegs may simulate a bromoderma or deep fungus infections such as coccidioidomycosis.

3. In **pemphigus foliaceus**, the typical bulla often is immediately adjacent to a unique acanthosis. Often the fluid accumulates between layers of the upper rete malpighii. If the accumulation of fluid is minimal, the cleavage may be sufficient to separate the uppermost portion of the epidermis by crude pressure of the thumb on the skin of the patient (Nikolsky's sign). The pegs are rounded and formed in congeries so that in a single section they may appear isolated in the deep dermis as in an early squamous cell carcinoma. This type of acanthosis resembles most of the epidermal proliferation seen often overlying myoblastomas. The epidermal proliferation is usually accompanied by a polymorphous cellular infiltrate of neutrophilic leukocytes and mononuclear cells.

Erythema multiforme bullosum may not be differentiable histologically from pemphigus, but clues are offered in the usually greater subepidermal, urticarial-like edema, hyperemia, and cellular infiltrate in the former. Clinical features such as the vivid erythema, frequently in a disproportionately large, irregular, symmetrically distributed area about a small vesicle, in contrast to pemphigus, are of some aid in making the prognostically important differential diagnosis.

Epidermolysis bullosa occurs soon after birth (congenital) or may first appear in the second or third decade (so-called acquired type). There are two varieties of epidermolysis bullosa: the simple, and the dystrophic. In the simple type, the lesions occur, after slight trauma, on any portion of the body, and regress, leaving merely temporary pigmentation but no permanent changes. The dystrophic type is characterized by lesions of the extremities provoked by minimal trauma and associated with pigmentation, milia (epidermal cysts), atrophy and destruction of nails. Both the simple and dystrophic type may be congenital or acquired. The histology is that of a pressure vesicle with cleavage often at the junction of stratum corneum and stratum granulosum or between the epidermis and dermis especially in the dystrophic type (Fig. 984). The inflammatory reaction within both the vesicle and underlying dermis is mild except in regions, such as the feet, that are easily traumatized and infected. The small epidermal inclusions lie in the dermis beneath or at the margins of the vesicles. Destruction of the dermal elastic tissue is said to occur in the dystrophic type. The evidence for this is not satisfactory.

Virus Vesicles.—Smallpox (variola), chicken pox (varicella), alastrim, vaccinia (cowpox), herpangina, herpes simplex, and herpes zoster (shingles) are described in Chapter 14. In contrast to the ease with which most of the exanthemata are differentiable clinically is the difficulty or impossibility of differentiating the vesicles histologically. Nevertheless, there are certain features common to each of these vesicles which at least permit their recognition histologically as a vesicle produced by a virus. These features include (1) reticular colliquation by which the epidermis becomes transformed into multiple locules bounded by a reticulum of drawn-out, stringy cytoplasmic septa and (2) ballooning degeneration, the formation of multinucleated giant cells in the lower layers of the rete malpighii (Fig. 988). It is stated that, in the vesicle of smallpox, reticular colliquation proceeds at a faster pace, particularly at the periphery of the lesion, than ballooning degeneration, and thereby accounts for the umbilication of this vesicle. In smallpox, Guarnieri bodies are found as eosinophilic, varying-sized, round, cytoplasmic inclusions, especially in those cells that are at the base of the vesicle, includ-

Fig. 987.

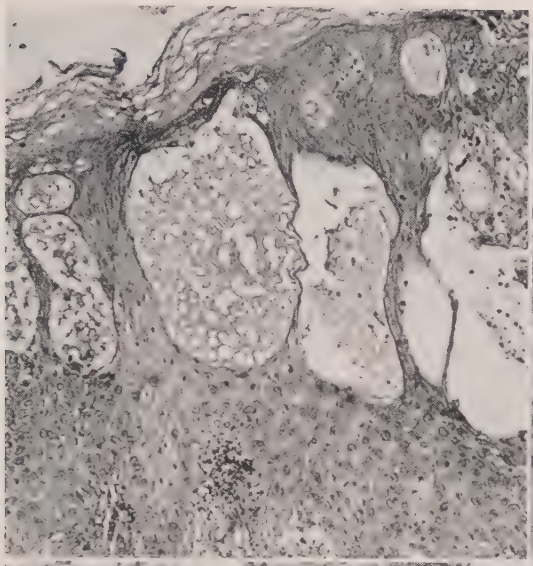
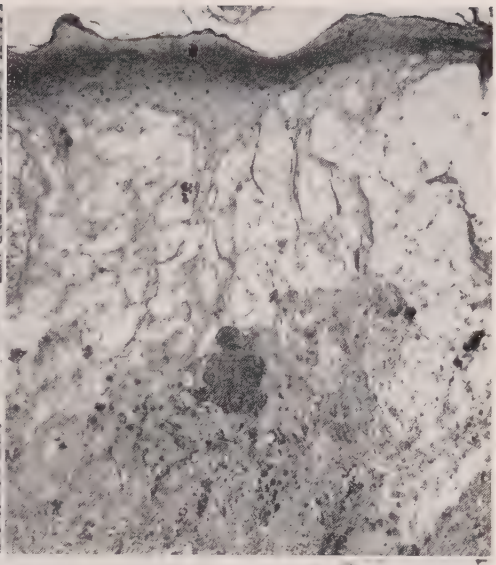


Fig. 988.



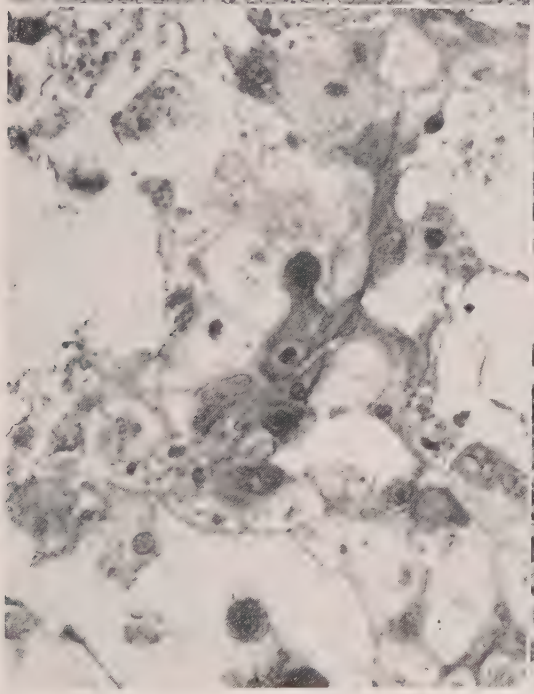


Fig. 989.

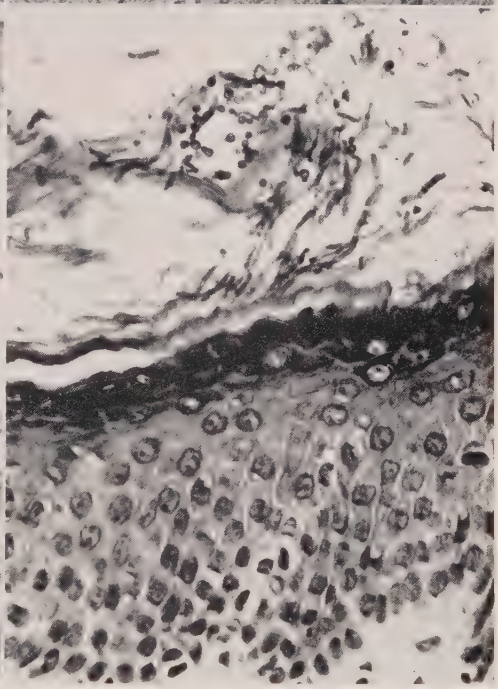


Fig. 990.

Fig. 987.—*Eczematous dermatitis* with vesiculation as a result of intercellular edema (spongiosis).

Fig. 988.—*Vesicle of hemorrhagic smallpox* characterized by reticular colliquation, and the giant cells of ballooning degeneration in the deeper portion.

Fig. 989.—*Vesicle of variola* with intranuclear and intracytoplasmic inclusions (Guarnieri bodies).

Fig. 990.—*Tinea versicolor* showing spores and hyphae of *Microsporon furfur*.

ing those undergoing ballooning degeneration. In addition, eosinophilic intranuclear inclusions with margination of the nuclear chromatin are common in these cells. In the vesicles of herpes, these intranuclear inclusions are referred to as "zoster bodies of Lipschütz," although they are morphologically similar to the intranuclear inclusions of the other virus vesicles (Fig. 989). The scarring that follows some of these vesicles, for example, those of herpes zoster and occasionally of smallpox, is an index of the prior inflammatory destruction of the upper corium. Edema and infiltrate of inflammatory cells as a rule are present in the upper dermis of most vesicles of the various virus diseases. The residual scarring, however, appears to reflect the greater intensity and destructiveness of the process. Very recently, a new entity referred to as *"herpangina"* has been described. It is a benign, febrile self-limited disease of virus etiology, affecting children chiefly, and characterized by a sudden onset of grayish-white, papulovesicular, oral or pharyngeal lesions with a surrounding red areola. Histologic studies of the vesicles are not available but one would anticipate that they would resemble the vesicles of herpes. Another controverted disease that now appears clearly virogenic is *Kaposi's varicelliform eruption.* This disease is really disseminated herpes simplex rather than generalized vaccinia as some have thought.[25]

Superficial Mycoses.—The mycoses (see also Chapter 15, page 352) are separated into the superficial type (ringworm, tinea corporis, favus) and the deep type (blastomycosis, coccidioidomycosis, actinomycosis, etc.). Superficial mycoses are divided, according to the region affected, into tinea capitis, barbae, corporis, cruris, and pedis or epidemophytosis. Several kinds of fungi may be responsible for the same clinical type of lesion. On the other hand, the form and chronicity of ringworm may vary considerably with the causative fungus; for example, Trichophyton infection of the feet presents as a dry, scaly dermatosis, whereas that due to Epidermophyton appears vesicular and moist. It has therefore been suggested that the etiology as well as the anatomic region be indicated in the name, as, e.g., tinea corporis trichophytica. However, usage sanctions the retention of additional names for varieties of ringworm infection which have distinguishing features of pattern, color, severity or chronicity of lesions, such as favus, kerion (ringworm of scalp complicated by abscesses), tinea imbricata, tinea versicolor, and others.

The fungus may be observed in wet smears of scrapings soaked in sodium or potassium hydroxide or they may be cultured on special media, such as Sabouraud's agar. However, with the exceptions of tinea versicolor and favus, it is rare to observe the fungus in a routine paraffin section of a lesion of ringworm. Generally, the histologic picture comprises merely the presence of scales or vesicles along with subepidermal hyperemia and slight perivascular cuffing by mononuclear cells. In tinea versicolor, the spores and hyphae of *Microsporon furfur* are usually abundant and confined to the stratum corneum; in favus, the large scutula, or matted scales, contain myriads of fungus (Fig. 990). The vesicle of ringworm, no matter where the lesion is located, is an eczematous vesicle, usually multiloculated, and the morphologic result of excessive spongiosis. This type of vesicle is the picture of the dermatophytid or allergic manifestation of the fungus infection. The dermatophytids are sterile of fungi and are caused by the cutaneous reaction to the products of fungi transported probably through the blood or lymph. For example, the dermatophytids following ringworm of the feet often occur on the hands. It has been suggested that sensitizing antibiotic therapy with preparations from fungi such as penicillin may be responsible in some measure for the dermatophytids following superficial mycoses.

Scabies.—Another lesion of the epidermis that is often recognizable in a fortunate histologic section is caused by *Acarus scabiei.* The disease is characterized by the occurrence of intensely pruritic papules, vesicles, pustules, and excoriations usually located in relation to the burrow, cuniculus, or gallery dug by the mite of the Acarus into the epidermis. These lesions tend to occur in the webs of the fingers, on the wrists, in the genital regions, and beneath the breasts. The disease is contagious and in most instances is transmitted by direct bodily contact with an infected individual. The diagnosis may be made clinically by picking the female mite out of the burrow and identifying it with the low power lens of the microscope. Histologically none of the lesions of scabies is diagnostic except the burrow with the tenant mite. However, often the mite may not be included in the section but the presence of ova or fecal material of the Acarus within the burrow or merely the presence of the gallery itself, is strongly presumptive evidence of scabies. The burrow is a superficial epidermal defect extending obliquely through the thickened stratum corneum which serves as a roof to shelter the Acarus. A form of scabies may be transmitted to man by mites which infest dogs, cats, birds, and monkeys.

Diseases Affecting Both Epidermis and Dermis

Lupus Erythematosus, Discoid.—Lupus erythematosus occurs in two principal forms: (1) acute and (2) chronic or discoid. The discoid variety is fortunately the more common and manifests itself by stationary or slowly progressive coalescent macules or plaques covered irregularly with fine, whitish or yellowish greasy scales and associated with focal gray patches of atrophy and keratotic plugging of follicles. The lesions are usually well-defined (hence discoid) and show a predilection for the malar areas and bridge of the nose distributed in the shape of a butterfly. The process is not limited to this area but may occur also on other parts of the face, the mucous membranes of the mouth, the neck, extremities, and elsewhere. In any location, the lesions are aggravated by exposure to sunlight. The lesions may regress completely but usually there is residual, rather typical superficial scarring without pigmentation or puckering. Acute changes may also be superimposed on the discoid lesions. Carcinomatous transformations (squamous cell) may occur

Fig. 991.

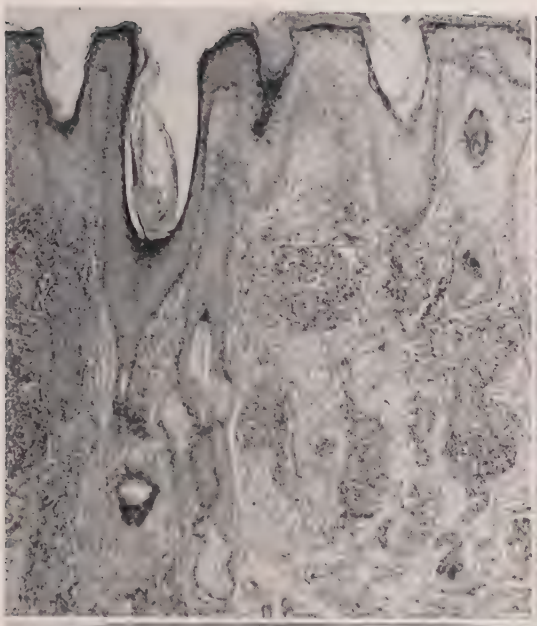
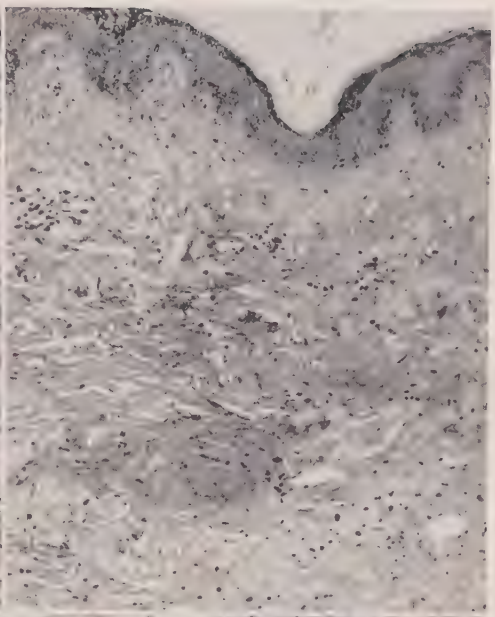


Fig. 992.



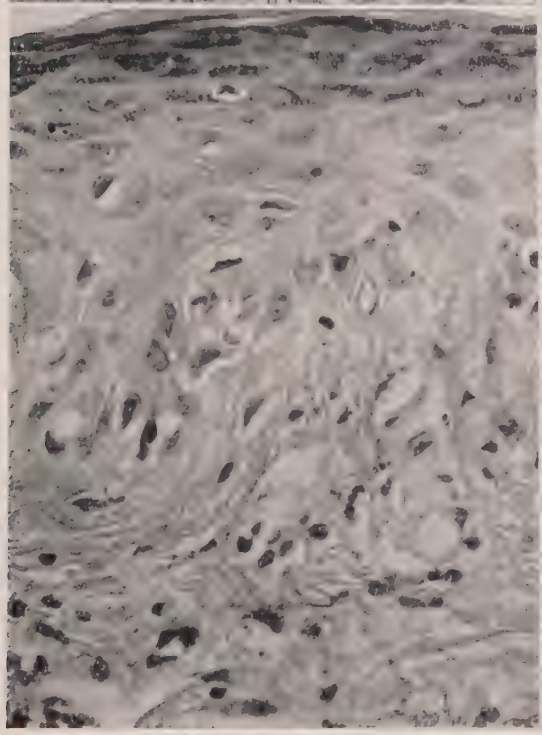


Fig. 993.

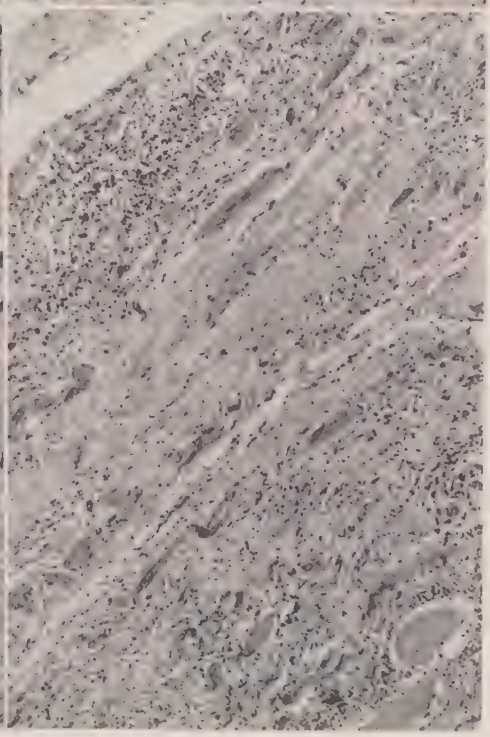


Fig. 994.

Fig. 991.—*Chronic discoid lupus erythematosus* with alternating acanthosis and atrophy, liquefaction degeneration, keratinous plugs in follicles, superficial telangiectasia, and dense collections of dermal lymphocytes. (From Arch. Dermat. & Syph. 57: 19, 1948.)

Fig. 992.—*Acute disseminated lupus erythematosus* with fibrinoid necrosis of dermal collagen, an uncommon finding in the skin in this disorder.

Fig. 993.—*Acute disseminated lupus erythematosus* with marked liquefaction degeneration at the epidermal-dermal junction.

Fig. 994.—*Dermatomyositis* with dense inflammatory cells interspersed among atrophic muscle fibers.

in the chronic process. For a long time it was thought that lupus erythematosus was in some way related to tuberculosis, probably a reaction to one of the toxic products of the tubercle bacillus. This erroneous impression was prompted by the incidental finding of pulmonary tuberculosis in patients who died of acute lupus erythematosus. This association of the two diseases was undoubtedly dependent on the common activation of tuberculosis in debilitating illnesses rather than a direct etiological relationship. The therapy of the disease is unsatisfactory. Gold and bismuth salts, and germanin have been used with occasional gratifying results.

The histologic features of the discoid variety of lupus erythematosus are easily recognizable in most cases. They include: (1) alternating acanthosis and atrophy of the epidermis with the acanthosis infrequently progressing to squamous cell carcinoma, (2) liquefaction degeneration of the basal layer, (3) hyperemia or telangiectasis of the papillary and subpapillary layer of the dermis, and (4) dense collections of mononuclear cells, principally lymphocytes, in the upper and midportions of the dermis, most concentrated about the appendages (Fig. 991). Basophilic "degeneration" of collagen in the upper dermis is a completely unreliable criterion of chronic lupus erythematosus inasmuch as it is found normally in the skin of the malar regions in the older age groups of patients. Changes in vessels, other than telangiectasis, is not part of the picture of discoid lupus erythematosus. The lesions of *rosacea* may occasionally offer differential diagnostic difficulty because of the presence of keratotic plugs and erythema. The epidermal changes and middermal masses of lymphocytes favor lupus erythematosus.

Acute Lupus Erythematosus.—The acute lesions of lupus erythematosus may occur as a focal, transient reaction to sunlight or may be part of the spontaneous fatal systemization of the disease. These acute lesions may be superimposed on the chronic process or may effect previously uninvolved skin. The chronic lesion is assumed to be complicated by the disseminated form in the rarest instances. However, while this may be the impression clinically, the histologic data belie this impression somewhat. In the acute cases, the skin becomes reddened, edematous, and sometimes purpuric, with patchy macules which may coalesce into an erysipeloid somewhat mottled malar flush. On the hands, the lesions may be erythematous or purpuric, macular or papular. Elsewhere the lesions may take other forms such as vesicles, bullae, scaling macules, and telangiectases. When the acute process complicates the discoid lesion, fresh superficial or even moderately deep ulcerations may occur, in addition to the other changes mentioned, particularly at the advancing periphery of the old lesion. As stated, the acute cutaneous phenomena may be a localized reaction to sunlight without systemic complications. In the disseminated variety, which occurs particularly but by no means exclusively in young women,[55] the constitutional signs and symptoms include fever, thrombopenia, leukopenia, excessive gamma globulinemia, splenomegaly, arthralgias, valvular disease (Libman-Sacks disease), anorexia, vomiting, diarrhea, dysphagia, abdominal pain, and lymphadenitis. Death may result from renal insufficiency, bacterial endocarditis, cardiac failure, pulmonary tuberculosis, sepsis, or pneumonia.

As with the discoid variety, the etiology of the disseminated type is obscure, although, because of clinical features (reaction to sunlight and occasional porphyrinuria) and histologic changes (fibrinoid degeneration of collagen, focal necrosis of lymph nodes) the underlying pathogenesis has been attributed by some investigators to an unexplained allergic mechanism. However, the overwhelming selection of females is difficult to reconcile with such a universal phenomenon as allergy unless, perhaps, the allergen is a product of a sex-linked compound.

The acute histologic changes in the skin are recognized by an exaggeration of the liquefaction degeneration of the basal layer of the epidermis with eosinophilic swelling of the cytoplasm of the basal cells, edema of the papillary and subpapillary layers, necrobiosis with karyorrhexis and nuclear distortion of inflammatory cells in the upper dermis, telangiectasis, and, occasionally, fibrinoid degeneration of foci of collagen in this region as well as of the walls of some of the arterioles. The latter change is inconstant and is surely not responsible for the other cutaneous alterations. Characteristic histologic changes occur in other organs in the disseminated disease. These include: (1) atypical verrucous endocarditis (Libman-Sacks disease) recognizable by the hematoxylin bodies of Gross (coalescent nuclear debris analogous to the phenomenon of the "L.E." cell naturally showing a positive Feulgen reaction for nucleic acids) and the extensive fibrinoid swelling of the cardiac valves, especially in the often overlooked pockets of the posterior mitral leaflet; (2) striking fibrinoid alteration of the interstitial collagen of the myocardium which may, but need not be, mistaken for Aschoff bodies; (3) concentric dense rings of collagen, apparently thickened reticulum, about the central splenic arterioles; and (4) focal fibrinoid swelling of the walls of glomerular capillaries ("wire loops"). With the exception of the splenic lesion, these changes are practically pathognomonic of disseminated lupus erythematosus and occur rarely in such provisionally closely related diseases as scleroderma and dermatomyositis. The splenic changes apparently do occur infrequently in mild form in other diseases. The glomerular alterations may be so widespread as to cause renal insufficiency and a clinical picture of glomerulonephritis in about a third of the cases.[51] The atypical verrucous endocarditis offers an optimal nidus for the implantation and growth of bacteria so that bacterial endocarditis is a common terminating event in this disease (Figs. 992, 993).

Undoubtedly, one of the most provocative discoveries in the field of cutaneous-visceral integration in the last few years has been the phenomenon of the "L.E." cell.[44] Cytologically the phenomenon is manifested typically by a rosette of neutrophilic leukocytes about a mononuclear cell, apparently a lymphocyte, or less

typically, by a neutrophilic leukocyte with a cytoplasmic vacuole or a cytoplasmic inclusion of a nuclear fragment; often there is excessive clumping of platelets. The essence of this phenomenon resides in the gamma globulin of the serum of patients with disseminated lupus erythematosus and may be observed not only with cells of the patient's marrow but with cells of the peripheral blood. It may also be observed with normal cells—human or animal—after mixture with the patient's serum. Similar cells are noted in a cantharides-induced blister in the skin of individuals with disseminated lupus erythematosus. It is of interest, but by now not surprising, to record the dramatic remissions in profoundly ill patients which are initiated by cortisone and ACTH; with this improvement, the number of "L.E." cells diminishes but does not disappear.[45, 47, 49, 52] Rare instances of a falsely positive "L.E." phenomenon have been recorded in multiple myeloma, leukemia, and recently in association with infection or contamination of serum with *Aspergillus niger* or *Trichophyton gypseum*.[46] There is no indication that cortisone or ACTH significantly alters the histologic reactions of disseminated lupus erythematosus or of scleroderma either.[47] It is of further interest that the "L.E." cell does not occur in scleroderma and dermatomyositis which together with disseminated lupus erythematosus have been gratuitously linked as diffuse vascular or diffuse collagen disease notwithstanding this and other discrepancies. Moreover, there is adequate reason to conclude that none of these diseases is either a diffuse vascular disease or a generalized disease of collagen. The review of the histology of even a small number of autopsies of these cases quickly reveals that the involvement of vessels or of collagen is as a rule, neither diffuse nor itself responsible for the clinical picture.[51]

Psoriasis.—Psoriasis is characterized by reddish-brown papules, covered with silvery-white micaceous scales with a predilection for symmetrical distribution on the extremities, especially on the knees and elbows. Lesions may occur also on the scalp, over the sacrum, the upper back, the face, and genitals. The nails are often involved and become thickened, dirty white, irregularly laminated, rigid, and brittle. The disease is notoriously chronic although remissions may occur spontaneously and after certain therapy, as following exposure to x-rays or to ultraviolet ray therapy, especially in conjunction with the application of crude coal tar ointment (Goeckerman treatment). Occasionally a widespread erythroderma or exfoliative dermatitis may complicate psoriasis, either spontaneously or more particularly after vigorous therapy. Another complication of psoriasis is arthritis, occurring usually in association with the generalized erythroderma. Occasionally the arthritis is deforming and persistently ankylotic, as in rheumatoid arthritis.

Cortisone and ACTH, these two agents with an incredible therapeutic versatility, are effective in at least temporarily alleviating the symptoms of psoriasis, including the arthritis. The cutaneous changes which may follow the administration of cortisone or ACTH include hyperpigmentation, hirsutism, striae, acneiform eruptions, delayed wound healing, alopecia, moon facies, nail pigmentation, and partial regression of keloidal scars. ACTH has also provoked a generalized erythroderma in psoriasis.[38]

The various qualifying terms such as psoriasis punctata, psoriasis guttata, psoriasis rupioides, psoriasis follicularis, psoriasis nummularis, and others reflect simply the predominant pattern of the lesions. Pustular psoriasis is a controverted entity, many dermatologists believing it to be really a pustular bacterid or related disorder. From the photomicrographs accompanying some of the articles, it is apparent that they are not all discussing the same condition. Pustular psoriasis, commonly associated with arthritis, has a histologic picture similar to keratoderma blennorrhagicum.

The histologic features of psoriasis are these (Fig. 978): (1) acanthosis with regular downgrowth of the rete pegs to about the same dermal level; (2) rounded test-tube shaped tips of the rete pegs; (3) prolongation of the papillae frequently with single vessels (venules) extending the length of the papillae as if rigid rather than tortuous; (4) thin epidermal plates over the elongated papillae which offer so little covering for the dilated vessels of the papillae that bleeding occurs when a scale is lifted (Auspitz's sign); (5) prominent parakeratosis usually extending the length of the lesion rather than patchy in distribution; (6) absence or sparsity of stratum granulosum; and (7) microabscesses (of Munro) in the upper rete malpighii. In addition there is an absence of spongiosis, as a rule, except in the immediate vicinity of the epidermal microabscesses; intracellular edema in the rete malpighii is common. The papillae are infiltrated chiefly with lymphocytes and histiocytes. In lesions that are in the early stage of development, some of these features, such as the rounding of the pegs and the elongation of the papillae with thin epidermal plates, may be absent. Furthermore, as in other dermatoses, recent therapy, trauma, or secondary infection will obviously modify the histology. However, in cases where there has been a superimposed exfoliative dermatitis, the basic histologic picture of the psoriatic lesion tends to persist and thereby may help differentiation from the exfoliative stage of *mycosis fungoides*, a problem that occasionally arises (Fig. 1036). Neurodermatitis may simulate psoriasis so closely as to be histologically indistinguishable; as a rule, however, the psoriasiform features listed previously are less developed in neurodermatitis or individual changes are lacking.

Parapsoriasis.—Parapsoriasis, notwithstanding the name, is not otherwise related to psoriasis. The disease is characterized by erythematous macules covered with fine scales and distributed on the trunk and extremities. The lesions are extremely resistant to therapy. Several varieties are described: parapsoriasis en gouttes, parapsoriasis varioliformis, parapsoriasis lichenoides, and parapsoriasis en plaque. The last named is of special importance because of the conviction of some observers that this type may evolve into mycosis fungoides. It is our impression that mycosis fungoides does not follow parapsoriasis in plaque—except by coincidence—but

that often the initial stage of mycosis fungoides is mistaken for parapsoriasis as well as other diseases.

The histologic changes of parapsoriasis are said to be quite nonspecific and to simulate psoriasis, seborrheic dermatitis, lichen planus, a macular syphiloderm, or the early stage of mycosis fungoides. While the changes may simulate these other diseases, the specific diagnosis of parapsoriasis may be made with considerable assurance in many of the cases on the basis of the histologic changes alone. These changes are spotty, thin areas of parakeratosis, slight to moderate acanthosis, vertical arrangement with some hyperchromatism of the basal layer along with slight liquefaction degeneration and, perhaps most revealing, the localization of inflammatory cells, mostly mononuclear, in the immediately subepidermal zone. The infiltrate hugs the epidermis tightly, and characteristically some of the inflammatory cells are located in the epidermis in their transepidermal migration (Fig. 979). The absence or sparsity of plasma cells and of endarteritis helps to eliminate syphilis as a possibility; the presence of parakeratosis and a minimal stratum granulosum as well as the shape of the pegs easily distinguish parapsoriasis from lichen planus.

Lichen Planus.—Lichen planus is generally easily recognized clinically by the irregular, violaceous, glistening, flat-topped, pruritic papules covered with a thin, horny, adherent film, and distributed symmetrically particularly along the flexor aspects of the wrists, forearms, and legs.

On careful examination, minute whitish points and lines (Wickham's striae) are seen on the surface of the papules. The disease is chronic, may last from months to years and is rarely associated with constitutional reaction except in some of the hyperacute cases. The principal varieties include lichen planus, lichen planus hypertrophicus, and lichen planus atrophicus. During World War II, many soldiers who had received Atabrine as a malarial suppressive developed cutaneous lesions which simulated lichen planus, more especially lichen planus hypertrophicus. However, Atabrine dermatitis differed from lichen planus in localization (face, scalp, and nails), in its greater severity, in its common association with eczematous and exfoliative dermatitis, and in its response following removal of the patient from tropical climates and withdrawing the drug. In addition, associated with Atabrine dermatitis, there were occasional severe or fatal systemic reactions including aplastic anemia, hepatitis, and necrotizing nephrosis.[51]

The histology of lichen planus is strikingly characteristic and comprises (1) hyperkeratosis, (2) prominence of the stratum granulosum, (3) acanthosis with elongated, saw-toothed rete pegs, (4) liquefaction degeneration of the basal layer, and (5) a mononuclear infiltrate consisting mostly of lymphocytes and histiocytes, sharply limited to the papillary and subpapillary layers of the dermis (Fig. 980). In the atrophic form, the pegs are flattened and the dermal infiltrate is sparse and replaced by an increased density of collagen containing somewhat thickened arterioles. Those lesions of Atabrine dermatitis that clinically resemble lichen planus carry that similarity into the histologic picture.

Keratoderma Blennorrhagicum.—Infrequently, perhaps about once in five thousand cases, there develops an ugly eruption following the contraction of gonnorrheal urethritis. This eruption is called keratoderma blennorrhagicum or gonorrheal keratosis and is associated with a nonsuppurative migrating arthritis and gonorrheal urethritis that persist in spite of chemotherapy. The cutaneous lesions appear several weeks following the urethritis, do not contain gonococci, according to most observers, and clear only after disappearance of the urethritis. The lesions of the skin are identical with those of *Reiter's syndrome*, which is associated with a presumed "nonspecific" urethritis, conjunctivitis, and nonsuppurative arthritis. Although the latter syndrome is said not to be due to the gonococcus, the matter cannot be considered settled conclusively, especially in view of the frequency of autotherapy with chemotherapeutic agents as well as of the spontaneous disappearance of gonococci in some cases of persistent urethritis. In both the keratoderma and Reiter's syndrome, the evolution of the disease is essentially similar; in both, the arthritis clears, as a rule, without residual damage to the joints. In the few cases tested the complement fixation test for gonorrhea was negative in Reiter's syndrome. More recently the pleuropneumonia or "L" organisms have been considered responsible for Reiter's syndrome.

The histologic features of keratoderma blennorrhagicum are: (1) prominent parakeratosis with excessive loosening of the scales so that they may be difficult to include in the histologic sections, (2) acanthosis with elongation and rounding of the ends of the rete pegs, very much as in psoriasis, so that pustular psoriasis may be a difficult differential diagnostic problem, (3) elongation of the papillae but generally not as strikingly as in psoriasis because the overlying epidermal plate is usually not as thinned as in the latter disease, (4) numerous polymorphonuclear leukocytes particularly in the upper rete malpighii and in the scales. These leukocytes tend not to be clustered densely into epidermal abscesses, but rather they are scattered more or less evenly and tend to occur in lacunae. The infiltration of the vascular papillae is principally of lymphocytes and histiocytes (Fig. 981). No gonococci are demonstrable by bacterial stains although they are said to have been cultured in a few instances. Moreover, notwithstanding the abundance of polymorphonuclear leukocytes, the commonplace staphylococci are so few in these lesions that often they, too, are not demonstrable even with special bacterial stains. It has been presumed that the development of the cutaneous lesions several weeks after the urethritis, the usual absence of gonococci in the lesions, the intractibility of the lesions to local therapy, their spontaneous resolution after the urethritis has been cleared, and the distribution of the skin lesions in the pattern of epidermophytids, all suggest an allergic basis for the eruption. It is, of course, well known,

but occasionally forgotten, that the histologic response to allergy may consist of vesicles and polymorphonuclear exudation in addition to the more generally recognized reactions of eosinophilia, plasmocytosis, and fibrinoid degeneration.

Diseases Principally of the Dermis

Urticaria Pigmentosa.—Urticaria pigmentosa is a chronic disease of the skin which begins usually in the first year of life but may start shortly after puberty or in later adult life, selecting particularly males of light complexion. The eruption, characteristically, is made up of oval, 0.5 to 2.5 cm., pigmented, yellowish- to reddish-brown, macular, papular, and even nodular lesions, occurring on the back especially, but also on the face, scalp, palms, and soles. Occasionally the eruptions may be sufficiently yellow to simulate xanthomatosis. The lesions are often intensely pruritic and when irritated become reddened, swollen, and urticarial; that is, they show evidence of dermographism. The lesions may persist for years and in many instances disappear spontaneously.

The histologic picture of urticaria pigmentosa is distinctive. In the more striking examples, the upper one-half to two-thirds of the dermis is replaced by a compact zone of mast cells which obscure the dermal landmarks (Fig. 995). The mast cells should be recognized in sections stained with the routine hematoxylin and eosin notwithstanding their simulation of ordinary histiocytes and of plasma cells. Frequently under high magnification, even with this routine stain, the cytoplasmic granules of mast cells may be discerned; these granules are, of course more clearly demonstrable in metachromatic stains, such as Giemsa's or toluidine blue. In some cases, mast cells are present in smaller numbers and are dispersed as clumps of ten to twenty cells about the mid-dermal vessels. In these instances, nice judgment may be required to differentiate the presence of mast cells in normal and abnormal numbers. In addition to the mast cells, there often are subepidermal edema (urticaria), chromatophores containing melanin in the upper dermis, and eosinophilic leukocytes scattered among the mast cells. The full-blown picture of urticaria pigmentosa closely resembles the so-called mastocytoma of dogs. In the latter disease, small foci of cellular infiltrations of mast cells are found also in the viscera; for example, in the spleen, liver, lymph nodes. Information as to whether or not the anticipated corresponding situation exists in urticaria pigmentosa is scarce but we have seen two cases in which abundant mast cells were present in the lymph nodes (histologic sections were made available by Drs. John A. Milne and R. Skahen). Routine histologic sections of urticaria pigmentosa are commonly mistaken for leukemia, nevi or malignant melanomas, and Letterer-Siwe's disease. Resignation to the teaching that mast cells cannot be detected or strongly suspected with stains of hematoxylin and eosin is in large part responsible for these serious errors.

Simple urticaria may be caused in a variety of ways: by drugs, allergenic foods, ultraviolet irradiation (*urticaria solare*), and fairly commonly by emotional disturbances. Urticaria solare follows immediately after exposure to light of sufficient intensity and of proper wave length, usually in the violet or blue part of the spectrum.

Erysipelas.—Erysipelas is an acute, contagious, infectious disease caused by the *Streptococcus hemolyticus* and characterized by a well-demarcated, erythematous, hot, swollen patch of skin in association with fever, chills, and malaise, occasionally of serious proportions. The eruption occurs commonly on the face but may select any part of the body (see Figs. 135 and 136, page 197).

The histologic reaction of erysipelas is that of a phlegmon in which numerous polymorphonuclear leukocytes are scattered loosely, rather than in clumps, throughout a markedly edematous dermis and beyond into the subcutaneous tissue. Numerous streptococci can be found in the interstitium and lymphatics. There is considerable dilatation of capillaries, venules, and lymphatic vessels. The edema may be so marked as to produce bullae. The lesions tend to heal without residua.

Diseases of Collagen.—

Keloid.—A keloid is a hypertrophic cutaneous scar which develops as a reaction to burns of various sorts, incisions, insect bites, vaccinations, and other stimuli. Negroes have a diathesis for the development of keloids although such formations are common also in the white race following burns. Partially ulcerated keloids are prone to undergo carcinomatous transformation of the epidermis after a long interval, particularly in those due to burns or associated with chronic sinuses as in osteomyelitis. The dermal portion of a keloid is not more liable to become sarcomatous than the dermis elsewhere. Rarely a keloid resolves spontaneously.

The histologic features of a keloid include thick, homogeneously eosinophilic bands of collagen admixed with thin collagenous fibers and large active fibroblasts. The lesions occupy more or less of the dermis. The sweat glands, sebaceous glands, follicles and arrectores pilorum are atrophic, destroyed, or displaced by the scar. The epidermis may be atrophic or only slightly altered by fusion and irregular pattern of the pegs. The ordinary scar of the skin is more cellular than a keloid and is composed of uniformly thinner collagenous fibers. In both instances, elastic tissue is diminished or absent. The keloidal reaction of hypertrophic collagenous bundles and large fibroblasts is characteristic of dermatitis papillaris capillitii (keloidal acne) which occurs particularly in the nuchal region of Negroes and, with the associated extensive plasmocellular reaction, represents a type of response to folliculitis.

Balanitis Xerotica Obliterans.—Balanitis xerotica obliterans constitutes another disease of collagen which appears clinically as whitish firm coalescent papules or a sclerotic plaque of the glans penis and foreskin and occurs often following circumcision. The disease is of some importance because the process tends to extend to the urethral meatus causing stenosis of the orifice. The lesion is to be differentiated from

Queyrat's erythroplasia and circumscribed scleroderma. There is some question as to whether or not balanitis xerotica obliterans is a form of kraurosis of the penis or of lichen sclerosis et atrophicus.

The histologic picture consists of (1) atrophic epidermis or epithelium with loss of rete pegs, (2) striking homogenization of the collagen for about one-third of the upper dermis, and (3) a more or less dense zone of lymphocytes and histiocytes beneath the homogenized collagen (Fig. 996). The small arteries and arterioles of the upper and middle dermis may show evidence of endarteritis obliterans, but this process is sufficiently inconstant as not to warrant the use of the qualification "obliterans" in the name of the disease. Furthermore, on the basis of other cutaneous atrophies, there is considerable reason to believe that the vascular change does not initiate the collagenous change but perhaps is an incidental secondary reaction as in other kinds of chronic inflammations; for example, chronic gastric ulcer.

Acrodermatitis chronica atrophicans presents the basic qualitative histologic features of balanitis xerotica obliterans, namely, atrophy of the epidermis, and a subepidermal homogenized zone of collagen beneath which is a dense zone of mononuclear cells (Fig. 997). The major difference lies in the constantly wider zones of homogenization and cellular reaction in balanitis xerotica obliterans. In addition the epidermis is hyperkeratotic; there is loss of dermal elastic tissue and atrophy of appendages in acrodermatitis chronica atrophicans. Clinically, however, there is no resemblance between the two diseases. Acrodermatitis chronica atrophicans begins as erythematous, slightly edematous macules which later become wrinkled, atrophic, and sclerodermatoid. As the prefix *acro* indicates, the disease tends to select the extremities, particularly the hands and feet and the extensor surfaces of the elbows and knees. The condition occurs predominantly in middle-aged women. It has been reported that individuals with this disease are prone to develop epidermoid carcinomas of the skin. However, thus far the statistical documentation lacks conviction just as it does for the corresponding complication in psoriasis.

Granuloma Annulare.—Granuloma annulare is a chronic eruption made up of papules or nodules grouped in a ringed or circinate arrangement with a tendency to occur on the dorsum of the fingers and hands, the elbows, neck, feet, ankles, and buttocks, particularly of children and young adults. The lesions can be palpated intracutaneously rather than subcutaneously as are the rheumatic nodules. The etiology of the disease is unknown although, with evidence that is not acceptable, many observers have attributed the lesions to tuberculosis. Because of the histology, a rheumatic basis for the disease comes to mind, but here, too, clinical evidence is lacking. Allergy is a probable factor. We have seen two cases associated with disseminated allergic granulomatous arteritis.

Histologically, granuloma annulare is characterized by an intradermal oval or circular focus of fibrinoid degeneration of collagen. About such a focus there are palisaded rows of epithelioid cells or histiocytes, some of which may be vacuolated by fat (Fig. 998). It is the combination of fibrinoid alteration of collagen and palisaded histiocytes that suggests a possible rheumatic etiology. In fact, the histologic features of granuloma annulare are identical with those of the rheumatic nodule, the only difference being the location of the latter in the subcutaneous tissue, adjacent to or within synovial membranes. Certainly the histologic picture is not that of tuberculosis although the characteristic fibrinoid degeneration of the collagen of granuloma annulare and the rheumatic nodule has been mistaken for the caseation of tuberculosis, a simulation that can usually be detected easily. There may be considerable difficulty, however, in recognizing early or small lesions of granuloma annulare where the only clue may be a minimal smudgy fibrinoid swelling of collagen with clumps of a few histiocytes, some vacuolated, others partially palisaded. These minute lesions may be confused with xanthoses, necrobiosis lipoidica diabeticorum, or leprosy. Of course, Aschoff cells are absent in granuloma annulare as they are in the subcutaneous rheumatic nodule; they are confined to the heart.

Necrobiosis Lipoidica Diabeticorum.—Necrobiosis lipoidica diabeticorum is a disease characterized by oval, circular, firm, sharply defined plaques with yellowish centers and violaceous peripheries, occurring predominantly on the legs but found also on the forearms, palms, soles, neck, and face. The centers of the lesions are prone to ulcerate. Trauma, often inconspicuous, may initiate the lesions. In about 80 per cent of cases the disease is associated with diabetes; in about 10 per cent, the lesions precede the onset of diabetes; in the remainder, diabetes does not develop. Obviously, the recognition of necrobiosis lipoidica diabeticorum can be of remarkable prophetic importance. Clinically the disease must be differentiated from other such focal diseases of collagen as granuloma annulare, amyloidosis, morphea, and lipoid proteinosis as well as the granulomas of sarcoid and erythema induratum which tend, also, to occur on the extremities.

The basic histologic change of necrobiosis diabeticorum consists of a degeneration of collagen occurring in irregular patches especially in the upper dermis. In well-developed foci, the altered collagen is swollen, somewhat granular, with loss of fibrils and with a diminution in nuclei of fibrocytes. At the periphery of the collagenous alteration are small collections of histiocytes often arranged about Langhans' giant cells and simulating sarcoid or tuberculosis (Fig. 999). This giant cell reaction occasionally may involve the walls of veins to produce a giant cell phlebitis reminiscent of the reaction in temporal arteritis. Vacuoles may be present in the cytoplasm of the giant cells and histiocytes, but fat is found infrequently within the cells of these lesions although extracellular fat is detectable about the altered collagen.

Scleroderma.—There are two basic varieties of scleroderma the differentiation of which is of great importance prognostically: (1) morphea or circumscribed scleroderma and (2) diffuse

scleroderma. Circumscribed scleroderma occurs as well-delimited, round or oval plaques with whitish, yellowish, or ivory-colored centers and violaceous peripheries. Occasionally the plaques correspond in distribution to the innervation of a cutaneous nerve, so a trophic origin has been suggested. *Morphea guttata* or *white-spot disease* is a modification of circumscribed scleroderma characterized by varying sized chalk-white patches on the chest and neck. Rarely does circumscribed scleroderma progress into the often fatal diffuse scleroderma. Usually the lesions clear with a barely noticeable thin, atrophic area as a residuum.

Fig. 995. Fig. 996. Fig. 997.

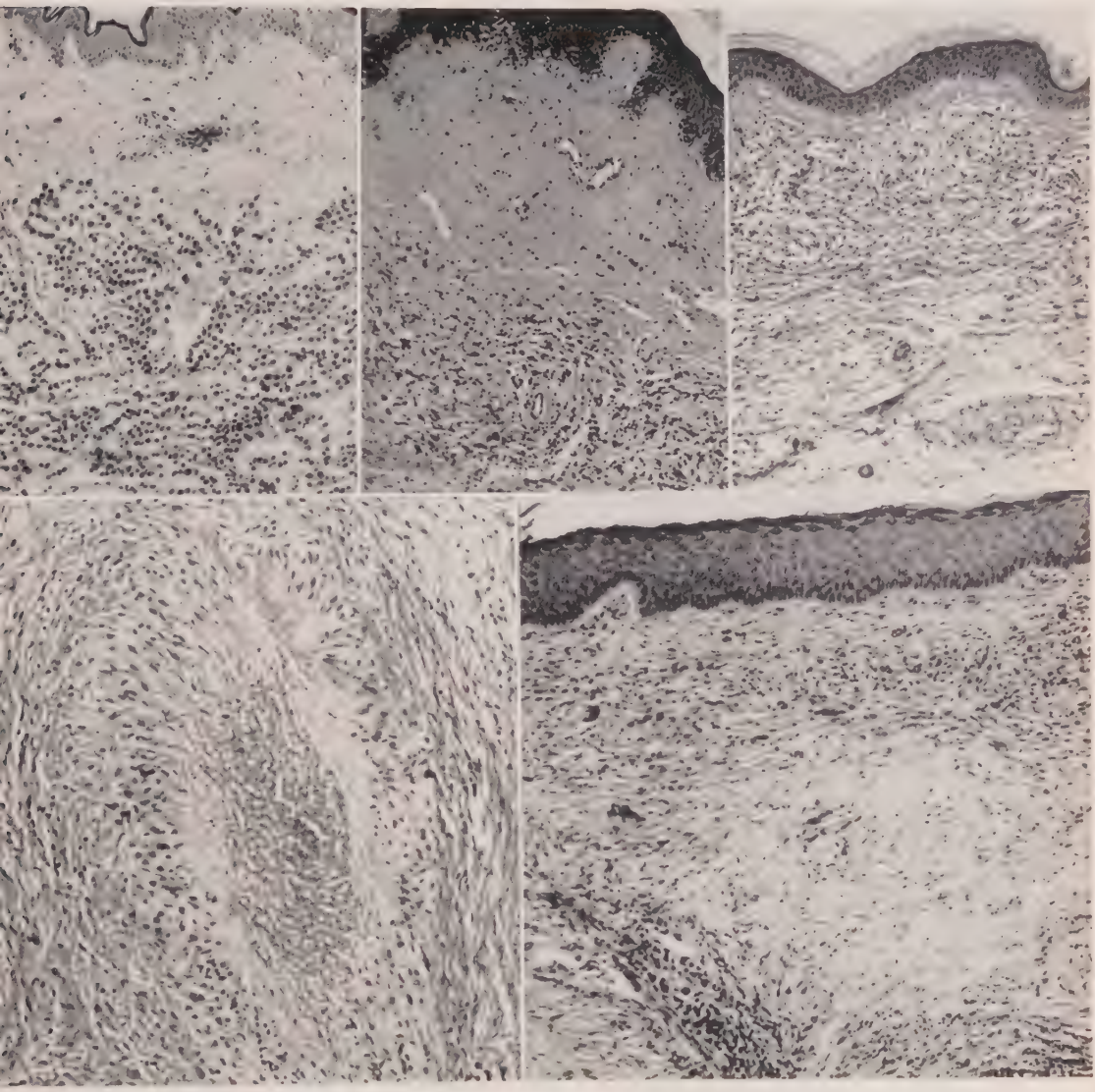


Fig. 998. Fig. 999.

Fig. 995.—*Urticaria pigmentosa* with superficial edema of cutis and extensive numbers of mast cells in the remainder of the dermis.

Fig. 996.—*Balanitis xerotica obliterans* with homogenization of subepidermal collagen over a zone of inflammatory cells.

Fig. 997.—*Acrodermatitis chronica atrophicans* with a thin zone of hyalinized subepidermal collagen and a deeper layer of inflammatory cells.

Fig. 998.—*Granuloma annulare* with central fibrinoid necrosis of dermal collagen surrounded by palisaded epithelioid histiocytes. (From Arch. Dermat. & Syph. 57: 19, 1948.)

Fig. 999.—*Necrobiosis lipoidica diabeticorium* with irregularly homogenized, degenerated dermal collagen and tuberculoid granulomas at the periphery.

Fig. 1000.

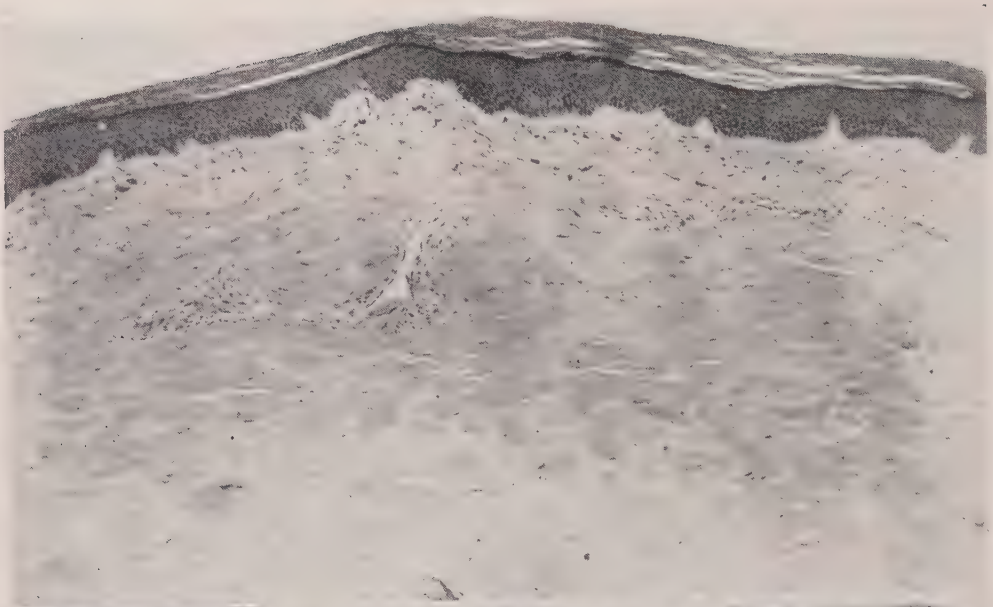
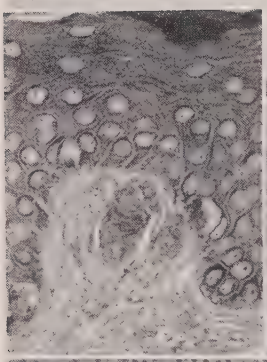


Fig. 1001.



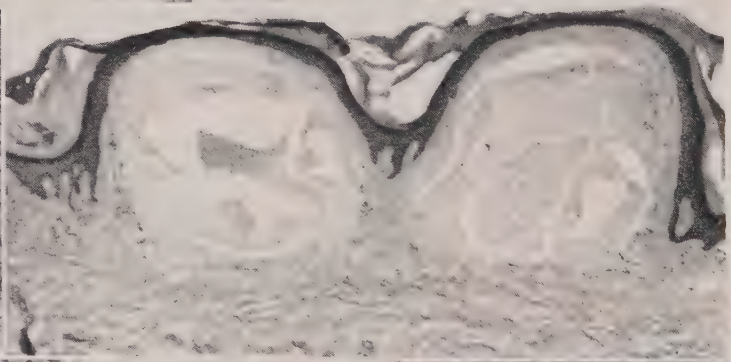


Fig. 1002.

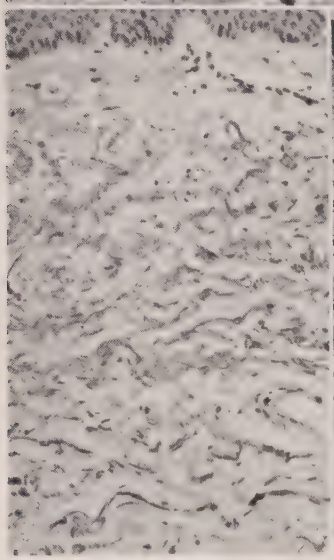


Fig. 1003.

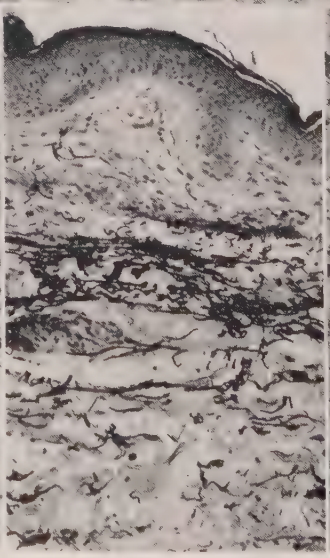


Fig. 1004.

Fig. 1005.

Figs. 1000-1005.—(*For legends see opposite page.*)

Diffuse scleroderma which affects women twice as often as men, begins insidiously, usually as edema of the hands, other parts of the extremities, or neck, and extends inexorably on to atrophy which stiffens, binds, and limits the mobility of the affected part. Ulcerations may occur over bony prominences; calcareous cutaneous deposits and pigmentation, the latter of a degree as to simulate Addison's disease, are frequent. The normal cutaneous lines become obliterated; diminution in sweating, hyperesthesias, and pruritus may occur. Sclerosis limited to the hands in association with the vasospastic symptoms of Raynaud's disease is called acrosclerosis or sclerodactylia. In actuality this symptom complex presents a phase of diffuse scleroderma although the progress to the fatal disease is not invariable. Death in diffuse scleroderma generally results from cachexia with intercurrent infection; rarely to renal or cardiac insufficiency; at times secondary to cystic fibrosis of the lungs.

The histologic sections of morphea cannot be differentiated from those of diffuse scleroderma. The principal changes involve the collagenous fibers, which become hypertrophied through edema and then atrophy. The atrophic fibers are no longer loosely disposed as in the normal dermis but are compressed into dense, compact, collagenous masses with diminution of fibrocytic nuclei and obliteration of spaces between collagenous bundles so that the thickness of the dermis is visibly decreased (Fig. 1000). Inflammatory reaction may be absent or abundant, particularly focal collections of mononuclear cells disposed about appendages. The appendages—hair, sweat glands, and sebaceous glands—are atrophic. Elastic fibers may be diminished or distorted but they represent the least informative alteration and are unduly emphasized in the literature. The epidermis may be normal but usually it is atrophic with flattened rete pegs and a hyperpigmented basal layer. Subepidermal melanin-containing chromatophores may be increased. In conjunction with the collagenous atrophy, small arteries and arterioles may become sclerotic. Calcific or even ossified foci (osteoma cutis) may replace the altered collagen of the dermis and subcutaneous septa. The deposits of calcium may be so extensive as to camouflage the primary diagnosis and be dismissed as "calcinosis." Atrophic myositis may accompany the cutaneous lesions, although uncommonly to the degree found in *dermatomyositis* or *poikilodermatomyositis,* in which the inflammatory reaction in the skeletal muscles may be extreme despite the usual nondescript subepidermal edema, and focal liquefaction degeneration in the latter diseases. Here again it is emphasized that neither *diffuse* vascular nor *diffuse* visceral collagenous changes occur in dermatomyositis or poikilodermatomyositis any more than they do in the vast majority of cases of diffuse lupus erythematosus or even scleroderma. This misapplication of the term "diffuse vascular disease" is further exemplified in the instance of the typhus fevers, particularly tsutsugamushi disease.[53] Sclerosis in scleroderma may involve portions of the gastrointestinal tract and the myocardium. The kidney infrequently is involved with vascular lesions simulating those of malignant nephrosclerosis and rarely the "wire-loop" form of glomerulitis.[51] Cystic changes in the lung with hyperelastosis occur occasionally.[48]

SCLEREDEMA ADULTORUM.—*Scleredema adultorum* (Buschke's disease) is to be distinguished from scleroderma. Scleredema is a self-limited disease characterized by a tough, nonpitting, uniform edema of the head and neck, producing a masklike expression and restricted motion that simulates scleroderma. The periphery of the process is sharply palpable. The disease runs its course in from several months to a year and a half, leaving no residuum. Recurrences have been recorded. The lesion differs from scleroderma in the absence of pigmentation, the rarity of involvement of hands and feet, and the complete resolution.

The histologic picture of scleredema is that of striking hypertrophy of tight collagenous bundles so that, despite the compactness of the bundles, the thickness of the dermis is distinctly increased over normal. The epidermis, vessels, elastic tissue, and muscle show no changes. The changes of *sclerema neonatorum* are, of course, altogether different from scleredema or scleroderma and consist of the precipitation of fatty acid crystals and foreign body reaction in the subcutaneous fat, possibly due to a deficiency of olein in the fat with consequent raising of its melting point. The localized, nodular sclerema, which some believe may result from birth trauma, is a self-limited disorder; the diffuse form, which may involve also visceral (e.g., periadrenal and perirenal) fat, is a fatal disease.[68] Scleredema and scleroderma are to be differentiated also from *myxedema,* either the circumscribed or diffuse type. In *myxedema,* unlike either scleredema or scleroderma, there is focal granularity, irregular vacuolization, and looseness of the collagen bundles due to the presence therein of mucin. The epidermis tends to be hyperkeratotic.

LIPOID PROTEINOSIS is another remarkable disease affecting dermal collagen and its vessels. The disease generally manifests itself in infancy and is characterized by verrucous yellowish plaques especially on the hands, feet, elbows, and face. The lesions may involve also the mouth and larynx; in the latter location the woody consistency of the lesions may cause a stenosis severe enough to require tracheotomy. Persistent hoarseness is a common symptom.

Fig. 1000.—*Scleroderma* with dense, thickened dermal fibers, atrophy of appendages and epidermis, and melanin pigmentation of the basal layer.

Fig. 1001.—*Amyloidosis* showing a metachromatic focus in the papilla. (Toluidine blue stain.)

Fig. 1002.—*Colloid milium* with characteristic nodules of altered collagen.

Fig. 1003.—*Senile elastosis.*

Fig. 1004.—*Hyperelastosis cutis.* (Weigert and van Gieson stain.)

Fig. 1005.—*Tattoo* with irregular deposits of black-appearing pigment.

Disturbances in phospholipids are inconstant. A familial tendency toward diabetes mellitus is occasionally present (Fig. 984).[9]

The histologic features are a hyperkeratotic and acanthotic epidermis overlying eosinophilic homogenized collagen in the upper dermis. The walls of arterioles and small arteries of this region are thickened. A fat stain reveals dense sudanophilic deposits in and about their walls as well as in the stroma. No foam cells are present. It is stated that the fat is combined with the protein of the collagen and therefore resists ordinary fat solvents. This property was not borne out in two of the author's cases.

Amyloidosis may be confined to the skin, or the cutaneous lesions may represent part of a systemic process. The eruption is characterized by pruritus, brownish papules, nodules, or plaques occurring particularly on the legs. Histologically there are focal areas of bland homogenization of dense collagen, occasionally scattered in the dermis but often located as subepidermal round masses which stain metachromatically with the ordinary stains for amyloid. The histologic picture may closely simulate *colloid milium,* in which, too, there is a homogeneous alteration, with swelling into nodular masses of the subepidermal collagen. However, the collagen of colloid milium does not stain metachromatically and, in addition, the fibers in this disease appear looser, more edematous, and more friable, than do those of amyloidosis (Fig. 1001). Clinically colloid milium appears as small, translucent papules from 1 to 5 mm. in diameter, occurring commonly on the face. Response of colloid milium to vitamin C has been reported (Fig. 1002).

Diseases of Elastic Tissue.—Although alterations in elastic tissue, especially diminution and fraying, occur in many dermatoses, there are three principal, primary disorders of elastic tissue: (1) cutis hyperelastica (Ehlers-Danlos syndrome), (2) pseudoxanthoma elasticum, and (3) senile elastosis.

Cutis hyperelastica is a familial disease characterized by hyperelastic velvety skin ("rubber skin") associated with hyperlaxity and hyperextensibility of the joints and the tendency of the skin to bleed, tear, and scar following slight trauma. Histologically, abundant compact masses of elastic fibers are demonstrable throughout the dermis by Weigert's stain for elastic tissue (Fig. 1004).

Pseudoxanthoma elasticum is another hereditary disease in which yellowish papules and plaques symmetrically distributed are found in abnormally lax skin of the neck, axilla, groin, and cubital and popliteal spaces. Other parts of the body are less frequently involved. In the histologic sections, the elastic fibers are easily detectable even in routine preparations stained with hematoxylin and eosin as masses of basophilic curved, small, partially calcified,[74] fragmented curlicues, with a tendency toward concentration near the mid-dermis. In about 50 per cent of cases of pseudoxanthoma elasticum there occur ophthalmoscopically visible "angioid streaks" in the retina which are said to be similar to the dermal changes histologically.[73] The histologic evidence, however, is very sparse.

Senile elastosis is the term used to describe the loss of elasticity of the skin of elderly people, as noted particularly on the face, and the dorsum of the hands, that is, the exposed portions of the body. This condition is found associated also with epidermal neoplasms, discoid lupus erythematosus, radiodermatitis, and other diseases. In the microscopic sections, the change is represented by a subpapillary zone of basophilic alteration of swollen elastic fibers. This form of elastosis may or may not be associated with atrophy of the epidermis and appendages (Fig. 1003). It is of interest that notwithstanding the increase in elastic tissue, such skin is characterized by a loss of elasticity as if the physical properties of these fibers had been altered.

Specific Granulomas.—Of the specific granulomas of the skin, the following should be mentioned briefly: tuberculosis, sarcoidosis, berylliosis, leprosy, brucellosis, syphilis, granuloma inguinale, leishmaniasis, and those due to deep fungi, such as sporotrichosis, blastomycosis, coccidioidomycosis, and histoplasmosis.

Tuberculosis cutis may take a large variety of clinical forms in which lupus vulgaris, scrofuloderma, tuberculosis cutis verrucosa, miliary cutaneous tuberculosis, and many kinds of tuberculids are a few examples. While differing prognostic implications usually make the precise diagnosis of tuberculosis of significance, the important service the pathologist is expected to render is to name the over-all tuberculous process. In this the problem is complicated by the difficulty with which the tubercle bacillus is demonstrable in paraffin sections of the skin, so that the tubercle is usually the basis of the diagnosis. However, often the tubercle is incompletely formed and reliance is then placed on such suggestions as epithelioid cells clustered or palisaded in the vicinity or in a matrix of caseated tissue, with or without giant cells. The cutaneous reaction of leishmaniasis and histoplasmosis is often tuberculoid, but the detection of the respective organisms in histiocytes and giant cells establishes the diagnosis.

The histologic diagnosis of *Boeck's sarcoid* is made on the finding of dermal hyperplastic tubercles, with or without giant cells, Schaumann or asteroid bodies, but in the absence of caseation. Usually the tubercles are surrounded by dense bands of collagenous stroma. No tubercle bacilli are detectable, but, nevertheless, the evidence appears to favor the concept that the process represents noncaseating tuberculosis. The term *Darier-Roussy sarcoid* is reserved for an essentially similar histologic process occurring in the deep dermis and subcutaneous fat, thereby resembling erythema induratum. Confusion arises from the simulation of the tuberculous process by the reaction of the tuberculoid form of leprosy, by the syphilitic gumma, and by the response to blastomycosis, coccidioidomycosis, leishmaniasis, and sporotrichosis. Moreover, in some instances of sarcoid a form of fibrinoid degeneration simulating caseation may occur. (See also discussion on page 670.) Sarcoidosis responds well to cortisone. A diagnostic test for sarcoidosis, called the *Kveim test* consists of injecting intradermally

a brei of tissue known to be involved with Boeck's sarcoid, and observing the delayed clinical and histologic reaction to the injection several weeks later, as in the lepromin (Mitsuda) test for leprosy. The histologic features of the Kveim test are similar to those of sarcoidosis. Extracts of normal splenic tissue and of leukemic lymph nodes also give a positive reaction. The tuberculin reaction tends to be negative in sarcoidosis and unlike the Kveim reaction, has a nonspecific histology. The Kveim reaction is positive in most cases of active Boeck's sarcoidosis; it is negative in the healed or inactive forms, and is uncommonly falsely positive. It is negative also in tuberculosis and leprosy.[75]

The granulomas of *berylliosis* (usually acquired by inoculation of the beryllium phosphors from broken fluorescent lamps) and of *brucellosis* are histologically indistinguishable from those of sarcoidosis. The brucella organisms may be recovered from culture or after animal inoculation of the diseased tissue.[80]

In *tuberculoid leprosy,* acid-fast bacilli are rarely found in contrast to nodular leprosy. In this connection it is important to recall that care must be taken in staining for the bacilli because the Hansen's bacillus is not as acid fast as is the tubercle bacillus. Histologic clues of leprosy include involvement of cutaneous nerves, the atrophy of the epidermis, and the presence of foam cells particularly about the appendages. Of course, these last two features are prominent in nodular leprosy in which the tuberculoid structure is absent. (See also discussion on page 267.) The lepromin test tends to be negative in tuberculoid leprosy and positive in nodular leprosy.[8]

The *syphilitic gumma* may be indistinguishable from tuberculosis except by the demonstration of the etiological agent with special stains. The more advanced the stage of syphilis, the greater is the difficulty of demonstrating the treponemata. Plasmocellular infiltrate and endarteritis obliterans are helpful clues suggesting syphilis in any of its stages. The plasmocellular infiltrate about dermal blood vessels or appendages may be the only histologic feature pointing to syphilis in the secondary lesions.

The histologic reaction in *granuloma inguinale* is more easily recognized in routine sections than is generally conceded. The two features suggestive of the disease are (1) large, isolated vacuolated histiocytes which contain the Donovan bodies in their cytoplasm; and (2) microabscesses containing about 6 to 12 polymorphonuclear leukocytes scattered throughout the body of the infiltrate. Leukocytes at the ulcerated surface are obviously of no diagnostic help. In addition, there is an associated dense inflammatory reaction occupying most of the dermis. Plasma cells and endarteritis obliterans may be as conspicuous as in a syphilitic chancre. The diagnosis of granuloma inguinale may be suggested with considerable assurance on the basis of these histologic criteria. The etiological organisms may or may not be discernible in sections stained with hematoxylin and eosin; the organisms are more easily seen with a Giemsa or a silver stain (e.g., Warthin-Starry), the latter being particularly useful because the capsules of the organisms adsorb the silver and, therefore, appear considerably larger than with other stains. (See page 289.)

Sporotrichosis may offer some histologic problem in diagnosis but, as a rule, the three zones of reaction in this disease are easily noted. These zones are (1) an inner core of purulent exudate; (2) a middle zone of giant cells both of the foreign body and Langhans' type; (3) an outer rim of lymphocytes with a few histiocytes.

Other deep fungal diseases, such as *blastomycosis, histoplasmosis, coccidioidomycosis,* and parasitic diseases, e.g., leishmaniasis, may provoke a tuberculoid reaction. In many such lesions, organisms may be sparse in histologic sections. The search for the fungi should be particularly meticulous in tuberculoid lesions in which there is striking pseudoepitheliomatous hyperplasia along with ulceration and intraepidermal abscesses. This latter epidermal picture is the common histologic feature of the reaction to halogens as in bromoderma and iododerma, although there is usually an accompanying dense mononuclear dermal reaction. The organisms of blastomycosis are distinguished from those of coccidioidomycosis by the absence of endospores and the occurrence of budding in the blastomyces. (For further discussion of the fungi, see reference[8] and Chapter 15.)

Pigmentations

The abnormalities of cutaneous pigmentation may be considered under two principal categories: (1) metallic and (2) nonmetallic. The exogenous pigmentations are chiefly those due to metals introduced into the body in a variety of ways, including ingestion, parenteral administration, inunction, and intradermal injection. In general, the metallic pigmentations provoke at least an increased deposition of melanin in the basal layer and chromatophores. The brown *arsenic pigmentation* due to the ingestion of either pentavalent or trivalent arsenic, as in Fowler's solution, sodium cacodylate, or arsenic trioxide, is often associated with keratosis of palms and soles. Histologically, there is relative hyperkeratosis with atrophy of the remainder of the epidermis, hyperchromatism, and a tendency toward palisading of the basal cells and increased melanin deposits in these cells as well as in the chromatophores of the upper dermis, which usually is edematous. *Argyria,* in which the skin is discolored bluish-gray, may follow the ingestion of silver nitrate, formerly used in the treatment of peptic ulcers, or the application of this drug as well as colloidal silver compounds (argyrol and neosilvol) to mucous membranes. The pigmentation is particularly marked in those areas of the skin exposed to light. The black granules of silver are noted especially in the argyrophilic basement membrane of the sweat glands but also in the connective tissue about sebaceous glands and hair follicles and just beneath the epidermis.

Chrysiasis, due to the parenteral use of gold preparations, as in the treatment of chronic lupus erythematosus, causes an ash-gray or mauve pigmentation which is characterized his-

tologically by irregular large, granules located chiefly in chromatophores and in the walls of blood vessels. A somewhat similar histologic picture is caused by pigmentation due to *bismuth* and *mercury*. In *tattoos*, the pigmentation is the result of the deposition of various metallic and vegetable pigments (e.g., cinnabar or red mercuric sulfide), both within chromatophores and extracellularly in irregularly large clumps sometimes surrounded by foreign body reaction (Fig. 1005). Discoid lupus erythematosus may selectively involve the red areas of tattoos (mercuric sulfide) and spare the blue; similarly, individuals sensitive to mercury may show allergic reactions in the red portions. Conversely, syphilitic lesions may spare these mercury impregnated red components of tattoos.

The nonmetallic abnormalities of pigmentation of skin include those due to hemochromatosis, Addison's disease, chloasma, melanosis of Riehl, ephelides (freckles), sunburn, pupuras, tinea versicolor, and pinta.

In *hemochromatosis* (bronze diabetes), hemosiderin and hemofuscin are deposited as brownish granules in chromatophores not only in the upper dermis but principally about sweat glands. In addition, there is increased melanin in the epidermis and adjacent chromatophores. This cutaneous lesion is commonly associated with deposits of the pigments in the pancreas, liver, and lymph nodes and the development of diabetes mellitus and cirrhosis of the liver. In *Addison's* disease, there is an excessive deposit of melanin in the basal layer of the epidermis and in underlying chromatophores. A similar histologic picture is found in the ordinary freckle (ephelis), sunburn, and chloasma (pigmented spots of pregnancy). *Melanosis of Riehl*, often associated with malnutrition, is characterized by brown macular discolorations of the face, neck, and, occasionally, hands. Histologically there is irregular pigmentation by melanin of the basal layer and chromatophores, in addition to telangiectasis, varying degree of hyperkeratosis, liquefaction degeneration of the basal layer, and partial obliteration of the rete pegs. A similar picture is seen in tar melanosis, the occupational dermatosis probably concerned with photosensitization. Recently there has been described a syndrome consisting of melanosis of the lips, oral mucosa, and digits in patients with gastrointestinal polyposis.

Increased pigmentation of the skin follows a variety of purpuras; *purpura annularis telangiectodes* (Majocchi's disease), *Schamberg's disease*, and *pigmented purpuric lichenoid dermatitis* of Gougerot and Blum. Each of these diseases occurs selectively on the lower extremities. The pigment in these cases is hemosiderin which is deposited in chromatophores in the upper dermis. *Angioma serpiginosum*, which is also rather loosely included in the category of cutaneous purpuras is really an inflammatory telangiectasia, and usually shows little or no hemosiderin. In all of these "purpuras," which are unassociated with hematologic disorders, there are inflammatory cells, principally lymphocytes and histiocytes localized in the upper dermis, especially about arterioles and capillaries, which may have swollen, and prominent endothelium. This latter finding is particularly true of Majocchi's disease. There is some question as to whether or not these conditions are actually different phases of the same basic disease. Occasionally, these purpuric lesions, particularly those of *Majocchi's disease*, may be confused histologically with the vascular changes of *erythema elevatum diutinum* (hyalinized, acutely inflamed capillaries and arterioles) *periarteritis nodosa*, or bacterial and rickettsial arteritis. The changes of *thrombophlebitis migrans* and of *thromboangiitis obliterans* are discussed elsewhere. Of great interest is another truly diffuse vascular disease characterized by thrombocytopenia, purpura, a usually fulminant, fatal course (although rare protracted cases have occurred), and a specific histologic picture of fibrinoid necrosis and plateletlike *verrucal* thickening of the walls of dilated arterioles and capillaries. In the past the disease has been called generalized platelet thrombosis or some variant of this term. However, the histogenesis of the entire lesion from the vascular walls[83] would seem to make the designation *generalized thrombocytopenic verrucal angionecrosis* more appropriate. These cases are rarely diagnosed clinically. Inasmuch as the vascular necrosis occurs in the skin as well as the viscera, a cutaneous biopsy is called for in obscure instances of thrombocytopenic purpura. There is strongly suggestive clinical and histologic evidence of a factor of hypersensitivity in this disorder.

Achromia should be mentioned among the abnormalities of cutaneous pigmentation. The congenital absence of pigment is referred to as partial or complete albinism or leukoderma. *Vitiligo* or acquired leukoderma is of usually unknown etiology. The depigmented patches are rimmed by hyperpigmented borders and the histologic sections reveal the depigmented and hyperpigmented basal layers in the respective portions. Vitiliginous areas may occur also in any lesion in which there is considerable liquefaction degeneration of the basal layer and encroachment onto this layer by inflammatory cells. Pinta and lichen planus in Negroes are cases in point; in both, the melanin is extracted from the basal layer, phagocyted by chromatophores, and carried away to regional lymph nodes. Vitiliginous patches occur in patients with tinea versicolor partly because the areas affected by the fungus prevent absorption of ultraviolet irradiation and partly because the fungus itself actively causes a degree of depigmentation.

Diseases of Appendages

Limitations of space permit no more than the briefest mention of the nonneoplastic diseases of the cutaneous appendages. The disorders of the *sweat glands* include hyperhidrosis, congenital or acquired hypohidrosis, miliaria (prickly heat, tropical or thermogenic hypohidrosis with keratotic or inflammatory plugging of the sweat ducts), bromhidrosis (fetid sweat), chromhidrosis (colored sweat), hidradenitis suppurativa of the apocrine glands, and Fox-Fordyce disease (pruritic papular chronic adenitis of sweat glands of axillae, nipples, pubic, and perineal regions). The diseases of the *sebaceous glands* include varieties of seborrhea, hyposteatosis or diminished secretion, comedones, acne in its several forms,

and rhinophyma. The abnormal conditions of the hair are many. Hypertrichosis, the alopecias of the cicatricial types (pseudopelade, folliculitis decalvans, chronic lupus erythematosus of the scalp) and the noncicatricial types (alopecia areata, ordinary male baldness, fungous infections, etc.), fragile hairs (fragilitas crinium), trichorrhexis nodosa, pili torti (twisted hairs), fungous infections such as piedra and trichomycosis nodosa, and trichostasis spinulosa (multiple lanugo hairs in a single follicle) constitute a few of the problems.

The diseases of the *nails* are of particular interest not only for the involvement of the nails themselves but for the accessory information they reflect on disorders elsewhere. *Beau's lines* are transverse furrows in the nail which date periods of severe acute illnesses or of inflammations near the nail fold leading to the arrest of function of the matrix. The discoloration and the thickening of the nail due to psoriasis, eczema, or fungi, the spoon nails (*koilonychia*) associated with trauma, eczema, and the Plummer-Vinson syndromes, the brittleness (onychorrhexis) following the use of certain chemicals or vitamin A deficiency, the loss of nails (onycholysis) after trauma or systemic disorders such as hypothyroidism, and the whitening of nails (leukonychia) denote systemic disease or obscure interference with nail growth. These and many other changes affect the nails.

Panniculitis

There are several diseases of the subcutaneous fat which simulate each other closely histologically but have different prognostic and etiological implications. These diseases are (1) erythema induratum (Bazin's disease), (2) nodular, nonsuppurative, febrile, relapsing panniculitis (Parkes Weber-Christian disease), (3) erythema nodosum, (4) nodular vasculitis, and (5) erythema pernio (chilblains). *Erythema induratum* appears as chronic recurring, often ulcerated, bluish-red nodosities of the calves of the legs particularly. The lesions are generally found in patients with frank tuberculosis elsewhere. Histologically, tubercles, as a rule of an incomplete or atypical variety, are found in the subcutaneous fat. Caseation may or may not be present. Fat necrosis, and fat atrophy associated with nonspecific inflammation of the fibrous septa, fat, and lower dermis are present. Endarterial and endophlebitic inflammation and proliferation are seen commonly. Tubercle bacilli are rarely found in these lesions although positive results have been reported from guinea pig inoculation of the tissue. *Nodular, nonsuppurative, relapsing, febrile panniculitis (Parkes Weber-Christian disease)* is observed preponderantly in women and is characterized by bluish discoloration of the skin over firm subcutaneous nodules on the extremities and trunk, usually associated with otherwise unexplained fever. Isolated cases have responded to chemotherapy (sulfapyridine and penicillin). Fatalities have occurred in several cases, but autopsy findings were not especially enlightening. In sections of what are regarded as typical cases, the fat itself is infiltrated chiefly with lymphocytes and histiocytes but the septa are relatively spared. So-called "wücher" atrophy of fat (replacement of atrophied fat by fat-laden histiocytes), foreign body giant cell reaction, and endophlebitis and endarteritis are also present. However, the septa, although relatively spared, are often infiltrated and edematous; therefore, the involvement of the septa cannot be used as a criterion for excluding the possibility of Parkes Weber-Christian disease, although, if they are free the evidence is considerable that the panniculitis belongs to this category. *Erythema nodosum* occurs clinically as tender, pale red to livid blue nodules, principally on the anterior aspect of the lower extremities. These lesions, unlike those of erythema induratum, do not ulcerate, and are transient, lasting for several weeks on an average, and are not necessarily associated with a tuberculous process elsewhere. The disease may be one manifestation of a variety of unrelated infections, including coccidioidomycosis, leprosy, syphilis, virus diseases (e.g., measles, "cat-scratch fever"), and ringworm, or may follow lymphomas, the ingestion of drugs, or the administration of a vaccine. The histologic picture is much like that of erythema induratum with the addition that there is a greater tendency in erythema nodosum for nonspecific inflammation of the middle and lower dermis, which is practically spared in erythema induratum. *Nodular vasculitis* occurs chiefly in older women and refers to the often recurrent nodosities which are more painful, of shorter duration, and have less tendency to ulcerate than the lesions of erythema induratum. The histologic picture is that of Bazin's disease. *Erythema pernio* occurs usually on the hands and feet as tender, red, pruritic macules provoked by cold. The histologic picture may also closely simulate that of erythema induratum, as may the lesions produced in response to cold allergy.

Xanthoses

The xanthoses of the skin include (1) xanthelasma, (2) juvenile xanthoma, (3) xanthoma tuberosum multiplex, (4) xanthoma disseminatum, (5) xanthoma diabeticorum, (6) lipoid proteinosis (Urbach), and (7) necrobiosis lipoidica diabeticorum (the latter two diseases discussed under diseases of collagen). Although many of these lesions are often classified with neoplasms, their usually obvious relationship to disordered fat metabolism would favor their inclusion among the dermatoses. The differentiation of the various xanthoses is important from the prognostic and therapeutic viewpoints, although, in many instances, the histology alone does not permit distinctions.

Xanthelasma appears as soft, yellow ovoid papules or plaques near the inner canthus of the eyelids in middle-aged persons who usually show an elevation of blood lipids, especially cholesterol. These lesions may be found alone or in association with other xanthoses. The histologic picture consists of poorly delimited nests of fat-laden histiocytes in the upper dermis with sparse inflammatory reaction (Fig. 1006). Touton giant cells, composed of a lipid cytoplasm rimmed by nuclei, are rare in these lesions. The *juvenile xanthomas* may be present at birth or in early childhood and tend to be familial. Except for these fea-

Fig. 1006.

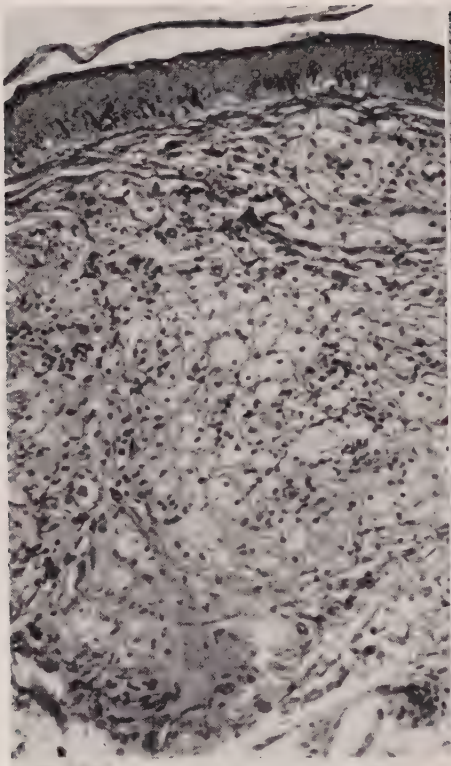
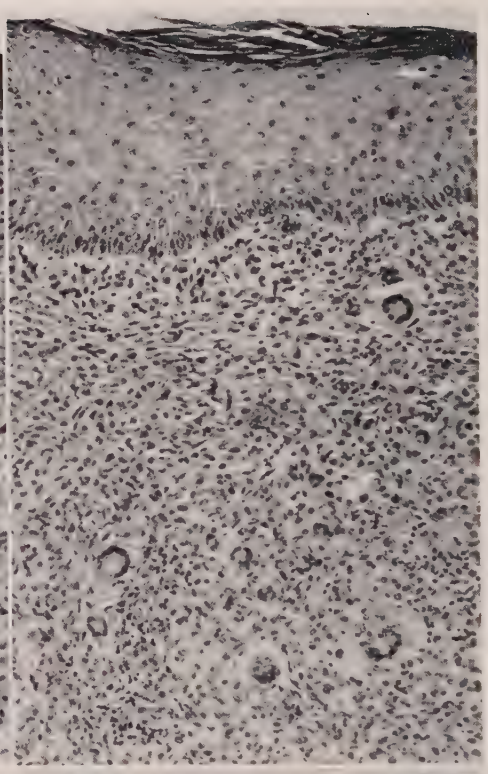


Fig. 1007.



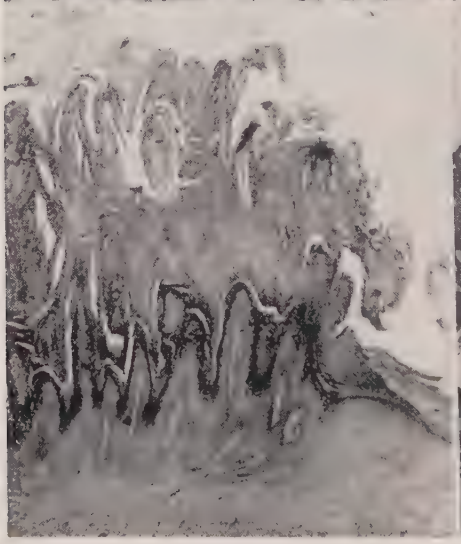


Fig. 1008.

Fig. 1009.

Fig. 1006.—*Xanthelasma* of eyelid with lipid-filled histiocytes.

Fig. 1007.—*Xanthoma tuberosum* with numerous lipid histiocytes, some of which are congregated as Touton giant cells.

Fig. 1008.—*Verruca vulgaris.*

Fig. 1009.—*Verruca pigmentosum* (seborrheic keratosis).

tures, the lesions are like those of *xanthoma tuberosum* or *xanthoma disseminatum. Xanthoma tuberosum multiplex,* which is the commonest of these diseases, appears as light yellow to brown papules and plaques. They are grouped particularly on the extensor surface of the extremities about the elbows, knees, and hips but may occur also on the palms and soles and even on the face. Tendon sheaths are frequently involved. The lesions develop slowly and tend to remain stationary for many years. Hypercholesterolemia is usually present, and the disease may be associated with fatty deposits in strategic visceral locations, of particular importance being the atherosclerotic plaques of coronary arteries. The lesions of *xanthoma disseminatum* tend to occur on the flexor surfaces of the extremities and are generally smaller and more uniform than those of xanthoma tuberosum. Xanthoma disseminatum may involve the mucous membranes of the pharynx and larynx. The values of cholesterol and cholesterol esters are not increased in this disease. Involvement of the pituitary gland and associated diabetes insipidus have been reported, yet there is stated to be no other evidence of Hand-Schüller-Christian disease in this condition. The histologic picture of the juvenile xanthoma, xanthoma tuberosum multiplex, and xanthoma disseminatum is essentially similar and consists of a nodular compact mass of fat-laden histiocytes with scattered Touton giant cells. The lesions of *xanthoma diabeticorum* appear as small, yellow to brown, discrete or confluent papules resembling those of xanthoma disseminatum but located predominantly on the extensor rather than flexor aspects of the extremities, and on the palms and soles. Other distinctive features include the suddenness of involution and evolution of the lesions, the marked pruritis, and the association with diabetes mellitus and marked lipemia, both usually of a severe degree. The lesions tend to respond to the therapy for diabetes mellitus. The histologic changes simulate those of xanthoma tuberosum except for the occurrence also of extracellular lipids, particularly following therapy (Fig. 1007). Although blood cholesterol levels as high as 1,300 mg. per cent have been reported in cases of xanthomatosis,[94] it is now coming to be appreciated that factors other than hyperlipemia are concerned with the deposition of fat in blood vessels as well as skin. These factors include the size of fat molecules, and the ratio of the concentrations of the various lipids to each other with consequent abnormality of emulsifying conditions.[92, 93] It is noteworthy that cases of sudden cardiac death have occurred in children with xanthoma tuberosum in association with marked coronary atherosclerosis.[95] The concept that cutaneous xanthomas may be associated with obstructive lipid deposits in biliary ducts cannot be substantiated. Cutaneous xanthomas occur in prolonged biliary cirrhosis of whatever cause because of the concomitant hypercholesterolemia.

NEOPLASMS OF THE SKIN

The deceptive simulation existing among neoplasms of the skin—a simulation that may jeopardize the prognosis for the patient—makes it more important than it is perhaps generally realized that the pathologist acquire a broad, firsthand knowledge of the histologic vagaries of these tumors. A discussion of some of the major principles and pitfalls of their microscopic analysis may serve in some measure as a diagnostic guide.

The following outline is based on the segregation of cutaneous neoplasms with respect to their location and/or histogenesis from epidermis, dermis proper, and appendages. In the ensuing discussion, several of the lesions are taken out of the order of the outline, for purposes of clarity of presentation.

Classification of Cutaneous Neoplasms

I. EPIDERMIS:

A. BENIGN:
1. Verruca (including vulgaris, digitata, filiformis, plantaris, juvenilis).
2. Verruca pigmentosum (seborrheic keratosis).
3. Condyloma acuminatum.

B. PRECANCEROUS:
1. Senile keratosis.
2. Leukoplakia.
3. Kraurosis vulvae.
4. Xeroderma pigmentosum.
5. Junctional nevus.
6. Bowen's disease.
7. Queyrat's erythroplasia.

C. MALIGNANT:
1. Basal cell carcinoma.
2. Squamous cell carcinoma.
3. Melanocarcinoma (melanoma).
4. Paget's disease.

II. DERMIS:

A. NEVUS:
1. Intradermal nevus (common mole).
2. Juvenile melanoma.
3. Compound nevus.
4. Blue nevus (Jadassohn-Tièche).

B. TUMORS OF VESSELS:
1. Lymphangioma.
2. Hemangioma.
3. Angiokeratoma.
4. Glomus tumor.
5. Hemangiopericytoma.
6. Kaposi's sarcoma.
7. Postmastectomy lymphangiosarcoma.
8. Sclerosing hemangioma (dermatofibroma lenticulare).
9. Dermatofibrosarcoma protuberans.

C. FIBROMA AND FIBROSARCOMA.

D. NEUROFIBROMA AND NEUROFIBROSARCOMA.

E. TUMORS OF MUSCLE:
1. Leiomyoma (arrectores pilorum).
2. Angiomyoma.
3. Myoblastoma.

F. OSTEOMA.

G. LYMPHOMAS AND ALLIED DISEASES.

H. METASTATIC NEOPLASMS.

III. APPENDAGES:

A. Sweat Glands:
1. Adenoma:
(a) Cystic.
(b) Solid.
2. Carcinoma.

B. Sebaceous Glands:
1. Adenoma.
2. Carcinoma.

C. Hairs:
1. Brooke tumor—trichoepithelioma or epithelioma adenoides cysticum.

D. Miscellaneous Cysts:
1. Dermoid.
2. Epidermoid.
3. Sebaceous.
4. Calcifying epithelioma.

Verruca (Wart)

The verrucae or warts represent thickenings or projections of epidermis to which are traditionally, if inconsistently, applied one of several adjectives in accordance with the shape, location, or other clinical feature of the lesion. For example, there are verruca vulgaris, verruca plantaris, verruca digitata, verruca filiformis and verruca plana juvenilis and verruca senilis.

The *verruca vulgaris* is the papillary wart common in children and found especially on fingers, palms, and forearms. They occur singly or in groups. There is some question as to whether or not these tumors merit inclusion under "neoplasms" inasmuch as they may disappear spontaneously or, as in some reported cases, under psychotherapy including placebos.[37] The possibility that these lesions are due to viruses is still strongly considered and fortified by evidence from electron microscopy of virus particles.[36] Histologically, the verruca vulgaris is characterized by a papillary acanthosis surmounted by friable keratotic material. The cells of the stratum granulosum are often acidophilic and vacuolated (Fig. 1008). A loose infiltration of various mononuclear cells may be present in the papillae. Carcinomatous transformation of these lesions is rare although occasionally a verrucal form of senile keratosis, or a squamous cell carcinoma with a prominent papillary hyperkeratotic surface is erroneously regarded as having arisen from a verruca vulgaris. The *verruca digitata* occurs chiefly on the scalp, face, and neck. It is distinguished from verruca vulgaris principally because the digitated lesion is made up of long fronds which may be separated down to the base of the lesion. *Verruca filiformis,* which occurs chiefly on the eyelid, is merely a single slender projection of skin, composed of a core of connective tissue representing the elongated dermal papilla covered by epidermis showing little acanthosis and hyperkeratosis. In this respect, these verrucae differ from the verruca vulgaris. The *verruca plantaris* clinically simulates a callosity of the sole of the foot. The two are distinguished by the observance in the plantar wart of the soft papillary verrucal acanthosis after the hyperkeratotic portion has been removed; in the callus, stripping of the horny material leaves the flat epidermis. The *verruca plana juvenilis* is generally a smooth relatively flat wart that is prone to occur on the dorsum of the hands of adolescents. It may closely simulate the lesions of epidermodysplasia verruciformis, although the latter differ in their distribution and in their occurrence in an older age group. Histologically, the verruca plana is characterized by acanthosis and hyperkeratosis; the acanthosis is relatively greater than in the callosity. Without knowledge of the clinical picture, verruca plana may be confused microscopically with various keratodermas although the vacuolization of the cells of the stratum granulosum may be of differential help. The "hard nevus of Unna" is essentially a verruca plana. *Acrokeratosis verruciformis* is the name applied to other verrucal lesions, hereditary in character and occurring symmetrically on the hands and feet. These lesions histologically tend to lack the loose basket-weave appearance present in the upper layers of the warts of epidermodysplasia verruciformis.

The *verruca senilis* is labeled, also, seborrheic keratosis or *pigmented papilloma.* These first two names are not well chosen for the reason that the lesions often appear in young people and acanthosis is the feature of note. Seborrheic keratosis is used by the dermatologists and emphasizes the greasy feeling to the touch imparted by the abundant fatty keratinous nests within the lesion. If the term verruca is to be retained, then perhaps *verruca pigmentosum* might be more representative. These lesions occur particularly on the trunk and forehead, are usually dark brown, elevated, and sharply delimited. The histologic picture is that of abruptly thickened epidermis which encloses nests of laminated keratin resulting from focal, irregular maturation of epidermis partially inverted within the core of the lesion. In places the central pearls are incompletely developed and present large mature squamous cells without the keratinous nests. The surrounding cells are usually focally pigmented with fine brown granules of melanin and superficially resemble basal cells. However, close examination often reveals residual intercellular bridges that help identify them as squamous cells notwithstanding statements to the contrary. Many of these *epithelial cells are dopa positive.* Rare cases of malignant transformation of the verruca pigmentosa have been recorded.[115a] A lesion that has many of the cellular characteristics of the verruca pigmentosa is the so-called "inverted papilloma" which grows downward rather than outward from the epidermal surface. The "inverted papilloma" is often associated with an inflammatory reaction of mononuclear cells at its base, very much as are the senile keratoses (Fig. 1009). Condyloma acuminatum has a histologic structure essentially similar to that of the verruca vulgaris, with perhaps a greater acanthosis than the latter. It differs from the latter in the marked therapeutic response of the condylomas to the resins of podophyllin in contrast to the verruca vulgaris.

Precancerous Lesions

The precancerous lesions of the skin include senile keratosis, Bowen's disease, kraurosis vulvae,

Queyrat's erythroplasia, and the active junctional nevus. Each of these entities is characterized by atypia or "dyskeratosis" of cells which, however, is confined to the limits of the epidermis. To such lesions the term "carcinoma in situ" is often applied. "Precancerous" as applied to these lesions connotes, in a crude measure, the relatively high degree of probability with which they are liable to undergo malignant degeneration rather than the inevitability of such a complication. For example, it has been estimated roughly that approximately 20 per cent of lesions of Bowen's disease become invasive cancer. There is no histologic method of determining with certainty which one of a given series of five such lesions is destined to undergo cancerous change. Fortunately, only a small percentage of junctional nevi become melanocarcinomas (see page 1167).

Experimentally, changes in the equilibrium of the chemical constitution of the epidermis are produced by the application of carcinogens such as methylcholanthrene. The changes include decrease in calcium, zinc, and biotin, decreased nuclear viscosity, increase in thymonucleic acids, alterations in alkaline phosphatase, in the cholesterol-protein ratio, and in the number of dermal mast cells among others.[102, 103] It is of interest that basal cells and basal cell carcinomas do not contain arginase which is present in prickle cells and squamous cell carcinomas.[104] These changes, which may be detected through the study of isolated strips of epidermis by fluorescent microscopy, spectroscopy, microincineration, and ultracentrifugalization, presage the onset of invasive cancer. It is to be expected that such methods will be applied to the human cancerous counterparts in an effort not only to learn if similar changes occur but possibly in the hope eventually to alter the chemical equilibrium and so to prevent further extension of the process. Furthermore, such analysis of the junction nevi, for example, might provide profitable insight into the extraordinary behavior of this most important precancerous lesion that gives rise to the melanocarcinoma (see page 1165).

Keratoses.—The *senile keratoses* are irregular brownish patches of epidermis roughened by horny scales, occurring characteristically on the dorsum of the hands of aged people. Histologically similar lesions may follow irradiation, and exposure to arsenic or to the elements of the weather. They may be single or several, or they may occur in great numbers over many parts of the body. Microscopically, they are characterized chiefly by dyskeratosis of the cells of the basal layer and adjacent layers of the rete malpighii. These cells show hyperchromatism, loss of polarity, increased numbers of mitotic figures, and irregularity of size and shape of nuclei. Hyperkeratosis and parakeratosis of varying degrees are responsible for the roughened surface. Inflammatory cells, principally mononuclear, are present in the subepidermal tissue. These cells often encroach onto the epidermis so as to obscure the integrity of the "basement membrane" and occasionally prompt the premature and erroneous impression of infiltrating carcinoma. The cutaneous horn, in most instances, represents a senile keratosis with an accumulation of keratinous material in the form of a projecting spur. The same type of horny projection may be superimposed also on the verrucae. *Leukoplakia* is the lesion of mucous membranes analogous to senile keratosis of the skin. Leukoplakia occurs as grayish-white thickened patches of mucosa frequently observed on the lips, buccal mucosa, and tongue (Fig. 1011). Irritation, such as from smoking and from ill-fitting dentures, is presumably responsible for many of the lesions of the lips and buccal mucosa. Syphilis should be considered a foremost possibility as a cause of leukoplakia of the tongue. Syphilitic leukoplakia is particularly prone to cancerous change. The histologic pictures of leukoplakia are similar to those of senile keratosis. However, inasmuch as a stratum granulosum is normally absent in mucous membranes, the horny covering of leukoplakic lesions is more likely to be parakeratotic than hyperkeratotic.

Kraurosis vulvae is a precancerous lesion of middle age or beyond, characterized by local tenderness and pruritus. The criteria for the distinction between kraurosis and leukoplakia of the vulva are not well defined (see also discussion on page 1098). Kraurosis vulvae may present one of the following forms: (1) atrophic glistening white areas with constriction of the vulval orifice; (2) ulcerations or fissures; (3) epidermal keratoses; or (4) squamous carcinoma. Corresponding to the clinical variations, the microscopic picture may show these features combined or singly, commonly in association with a subepidermal infiltration chiefly of mononuclear cells, as in senile keratosis or leukoplakia. It is likely that in many instances the atrophy represents an early stage in the formation of the hypertrophic keratoses and finally of the carcinomas. On the other hand, carcinomas following directly on the atrophic phase occur in kraurosis vulvae, a phenomenon reminiscent of the carcinoma developing in atrophic patches of xeroderma pigmentosum.

Xeroderma pigmentosum is a precancerous familial disease of the skin usually first manifested early in childhood. It is characterized clinically by areas of atrophy as well as isolated and coalescent scaly patches of keratosis showing varying amounts of pigmentation. Histologically the changes are those of irregular atrophy, acanthosis, and hyperkeratosis, with excessive deposits of melanin in the basal layer and lowermost layers of the stratum spinosum as well as in chromatophores in the upper dermis (Fig. 1010). Xeroderma pigmentosum may be complicated by junctional nevi, basal cell or squamous cell carcinoma, or melanocarcinoma.

Bowen's disease occurs as irregular, scaly, slowly progressive usually brownish patches on the trunk, buttocks, and extremities. Microscopically the principal feature of these lesions is the presence of isolated dyskeratotic cells scattered haphazardly in all layers of the epidermis. These cells often have large, hyperchromatic single or double nuclei surrounded by cytoplasmic halos. Mitotic figures are numerous in these altered cells. Hyperkeratosis or parakeratosis may be marked. The acanthosis is usually uniform, but irregular thickening may be present (Fig. 1012). Similar histologic changes occur in *Queyrat's erythroplasia,* the precancerous lesion occurring principally on the glans penis but also on the vulva and mucous membranes of the mouth. In addition, the acanthotic thickening associated with

Fig. 1010.
Fig. 1012.

Fig. 1011.

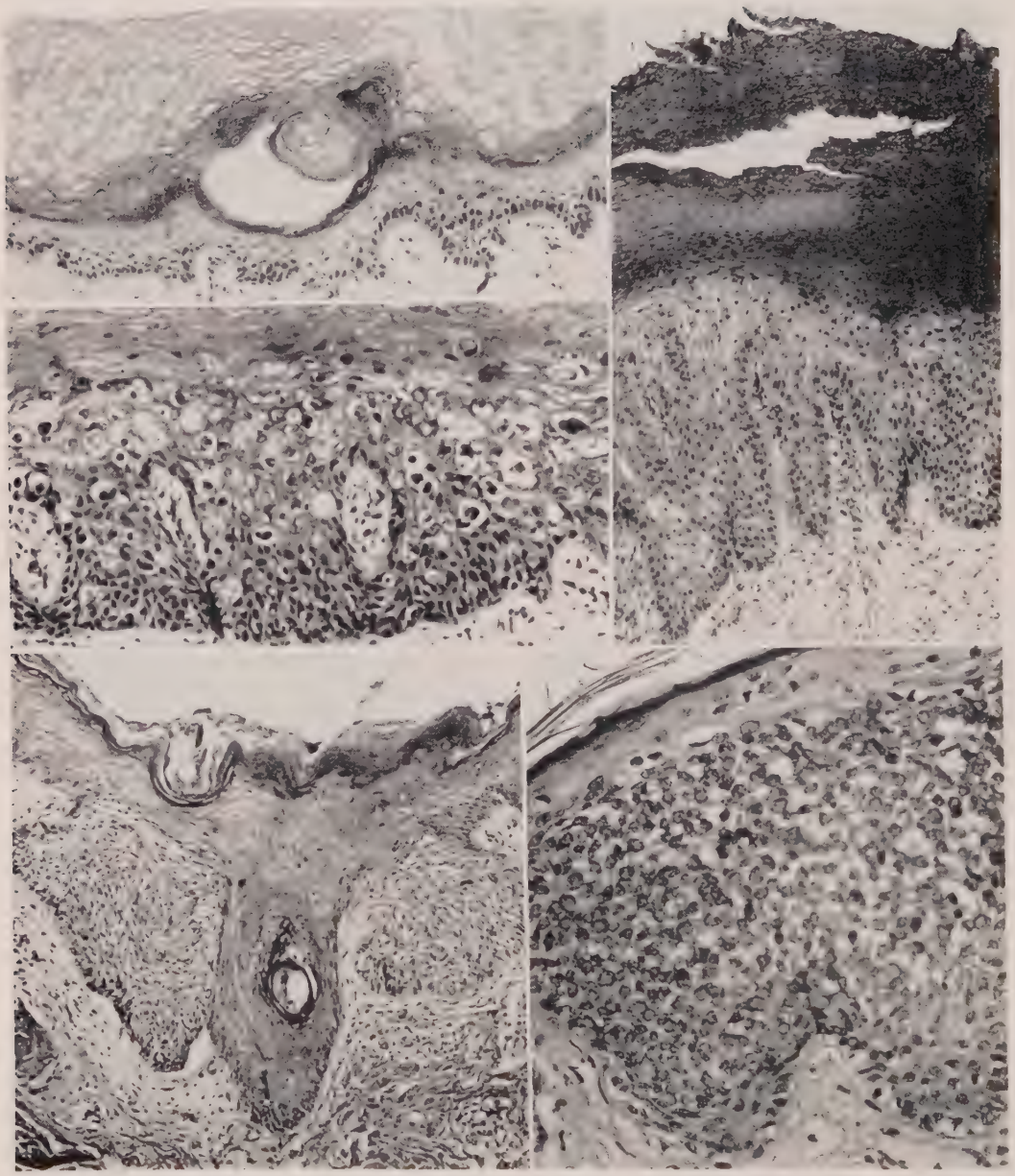


Fig. 1013.

Fig. 1014.

Fig. 1010.—*Xeroderma pigmentosum* showing hyperkeratosis, and epidermal atrophy and pigmentation. (AFIP No. 97125.)

Fig. 1011.—*Leukoplakia* with marked parakeratosis, acanthosis, some basalar atypia, and subepithelial inflammation.

Fig. 1012.—*Bowen's disease* with diffuse cellular atypia.

Fig. 1013.—*Basal cell carcinoma* (superficial epitheliomatosus, multicentric basal cell carcinoma).

Fig. 1014.—*Intraepidermal basal cell carcinoma* (Jadassohn type).

erythroplasia is often characterized by long rete pegs which are psoriasiform or attached to each other in a reticulated pattern. A cytologic pattern similar to that of Bowen's disease and Queyrat's erythroplasia occurs in the nipple and adjacent areas of the female breast in *Paget's disease* (see Fig. 967). However, unlike the precancerous lesions already described, Paget's disease is associated with carcinoma of the underlying mammary ducts and therefore demands treatment by radical mastectomy as for other mammary cancers. Furthermore, the intrammary neoplasm of Paget's disease is a ductal carcinoma of one or other types; the cancer that develops from kraurosis vulvae, leukoplakia, senile keratosis, Bowen's disease, and Queyrat's erythroplasia is of the squamous cell variety. Rarely a basal cell carcinoma complicates senile keratosis. Extramammary Paget's disease is reported fairly frequently, but it has become obvious that included under this diagnosis are melanocarcinomas, Bowen's disease, Queyrat's erythroplasia, and intraepidermal basal cell carcinomas. True extramammary Paget's disease, as defined, with carcinoma arising in underlying sweat ducts, is extremely rare, if, indeed, it occurs at all.

Malignant Lesions of the Epidermis

The malignant lesions of the epidermis include basal cell carcinoma, squamous cell carcinoma, Paget's disease, and, in the opinion of the author, melanocarcinoma.

Basal Cell Carcinoma.—The term "carcinoma" is preferred to "epithelioma" in connection with the basal cell tumors that belong to the general group of rodent ulcers. If left untreated, these neoplasms will progress, erode, and infiltrate neighboring bone and cartilage in a manner that would seem to merit the designation "cancer" notwithstanding the infrequency of metastasis. The term epithelioma might best be reserved for the form of basal cell proliferation that does not show these invasive characteristics; namely, the trichoepithelioma, otherwise known as epithelioma adenoides cysticum or Brooke tumor (page 1182).

It is of interest that although basal cell carcinomas are considered to occur predominantly in people in middle or old age, approximately 1,500 basal cell carcinomas occurring in soldiers were received and examined by us at the Army Institute of Pathology during World War II. In other words, about 1 in every 6 lesions of the skin examined histologically—both inflammations and neoplasms—was a basal cell carcinoma. It is likely that this unexpectedly high incidence is to be explained not necessarily by exposure of the soldiers to unfavorable meteorological conditions, but rather to the fact that a soldier would be more likely to have a small tumor removed and examined by a pathologist than would his fellow civilian in a similar economic status.

The basal cell carcinomas occur predominantly in blond, fair-skinned people, in the region of the face bounded by the hairline, ears, and upper lip. A tumor of the skin of the tip of the nose, however, is more likely to be a squamous carcinoma. Basal cell tumors are not confined to the face but may, in small numbers, occur in the skin of any part of the body, although there is a tendency to desmoplasia in those located away from the face. The basal cell carcinoma begins as a smooth, slightly elevated papule which may be scaly at first but tends soon to ulcerate centrally as the lesion spreads peripherally beneath the epidermis. Characteristically, the ulcer is rimmed by a waxy, smooth, firm, rolled border representing the intact epidermis which is wrapped over but not yet invaded by the underlying and undermining neoplastic nests. If neglected, the tumor may advance to a grotesque erosion of large portions of the soft tissue as well as the cartilage and bone of the face (see Fig. 308, page 425). Early treatment by either irradiation, excision, or by the various other means of local destruction is usually adequate. The advantage of treatment of neoplasms by excision is that it then becomes possible to know by histological examination not only the precise type of tumor present but whether or not the excised tumor is bounded by normal tissue.

Histologically, while there is considerable variability to the pattern of the basal cell carcinomas, there are sufficient characteristics in common as to make them recognizable with relative ease. They are made up of nests of closely packed cells of uniform size and oval shape, with dark nuclei separated by a small amount of spineless cytoplasm. The nests are often rimmed by a single layer of similar cells, arranged, however, in a neat radial pattern and strongly reminiscent of the more or less vertically arranged basal cells forming the lowermost layer of the normal epidermis or of the hair shafts. Mitotic figures are usually fairly common. Such nests may be observed arising not only from the basal portion of the epidermis but also from the corresponding layer of the hair shaft, or from both sources in the same tumor. The presence in these tumors of cells of the same type as those which line both the epidermis and the hair shaft would appear to account for the origin of these neoplasms from either of these structures. This is by no means equivalent to maintaining that embryonic rests of hair matrix, in one or other phase of its development, are the source of basal cell carcinomas. The basal cells of *adult* epidermis do have a limited range of reaction to *carcinogenic* stimulation. One major form such a reaction takes is to produce hair matrixes in the disheveled manner of a basal cell carcinoma, just as in response to *normal* growth stimuli the basal cells produce the orderly components of hair. In other words, when carcinogenic agents such as arsenic or x-irradiation produce basal cell carcinomas, they do so not by activating embryonic rests of hair follicles but by provoking neoplastic change in previously normally situated, *adult* basal cells.

The histology of basal cell carcinomas may vary by the presence of edematous stroma rimmed by neoplastic cells to form the *alveolar or cystic* type; by excessive, dense hyalinized stroma between nests of basal cells to give the *morphea* type; and by the presence of foci of squamous cells or pearls, occasionally calcified, in the centers of nests of basal cells. This last modification has been called *basosquamous cell* (transitional or metatypical cell) *carcinoma.* There is, in addition, the *comedo* type of basal cell carcinoma in which the cores of the masses

of basal cells are necrotic. In terms of prognosis, it has yet to be shown with any degree of credibility that there is any significant difference in these types. This matter is emphasized because of the general belief to the contrary. In particular, it is commonly stated that a basal cell carcinoma with areas of squamous cells represents a tumor with a more precarious prognosis than the ordinary basal cell carcinoma. This concept is based on the assumption that the squamous element of the neoplasm is prone to metastasize. The author's experience does not confirm this impression. It is much more reasonable and in accord with their behavior to regard such areas of squamous cells simply as evidence of maturation of the central portion of the collection of basal cells rather than as an indication of dedifferentiation. On the other hand, it is true that infrequently there is observed in the same histologic field evidence of a true squamous cell carcinoma alongside a basal cell carcinoma. Such a squamous cell carcinoma would, of course, not be expected to behave as innocently as the squamous portions of a basosquamous carcinoma. Occasionally, some spindle cell areas of squamous cell carcinoma superficially resemble basal cell nests and a misinterpretation of this resemblance is in some cases responsible for the notion that basosquamous cell carcinomas have a greater tendency to metastasize than do the pure basal cell cancers. This is not to say that the variations in the histologic pattern of the basal cell lesions have no therapeutic significance at all. If the tumor is to be irradiated, the therapist may be interested to know of the amount and character of the stroma and may want to modify the dosage accordingly. However, in actual practice, competent radiotherapists usually do not feel the need to vary the dosage with the histologic character of the basal cell carcinoma inasmuch as a sufficiently destructive dose is used to take care of such variations.

Superficial epitheliomatosis or multicentric basal cell carcinoma is a special variety of the basal cell tumors. These lesions occur predominantly on the trunk as dry and scaly, or moist and eczematous, slowly enlarging plaques. Histologically, the lesions are small basal cell carcinomas arising from multiple foci in the basal layers of epidermis. The lesion is differentiated from the Jadassohn type of intraepidermal basal cell carcinoma in which the neoplastic cells appear to be growing upward toward the surface from the basal cell layer instead of into the dermis. In these superficial lesions as well as in other cutaneous "carcinomas in situ" arsenic should be suspected as a possible etiological factor. (Figs. 1013-1016.)

Squamous Cell Carcinoma.—The squamous cell carcinoma may occur in the skin of any part of the body but there is a predilection for the exposed areas, particularly the face and hands. Certain sources of chronic irritation definitely predispose to squamous cell carcinoma. These include smoking of pipes, particularly clay pipes; irritation to the scrotum incurred by chimney sweeps; the exposure to arsenic, to tar and to carcinogenic oils which soak the clothes and abdomen of the mule spinner; the constant contact of the abdomen with the small charcoal heaters causing the so-called kangri cancers observed in the Kashmir regions; the exposure of susceptible blond skins to actinic rays and other elements of the weather; the unexplained cancerous irritant that is present in old scars as from burns or osteomyelitis; the vague irritant of syphilitic leukoplakia, and a variety of others. However, in most instances of squamous cell carcinoma, the source of irritation or stimulation is not apparent.

Clinically, the lesion begins as a superficially scaly, slightly indurated area which bleeds, crusts, and resists casual therapy. With growth, the surface becomes ulcerated or hornified and the base indurated. The ulceration may extend to a deforming depth. The sectioned surface is granular, grayish-white, and flecked with yellow. Usually, the limits of the neoplasm may be determined even by gross inspection of the cut surface. Microscopically these carcinomas are characterized by irregular nests of epidermal cells which have infiltrated the dermis for varying depths. The nests of a squamous cell carcinoma may include cells representing any layer of the epidermis from the basal layer to the stratum corneum. In well-differentiated lesions the intercellular spines and the central keratinous nests, or the "epithelial pearls," easily identify the origin of the tumor from squamous epithelium. In highly anaplastic lesions these elements may be altogether lacking. Indeed, the anaplasia may be so extreme in occasional squamous cell carcinomas that they may be almost indistinguishable from spindle cell sarcomas. These spindle cell *carcinomas* almost always follow irradiation and are controlled with difficulty; they are not to be confused with the unimportant, focal areas of spindle cells occurring in many basal cell carcinomas. Another variety characterized by intercellular edema, particularly affecting the central cells of the neoplastic nests which are rimmed by basaloid cells, is occasionally mistaken for sebaceous or sweat gland carcinomas or even adamantinomas.

Often of greater practical importance than determining the precise type of carcinoma is the decision as to whether or not an isolated nest of cells represents actual carcinomatous invasion or is merely an obliquely cut rete peg in an area of *pseudoepitheliomatous hyperplasia.* In some instances the decision may be most difficult to make. However, the cells of a peg in hyperplastic epidermis are quite differentiated and tend to resemble very closely the cells of the neighboring, obviously benign pegs and epidermis. The neighboring pegs, elongated, curved, yet attached to the epidermis and cut perpendicularly, help to indicate that the isolated nest of cells actually represents an obliquely cut peg rather than cancer. Another problem arises when abundant subepidermal inflammatory cells are present, some of which may have migrated across the "basement membrane" and lower epidermis, thereby obscuring the integrity of or even actually interrupting the "basement membrane." Since disruption of the basement membrane is one of the standard, if unreliable, criteria for provoking at least the suspicion of carcinoma, it becomes of some limited importance to judge, particularly by the

Fig. 1015.

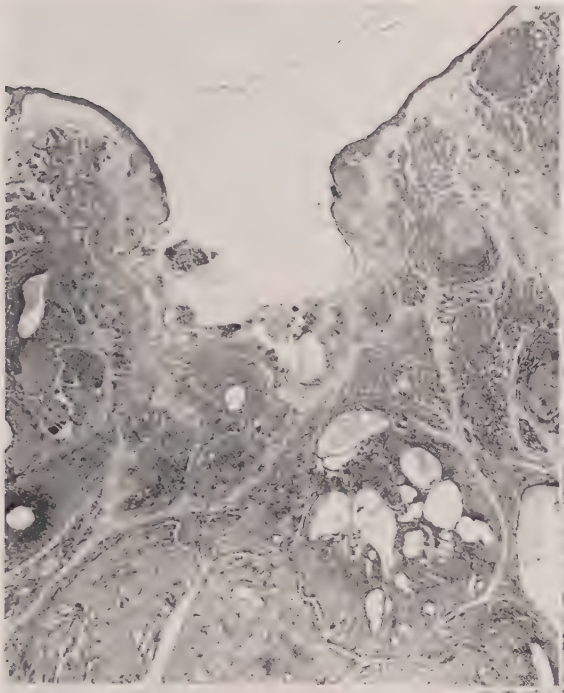
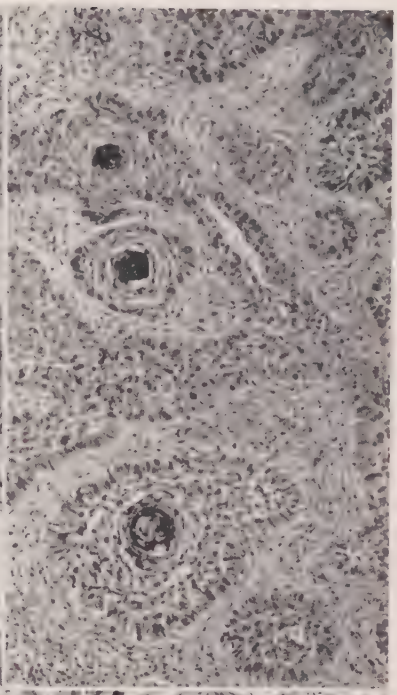


Fig. 1016.



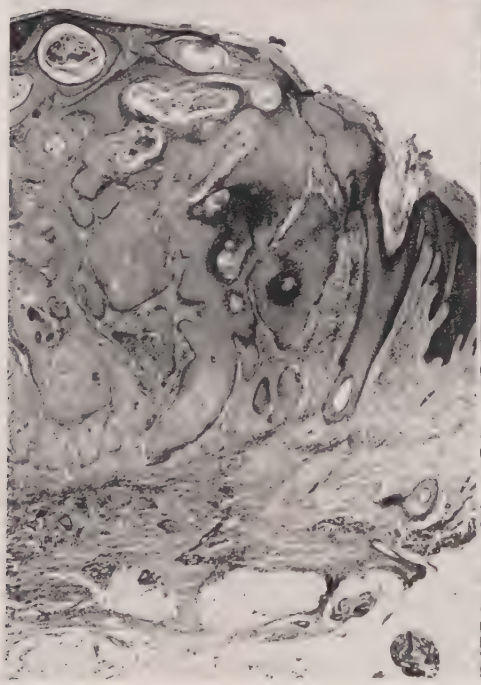


Fig. 1017.

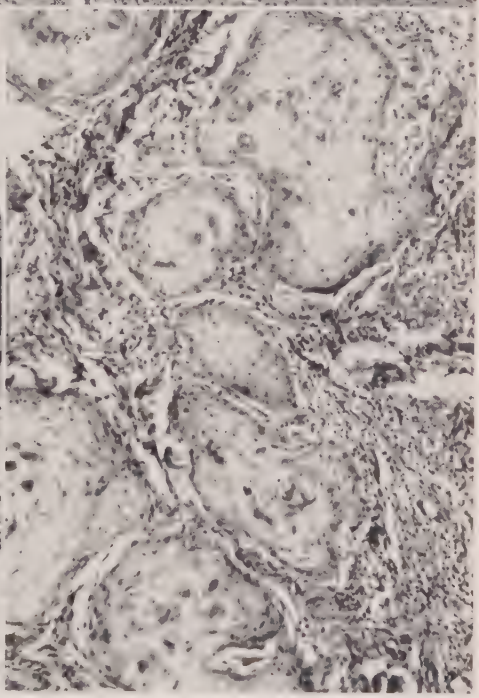


Fig. 1018.

Fig. 1015.—*Basal cell carcinoma* with central ulceration, smooth borders (clinically waxy), and variegated picture of the neoplasm.

Fig. 1016.—*Basal cell carcinoma,* so-called baso-squamous cell carcinoma with central, mature, squamous nests.

Fig. 1017.—*Squamous cell carcinoma.*

Fig. 1018.—*Squamous cell carcinoma.*

Fig. 1019.

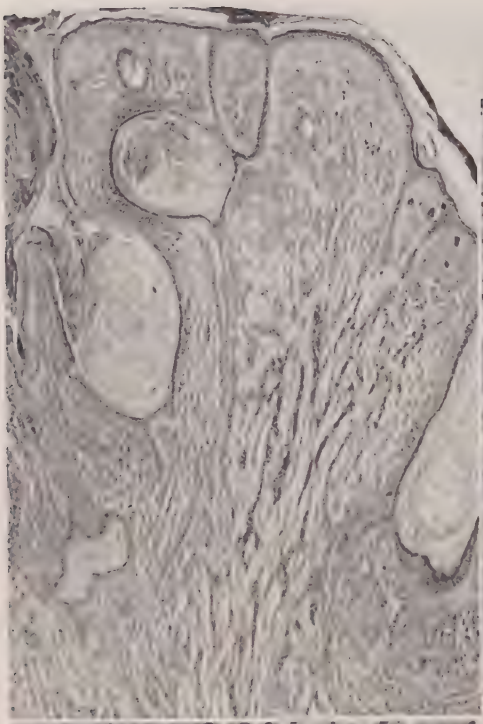
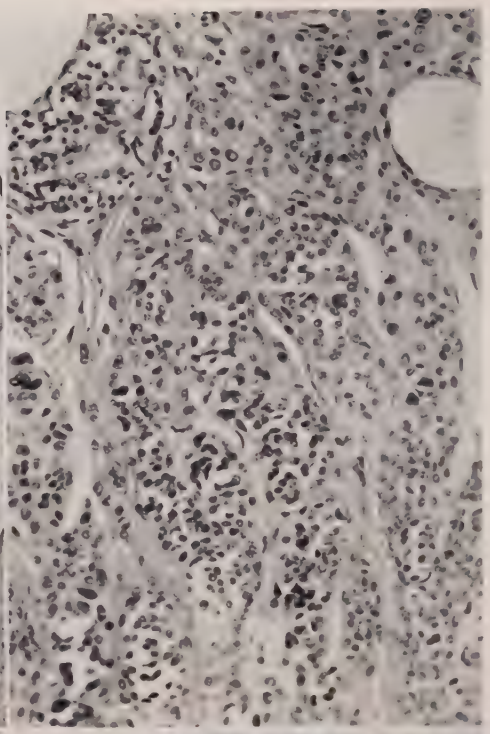


Fig. 1020.



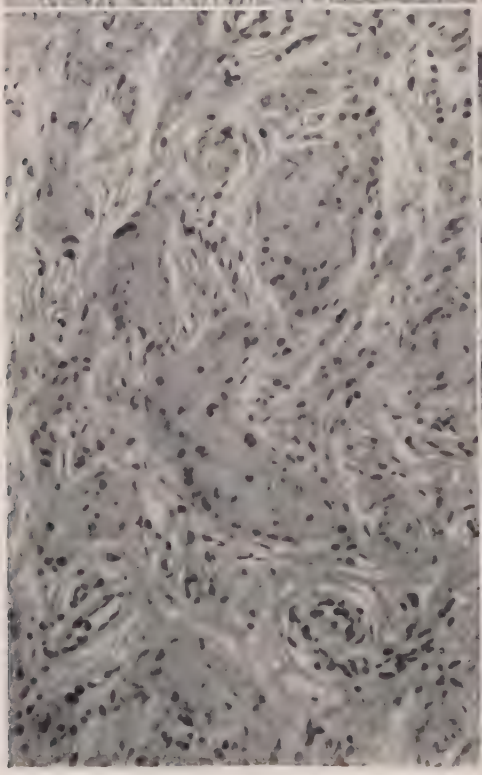
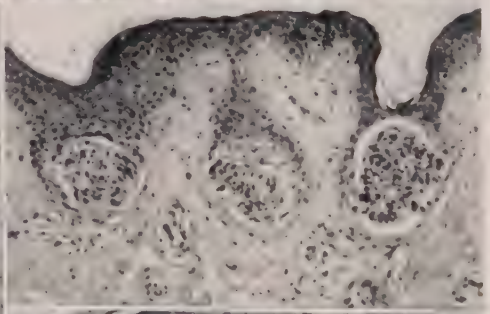


Fig. 1021.



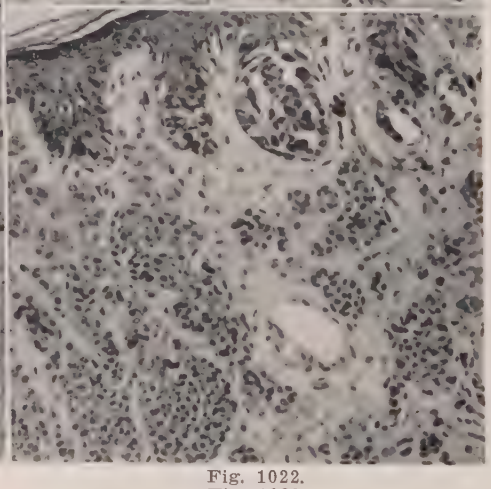


Fig. 1022.
Fig. 1023.

Figs. 1019-1023.—(*For legends see opposite page.*)

anaplasia of the epidermal cells involved, whether or not the disruption is due merely to inflammation or to early cancer. (Figs. 1017, 1018.)

The squamous cell carcinomas of the skin are, as a rule, not as anaplastic as the corresponding lesions of mucous membranes such as lip, or cervix of the uterus. Accordingly, metastases are considerably more common following squamous cell carcinoma of the mucous membranes than of the skin. While this difference is the rule, there are conspicuous exceptions. One of the most anaplastic squamous cell carcinomas of our experience occurred in a scar following a burn of the skin of the leg; the tumor metastasized widely to the viscera.

Pigmented Nevi.—The term *nevus* is used by dermatologists to refer to any congenital blemish. Therefore, they refer not only to pigmented nevi but also to vascular nevi, sebaceous gland nevi, sweat gland nevi, and others. However, to the general pathologist and to those who are not dermatologists, "nevus" denotes a neoplasm derived from pigmented or, at least, dopa-positive cells. These nevi include:

1. The junctional nevus (dermo-epidermal or marginal). (Fig. 1022.)
2. The intradermal nevus (common mole). (Figs. 1019-1021.)
3. The compound nevus. (Fig. 1023.)
4. The juvenile melanoma. (Fig. 1026.)
5. The blue nevus (Jadassohn-Tièche). (Figs. 1024 and 1025.)

Junctional Nevus.—The junctional nevus, also known as dermo-epidermal or marginal nevus, should be of the utmost concern because it is a direct forerunner of the melanocarcinoma.[115] The uncomplicated junctional nevus occurs as a flat, smooth, generally hairless, light- to dark-brown mole. The lesions may be single or multiple. Their smooth appearance may be altered by their combination with an underlying intradermal nevus (compound). *Unfortunately, it is not always possible to recognize them clinically.* However, it may be assumed that pigmented moles on the ventral surface of the hands and feet, and on the genitalia are junctional nevi or, at least, have a junctional component in the form of a compound nevus. Histologically the junctional nevus is easily recognized by the clusters of enlarged, rounded, loosened cells of the basal and adjacent prickle cells of the epidermis. In addition, these cells lose their prickles and cohesion with neighboring cells and many become powdered with fine granules of melanin. If mitotic figures are present and the nuclei show any noteworthy anaplasia, the lesion may be assumed to have been on the verge of melanocarcinomatous transformation. The process may be diffuse along a strip of epidermis or it may be focal, with normal or skipped areas of epidermis intervening between involved portions. In the latter case, judgment as to the adequacy of normal margin bordering the lesion must be made with caution inasmuch as the section may be removed through one of intervening, unaltered areas (Fig. 1022).

It is generally believed that the cells of the junctional nevus are derived from specialized nerve endings intercalated in the basal layer as clear cells. These cells are regarded by most observers as similar to or identical with Merkel-Ranvier corpuscles. However, it seems that such a restricted view disregards the occurrence of cells of the junctional nevus (many dopa-positive) not only in a continuous row in the basal layer, but also as isolated cells high in the prickle cell layers, the stratum granulosum, and even well into the stratum corneum. This phenomenon is believed to occur not by proliferation of neurogenic cells within the epidermis, many have felt, but by the alteration in situ of the pre-existing epidermal cells, as a few formerly thought.[111, 112] For one thing, this is indicated by the absence of increased thickness of the epidermis in most of the ephelides. Moreover, as stated, a *continuous* row of basal, dopa-positive melanoblasts occurs not only normally in dark-skinned people but also after irradiation, in Addison's disease, in acanthosis nigricans, etc. Surely the enzyme concerned—dopa-oxidase or tyrosinase—does not diffuse horizontally exclusively throughout the basal layer from the isolated, supposedly neurogenic clear cells, rather than at least partially upward through the epidermis. In addition, as further evidence against the neurogenesis of epidermal melanoblasts, it has long ago been clearly shown[118] that their dendrites, which to many seem automatically to connote neurogenesis, may be entirely absent in many of these cells. It is anticipated that this observation will be circumvented by the ever-handy tenuous hypothesis that such melanoblasts must be in an embryonic predendritic phase of development. Finally, unlike truly neurogenic dendritic cells of neurons, which are attached to axone fibers for the transmission of impulses, or, for that matter, unlike true cutaneous nerve endings such as Meissner's or Pacinian corpuscles, such fibers are found rarely, if unequivocally ever, leading to or from dendritic melanoblasts; on the other hand, the axone fibers of neurons of Meissner's or Pacinian corpuscles are demonstrable with relative ease and constancy by silver preparations. Actually, when the dendrites of melanoblasts are seen with silver stains, they are made evident *not because of an intrinsic argyrophilia* possessed by cells of neurons, *but because of the argyrophilia of the contained granules of melanin.* It is, of course, a brilliantly established fact that the pigment of skin, hair, and feathers may be controlled by the transposition of the embryonic cells of the neural crest. That neural *control* of many varieties of pigmentation exists is obvious. However, to conclude from this that the cells of the neural crest are incorporated in the epidermis as melanoblasts is to fail to distinguish the artist from his pigments.

Fig. 1019.—*Intradermal nevus.* (From Cancer 2: 28, 1949.)

Fig. 1020.—*Intradermal nevus.*

Fig. 1021.—*So-called "lâmes foliacées,"* which are really no more than foci of collagenization about nevus cells. These become more prominent with increasing age and are practically absent in children. (From Cancer 2: 28, 1949.)

Fig. 1022.—*Junctional nevus.* (From Cancer 2: 28, 1949.)

Fig. 1023.—*Compound nevus* showing the junctional and intradermal components.

The addition of these facts, supplemented by the evidence from the direct examination of many junctional nevi and melanocarcinomas—a gainful procedure possibly not always adequately utilized by all the observers—indicates that basal cells principally but also prickle cells may become converted to melanoblasts, and that the junctional nevi are derived from these cells. It is of extreme interest that corticotrophin (ACTH) has been reported to have produced junctional nevi[117]; what remains to be done is to discover an agent with a counter-effect, namely, the prevention of the junctional change.

Intradermal Nevus.—The *intradermal nevus*, or common mole, is the ordinary pigmented spot of which few white people are spared altogether. The mole may be flat or raised, with or without hairs, papillary and keratotic. These lesions may be present at birth or may develop in later years. They tend to become more prominent at the time of puberty. Histologically, the tumor is composed of nests and cords of cells with round moderately chromatic nuclei and surrounded by an even, easily seen rim of cytoplasm. Melanin pigment, when present, is usually limited to the superficial cells; similarly, the cells in the upper part of the lesion are more likely to be dopa-positive than the deeper ones.* Mitotic figures are seen rarely in these nevi in adults. Occasionally, hyperchromatism and enlargement of nuclei are simulated by mere agglutination of nevus cells. The nevus cells characteristically trail off into the depths of the dermis without sharp limitation. The overlying epidermis is usually thinned and may be flat or papillary, with or without hyperkeratosis. (Figs. 1019-1021.)

The origin of the cells of the common mole is still unsettled. The possibilities include: (1) the ordinary epidermal cells, (2) specialized "nerve-endings" similar to Merkel-Ranvier corpuscles, and (3) dermal nerves. Those who subscribe to the epidermal origin of the intradermal nevus assume that the altered epidermal cells drop off ("abtropfung") and migrate into the dermis. Those who believe in the neurogenesis of pigmented nevi suggest that the nevus cells arise from dermal nerves, or their sheaths, as well as from the intraepidermal nerve endings.[120] The frequency with which intradermal nevi are associated with loosened nests of epidermal cells that appear about to drop off (junctional changes) makes the epidermal origin of the common mole the likeliest possibility. This frequent association of the junctional change with the intradermal nevus can hardly be fortuitous inasmuch as the change is rarely seen with blue nevi, yet is infrequently absent in the moles of children, normally diminishing in frequency and prominence after puberty. There is impressive histologic basis for the conclusion that the ordinary intradermal mole that is *not* overlain by a junctional nevus rarely if ever becomes malignant.

Compound Nevus.—In about 98 per cent of the intradermal nevi occurring prior to puberty[114] and in about 12 per cent of nevi of adults,[115a] there is an associated junctional change. For lesions with this combination of features the term "compound nevus" is suggested. Clinically, there is no way to be certain as to whether or not an intradermal nevus is compounded with a junctional nevus. This fact emphasizes the importance of histologic examination of all excised nevi. As is indicated in the discussion of melanocarcinomas, the compound nevus has the capacity for undergoing malignant transformation by virtue of its precancerous junctional component.[115a, 115b, 122]

Juvenile Melanoma.—In children, until the age of puberty, the occurrence of metastasizing melanomas is a rarity. This clinical fact has been appreciated for years by a number of observers. Nevertheless, the histologic diagnosis of malignant melanoma in children is still rendered fairly frequently by pathologists and on the basis of such histologic diagnosis, unnecessarily radical surgery continues to be done for such lesions. The situation represents one of several in which there is a disparity between clinical behavior and histologic appearance.[116] There do occur pigmented cutaneous lesions which, although they resemble histologically the malignant melanomas of adults, nevertheless fail to metastasize and therefore should be treated by conservative local excision. To these nevi the name *juvenile melanoma* is applied. The histologic characteristics of the juvenile melanoma were defined for the first time by Sophie Spitz in 1948.[114] It has become reasonably apparent that this much needed definition has served in a most practical way to clarify portions of a gravely confused problem. Briefly the distinguishing features of the juvenile melanomas are those of the compound nevi with the addition of myogenous-appearing, single and multinucleated giant cells with abundant basophilic cytoplasm, often loosely dispersed in an edematous upper cutis. In other words, before puberty the melanocarcinomatous-like cell does not have the cancerous potentiality that it has in adults. In this remarkable phenomenon of the relatively marked immunity of sexually immature individuals to the metastases of cutaneous melanocarcinomas, there must be concealed information of basic importance in the comprehension of the behavior and, perhaps, therapy of the melanomas. It is worth noting that metastases from melanocarcinomas of mothers have been transplanted across the placenta to the viscera of infants and subsequently have caused their death. This fact implies that while the cells of juvenile melanoma are histologically similar to those of the adult melanocarcinoma, they lack the virulence of the latter, perhaps because of hor-

*The dopa-positive cells are melanoblasts (or melanocytes). These cells, both pigmented and nonpigmented—especially the latter—contain an enzyme, thought by some to be a dopa-oxidase, and by others (Figge, initially in 1941[121]), an inhibited tyrosinase, which reacts with dihydroxyphenylalanine (dopa), to produce a black pigment in the dopa-positive nevus cells. Polymorphonuclear leukocytes give a similar reaction. The reaction is done with frozen sections on fresh tissue or tissue fixed for several hours in 5 per cent formalin. The frozen sections are incubated at 37° C. with dopa in solutions buffered at pH 7.4 for about four to five hours. Paraffin sections may be cut from a thin block of tissue after incubation in dopa solution.

Chromatophores are merely phagocytes which engulf and transport melanin. Chromatophores are dopa-negative. A pigmented nevus cell or melanoblast may be dopa-negative because its enzyme has been completely utilized. The cells of a nonpigmented (amelanotic) melanoma may be dopa-positive.

monal blockage. To test this hypothesis one would like to know if transplantation of the cells into adults would alter their virulence. Some information would be gained if we knew even the natural history of a juvenile melanoma after puberty. This information is not easily available because the juvenile melanoma is not recognized clinically with any certainty, and, of course, very few are left only partially excised (Fig. 1026). However, our recent histologic studies[115b] have indicated that approximately 6 per cent of the adult melanocarcinomas arise from pre-existing juvenile melanomas.

The frequency of juvenile melanomas is not known, but they appear to be fairly common lesions; there were 13 cases at Memorial Hospital.[114] As previously stated, many of the juvenile melanomas are histologically indistinguishable from the adult melanocarcinomas. However, with increasing experience it has become possible to detect telltale differences in an appreciable number of cases. This observation has extended the scope of significance of the lesion because occasionally the characteristics of the juvenile melanoma are noted in patients beyond puberty, although rarely over 25 years of age. Such lesions are regularly called malignant because the patient is past puberty, when, in fact, they are quite benign notwithstanding the age of the patient.[115b]

Frequently, it is possible to estimate the approximate ages of individuals from certain histologic features of their nevi. These features include the quality of the junctional changes (often abundant yet qualitatively torpid looking in children), the compact cellularity of the intradermal component of the nevi in children notwithstanding recent contrary statements, the increasing prominence because of collagenization, of the "lames foliacées" of Masson (Fig. 1021) with increasing age and their virtual absence in children,[114] and the elements of the juvenile melanoma as outlined above.[115a, b]

Blue Nevus.—The blue or Jadassohn-Tièche nevus appears as a flat or slightly elevated blue or bluish-black lesion occurring particularly on the trunk and extremities and often mistaken clinically for a malignant melanoma. It is structurally the same as the *Mongolian spot* which is found in the sacral region in the last half of embryonic life or the first year of infancy, disappearing thereafter. Histologically both the Mongolian spot and the blue nevus are composed of interlacing fasciculi of spindle cells with long cytoplasmic processes and oval fibrocytoid nuclei. If the pigment were not present, the histologic picture would be that of a dermal neurofibroma and, indeed, it is likely that the basic morphogenesis of the two is similar. However, many of the cells of the blue nevus and the Mongolian spot are dopa-positive. Abundant melanin pigment may obliterate the details of most of the cells of the blue nevus. In addition, the neoplastic cells are interspersed with numerous pigment-laden chromatophores. Usually the nevus cells lie deep in the dermis, or occasionally they are directly apposed to the epidermis. The color of the nevus is, of course, dependent not only on the amount of pigment present but on the distance of the lesion from the epidermis. Infrequently the blue nevus is combined with the ordinary intradermal nevus (common mole) and with the junctional nevus.

There is a striking cellular variant of the blue nevus which is frequently incorrectly diagnosed as melanosarcoma. This lesion occurs in about 50 per cent of cases in the skin of the buttocks, and the dorsum of the hands or feet. The epidermis is unchanged. The cells of this tumor show no significant anaplasia and mitotic figures are almost always absent. Fused nuclei often simulate the hyperchromasia of activity. One of the features which characterize the lesion is the cross sections of fasciculi surrounded by a clear zone, giving the illusion that the whorls are metastases in lymphatics when they actually represent artifactitious shrinkage and cleavage of the fasciculi (Figs. 1024, 1025).

Blue nevi undergo malignant change with consoling rarity. The author personally has seen only four examples of a malignant blue nevus in which metastasis occurred. While it appears obvious that the diagnosis of sarcomatous transformation of a blue nevus is often made unjustifiably, it is incorrect to assume that such cancers do not occur.[115a, b, c]

Melanocarcinomas.—The melanocarcinoma *(malignant melanoma)* (usually abbreviated melanoma) of the skin ranks with the choriocarcinoma for the inexorably widespread metastases to which it gives rise. We have classified the malignant melanomas as follows[115b]:

1. Melanocarcinomas (from junctional nevus, compound nevus, or juvenile melanoma).
   a. Superficial.
   b. Deep.
2. Malignant blue nevus.

Clinically, the melanoma is preceded usually by a flat, hairless mole, pigmented light to dark brown. When such a mole, which may have appeared the same for years, begins to darken, it probably has already undergone at least local malignant transformation; the added change of ulceration and bleeding indicates an almost hopeless ultimate prognosis. A mole which is hairy, elevated, and papillary is uncommonly the site of cancer although the insurance is by no means absolute, for the histologic reasons to be explained. In some instances, the neoplasm appears to arise de novo, especially on the scrotum, palms, and soles. In these regions, the common (intradermal) mole rarely occurs, but the small, flat, often unnoticed, frecklelike junctional nevus is frequently present. In many instances the benign, deeply pigmented blue nevus is mistaken for a developing malignant melanoma. As stated, metastasizing melanomas are rare prior to the age of puberty, although we have recorded several such cases.[115b] In each of these instances the histologic picture could be distinguished from that of the juvenile melanomas.

Melanocarcinomas in Negroes.—Melanomas are said also to be uncommon in Negroes, a phenomenon which has been considered analogous to the frequency of the melanoma in white or gray horses in contrast to the incidence in darkly pigmented ones. However, the statistics on this matter are not clearly presented, usually for the reason that the ratio of the white to Negro popula-

Fig. 1024.

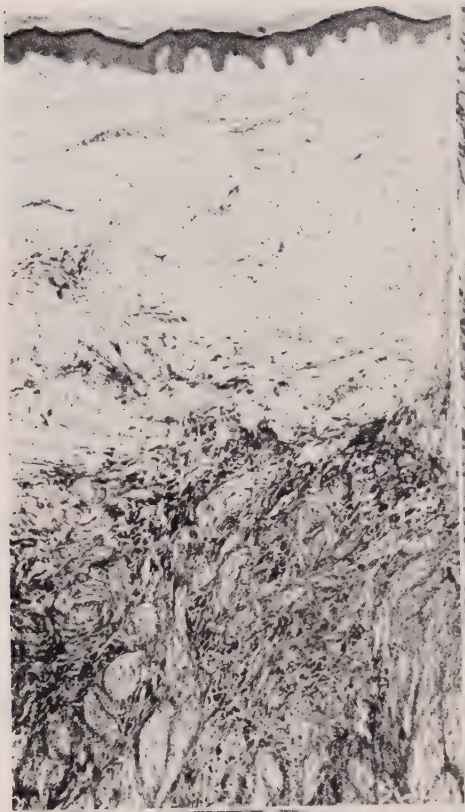
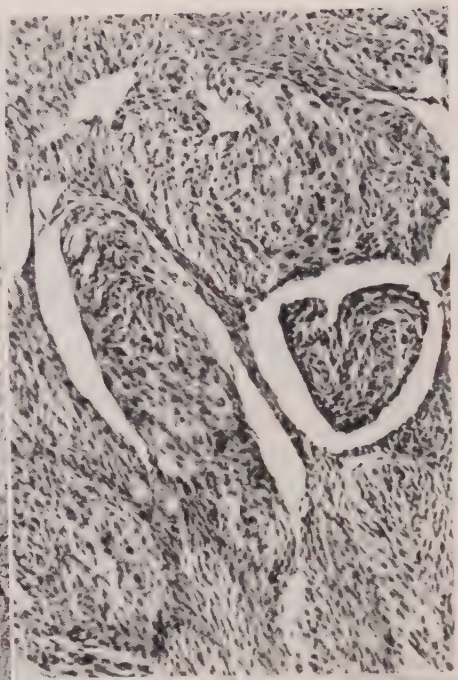


Fig. 1025.



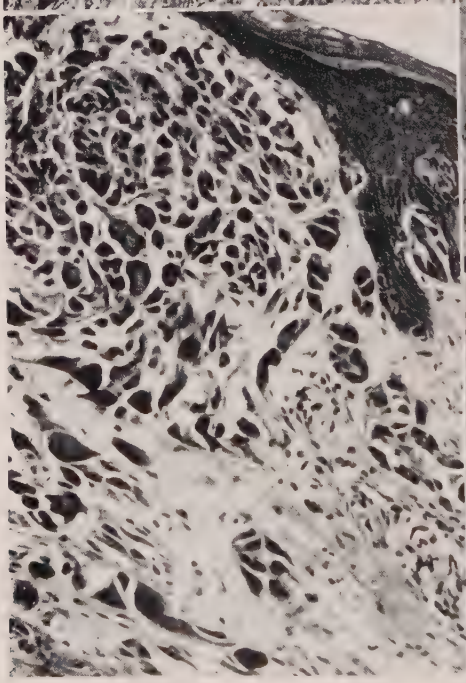


Fig. 1026.

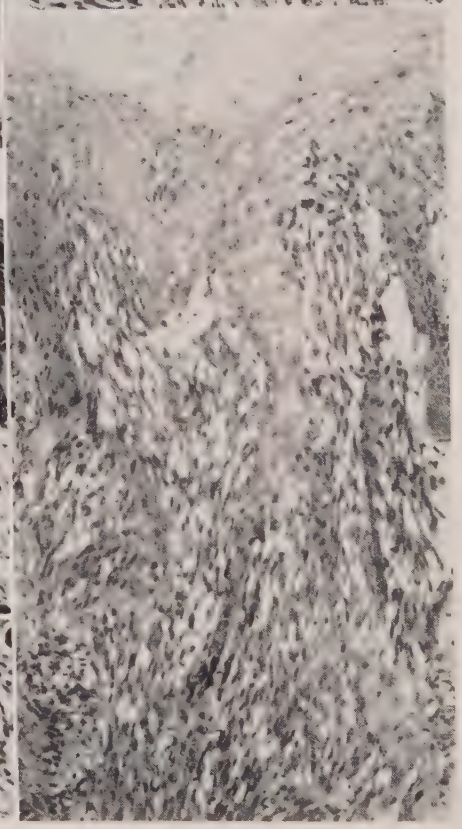


Fig. 1027.

Figs. 1024-1027.—(*For legends see opposite page.*)

tion in the particular institution is not taken into account. In a study in which this ratio was properly considered,[119] the relative incidence in the white group was about four times that of the Negro; in another study, the ratio was even lower.[123] In the South African Negro a high incidence is recorded, although, curiously enough, it is emphasized that the lesions tend to remain localized despite the histologic features of malignancy. This fundamental phase of the problem surely merits further study. A large percentage of the melanomas of the South African native occurs on the feet, a fact which has been attributed to the trauma undergone by the bare feet. Moreover, the chronic irritation of a shoe, belt, or shoulder strap, or the stimulation of an electrocoagulating current used in excisional therapy has been vigorously blamed, and possibly with justification, for the change of a mole into a malignant melanoma. Nevertheless, this impression, too, needs statistical testing.[115b]

Histology and Histogenesis.—There is considerable variation in the cellular pattern of the melanocarcinomas. The primary lesion may simulate a squamous cell carcinoma, a spindle or basal cell carcinoma, an adenocarcinoma, a neurofibrosarcoma, or other neoplasms. The usual melanocarcinoma is composed of cells arranged as compact masses with some cords and alveoli. The cells are likely to be more or less uniform in size and shape. The nuclei of the primary lesion commonly do not exhibit the classical evidence of anaplasia; mitotic figures may not be numerous despite the aggressiveness of the neoplasm. Often, the nuclei are vacuolated and contain large acidophilic nucleoli resembling inclusion bodies. Melanin pigment may be present or absent without prognostic influence. In the neoplastic cells the pigment tends to be of a uniform fine gradularity whereas in the chromatophores the pigment granules are likely to be more irregular in size and shape. One of the most helpful histologic aids in diagnosis is the active junctional change overlying and continuous with the dermal portion of the cancer. With rare exceptions, malignant melanoma is accompanied by this junctional pagetoid loosening of the cells. The cells of the pegs may be so loosened as to be incorporated in the dermal neoplasm with consequent partial dissolution of the pegs. Isolated, spherical, haloed cells, often powdered with fine melanin granules, may be found as far up as the stratum corneum. Such intracpidermal cells represent the junctional change and are considered by the author the source of the melanocarcinoma. These cancerous cells are not related to Langerhans cells or Merkel-Ranvier corpuscles but actually seem to have been, originally, cells derived from various layers of the epidermis. Nor is it true, as some believe, that these cells within the epidermis are metastatic from the underlying tumor within the dermis. Evidence for the autochthonous epidermal origin is found not only in the occurrence of such cells within the epidermis alone in early junctional nevi, or superficial malignant melanomas but in their absence in the epidermis overlying a snugly apposed dermal metastasis of a melanoma (Figs. 1027-1030), a criterion which distinguishes the primary from the metastatic melanocarcinoma.[115a, b, 122]

Approximately 12 per cent of the intradermal nevi of adults are overlain by this curious epidermal dysplasia or junctional change. This generally disregarded combination of the junctional and intradermal nevi (compound nevi) would seem to explain the widely held but apparently erroneous impression that the intradermal nevus cells of the common mole are the ones which give rise to the malignant melanomas. It is our conviction that when a malignant melanoma appears to be superimposed onto a benign intradermal nevus, there was originally present a clinically obvious or latent junctional nevus which itself was the source of the malignant melanoma. Routine studies of the epidermis of the primary melanocarcinomas of skin (and mucous membranes including conjunctiva) demonstrate this junctional change. In other words, the melanoma arising in the skin would actually seem to be a peculiarly virulent variant of an epidermogenic carcinoma, a view originally expressed decades ago by Unna in 1893. Why the malignant melanoma behaves fundamentally differently from other epidermal carcinomas is not yet known. Occasionally it becomes a problem to decide if a given lesion is still in the stage of junctional nevus or whether it has become malignant. The histologic diagnosis of such a *superficial melanocarcinoma* must, in the last analysis, depend on finding evidence of invasion of the dermis by the cells of the active junctional nevus. The presence of merely a single mitotic figure in a junctional nevus of an adult, of pagetoid, spongy cells scattered in different levels of the epidermis, and of even minor degrees of anaplasia should lead to a painstaking search for dermal invasion with the help of multiple sections. Actually, the histologic criteria for the distinction of a superficial melanocarcinoma from an active junctional nevus, on the one hand, and a deep melanocarcinoma on the other, are essentially similar to those used for distinguishing a superficial squamous cell carcinoma from leukoplakia and from a deeply infiltrating carcinoma. Incidentally, the marked degree of pseudoepitheliomatous hyperplasia so commonly associated with melanocarcinomas is largely responsible for mistaking these neoplasms for squamous cell carcinomas. Such epithelial hyperplasia constitutes, in this instance, an

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Fig. 1024.—*Cellular blue nevus.* The epidermis is intact. (From Cancer 2: 28, 1949.)

Fig. 1025.—*Cellular blue nevus.* The appearance of invasion of lymphatics here shown is an illusion characteristic of this lesion and is secondary to artefactual shrinkage. (From Cancer 2: 28, 1949.)

Fig. 1026.—*Juvenile melanoma,* a special form of compound nevus simulating the melanocarcinoma. (From Spitz, Am. J. Path. 24: 591, 1948.)

Fig. 1027.—*Melanocarcinoma,* spindle cell form, showing origin from the epidermis. (From Cancer 2: 28, 1949.)

additional increment of evidence in favor of the epithelial genesis of melanocarcinomas.[115b, 122]

PROGNOSIS.—From an analysis of a personally reviewed, rather large series of cases[115b] it appears that the prognosis of melanocarcinomas, while always serious, is not quite as hopeless as generally believed. The following are factors in the prognosis:[115b]

1. Superficial melanocarcinomas. The survival rate in patients with superficial melanocarcinomas is about 75 per cent as opposed to from 10 to 39 per cent (depending on age and sex) in those with deep melanocarcinomas.

2. Sex. The over-all prognosis is considerably better for women, exclusive of those with melanocarcinomas of mucous membranes.

3. Location. The skin of the head and neck region appears to be the most favorable site.

4. Regional node metastasis. Of course, regional node metastasis is an ominous prognostic

Fig. 1028.

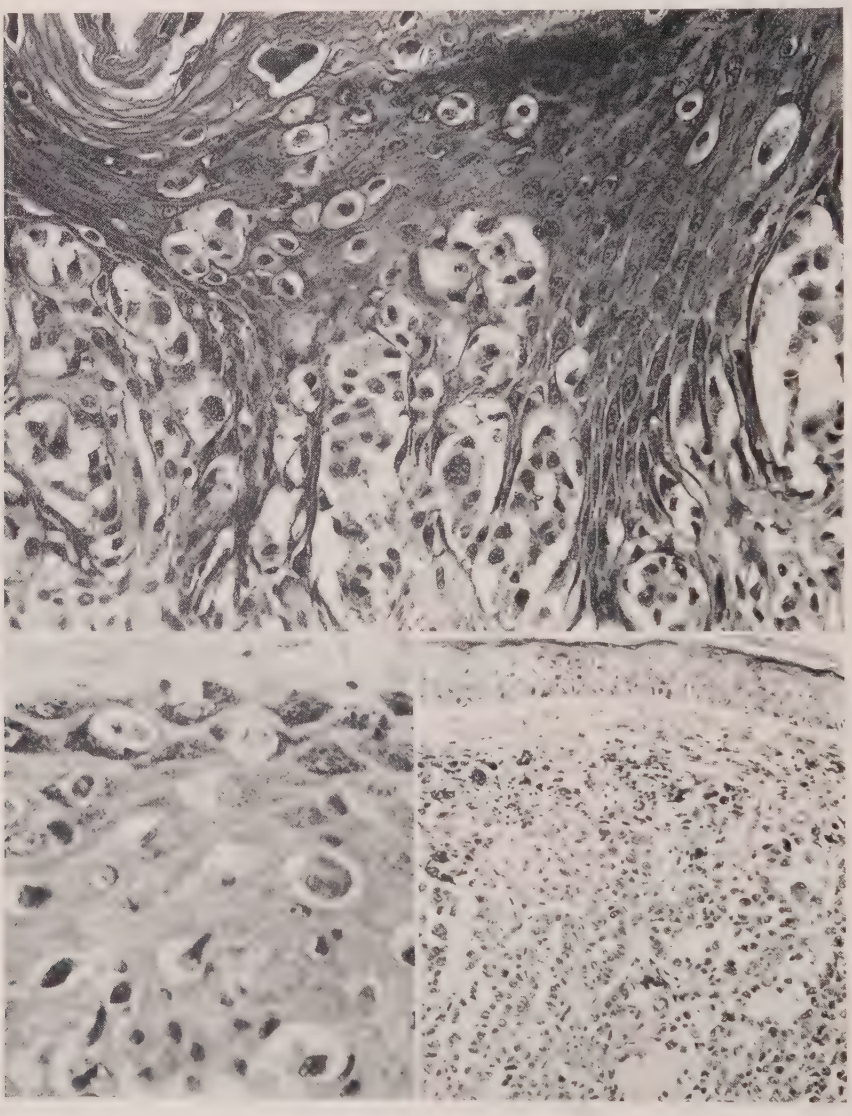


Fig. 1029. Fig. 1030.

Fig. 1028.—*Melanocarcinoma* showing the conversion of epidermal cells into melanocarcinomatous cells. (From Cancer 2: 28, 1949.)

Fig. 1029.—*Melanocarcinoma* illustrating in situ transformation of epidermal into melanocarcinomatous cells. (From Cancer 2: 28, 1949.)

Fig. 1030.—*Metastatic* melanocarcinoma to skin showing the overlying intact epidermis—the criterion for primary versus metastatic melanocarcinoma. (From Cancer 2: 28, 1949.)

portent but such metastasis does not preclude survival.

5. Five-year survivals. Survival of the tumor for five years is not necessarily tantamount to cure. Approximately 13 per cent of patients died of metastases five years or longer after the diagnosis was made or after the initial therapy.

6. Although adequate statistical evidence is lacking, pregnancy is probably a detrimental factor in the activation of junctional nevi or acceleration of growth of melanocarcinomas.

7. Local recurrences are usually the result of either the failure to remove the junctional change at the margins of the tumor or the reactivation of junctional change at or near the margin of excision. Patients with a melanocarcinoma appear to have a systemic diathesis for activation of junctional nevi which in a considerable percentage of cases (3.5 per cent) leads to multiple primary melanocarcinomas.

8. Such histologic features as the content of melanin and the absence of appreciable polymorphism or mitotic figures are not significantly contributory in the evaluation of the prognosis.

9. Prophylaxis. In view of the fact that moles in these locations are generally junctional or compound nevi, it would seem wise, prophylactically, to remove, when feasible, nevi of the soles, palms, and genitalia, preferably prior to puberty; moles in regions chronically irritated, as by straps and belts, should also be included in this category.

10. Melanocarcinomas of the mucous membranes of the oronasopharynx, the larynx, bronchus, esophagus, genitalia, and anorectal region are almost uniformly fatal. Undoubtedly some of the contributory reasons for their grave prognosis is the delay in detection and in accurate histologic diagnosis, the frequent injudicious therapy, the difficulties in adequate operative removal, and possibly such extraneous factors as chronic infection and repeated trauma. In approximately 15 per cent of 337 patients, the tumors arose in these various mucous membranes (exclusive of the conjunctiva). The ulceration of the junctional change and the absence of appreciable amounts of pigment in about 50 per cent of the melanomas of mucous membranes increase the difficulties of histologic diagnosis.

Tumors of Vessels

Lymphangioma.—The number of histologic and clinical variants as well as the difficulty in distinguishing neoplasia of lymphatic vessels from ectasias, anomalies, and proliferations due to stasis has led to the application of needlessly confusing names. The same situation exists with respect to the angiomas, but in both instances it has existed so long that scrapping of terminology at this point would add to the confusion.

The *lymphangioma simplex* is a soft, compressible, grayish-pink nodule. These nodules are often multiple and grouped irregularly. The skin of the genitalia is the common site for these tumors but they are found also on the lips and tongue and may be associated with a macroglossia or macrocheilia. They are composed of varying-sized, endothelium-lined, thin-walled vessels, either empty or containing lymph with occasional leukocytes. Some of the channels may contain a few red blood cells. In a proportion of the tumors there is an abundant proliferation of endothelial cells to which the designation *lymphangioma tuberosum multiplex* or *lymphangioendothelioma* has been applied.

Lymphangioma cutis circumscriptum occurs in the skin of the face, chest, or extremities in the form of a single tumor or multiple, projecting, somewhat papillary verrucose nodules. They may resemble opalescent vesicles and there may be an associated telangiectasis. Histologically they are composed of dilated lymphatic vessels in the upper dermis and are so closely linked to the epidermis as to appear incorporated in it. The overlying epidermis may be irregularly atrophied and acanthotic as well as hyperkeratotic in a papillary manner so as to simulate the angiokeratomas.

The *lymphangioma cavernosum* may be small and circumscribed, or it may extend diffusely over an extensive area, causing macrodactylia, for example. Histologically the lymphatic channels are markedly dilated and may extend into fat and muscle, as do the so-called infiltrating angiomas. The unencapsulated extensions are in neither instance evidence of malignant transformation but do complicate local removal.

The *lymphangioma cysticum colli* or *hygroma* is a congenital lesion which arises usually in the neck and submaxillary regions and is histologically similar to the lymphangioma cavernosum in both structure and extension. The hygroma may ramify widely upward to the parotid area, downward as far as the mediastinum, and inward to lie precariously close to the trachea and adjacent structures. The lymphangioma cysticum may occur also in the region of the sacrum. It may be impossible histologically to differentiate neoplasms or dysontogenetic tumors of lymphatic vessels from the focal, occasionally nodular lymphangiectasis which follows stasis due to scarring of skin or inflammatory reactions within lymph nodes. The differentiation may be dependent on a complete clinical picture. Often there is an associated telangiectasia which may complicate the interpretation, as may the accidental presence of a few red blood cells in the lymphatics. The over-all impression of these tumors of the lymphatic vessels is that they represent ectasias, either congenital or acquired, and are occasionally concomitantly associated with venous dilatation. Certainly the occurrence of multiple benign tumors of lymphatic vessels in an irregular group does not suggest multicentric neoplasia as much as simple ectasias due either to faulty intrinsic development of the vessels or to errors in development of related structures such as lymph nodes, with resultant changes in lymphodynamics. However, the pressure of time-honored usage seems to compel the retention of at least the nomenclature outlined.

Hemangiomas.—The problems of the pathogenesis and terminology of tumors of blood vessels are even more complicated than those of lymphangiomas. Theoretically, a true hemangioma is to be differentiated from a simple

dilatation of blood vessels by its independence from the adjacent normal circulatory channels. A hemangioma enlarges, therefore, by growth of its own elements rather than by incorporation of near-by vessels. In practice, however, these criteria are seldom applied, and accordingly many ectasias, hyperemias, and hyperplasias are included as neoplasias. The hemangiomas may be classified simply as *capillary cavernous,* or *mixed.* The *capillary angioma* corresponds clinically to the familiar "port wine" stain common on the face and neck but it exists also as simple small "vascular nevi" or birthmarks. In infants such angiomas may be composed of compact masses of endothelial cells in which the capillary lumina are obscured in many areas. These proliferations often extend from the dermis into the subcutaneous tissue. The extension of the lesion beyond the dermis and its rich cellularity may provoke the erroneous diagnosis of angiosarcoma. However, such angiomatous formations are usually sufficiently characteristic as to make possible the diagnosis of benign *infantile angioma* on the basis of histologic appearance alone. The capillary angioma may be confused histologically also with granuloma pyogenicum, particularly if the former is ulcerated and inflamed, as the latter usually is. The granuloma pyogenicum, however, is characteristically polypoid and generally has been present for no longer than one to three months and bleeds easily and repeatedly. The histology of the granuloma pyogenicum is identical with the so-called "pregnancy tumor" that occurs in the oral mucosa during the period of gestation.

The *sclerosing hemangioma* appears to be a special variety of capillary angioma although few dermatologists subscribe to this interpretation. They prefer to regard the lesion as a dermatofibroma lenticulare, histiocytoma, or merely subepidermal fibrosis. The lesions occur chiefly on the extremities and present clinically as single, firm, slightly elevated intracutaneous nodules, averaging several millimeters to a centimeter in diameter. Their sectioned surface is smooth and yellow. Histologically, more or less of the dermis is replaced by spindle cells arranged generally in tight curlycues, although in some areas these cells appear to enclose tiny spaces suggestive of the lumina of capillaries. In a few cases, the lumina are so large and numerous as to make the vascular nature of this lesion obvious. Usually the cells are vacuolated by lipid and in some cases the fat content is the most striking feature. Dark brown granules of hemosiderin are often present in many of the cells. At times, the iron pigment may be so abundant that pathologists, confusing the pigment with melanin, have succumbed to the serious error of labeling the lesion a malignant melanoma. The overlying epidermis may be normal, atrophied, or moderately acanthotic. In some instances a sharply delimited subepidermal zone of the dermis is spared. A similar free zone is seen in the dermal neurofibroma, although perhaps not as frequently (Figs. 1031, 1032). The sclerosing hemangioma may sometimes be justifiably confused with the neurofibroma when, as not infrequently occurs, the deeper portion of the lesion is composed of fasciculi of spindle cells such as characterize the neurofibroma. Occasionally the sclerosing hemangioma, particularly of the trunk, recurs locally with formation of satellite nodules. Usually such tumors originally extended in the subcutaneous fat and were removed incompletely. These tumors, called *dermatofibrosarcoma protuberans,* give rise to distant metastases in the rarest instances. The author is personally familiar with two such instances.

The *cavernous hemangiomas* are histologically similar to the cavernous lymphangiomas except for the presence of blood in the congeries of vessels. The vessels may ramify progressively in the subcutaneous fat, fascia, and the intermuscular septa. The extensions may be so wide and inaccessible as to make surgical removal an exceedingly difficult procedure. The term, infiltrating angioma, is more aptly applied to such tumors than angiosarcoma. Clinically the cavernous hemangiomas present on the skin surface as purple, single, globular or multilobular tumors, or as the flat or slightly elevated "strawberry" nevus of infants. The angiomas may be multiple and may cause, or at least be associated with, enlargement and distortion of an area of the body in the vicinity of the tumors. The distortion from edema and hypertrophy of an arm (*Parkes Weber* syndrome, 1907) may be so great as to require amputation because of the sheer weight of the extremity. Other syndromes associated with anomalies of blood vessels include the Sturge-Parkes Weber syndrome (nevus flammeus of the face, cerebral angiomatosus, hemiplegia, and mental retardation),[143] the Maffucci syndrome (angiomas with dyschondroplasia), and heredofamilial angiomatosis (Rendu-Osler-Parkes Weber disease). Cutaneous angiomas may also be part of the complex of *multiple congenital angiomas* found in the viscera, particularly in the cerebellum and retina, and known as *von Hippel's disease.*

The *angiokeratoma* or telangiectatic wart represents a variety of cavernous hemangioma which is structurally similar to the lymphangioma cutis circumscriptum. The dilated blood channels are located high in the papillae and are so intimately associated with the epidermis as to appear actually within it in many places. The overlying epidermis is usually papillary, acanthotic, and hyperkeratotic. Clinically the lesions are dark purplish-red, firm, the size of a pinhead or a split pea, and located in the scrotum, ears, fingers, and toes. The lesions are often associated with some circulatory disturbance such as might follow chilblains and varicosities. This type which tends to occur on the extensor surface of the extremities is known as the *Mibelli* type of angiokeratoma as opposed to *Fordyce's* type without associated pernio. Telangiectasis or small cavernous hemangiomas subjected to chronic irritation may duplicate the histologic picture of angiokeratoma.

Spider "angiomas" which are really small telangectasias, possibly with arteriovenous shunts, occur with chronic hepatic damage as in Laennec's cirrhosis and in pregnancy. They are thought to be an effect of excess of estrogenic hormones.

Fig. 1031.
Fig. 1032.

Fig. 1033.

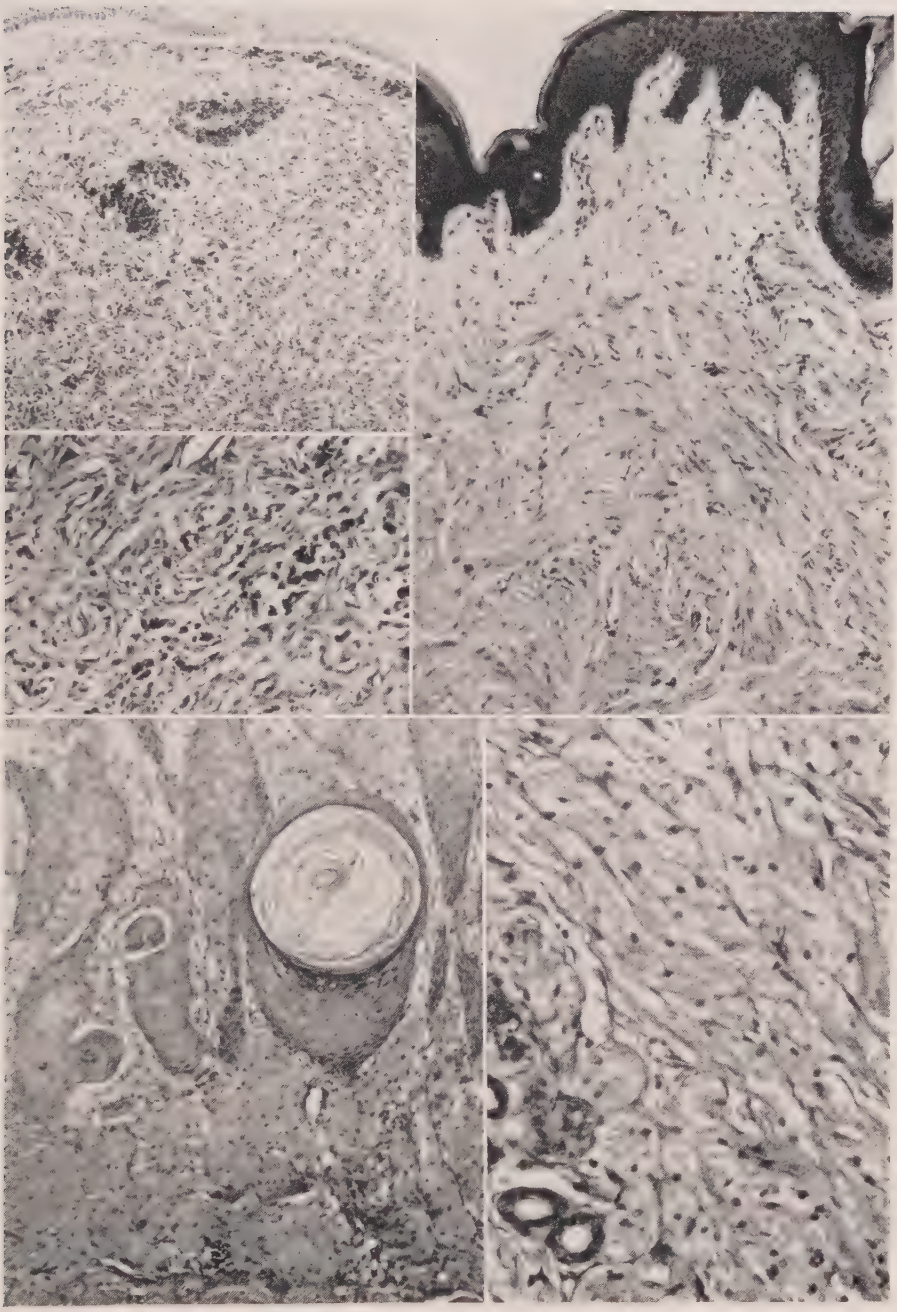


Fig. 1034.

Fig. 1035.

Fig. 1031.—*Sclerosing angioma* showing abundant hemosiderin.
Fig. 1032.—*Sclerosing angioma* with the vascular nature evident.
Fig. 1033.—*Leiomyoma of cutis,* derived from arrectores pilorum.
Fig. 1034.—*Myoblastoma* with characteristic pseudoepitheliomatous hyperplasia.
Fig. 1035.—*Myoblastoma*—high power of the granular cytoplasm and uniform small nuclei.

The term hemangioendothelioma is rather gratuitously applied to hemangiomas in which there is a relative prominence of endothelial cells with or without atypia. The implication in its use is that the neoplasm shows greater activity and therefore presents more likelihood of local recurrence than the ordinary hemangioma. The evidence for this presumption is questionable. A similar situation exists with respect to the use of "lymphangioendothelioma." Unfortunately, the name "hemangioendothelioma" rather than angiosarcoma has been applied to the frankly malignant tumor.

Angiosarcoma.—Primary solitary angiosarcoma of the skin, exclusive of Kaposi's hemorrhagic sarcoma, is rare. However, several cases have been recorded in which visceral metastases have occurred.[146] The metastases tend to be more cellular and anaplastic than the original growth. Others have been reported as malignant vascular tumors of skin under the title hemangioendothelioma, but, in most instances, evidence of origin from dermis as well as of the cancerous characteristics is not convincingly presented. Knowledge of the rarity of such tumors is of practical importance because of its tempering effect on the tendency to call sarcomatous those nonmetastasizing angiomas with abundant endothelial cells, or those that have infiltrated into the subcutaneous fat and beyond into the muscles. The Kaposi sarcoma, on the other hand, represents a process of vastly different significance.

Kaposi's Idiopathic Hemorrhagic Sarcoma.—Kaposi's sarcoma begins as reddish- to purplish-brown, discrete or grouped, painful, tender nodules varying from 1-2 mm. to about 1 cm. They occur particularly on the hands and feet although they may start in the skin of any part of the body. The incidence is about ten times as great in men as in women, and is seen especially in elderly patients, although the disease has been described in children. The surface of the nodules may be telangiectatic but often it is verrucose. Local purpura and bullae may be associated with the lesions. Lymphatic blockage with elephantiasis of the extremities is common. The course of the disease is slow, the nodules often involuting, with resultant atrophic scarring and pigmentation. The condition may last from one to fully twenty-five years, although the average duration is from five to ten years. The disease is found chiefly in Italians and Jewish people.

The lesions may involve extensive areas of the skin and nearly every organ of the body. The gastrointestinal tract, mesenteric nodes, liver, and lungs are most commonly involved although even the osseous and central nervous systems may be affected. The question is unsettled as to whether these lesions are truly metastases, or actually multicentric foci of a neoplasm. The intestinal lesions of Kaposi's sarcoma, unlike most other metastatic lesions excepting melanomas particularly, have a predilection for the inner coats rather than the serosa. In this location the tumors give rise to profuse hemorrhage. This difference in location in the intestinal tract between the Kaposi sarcoma and other metastatic tumors is a bit of evidence in favor of the multicentric origin of the former. Visceral tumors histologically identical with Kaposi's sarcoma have been found without cutaneous involvement. Patients with Kaposi's sarcoma die of hemorrhage from an intestinal lesion, intercurrent infection, extensive visceral involvement, or complicating malignant lymphomas.

The Kaposi sarcoma is a form of angiosarcoma that is so varied histologically as frequently to cause difficulty in the interpretation of a given slide. In one phase, perhaps the earliest, the picture is that of a simple hemangioma or of foci of hyperemic, nonspecific granulation tissue characterized by clusters of capillaries placed closely together with or without a sprinkling of mononuclear cells and histiocytes containing hemosiderin in the intervening, often edematous stroma. At this stage the endothelial cells may be quite regular without mitotic figures or other evidence of anaplasia. The important histologic clue is the disposition of these vascular foci not only near the epidermis but isolated about appendages in the deeper layers of the dermis. The presence of such vascular foci at a distance from the surface of the skin is suspiciously unlike the ordinary pattern of the response of skin to inflammation. In more advanced lesions there occurs proliferation of spindle cells and fibroblasts in association with scattered lymphocytes and histiocytes. The cells appear to form abortive capillaries and in the actively growing lesions these cells are large, hyperchromatic, and contain mitotic figures. In the later stages there is a tendency toward focal necrosis of the neoplastic tissue and subsequent fibrosis. These variegated pictures may be observed not only at different stages of the disease, but often within a single lesion.

Relation of Kaposi's Sarcoma to Malignant Lymphomas.—There is an increasing number of reports in the literature of the simultaneous occurrence of Kaposi's sarcoma with one or another of the malignant lymphomas including Hodgkin's disease, lymphatic leukemia, lymphosarcoma, and mycosis fungoides. In our material, there are five examples of this concomitant association. For both statistical and histological reasons, the latter comprising what seems to be evidence of transition of the two processes within the same lesion, we believe that the association is not coincidental.

Postmastectomy Lymphangiosarcoma.—In 1948, an entity described as lymphangiosarcoma was recorded[144] as a complication of postmastectomy lymphedema of the upper extremity. The lymphangiosarcoma in the skin of the edematous arm developed 6 to 24 years after the mastectomy, the lymphedema having existed during the entire latent period. In one instance, the tumor of the breast was benign. There was no relationship between the use of x-irradiation and the development of the lymphangiosarcoma. Histologically, the sarcoma has a range of variation quite equal to that of Kaposi's sarcoma and indeed in many sections one cannot be certain that the neoplastic elements are lymphatic vessels rather than blood sinuses. The tumor is capable of metastasizing. No record of lymphangiosarcoma as a complication of the lymphedema of

filariasis has been recorded so that the mechanism of cancerogenesis in the cases of postmastectomy lymphedema is obscure. Postmastectomy lymphangiosarcomas have since been reported by other observers.

Glomus Tumor.—In the corium of the skin of the finger tips, particularly in the nail beds, around the joint of the extremities, and over the scapula and coccyx, there are normally arteriovenous shunts, or glomera. These are composed of an afferent artery, the Sucquet-Hoyer canal or shunt, and an efferent vein. The artery is surrounded by several layers of small, spherical, uniform glomus cells which superficially resemble the cells of the intradermal nevus and which are presumed to control the flow of blood by their contractility. Nonmedullated nerves and bundles of smooth muscle are intimately associated with the shunt. Tumors of this structure are called glomangiomas, angiomyoneuromas, glomus tumors, or neuromyo-arterial aneurysms. They are most common in the nail bed, but occur elsewhere on the extremities and trunk, and even deep to the skin in muscles and joints. No instance of tumor occurring in the coccygeal glomus has been observed. Glomus tumors appear as purplish-red spots several millimeters in diameter, which are often clinically diagnosable by a characteristically lancinating pain, remarkably severe in view of the small size of the tumors. Not all glomangiomas, however, are associated with this characteristic symptom. Histologically, the glomus tumors range from compact masses of uniform glomus cells with few vascular channels to cavernous skeins of vessels cuffed by these cells. The vessels of the tumors tend to be small especially in the nail bed. The identifying features are the several rows of peritheliomatously arranged glomus cells in which mitotic figures are rare or absent; these cells may be so numerous as to obliterate vascular lumina and to resemble a basal cell tumor or a variety of sweat gland adenoma. Nonmedullated nerves are usually discerned, but there appears to be no apparent relationship between the pain and the number or location of these nerves. Occasionally, glomus tumors are called simply hemangiomas or glomangioid tumors because of the presence of only two or three perivascular rows of glomus cells. However, such tumors have been observed with the typical symptomatology of glomangiomas.

Hemangiopericytoma.—Recently, a tumor has been described which is morphogenetically related to the glomangiomas but which lacks its organoid structure. This tumor has been called a hemangiopericytoma.[149] Its cells are said to be derived from the pericytes of Zimmerman, which normally are located just outside the basement membrane of capillaries. The pericytes, like the glomus cells, are presumed to have a contractile function. Clinically, these tumors present as nodules on the skin which may be grossly indistinguishable from many other tumors of the skin. The hemangiopericytomas lack the pain of the glomus tumors. Histologically, they are characterized by endothelial sprouts filled with blood and rimmed by rounded pericytes. Proof that the neoplastic cell is in fact derived from pericytes is not altogether clear-cut. These lesions are generally benign, but one deeply infiltrating example and one with a metastasis have been described.

Tumors of Muscle

Three varieties of tumors of dermal muscle are described: (1) leiomyoma (arising from arrectores pilorum), (2) angiomyoma, and (3) myoblastoma.

The **leiomyoma cutis** occurs singly or in groups of as many as dozens of firm, usually pea-sized nodules, which are often tender and painful. Histologically they are composed of interlacing sheets of smooth muscle which may resemble a haphazard compact collection of arrectores pilorum (Fig. 1033). Infrequently, the nuclei are large, irregular in size and shape, and hyperchromatic so as to merit the term *leiomyosarcoma cutis* or *dermatomyosarcoma.* However, these lesions rarely metastasize, although recently the author had the opportunity to observe an example of dermatomyosarcoma exhibiting striking venous invasion of subcutaneous vessels; the lungs were not yet involved clinically.

The **angiomyoma** presents as a small nondescript nodule which microscopically is made up of circular masses of smooth muscle strongly reminiscent of the media of arteries. The residual arterial lumen is discernible in the core of many of the masses of muscle. These lesions remain benign.

The **myoblastoma** is found as a nodule in the skin of various parts of the body as well as on the mucous membranes, particularly of the tongue. Histologically the tumors are composed of nests and alveoli of large cells with small centrally placed nuclei in cytoplasm loosely stippled with eosinophilic granules. The cells closely resemble those of a xanthoma but fat stains are negative. On close examination it is observed that the cytoplasm is not actually vacuolated as are lipoid histiocytes. The loose dispersion of granules which simulate vacuoles are stated to represent embryonic fibrils of striated muscle cells. Such an hypothesis is open to question inasmuch as these tumors are present in the corium where striated muscle does not occur. The same objection may be leveled at the hypothesis that these cells represent degenerated adult striated fibers, although in sites where striated muscle is normally present, such as the tongue, this kind of transition is occasionally suggested. The evidence for the neurogenesis is altogether inadequate. The concept of a fibroblastic origin has recently been advanced.[139] In any event, whether or not these tumors are proved eventually to be myogenic, it is clear that they are easily recognizable histologic entities which rarely metastasize. Most of the so-called malignant granular cell myoblastomas are in reality unrelated rhabdomyosarcomas in which some of the cells happen to be granular. One of the remarkable and distinctive features of many of the myoblastomas is the characteristic epithelial or epidermal acanthosis that overlies the lesion. This feature is not present in association with frank cutaneous leiomyomas. As a rule, dermal

neoplasms leave the epidermis essentially unaltered or cause its atrophy through compression; the myoblastomas, on the other hand, appear to provoke a degree of acanthosis that may simulate squamous cell carcinoma. It is as if some epidermal irritant were present in the cells of the myoblastoma. (Figs. 1034, 1035.) (See also page 747 and Fig. 660.)

Fibroma

The diagnosis of cutaneous **fibroma** is usually found on careful review to include dermatofibroma lenticulare or sclerosing hemangioma, neurofibroma, leiomyoma, keloids, and other scars. This confusion does not apply to the pedunculated soft lipofibromas (fibroma molle) in which the fibrous component closely simulates the normal dermal collagen. These tumors are as likely to remain as benign as is normal skin. Occasionally a highly cellular neoplasm composed of compact spindle cells situated in the lower dermis appears to be truly a fibroma although differentiation from neurofibroma is difficult. The abundant cellularity of such possible fibromas and their tendency to extend into the subcutaneous tissue frequently prompts the diagnosis of fibrosarcoma. These tumors, however, metastasize with extreme rarity, so that a qualifying note to this effect should be appended to such diagnoses to forestall radical therapy. Undoubtedly, some of the spindle-shaped squamous cell carcinomas have been mistaken for fibrosarcomas of skin and so have contributed to the exaggerated impression of the capacity of the latter to metastasize.

Neurofibroma.—Neurofibroma may occur in the skin as a single tumor or multiple nodules. In the latter condition, the entity is classified as neurofibromatosis or von Recklinghausen's disease and may be associated with café-au-lait pigmented spots and neurofibromas of the sympathetic system as well as of motor and sensory nerve trunks. The tumors of the skin may be so numerous as to cover about the entire body from scalp to feet. The histogenesis of the tumors is complex. The axis cylinders as well as the nerve sheaths (neurilema) and endoneurium participate to a varying extent, so that the histologic picture may be altered accordingly. The tumor derived predominantly from nerve sheaths (neurilemoma) tends to manifest more obvious palisading of cells (Antoni A structure), degenerating, edematous microcystic foci (Antoni B), and hyaline Verocay bodies. Occasionally the neurilemoma presents marked central necrosis and such excessive telangiectasis as to be mistaken for an angioma. An examination of the periphery of these degenerated tumors usually reveals the telltale palisading of the neurilemoma. A small percentage of the cutaneous neurofibromas show sufficient hyperchromatism and irregularity in size and shape of nuclei as to suggest sarcomatous degeneration. However, here, too, metastases from these neoplasms of the skin are rare although local recurrence is fairly frequent. On the other hand, malignant changes in the visceral neurofibromas are common and may take the form of extensive, fatal local infiltrations or metastases. (See also page 1302.) The benign neurilemoma (Schwannoma) undergoes malignant change with extreme rarity. However, malignant neurilemomas occur but these are presumed not to have developed from a benign neurilemoma but to have been malignant from the start.

Osteoma

Osteoma cutis, an example merely of heterotopic bone, represents a metaplastic change of dermal collagen rather than true neoplasia. The lesion occurs as small nodules, as a rule, in scleroderma, syphilis, in association with acne, intradermal nevi, following trauma, after cystotomies, because of the osteogenic potentialities of urinary tract epithelium, or without apparent reason. The histologic picture may include fat and even marrow cells in addition to the bony trabeculae.

Lymphomas and Allied Diseases

The lymphomas and allied diseases of the skin include: (1) mycosis fungoides (?), (2) Hodgkin's disease, (3) lymphosarcoma, and (4) leukemia.

Mycosis fungoides (also known as granuloma fungoides—both names inaccurately chosen) is a fatal disease primarily and principally of the skin which is characterized clinically by three stages: (1) the premycotic, (2) the infiltrative, and (3) the stage of fungoid tumefaction. The premycotic stage is characterized by eczematoid, severely pruritic, erythrodermic, red, scaly, well-defined patches, or a generalized erythrodermia. The eruption in this phase may simulate eczema, psoriasis, parapsoriasis, seborrheic dermatitis, or a nonspecific exfoliative dermatitis. This stage may persist for months or years and may be impossible to diagnose with assurance either clinically or microscopically. In the second or infiltrative stage, firm, slightly elevated bluish-red plaques arise both in the previously involved and uninvolved areas. Partial or incomplete loss of hair from the scalp and other regions may occur. The last or fungoid stage follows the infiltrative period by several months. The tumors vary in diameter up to about 10 cm. or larger, and are prone to ulcerate. In each of the stages spontaneous remissions may be noted, but these are temporary. The diagnosis in the few reported instances of cure must be questioned. In some cases, the preliminary two stages do not develop; this form is called mycosis fungoides d'emblée. True instances of mycosis fungoides d'emblée must be exceedingly rare. Undoubtedly most of the recorded cases are, in reality, examples of Hodgkin's disease, reticulum cell sarcoma, or leukemia. As with Hodgkin's disease, mycosis fungoides may show appreciable, if temporary, regression following the administration of nitrogen mustard.[130] ACTH also produces an initial, temporary incomplete involution of lesions of mycosis fungoides and Hodgkin's disease.

The histologic picture of the first or premycotic stage is usually not diagnostic and may resemble one of the many conditions simulated clinically. However, even in this phase of the disease there is a tendency for the infiltrate to

be confined as a zone in the upper dermis and for the epidermis to appear psoriasiform. Occasionally, large, single or binucleated hyperchromatic cells are observed as well as a rare infiltrative cell in mitosis, which afford a clue. In the subsequent stages, the infiltrate, still selecting the upper dermis principally, becomes dense and polymorphous. The presence in this variegated infiltrate of eosinophilic leukocytes and cells that simulate the Sternberg-Reed cell of Hodgkin's disease and often an abundance of small and large (Marschalko) plasma cells constitutes the evidence for mycosis fungoides. In addition, there is a tendency toward scattered clumping of cells of the infiltrate. The epidermis tends to be moderately acanthotic and psoriasiform with focal spongiosis and small intraepidermal "microabscesses of Darier-Pautrier." These "microabscesses" are actually foci of tumor cells which have extended into the epidermis. Their absence does not preclude the diagnosis (Figs. 1036, 1037.) The quality of the infiltrate may be indistinguishable from that of Hodgkin's disease; the cutaneous infiltrate of Hodgkin's disease is irregularly distributed in various parts of the dermis rather than essentially in the upper dermis. However, this feature does not seem to be sufficient basis for segregating the two diseases, and it should be admitted that the relationship between them is obscure. To conclude that mycosis fungoides is simply torpid, cutaneous Hodgkin's disease is to neglect the indisputable fact that some cases of the former terminate as cutaneous reticulum cell sarcoma. This occurrence in Hodgkin's disease is questionable. Potentially the most revealing and yet most disputed morphologic clues to the nature of mycosis fungoides are the findings at autopsy. It is generally stated that mycosis fungoides invariably or almost always terminates with the visceral involvement by Hodgkin's disease, lymphosarcoma in its various forms or leukemia. This has not been our experience. Of 19 clinically typical cases collected by the author, only 3 showed evidence of isolated lymph node or visceral lymphomatous involvement at autopsy: one with Hodgkin's granuloma of a single lymph node, and the others with lymphosarcoma (lymphocytic type) localized to a small area. The peripheral lymph nodes are often enlarged because of their drainage of pigment, etc., from the infiltrated skin. Such nodes—now called "dermatopathic lymphadenopathy"—show partial obliteration of their architecture by reticulum cell hyperplasia, deposits of melanin and fat, and, what is an especially common and presumptive clue in mycosis fungoides, namely, numerous plasma cells. Similar plasma cells are generally in the bone marrow and spleen, and occasionally even contain Russell bodies. These nonspecifically altered lymph nodes of Pautrier and Woringer[135] may easily be mistaken for those of Hodgkin's disease. In this country, they were first adequately described again by Hurwitt in 1942.

In conclusion, it is our observation (1) that although the cutaneous tumefactions of mycosis fungoides may closely simulate or be indistinguishable from Hodgkin's disease or reticulum cell sarcoma, the *viscera are uncommonly involved* in properly documented cases; (2) that mycosis fungoides in the early stages prior to tumefaction is usually diagnosable by the integrated histologic changes in the epidermis and dermis; (3) that the plasma cell is one of the chief components of the infiltrate of the skin and viscera and the reasons for its presence should be investigated from the points of view particularly of altered blood proteins and reactions to allergens.[131]

The criteria for the histologic recognition in the skin of Hodgkin's disease, lymphosarcoma, and the various leukemias, are the same as are used for the visceral lesions. Additional clues are offered by the almost constant denseness of the infiltrate, immediately noted with low-power magnification, and the selectivity of the infiltrate for the upper dermis in some instances of leukemia. (Fig. 1039.) An important deceptive feature of the lymphomas is the occurrence also of quite nonspecific cutaneous reactions in which neoplastic cells are absent or unrecognized also of quite nonspecific cutaneous reactions in which neoplastic cells are absent or unrecognized. These reactions may take the clinical form of toxic erythema, excoriated pruritic exfoliative erythrodermia, generalized pigmentation, urticaria, and herpes zoster. Severe nonspecific cutaneous reactions lead to the changes in the regional lymph nodes, dermatopathic lymphadenopathy, which may become so enlarged as to be clinically indistinguishable from lymphomas. Undoubtedly one of the most difficult neoplasms to evaluate from a biopsy specimen of skin is Letterer-Siwe's disease of infancy or the related malignant histiocytoses of childhood, i.e., the so-called reticuloendothelioses, or lipid and nonlipid histiocytoses. The crux of the problem is the decision as to whether or not the cutaneous lesion indicates visceral involvement and a fatal prognosis, or merely a local histiocytosis or variant of xanthomatosis. As previously stated, urticaria pigmentosum should not cause the differential histologic diagnostic difficulties it often does. In the briefest terms, it may be stated that, in general, the degree of anaplasia and the compactness of the infiltrate of the monocytoid cells in the upper dermis are of great importance in suggesting the grave nature of the disease. However, remarkable disparities have been noted.[116]

Another source of clinical and histologic confusion is the entity known as *Spiegler-Fendt sarcoid,* which is characterized by grouped, local or disseminated, bright-red nodules. The histologic diagnosis is based principally on the finding of mature lymphocytes, and reticulum cells either scattered or as germinal centers of follicles. Anaplasia of the infiltrate or histologic evidence of appreciable activity is lacking. It is obvious that differentiation of this lesion from lymphosarcoma must at times require a great nicety of judgment; indeed, some of the cases originally but erroneously considered to be Spiegler-Fendt sarcoid have been recorded as having terminated in lymphosarcoma. Further confusion results from the use of the term *"benign lymphocytoma"* which is popular in dermatologic literature. This lesion, which may be single or multiple, resembles Boeck's sarcoid,

Fig. 1036.

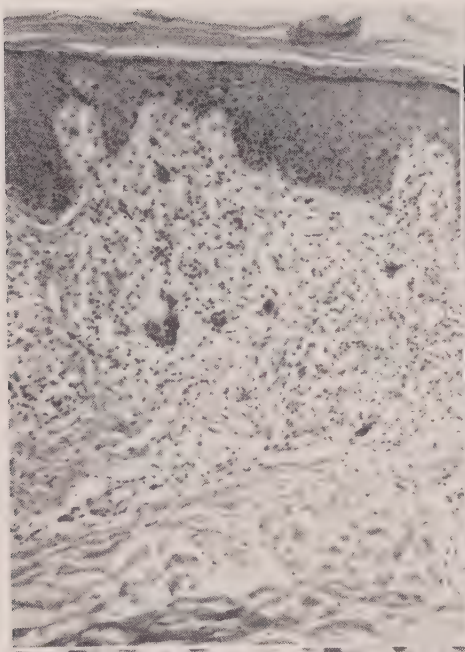
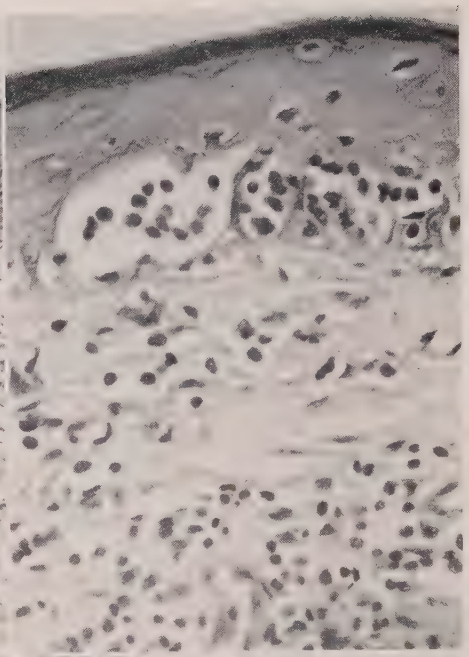


Fig. 1037.



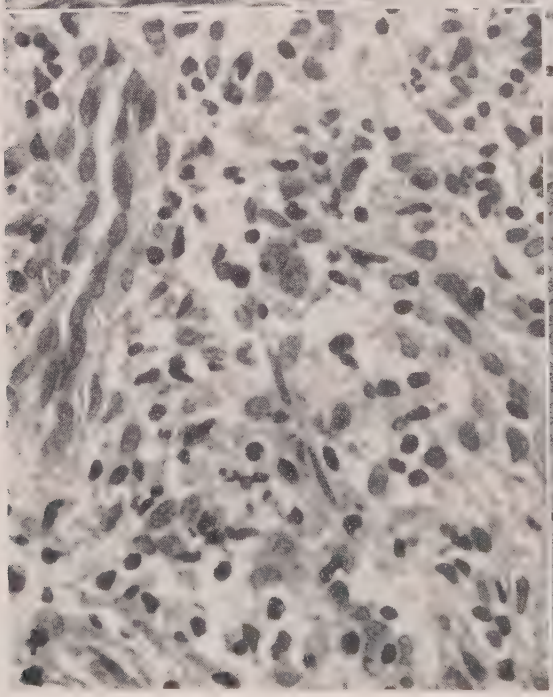


Fig. 1038.

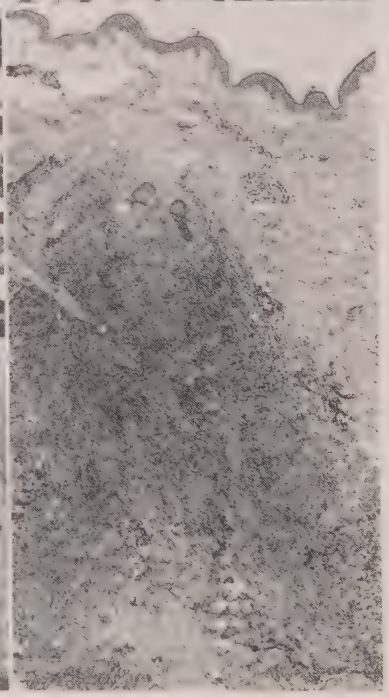


Fig. 1039.

Fig. 1036.—*Mycosis fungoides* in the so-called "premycotic" stage.

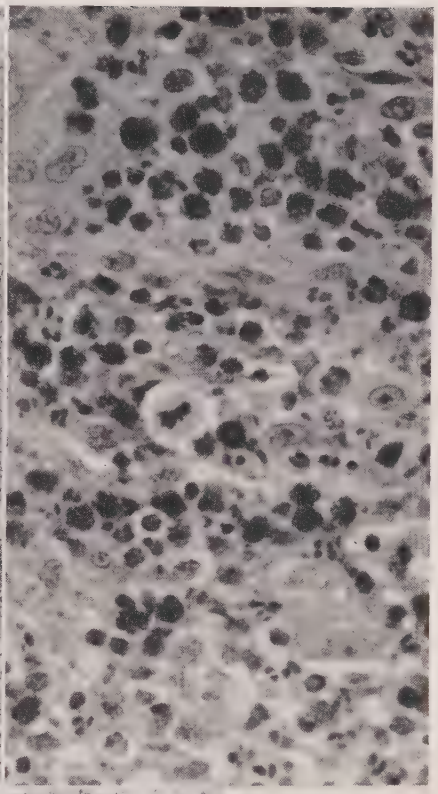
Fig. 1037.—*Mycosis fungoides* illustrating the pautrier "microabscesses," consisting of infiltrate extending from the dermis into the epidermis.

Fig. 1038.—*Mycosis fungoides* in tumor stage.

Fig. 1039.—*Lymphosarcoma* of skin showing density of infiltration without relationship to the epidermis as exists in mycosis fungoides.

Fig. 1040.

Fig. 1041.



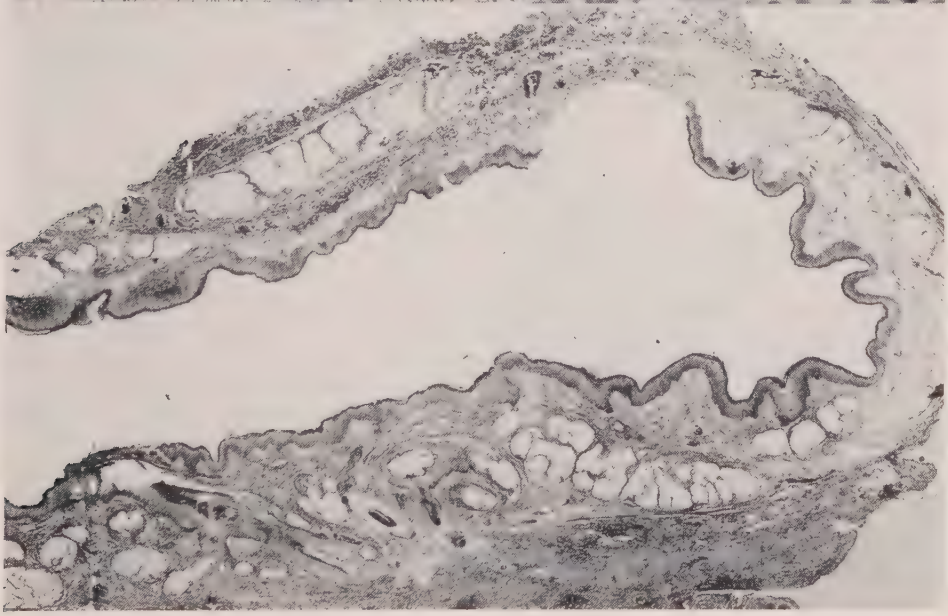


Fig. 1042.

Fig. 1040.—*Tick bite* with pseudoepitheliomatous hyperplasia simulating squamous cell carcinoma. (From Am. J. Path. 24: 367, 1948; AFIP No. 95767.)

Fig. 1041.—*Tick bite* showing dermal reaction reminiscent of Hodgkin's disease. A mitotic figure is near the center of the field.

Fig. 1042.—*Dermoid cyst* of the skin showing numerous sebaceous glands and hair follicles.

leukemic infiltration, or discoid lupus erythematosus clinically; histologically, it consists essentially of dense masses of mature lymphocytes which may be arranged in follicles with germinal centers. As would be anticipated, the lesions are highly radiosensitive.

Still another lesion commonly mistaken for one of the lymphomas is that produced by the bites of insects and ticks. The reaction usually consists of eosinophilic leukocytes, histiocytes, plasma cells, and reticulum cells, the latter occasionally binucleated and even in mitosis. In some lesions there are also prominent lymphoid follicles with germinal centers. Many patients with such an innocuous reaction have been given the grave diagnosis of Hodgkin's disease, mycosis fungoides, or lymphosarcoma. Part of the reason for the error is that it is not generally appreciated that the reaction to arthropods may persist for many months. The presence of only a single lesion is suggestive evidence, in doubtful cases, of an insect bite; on the other hand, an isolated lesion may occur also in the neoplastic conditions. Incidentally, another deceptive reaction to the venom of insects and ticks is the pseudoepitheliomatous hyperplasias which may be mistaken for squamous cell carcinoma.[127] (Figs. 1040, 1041.)

Metastatic Tumors in Skin

Cancerous metastases reach the skin by direct invasion, or through the lymphatics or blood vessels. The most common metastases include those from carcinomas of the breast, uterus, lung, gastrointestinal tract, pancreas, thyroid, and prostate gland, in addition to those from melanomas, epidermoid carcinomas and lymphomas, and sarcomas of bone, muscle, and fascia. There is generally little difficulty in recognizing the metastatic character of a tumor in the skin, except, of course, in the case of the lymphomas and in Kaposi's sarcoma. In both of these instances, the possibility of autochthonous multicentric origin is to be considered. Plasma cell myeloma occasionally involves skin. A nodule of melanoma may usually be so recognized as metastatic by the presence of an overlying intact epidermis showing no evidence of junctional change. Occasionally, a metastatic focus of adenocarcinoma is mistaken for a primary cutaneous carcinoma of sweat gland origin.

Tumors of Dermal Appendages

Sweat Glands.—There is an abundance of histologic variants of tumors presumably of sweat gland origin. As a result, a profusion of terms has arisen which are often used ambiguously and are applied inconsistently. It would seem that no practical purpose would be denied if all the benign neoplasms of sweat glands were labeled simply as solid or cystic syringadenoma or syringocarcinoma. However, the range of histologic variation is so great as to lead not infrequently to serious diagnostic errors, such as the mistaking of a sweat gland adenoma for a basal or a squamous cell carcinoma, malignant melanoma, or synovioma. It may be worth while, therefore, at least to mention and illustrate the various sweat gland adenomas. Despite their histologic variegations, in almost all instances there are foci of cells which indicate their source by their resemblance to sweat glands or ducts. In many instances of the solid syringadenoma, the hard, smooth, hyalinized, collagenous stroma is a clue to the nature of the tumor; in others, large cells with abundant acidophilic cytoplasm—cells which some observers on insecure evidence believe to be myoepithelial—suggest origin from sweat glands (Fig. 1045). In a considerable number of the cystic syringadenomas, the stratified epithelium is frequently papillated and the individual cells vacuolated with glycogen (Fig. 1050). In another variety of cystic syringadenoma (so-called hidrocystadenoma papilliferum) the papillary folds are closely set, covered by only two layers of epithelial cells, and associated with lymphocytic and histiocytic subepithelial reaction (Fig. 1043). These lesions are often overlain by a thickened acanthotic and hyperkeratotic epidermis which obstructs the orifices of the appertaining sweat ducts and thereby appears to contribute to the cystic dilatation and papillary proliferation in these lesions. Another clue is the presence of a hyalinized inner luminal zone of cytoplasm in the neoplastic acini or ducts that is reminiscent of normal sweat coils and ducts (spiroadenoma). In still another variety, the tumor consists merely of dilated isolated small dermal sweat coils, occasionally with squamous metaplasia of its lining and keratinous contents in the lumina (syringoma). These may be easily confused with the Brooke tumor (trichoepithelioma) (Fig. 1053). In yet another kind of sweat gland tumor the predominant histologic feature is the thick hyalinized band of collagen that rims each nest of cells and also ramifies among the individual cells ("turban" tumor, nevus epitheliomatocylindromatosum) (Fig. 1044). A final interesting variant of the sweat gland adenoma is the one in which islets of hyaline cartilage are included (so-called mixed tumor of skin) (Fig. 1049). The source of the cartilage in these lesions has been attributed to some effect of dysembryogenesis. However, it appears much more probable that the cartilage in the so-called mixed tumors of skin as well as parotid, and minor salivary glands and lachrymal glands is derived from two sources: chondral metaplasia of stroma and of adult acinar epithelium.[156] Another interesting variant is the syringadenoma of the vulva which may be mistaken for primary or metastatic adenocarcinoma.

Syringocarcinoma.—There is a tendency to diagnose sweat gland adenomas as malignant not because of anaplasia of the cells but on account of the irregular, ramification of nests of cells into adjacent dermis. On the other hand, some of the basal and squamous cell carcinomas characterized by small discrete nests of cells are mistaken for sweat gland tumors. As a rule, the uncommon sweat gland carcinomas are of a low grade of virulence, as are carcinomas of appendages generally.

Sebaceous Glands.—Adenomas of sebaceous glands occur as small yellowish papules principally on and beside the nose, the cheeks, and

the forehead. In many cases there are associated verrucae, neurofibromas, subungual fibrosis, and nevi, and in some cases the patients develop tuberous sclerosis of the cerebral cortex and present the triad of sebaceous adenoma, mental deficiency, and epilepsy (see page 1289). These patients may also have visceral tumors such as renal angiolipomas and others. The histologic picture is that of an overgrowth of sebaceous glands without apparent linkage to the hair apparatus. Often it is difficult to be sure that the process is not simple hyperplasia rather than neoplasia. There is another histologic form of sebaceous adenoma characterized by a proliferation of the basal cells lining the sebaceous glands interspersed with isolated sebaceous cells. Rarely a metastasizing, sebaceous gland carcinoma develops in which at least a few scattered sebaceous cells help to identify the source. (Figs. 1051, 1052.)

Fig. 1043.

Fig. 1044.

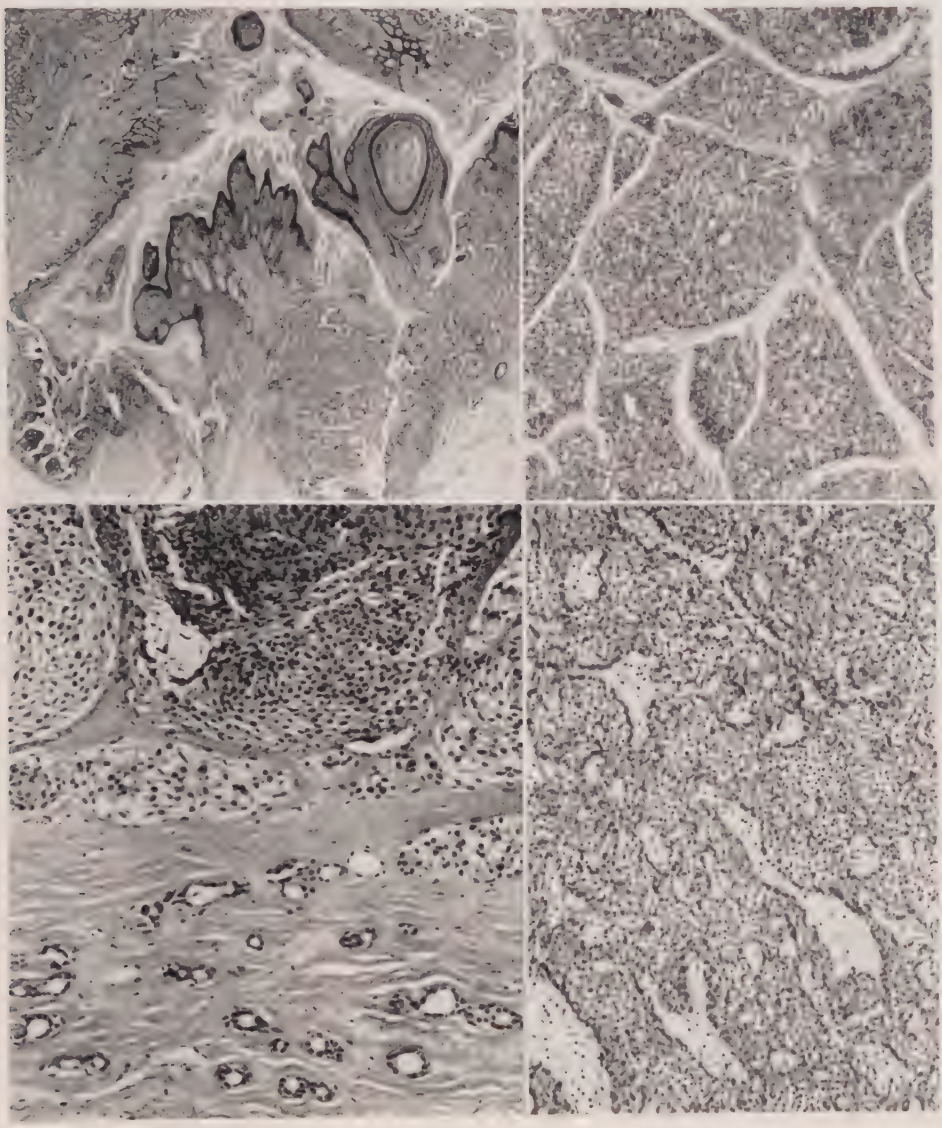


Fig. 1045.

Fig. 1046.

Figs. 1043-1050.—Varieties of sweat gland adenomas.
Fig. 1043.—*Syringocystadenomatous papilliferus.*
Fig. 1044.—*Turban tumor.*
Fig. 1045.—*Syringadenoma*—usually labeled "myoepithelioma" on questionable evidence.
Fig. 1046.—*Syringadenoma.*

Tumors of Hair Follicles.—There is a divergence of opinion as to the types of neoplasms that may arise from hair follicles. Many observers believe that basal cell carcinomas are derived from embryonic hair follicles. However, as previously stated, the histologic evidence favors the view that basal cell carcinomas arise from the mature basal cells wherever they lie—at the base of the epidermis, at the periphery of sebaceous glands, or in the outermost layer of the hair follicles. However, the tumor that probably does arise from hair follicles is known synonymously as a *trichoepithelioma, Brooke tumor,* or *epithelioma adenoides cysticum* (Fig. 1053). Some observers feel that the origin of this tumor from sweat or sebaceous glands is a possibility. The lesion tends to be familial and appears as multiple

Fig. 1047.

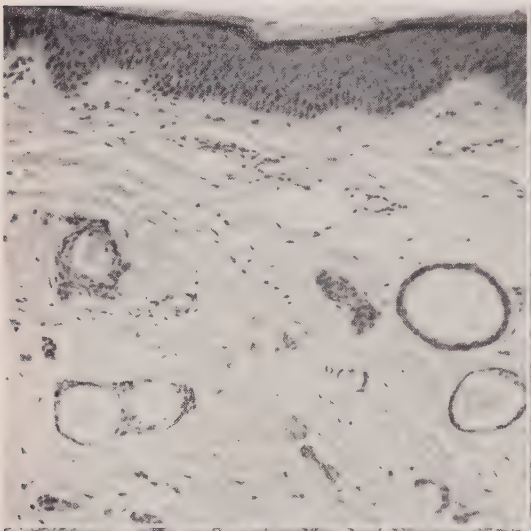
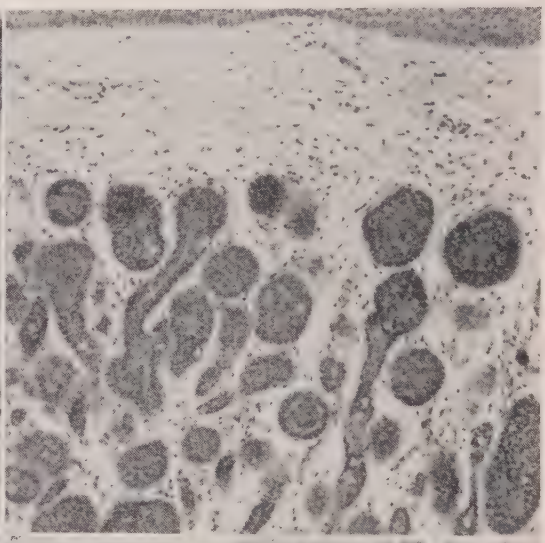


Fig. 1048.



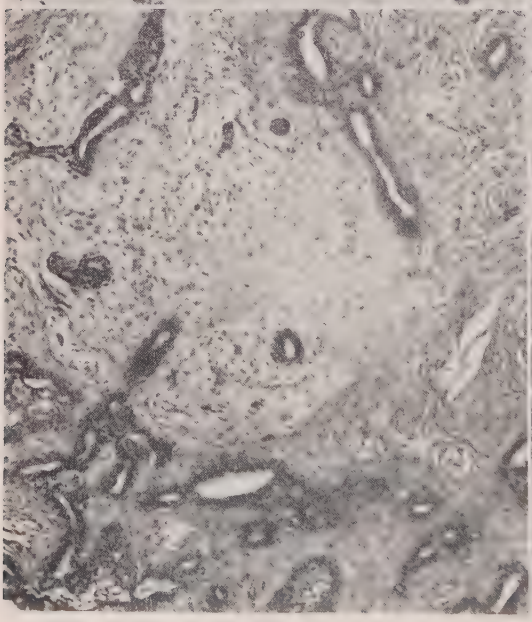


Fig. 1049.

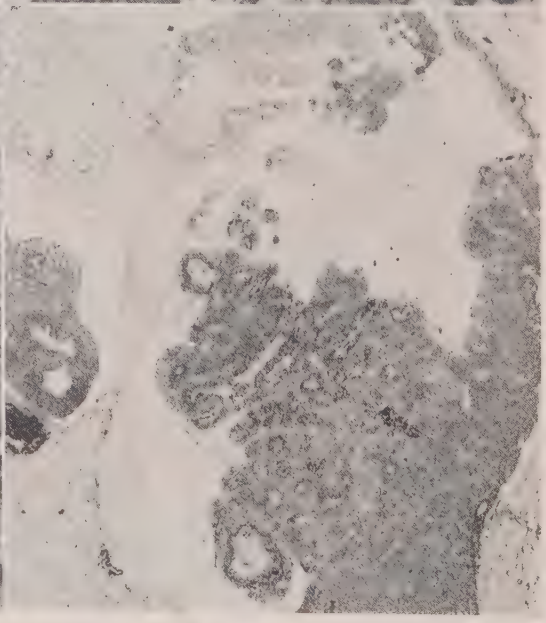


Fig. 1050.

Fig. 1047.—*Syringadenoma* (hidrocystoma).

Fig. 1048.—*Spiroadenoma.*

Fig. 1049.—*Syringadenoma* with chondral metaplasia ("mixed" tumor) such as occurs in salivary and lacrimal glands.

Fig. 1050.—*Syringocystadenoma.*

smooth nodules on the face and chest. Histologically, the tumor is overlain by intact epidermis unlike most basal cell carcinomas. The lesion is made up of varying-sized units of cysts filled with keratin and lined with stratified squamous epithelium, from which nests of basal cells proliferate. The trichoepithelioma is benign and does not infiltrate as do the basal cell carcinomas.

Fig. 1051.

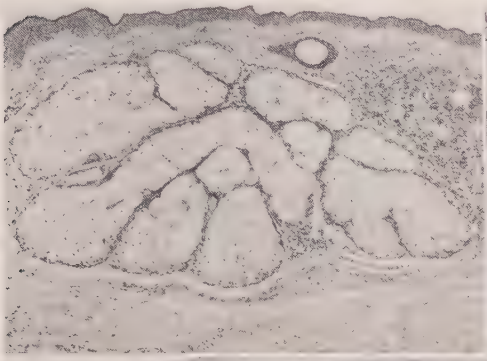
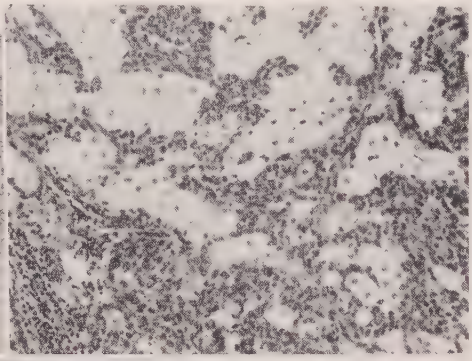


Fig. 1052.



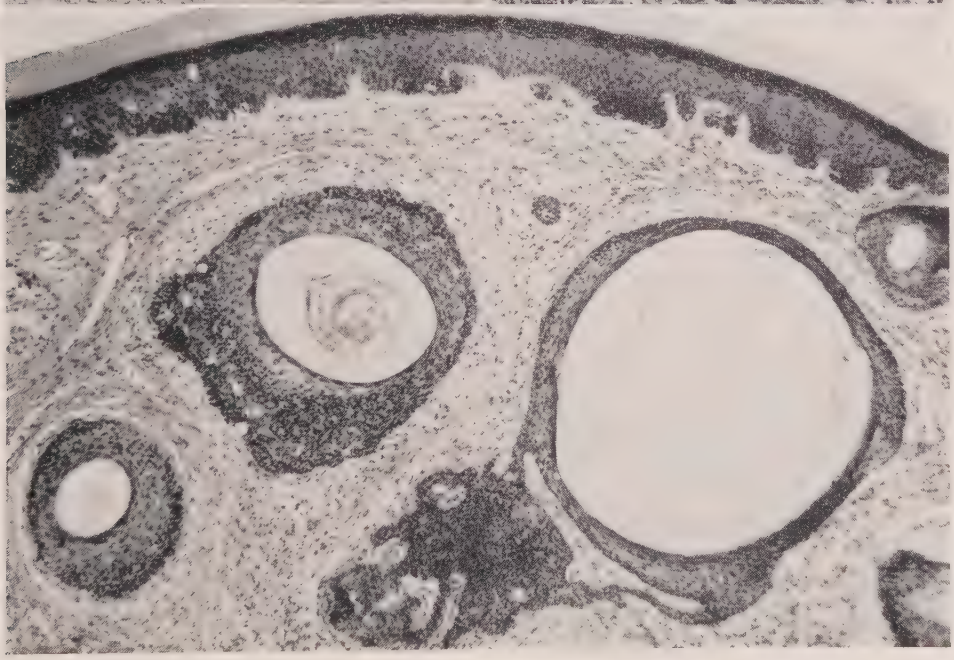


Fig. 1053.

Fig. 1051.—*Sebaceous gland adenoma.* (AFIP No. 97228.)
Fig. 1052.—*Sebaceous gland carcinoma*—low grade.
Fig. 1053.—*Trichoepithelioma* (Brooke tumor, epithelioma adenoides cysticum).

Cysts

The **dermoid cyst** is a congenital cutaneous inclusion occurring usually in the skin of the forehead especially in the supraorbital region or midline. **Sebaceous cysts** may occur on a dysontogenetic basis or may follow occlusion of the gland; **epidermoid cysts** may also be congenital and familial, particularly *steatocystoma multiplex,* but commonly are the result of trauma (including insect bites) or inflammatory downgrowth, with separation and eventual isolation and encystment of a fragment of epidermis.

Grossly the dermoid cyst cannot be differentiated from sebaceous and epidermoid cysts. Histologically, the wall of the cyst is actually skin with all of its appendages, often with a prominence of sebaceous glands. The epidermoid and sebaceous cysts differ from the dermoid cysts in that the former lack the appendages and their walls are made up of stratified squamous epidermis surrounded by fibrous tissue. As a rule, it is impossible to

distinguish the epidermoid from the sebaceous cyst. Infrequently, evidence of the relation of the cyst to a contiguous sebaceous gland may persist. The criteria that have been set up for the differentiation are unreliable. The epithelium of both tends to be nonpigmented.

The contents of each of the cysts is predominantly a beige-colored greasy keratin, representing in reality the stratum corneum which in these instances cannot be shed but accumulates in the epidermal enclosure. There is also much fat within the laminated keratin which may either not be demonstrable in routine sections or may be seen as cholesterin slits. In the dermoid cysts hairs may be included. Occasionally, the lining epithelium may proliferate as papillary buds either externally, or inward toward the lumen of the cyst. Because of the irregularity of these proliferations and perhaps because of their superficial resemblance to the carcinomas of epidermis, there is a tendency to classify these hyperplasias or benign proliferations as cancer—a tendency not warranted by their behavior.

The *calcifying epithelioma* is an exaggeration of this process of proliferation which frequently is misinterpreted as cancer. Histologically this lesion is usually a sharply circumscribed mass of disheveled fragments of epithelium many of which are necrotic and often partially calcified. The epithelial cells have a basaloid character, although it is likely that they are predominantly of prickle cell origin. A foreign body reaction, associated with cholesterin deposits, is common, as are calcification and even extensive ossification of the stroma. From the observation of early and transitional stages in the development of these lesions, it appears that they arise from the proliferation of the lining of epidermal and sebaceous cysts and infrequently even of cysts of sweat glands. Actual cancerous transformation of the lining of cysts is an infrequent occurrence; the incidence of 1 to 6 per cent quoted in the literature is probably high; a figure of about 0.5 per cent would appear to be more representative.

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Chapter 42

THE BONES

Granville A. Bennett

For convenience in presentation, the skeletal system may be divided into two parts: the osseous tissue and the articulations. Although many pathologic disturbances affect both of these structures, it is necessary to consider separately each anatomic unit and to describe the disease states that primarily or predominately affect it.

Osseous tissues are susceptible to most, if not all, the deleterious agents and unfavorable circumstances that affect the soft tissues of the body. Thus, bone reacts to physical and chemical injuries, to nutritional, metabolic, and endocrine disturbances, and to circumstances that are related to environment and heredity. In addition, the cellular components that are incorporated in osseous tissue give rise to a variety of neoplasms.

In its reaction to adverse conditions, bone often behaves quite differently from the other tissues and organs of the body. Such differences are attributable, in most instances, either to the peculiar mechanisms that are responsible for bone development and growth or to the special anatomic and physiologic characteristics of this interesting tissue. It is necessary, therefore, that the known facts related to the embryology, anatomy, and physiology of bone be kept in mind in the study of all skeletal lesions.

NORMAL OSSEOUS TISSUE

Bone is to be regarded as a highly specialized form of connective tissue. Developmentally it emerges from primitive connective tissues either by direct transformation of undifferentiated mesenchyma into bone, or by the more complicated process of endochondral bone formation. Irrespective of its mode of formation, bone, when fully developed, differs from ordinary connective tissue in several important details. It is relatively cell-poor, and such cells as are present are either widely separated from one another and segregated in lacunar spaces as osteocytes, or they are distributed as a single layer of cells upon the bone surfaces, where they form a continuous envelope surrounding all bony structures. The latter cells, depending on their position, constitute either the periosteal or endosteal layer.

In their resting state, the endosteal and periosteal cells resemble unstimulated fibroblasts. They are elongated and flattened in shape and contain small, darkly staining, rod-shaped or oval nuclei. There can be little doubt that this cell layer plays an important rôle in the exchange of metabolites between the vascular system and the more distant osteocytes enclosed within the lacunar spaces in the adjacent bony tissue (Figs. 1054 and 1055). This function is made possible by the intercommunicating channels (canaliculi) that range between the bone surfaces and the lacunar spaces which enclose the segregated osteocytes in the more distant parts of the bone lamellae or haversian systems forming the compact bony structures.

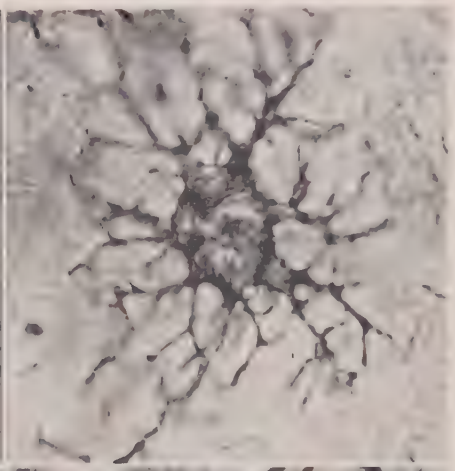
The intercellular substance of bone is comprised of collagenous fibrils that are embedded in a homogeneous-appearing matrix. The fibrillar components are arranged in a series of layers each of which has a predominating orientation of fibrils. Thus, in a given series of lamellae, one observes intermittent longitudinal and circular layers of fibrils. Such layers are scarcely observable in decalcified hematoxylin and eosin stained sections (Fig. 1056) but they are prominent in preparations after silver impregnation[1] or when examined with the aid of polarized light. Dense collagenous fibrils (Sharpey's fibers) are also evident at the sites of ligamentous or fascial insertions into compact bone. All of these fibrillar constituents of the organic substance of bone are incorporated in a more homogeneous ground substance which, in decalcified hematoxylin and eosin stained sections of newly formed bone, appears hyaline and acidophilic. In older bone prepared by similar techniques, this material is less homogeneous and takes a reddish-purple stain. Neither the chemical composition nor physiology of this material has been fully determined. In it is deposited the complex inorganic compound that is known as bone salt. Although the exact composition of bone salt is still uncertain[2] it has been stated that it consists of calcium phosphate and calcium carbonate in a manner represented approximately by the formula $[Ca_3(PO_4)]_N CaCO_3$. N is about 3 in the bone from young animals of some species, and approaches 2 in adult bone from most of the species studied.[3] The inorganic portion of bone is also known to include magnesium, sodium, and potassium.[4] Thus it will be seen that two minerals are specifically utilized in the formation and maintenance of bone. These are calcium and phosphorus.

Calcium is required in varying amounts depending on the age, size, and physiologic state

of the individual. Thus, a daily intake of approximately 1 gram is required by children less than 12 years of age, 1.4 grams for boys from 12 to 20, and 0.8 gram for adults of average size. During pregnancy and lactation, a woman may require from 1.5 to 2.0 grams.[1] The normal serum values range from 10.4 to 10.6 mg. per 100 c.c. In the form of phosphate and carbonate, calcium forms the principal inorganic constituent of bone, dentine, and tooth enamel. More than 99 per cent of the calcium of the body is contained in these structures.[5] It will be seen, therefore, that calcium in adequate amounts is necessary for the proper composition of the skeletal parts. Furthermore, it is evident that when the balance of ingestion and

Fig. 1054.

Fig. 1055.



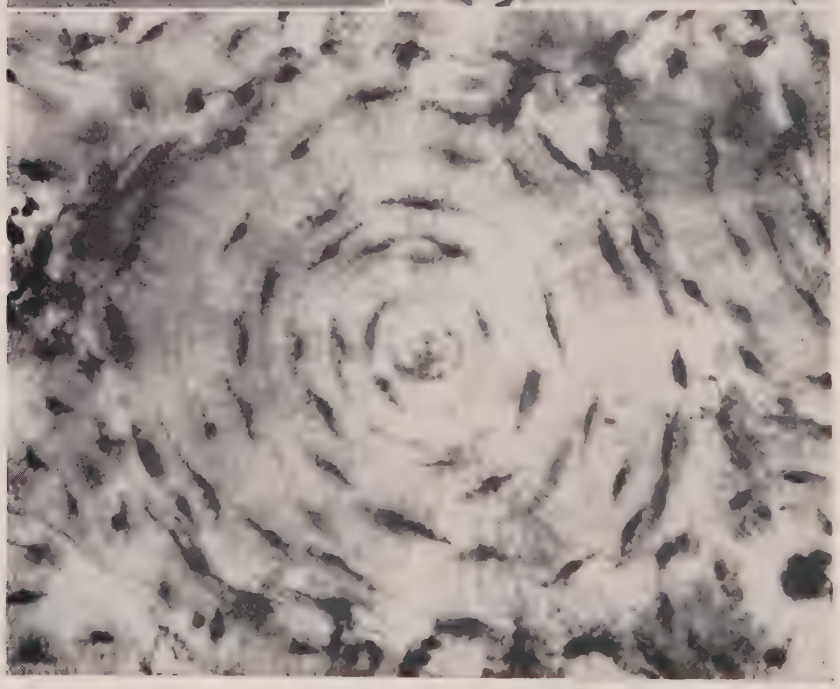


Fig. 1056.

Fig. 1054.—Osteocyte enclosed in a lacunar space from which canaliculi extend into the adjacent bone. (Hematoxylin-eosin stain. ×1,350.) (Photograph supplied by Drs. Weinmann and Sicher.)

Fig. 1055.—Branching canaliculi emerging from a lacunar space in compact bone. (Ground section ×1,350.) (Photograph supplied by Drs. Weinmann and Sicher.)

Fig. 1056.—The cellular and lamellar arrangement in compact bone is demonstrated in this ground section. (×360.) (Photograph supplied by Drs. Weinmann and Sicher.)

excretion is disturbed in such a way as to lower the serum values, this essential mineral will be mobilized from the bony storehouse to correct the deficits.

Phosphorus, like calcium, is indispensable in bone formation and in certain other physiologic activities. Phosphorus is present in large amounts in bones and teeth (calcium : phosphorus ratio approximately 2:1). It is also present in the serum, chiefly in the form of inorganic phosphate. The daily requirement of a normal adult is approximately 1.3 grams. Children need slightly less and women during pregnancy and lactation require more. The normal serum values for adults range between 3.0 and 4.0 mg. per 100 c.c. In children the value is slightly higher.

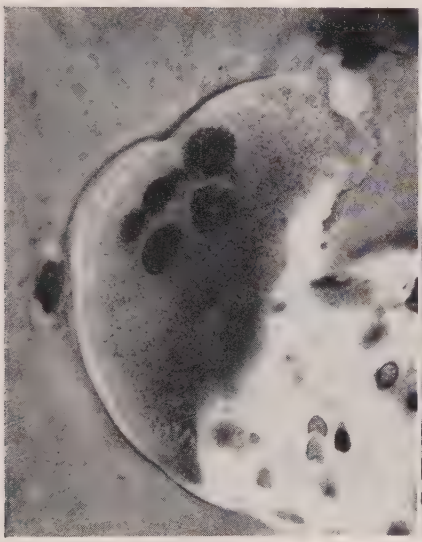


Fig. 1057.

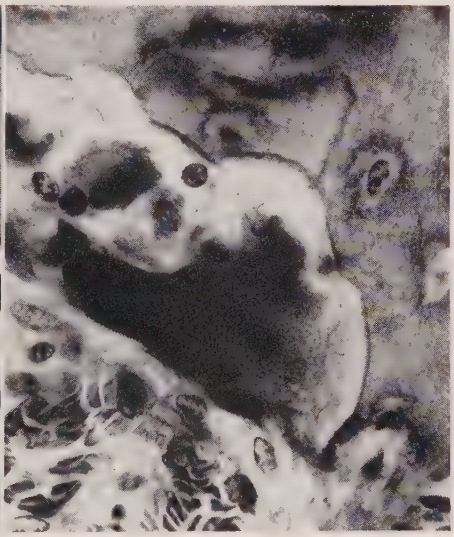


Fig. 1058.

Figs. 1057 and 1058.—Osteoclasts in Howship's lacunae are shown in these photomicrographs. (×700.) Note the sharp margins of the resorbing bone. (Photographs supplied by Drs. Weinmann and Sicher.)

Phosphorus is abundant in ordinary foods and a deficiency in intake is less likely to occur than in the case of calcium. The absorption of phosphorus from the intestinal tract is regulated in part by the amount of calcium in the diet and by the mechanisms that have to do with calcium absorption. In this way it is possible to have phosphorus deficiency in combination with calcium deficiency.

In the disturbances that lead to excessive mobilization of calcium from the bones, as for example, hyperparathyroidism, phosphorus is also mobilized. It is apparent, therefore, that the metabolism of calcium and phosphorus, including mechanisms of assimilation, excretion, and utilization, is so intimately related that both substances must be considered in all pathologic disturbances affecting one or the other substance.

Among the more important and revealing microscopic features of bone are the linear markings that remain after decalcification and stain intensely with hematoxylin. Such markings are called cement lines since it is evident that they represent the zones of junction between lamellae or between layers of bone that have been formed at different times. Thus, like the growth rings of trees, these lines furnish records of growth that can be interpreted by the morphologist. In the case of bone such markings also provide a means of estimating the amount of change in architecture that has resulted from resorptive and formative activities. It will be noted subsequently that the characteristic microscopic features of Paget's disease are dependent to a large extent on the increased number and bizarre design of these cement lines.

The structural pattern of osseous tissues is subject to change in accordance with functional demands. The precise mechanisms that may be responsible for the resorptive processes are as yet unknown. Some observers believe that endosteal and periosteal cells are capable of removing bone in addition to forming it. Still other observers hold that the salts and matrix of bone may be removed by "humoral" mechanisms. It is generally conceded, however, that osteoclasts are in some manner directly concerned with the resorption of osseous tissues. (Figs. 1057 and 1058.)

The functions of the bony structures of the body are well known. They include weight-bearing, provision of a means of locomotion, provision of protected compartments for vital organs, provision of well-adapted sites for hematopoiesis, and the provision of a readily available store of calcium and phosphorus. The morphologist, being aware of these functions, can frequently observe gross and microscopic alterations in cellular and structural patterns that permit an evaluation of the kind and

amount of disturbance of physiology that is taking place or has occurred previously. The chemist, by suitable studies on calcium and phosphorus metabolism and phosphatase, may be able to demonstrate altered values that conform with the morphologic patterns. Such relationships are best exemplified by the combined mineral metabolism and histologic studies in hyperparathyroidism, renal rickets, and rickets.

DISEASES OF BONE

Nonspecific Pathologic Disturbances

Atrophy and Osteoporosis.—Diminution in the gross density of bone occurs in association with a variety of unrelated disorders. In rare instances a single bone may atrophy without any demonstrable local or general cause.[6] Localized atrophy may result from pressure applied to bone from without or from within. Examples of atrophy resulting from compression are found in expanding aneurysms (Fig. 1059), benign or malignant tumors, and localized collections of abnormal cells such as those that are observed in certain lipoid storage diseases. Osteoporosis limited to one or several bones may result from disuse. This is frequently noted in roentgenograms that are made following rigid splinting or mechanical fixation of an extremity. It is also observed in conjunction with ankylosis of joints from rheumatoid arthritis or other causes. Reduction in blood flow to an extremity may result in osteoporosis but it is probable that hyperemia of traumatic or inflammatory origin may also be attended by osteoporosis. It is also well known that destruction of the peripheral nerve supply, such as occurs in leprosy, will be followed by localized osteoporosis or even complete resorption of the bony tissues distal to the nerve lesion. The actual mechanisms involved in local bone absorption are not known. It is probable, however, that impairment of nutrition mediated through diminished blood flow is one important factor and that increased pressure upon the bone surfaces is another. While evidence of osteoclastic activity (lacunar absorption) may be observed on microscopic examination in some specimens, it seems probable that other mechanisms must be operative to account for the numerous examples of bone atrophy in which osteoclasts are not in evidence.

Generalized osteoporosis is observed in certain nutritional disturbances, as for example in scurvy, in which the mesenchymal cells, including osteoblasts, are unable to form or maintain the normal amount of intercellular substance. It is seen also in disorders of mineral metabolism such as hyperparathyroidism, rickets, osteomalacia, and long-standing hyperthyroidism. Women in the postmenopausal period sometimes develop osteoporosis that is most marked in the spine.[7] Some degree of generalized atrophy of bone (osteoporosis) frequently accompanies the onset of old age (senile osteoporosis). Hypercalcinemia is not a feature of the osteoporosis associated with either senility or the postmenopausal state.[8]

The mechanisms that may be held responsible for generalized osteoporosis include at least three possible disturbances operating singly or together. They are: (a) inadequate amounts of available minerals, (b) excessive mobilization of bone salt, (c) inability of osteoblasts to form and maintain the organic matrix of bone. The latter defect may result either from hormonal influences or from general or specific inadequacies in nutrition. Osteoclastic (lacunar) absorption is prominent in certain examples of generalized osteoporosis, as for example, hyperparathyroidism, but in other diseases such as senile osteoporosis no such mechanism is apparent in the majority of instances. It is possible that the rate at which the resorptive process is taking place may be of importance in determining the number of observable osteoclasts.

Hypertrophy.—Isolated bones of excessive size or density are occasionally observed in persons whose skeletons are otherwise normal. Such lesions may arise from the stimulation of the bone-forming cells (periosteal or endosteal layers) because of low-grade inflammation that is caused by infectious agents or trauma. In a similar fashion, slowly growing neoplasms may stimulate excessive growth of bone leading to well-defined hyperostosis. This is frequently noted in meningiomas.[9] Hypertrophy of bone may result from excessive blood flow from congenital or acquired malformation of vessels. Abnormalities in endochondral ossification may give rise to single or multiple sites of osseous overgrowths that remain as permanent deformities.

Among the localized overgrowths of bone, one of the most common is the enostoses of the calvaria. This is a lesion of uncertain origin that consists of irregular knobs and ridges of bony tissue converging toward the nasal end of the metopic suture on the interior surface of the skull. Usually these bony masses are exceedingly dense and the diploë is obliterated in the involved portion of the skull. Occasionally, however, they are made up of porous or cancellous bone. The dura mater is usually adherent to the affected parts. Enostosis of the calvaria was observed in 7 per cent of 3,250 autopsied subjects and the incidence was highest in the sixth and seventh decades.[10] (See also page 966.)

Bone hypertrophy affecting a few or many of the bones of the extremities is seen in secondary osteoarthropathy and in osteitis deformans (Paget's disease) where the skull may also be affected.

Generalized overgrowth of the osseous parts forms the most striking feature of acromegaly and the gigantism caused by pituitary dysfunction. These disturbances will be referred to elsewhere.

Lines of Arrested Growth.—Roentgenograms of the long bones of children will occasionally contain one or more transversely placed lines of increased density in the expanded metaphyseal ends of the shafts. Such markings are known as arrested growth lines since they can be correlated with periods of illness or periods of malnutrition. Anatomic studies, including the microscopic examination of appropriate sections, have revealed that these lines are caused by the presence of heavy and transversely placed trabeculae. The latter result from a slowing or cessation of the normal sequences of endochondral ossification. When normal endochondral

bone growth is re-established, the relatively dense layer of calcified cartilage and bone that has formed during the illness remains and can be demonstrated in the x-ray films or in microscopic sections that are examined under very low magnification. Through the usual process of growth and remodeling of the bone shaft, these lines are gradually reduced and finally destroyed.

Lesions Produced by the Ingestion of Lead and Fluorine.—

LEAD.—Roentgenograms of the long bones of infants and children who have ingested sufficient quantities of lead will show broad bands of dense bone at or near the metaphyseal ends of the diaphysis. These densities occur in normally arranged but somewhat thickened trabeculae. It has been noted that the trabeculae corresponding to the zone of increased density in the x-ray film are comprised mainly of calcified cartilage and that large and acidophilic giant cells are present between them. It seems probable that the lead is deposited simultaneously with the bone salt and that the calcified cartilage matrix so impregnated resists the resorptive mechanisms by which it is normally removed as new osteoid tissue is laid down. The increased density in the x-ray shadow is probably caused in part by the excess opacity of the heavy metal as compared to normal bone salt.

Similar changes may result from the ingestion of other heavy metals such as phosphorus and arsenic.

FLUORINE.—Ingestion of excessive quantities of fluorine by children results in the formation of tooth enamel that contains chalky-white patches that may later acquire a brownish stain (mottled enamel). The observation that teeth affected in this manner have an increased resistance to decay has led dentists and public health workers to undertake an evaluation of the effectiveness of controlled administration of fluorine in drinking water as a preventive measure against dental caries. See also discussion on page 156.

The effects of fluorine upon osseous tissues has been noted in workers in cryolite factories, in people in certain regions in India,[11] and in

Fig. 1059.—Pressure erosion of the vertebral bodies caused by an aneurysm of the arch of the aorta. Note the somewhat better preservation of the nonvascular intervertebral discs.

animals experimentally treated[12] or spontaneously exposed while grazing near factories or volcanoes where fluorine-containing gases were emitted.[1] It seems probable that the anatomic changes resulting from fluorine intoxication vary greatly according to the age of the animal and the dosage of the mineral. In older animals the bones may become dense and sclerotic, whereas, in the young animals, especially when given large doses of fluorine, the osseous tissues are likely to show excessive porosity. Abnormality in calcium deposition in bone is indicated by the presence of small and large isolated crystals. Interpretation of the pathologic changes is made difficult by the frequent association of renal damage, metastatic calcification, and hyperplasia of the parathyroid glands.[1]

Congenital, Developmental, and Hereditary Abnormalities

Localized Deformities

A wide variety of localized abnormalities have been recorded. Some of these may originate from fetal or postfetal injuries, while others may result from inherited traits. Certain bones, especially those of the extremities, may fail to develop (aplasia). One or more limbs may be absent (amelus), and deformities in which the hands and feet are attached directly to the trunk (phocomelus) have been described. Fusion of two contiguous or closely placed bones or branching of a single bone may also occur as developmental faults. In contrast to these local disturbances there are a number of symmetrical or generalized malformations of bone that are of greater interest to the pathologist.

Symmetrical or Generalized Deformities

Cleidocranial Dysostosis.—This is a familial and usually hereditary disturbance in which, in association with retarded closure of the fontanels, one or both clavicles are absent or hypoplastic. In addition, in some cases, there is protrusion of the mandible and hypoplasia of the lacrimal and zygomatic bones. The hypoplasia or aplasia of the clavicles enables the affected subject to move his shoulders abnormally, even to the point of touching them together in front of the sternal notch.

Chondrodystrophia Fetalis (Achondroplasia or Chondrodysplasia).—Chondrodystrophia fetalis is a skeletal disease in which there are profound disturbances in endochondral ossification. The disease is hereditary and is said to be transmitted as a simple dominant mendelian factor. As a result of the defective growth and maturation of cartilage, the bones of the extremities are short and thick (Figs. 1060 and 1061). Similar changes occurring at the base of the skull lead to a reduction in the length of the cranial base, deep saddling deformity of the nose, and relative or actual protrusions of the mandible and frontal bones. Most circus casts include one or several such achondroplastic dwarfs, so that the composite picture of the deformity is well known.

The achondroplastic dwarf possesses normal intelligence and shows no evidence of glandular dysfunction. Although many die at birth or shortly thereafter, others live to become adults and to propagate the inherited traits.

Examination of the skeletal tissues indicates that the primary disturbance resides wholly, or in large part, in the proliferating cartilage. The cells of the growth cartilage fail to align themselves into columns and to pass through the normal stages of proliferation, maturation, retrogression, and invasion in an orderly manner by the capillaries from the adjacent bone. Instead, irregular masses of cartilage are built up, producing thick, nodular, and bulky epiphyses that undergo calcification and ossification irregularly (Figs. 1060 and 1061). This results in the formation of short bones that are wide and dense. The ends of the bones are often expanded to such an extent that they have been likened to collar studs. All bones that are developed in cartilage are affected to greater or lesser extent. The ribs show deformities at the costochondral junctions and the pelvis may be of small size or flattened in one or more directions.

Chondro-osteodystrophy (Morquio's[13] Disease).—This disorder of skeletal growth is similar in many respects to chondrodystrophia fetalis. Although congenital, the signs and symptoms of the disease may not be recognized until a few years after birth, when it is noted that the vertebral bodies are wedge-shaped and otherwise deformed. This gives rise to kyphosis that becomes noticeable as the child assumes an upright position.[14] Other skeletal deformities such as depression of the sternum, enlargement of the costochondral junctions, enlargement of the wrists and knees, and distortion of the cranial base, may be observed. Roentgenographic examination reveals distortion and irregular calcification of the cartilaginous epiphyses and this is confirmed by pathologic examination. This form of chondrodystrophy is apparently hereditary in origin and sex-linked. Males are affected, and twenty cases were observed by Jacobson[15] in five generations of one family.

Hereditary Multiple Exostoses.—Unlike chondrodystrophia fetalis, which is apparent at birth, this skeletal disorder develops gradually during childhood. About half of the offspring of an affected subject manifest the disorder. The disease may be transmitted through unaffected females.[16] Males are affected oftener than females (in a ratio of about 7:3). The pathologic disturbances arise from the growth of multiple cartilaginous exostoses at or near the bony epiphyses. Chondrosarcomas sometimes arise from one or more of these lesions, particularly in adults. Individually the overgrowths are no different from osteochondromas that arise singly, and for this reason they require no further comment at this time.

Ollier's Disease.—This poorly defined disturbance in skeletal growth and development may represent a variant of the other diseases affecting endochondral ossification.[17] Skeletal involvement may be limited to a single bone or to several long bones on one side of the body. In some instances the disorder is more widespread. Abnormalities in endochondral ossifica-

Fig. 1060.

Fig. 1061.

Fig. 1060.—Chondrodystrophia fetalis. A midsagittal section of a tibia from an infant is shown. The diaphysis is short, wide, and dense. The epiphyses are enlarged and nodular, and show multiple centers of calcification.

Fig. 1061.—Chondrodystrophia fetalis. Imperfect alignment of epiphyseal cartilage cells, and consequent irregularity in calcification and ossification associated with achondroplasia is shown. (×230.)

tion, beginning in the first or second year, give rise to deformities which remain after skeletal growth has been completed. No convincing evidence of hereditary transmission has been furnished.

Fig. 1062.—Marble bone disease. Roentgenogram of the pelvic bones and femurs of a 5-year-old child. There is well-marked clubbing and transverse layering of the femurs. (After W. M. Clifton, A. A. Frank, and S. Freeman: Am. J. Dis. Child. 56: 1020, 1938.)

Melorheostosis.—Derived from two Greek words meaning "limb" and "I flow," this term refers to an obscure disorder of bone which was described by Léri and Joanny in 1922.[18] Melorheostosis may be regarded as a form of developmental hyperostosis which begins in infancy or early childhood and progresses slowly thereafter. Usually one or more bones in either one upper or lower extremity are affected but occasionally the process may be bilateral in distribution and more generalized. The affected bones are thickened and have flat, irregular and overhanging cortical overgrowths that are reminiscent of the wax drippings along the surface of a partially burned candle. Microscopically, the thickened cortex is excessively dense and shows an irregular lamellar pattern. Occasionally the bony overgrowths are capped with cartilage in a fashion similar to chondral exostoses and this feature may indicate the manner of initial development of the hyperostosis.

Gargoylism (Hunter-Hurler Disease, Dysostosis Multiplex, Lipochondrodystrophy).—This disorder represents an atypical chondrodystrophy combined with a disturbance of lipoid metabolism (see Skeletal Changes Associated With Storage of Lipoids, page 1215). In its complete form gargoylism is manifested by striking clinical, radiologic, and pathologic features.[19] Mental retardation, coarse facial features, enlargement of liver and spleen and bizarre deformities of the trunk, extremities, and head comprise the more obvious abnormalities. Corneal opacities are frequent. Pathologic examination of the skeletal parts reveals irregularities in endochondral ossification, variations in size, shape, and density of the diaphyses of long bones and varying degrees of fibrosis and lipoid storage in marrow tissues. Abnormal deposits of lipoid in nerve and in certain parenchymal cells and in reticulo-endothelial cells suggest a relationship of gargoylism to other disturbances of lipoid metabolism. The disorder is believed to have a genetic origin dependent upon a recessive factor.[19]

Marble Bone Disease (Albers-Schönberg Disease or Osteopetrosis).—This uncommon but exceedingly interesting hereditary disorder of the skeleton appears to be transmitted as a simple recessive mendelian character. Not infrequently the disease has been observed in the offspring of parents who are closely related. The disturbance is usually congenital but its manifestations may not be recognized until some time after birth. The symptomatology is related to the fragility of bone (fractures), to the sclerosis of the skeletal parts (osteosclerotic anemia), and to the narrowing of the foramina (deafness, and impairment of vision). In spite of the excessive density and increased hardness of the osseous tissues, fractures from trivial causes are frequently observed. In association with anemia there may be extreme degrees of extramedullary hematopoiesis. In the case represented by Figs. 1063-1066, anemia was the dominant symptom. Biopsy of one of the enlarged superficial lymph nodes disclosed pronounced hematopoiesis. Subsequently, at autopsy, it was noted that all lymphoid tissues, as well as the liver and kidney, were the sites of blood cell formation.

Roentgenograms of patients with marble bone disease show remarkably dense bony structures in all skeletal parts that are formed in cartilage (Fig. 1062). In some instances the distal portions of the shafts are club-shaped and present alternating transverse zones of bone of varying densities (Fig. 1062). The bodies of the vertebrae, pelvic bones, and ribs are conspicuously affected. On gross examination the bones are extremely dense, and sawing is difficult because of the unnatural hardness. Cross section through the diaphysis of the long tubular bones reveals that the medulla is filled with the same dense bony tissue that forms the cortex. No marrow spaces are visible. While it is difficult to section such a bone with the saw, it is easy to induce a fracture by the application of moderate stress. The fracture occurs suddenly, indicating

unnatural fragility. Indeed, one is reminded of the manner in which a stick of hard candy breaks under slight to moderate tension.

Microscopic examination of cross and longitudinal sections of the bones that are formed in cartilage reveals a picture that is monotonous in its regularity. At the epiphyseal cartilage plates one observes dense and heavily calcified spicules of cartilaginous matrix that are wider than normal (Fig. 1063). Such spicules remain throughout the shaft and become surrounded by osteoid matrix which becomes heavily calcified (Fig. 1065). In cross section it is noted that little or no marrow tissue exists (Fig. 1064). These morphologic features seem to imply that the cartilaginous matrix in the provisional zone

Fig. 1063. Fig. 1064.

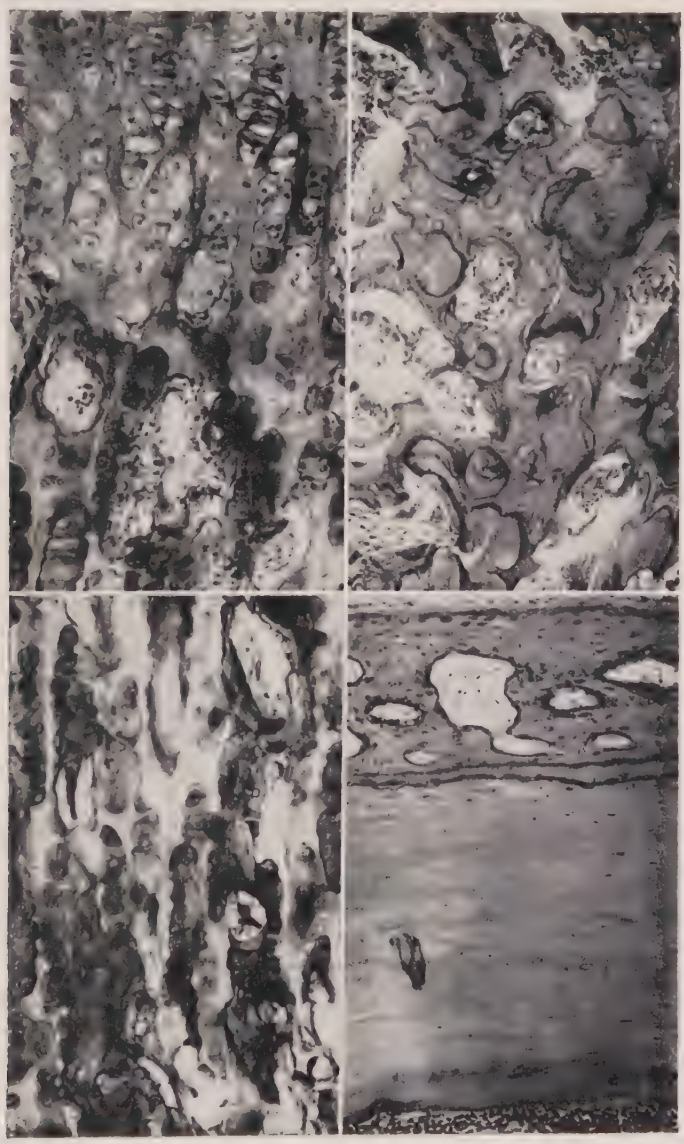


Fig. 1065. Fig. 1066.

Figs. 1063, 1064, 1065, and 1066.—Abnormalities of architecture in bone formed in cartilage are illustrated in these reproductions (×210). The increased amount of calcified cartilage matrix at the zone of endochondral ossification and the irregular penetration of marrow blood vessels are indicated in Fig. 1063. Persistence of these columns of calcified cartilage matrix and addition to osteoid matrix to further narrow the marrow spaces are illustrated in sections (longitudinal, Fig. 1065, and transverse, Fig. 1064) from the midshaft regions of the femur. In a section of the membranous bone of the skull (Fig. 1066) the osseous tissue is well formed and devoid of the characteristic features of marble bone disease (Fig. 1066, ×130).

of the epiphyseal plate is excessive in amount and heavily calcified. Furthermore, it is evident that the normal remodeling processes do not occur and that the calcified cartilage matrix is not removed. Osteoclasts are rarely observed. It seems likely, therefore, that this skeletal disorder results from an imbalance between the formative and resorptive mechanisms that are normally present. Membranous bones, such as the flat segments of the skull, are altered little, if at all, in marble bone disease (Fig. 1066).

Osteogenesis Imperfecta.—This hereditary disorder is apparently transmitted by a dominant gene. In one family of 51 members in five generations, 27 persons were affected.[20] Although the disease is usually apparent at the time of birth, it may not be recognized until later in childhood (osteogenesis imperfecta tarda, osteopsathyrosis). In the congenital form, the manifestations are striking and in numerous instances the infant is stillborn or lives only a short time after birth. The pre-

Fig. 1067.—Osteogenesis imperfecta. A hemisection of the body of an infant deformed as a result of osteogenesis imperfecta. The skull is thin and transparent. Multiple fracture sites are apparent in the ribs, and the upper and lower extremities are deformed as a result of old and recent fractures.

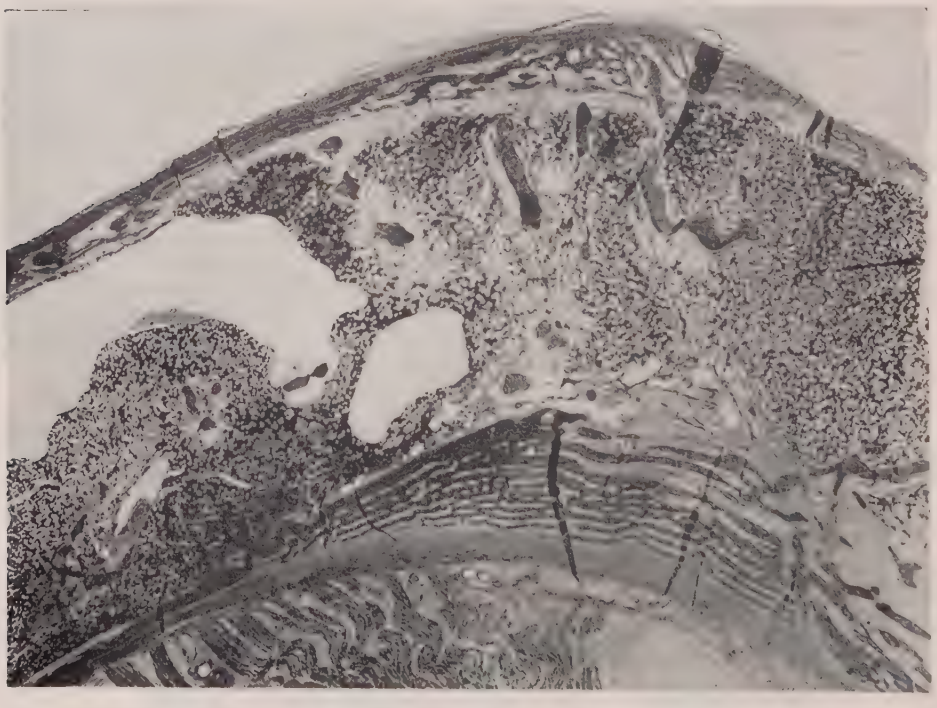


Fig. 1068.—Longitudinal section of tibia through the site of an old fracture. The cortex is extremely thin and delicate. It is clearly apparent that the fracture has healed and that new layers of bone are forming on the concave surface, a mechanism by which such deformities are usually corrected or modified. (×9.)

dominant manifestations of the disease (fractures) are related to the porosity and fragility of bone. Multiple fractures are usually present at the time of birth and deformities indicative of fractures acquired in utero are frequently observed (Fig. 1067). In surviving children, there is often a lessened susceptibility to fracture at and after puberty.

Some observers have elected to regard osteogenesis imperfecta as a disorder in which there is hypoplasia of the mesenchyma in general. In support of this contention it is noted that the sclerae of the eyes may be thin, allowing the pigmented layers to show through (blue sclerotics), that the dentinal structures are poorly formed (dentinogenesis imperfecta), and

Fig. 1069. Fig. 1070.

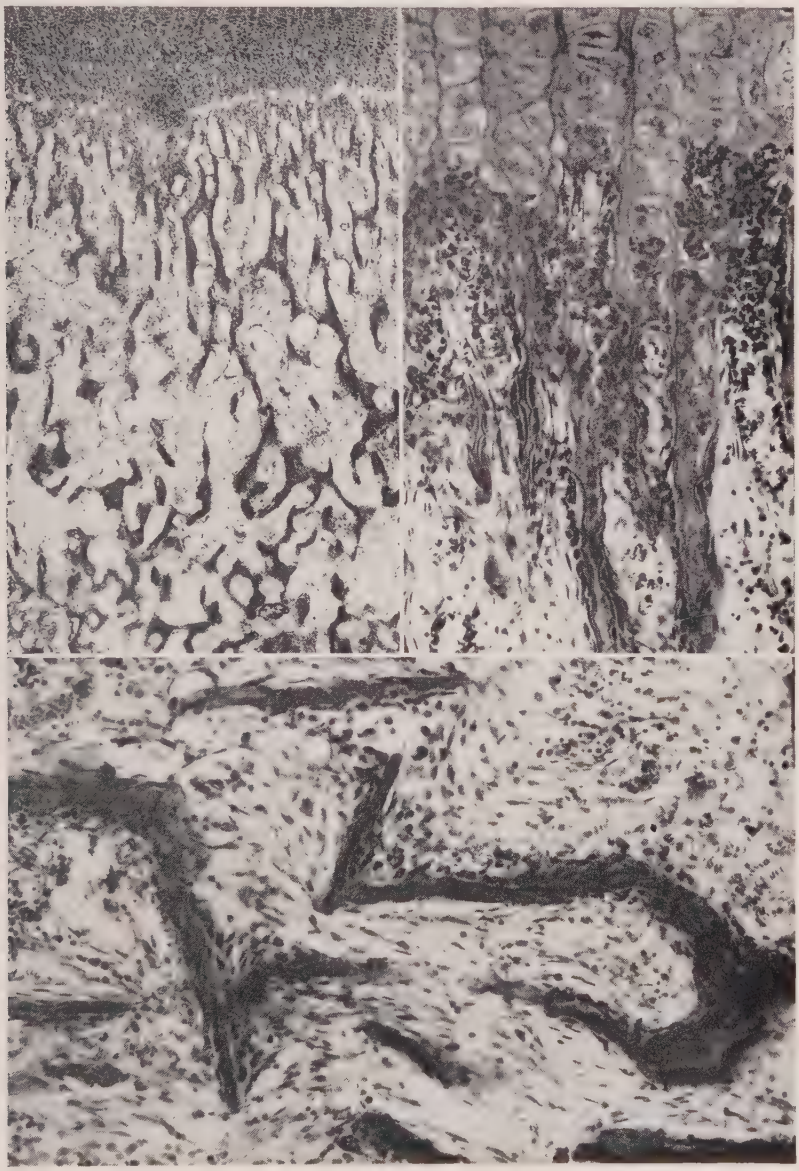


Fig. 1071.

Figs. 1069, 1070, and 1071.—Osteogenesis imperfecta. The normal mechanisms of endochondral ossification are clearly apparent in Fig. 1069 (×40) and Fig. 1070 (×250) from the femur of an infant with osteogenesis imperfecta. The individual trabeculae are delicate, and often fractured, Fig. 1071 (×250). Note the increased cellularity of the bony tissue and the relative scarcity of matrix.

that certain other connective tissues may be delicate and thin.

Roentgenologic and macroscopic examination of the skeletal parts reveal extremely porous and delicate bones. Deformities from recent, old, and unhealed fractures are also apparent. It is possible in some instances to section the undecalcified bones with a knife. Care must be taken, in performing an autopsy, to prevent additional postmortem fractures.

Microscopically, the bony tissues are thin and delicate (Figs. 1068-1071). The cancellous trabeculae are few in number and may show microscopic fractures (Fig. 1071). Individual spicules of bone contain numerous, closely placed osteocytes that are surrounded by only small amounts of matrix (Figs. 1070 and 1071). Fractures heal readily but the newly formed trabeculae are thin and fragile like the original bone (Fig. 1068). No disturbances are noted in the sequences of endochondral ossification (Figs. 1069 and 1070).

This skeletal disease bears no apparent relationship to any endocrine dysfunction or to disturbances in mineral metabolism. It seems probable that imperfections in the quality and quantity of intercellular matrix of certain mesenchymal tissues are the essential defect.

Traumatic Injuries

When a bone is traumatized, the endosteal and periosteal cells respond in a characteristic manner. Morphologically they change to plump, rounded or cuboid-shaped cells, and mitotic figures appear. These stimulated cells are capable of producing the intercellular matrix of bone (osseomucin) and they are presumed to give rise to an enzyme (phosphatase) that plays an important role in bringing about the deposition of bone salt. Thus, the embryologic sequences responsible for intramembranous bone formation are reestablished as the result of injury, or as the result of stimulation of these specialized cells which form the immediate covering of osseous tissue.[21]

Fractures.—From the time at which a bone is fractured until complete functional and anatomic restoration has been accomplished, one may observe morphologic changes of a reparative nature. It is almost certain that these structural alterations are accompanied by chemical and physiologic adaptations that, although less obvious, are of equal or perhaps greater importance. The experiments of Stirling[22] and others have clearly indicated the importance of some of these mechanisms in the early stages of bone repair.

Although the processes by which a fractured bone is restored to normal are continuous, it is convenient to discuss them in four stages depending on the length of time since injury:

1. Development of Hematoma and Traumatic Inflammation.—Simultaneously with the occurrence of a fracture, the soft tissues within and around a bone are injured. The periosteum is torn or detached from the outer surface of the cortex, the endosteum is stripped from the surfaces of the marrow or vascular spaces within bone, and the marrow tissue is disrupted. Blood vessels and capillaries in all the adjacent soft tissues, as well as within the intraosseous vascular channels, are injured or disrupted. Such an injury results in the production of a hematoma surrounding the ends of the fractured bone. Concomitantly there is hyperemia, extravasation of edema fluid and beginning inflammatory cell infiltration. Fibrin is formed at the periphery of the hematoma beneath the detached periosteum and between the ends of the fractured bone. The injured parts are thus cemented together by a loose-meshed fibrinous framework which serves as a scaffold upon which the subsequent granulation tissue may grow. In a fracture the detachment and displacement of the periosteum are greater at the level of the break than they are at more distant points. Thus, the area of hemorrhage and exudation assumes, at an early stage, a fusiform shape which is usually maintained throughout the process of healing.

2. Organization.—During the first twenty-four to forty-eight hours after injury the inflammatory and exudative changes increase. Leukocytes accumulate in large numbers. The tissues become swollen and indurated from the extravasation of blood and edema fluid. Fibrin precipitation increases steadily. These exudative phenomena are accompanied almost from the time of injury by increasing signs of stimulation of the fixed tissue cells. These cellular alterations represent the earliest demonstrable stages of repair. The fibrin clot between the ends of the fractured bone undergoes organization by means of an ingrowth of proliferating connective tissue cells and tubular sprouts of budding capillary endothelium (granulation tissue). In

addition to the numerous polymorphonuclear leukocytes that are present during the early stages, one now observes increasing numbers of mononuclear phagocytes that are apparently engaged in phagocytizing necrotic cells and tissue debris. Up to this point, one is unable to detect any noteworthy difference between the repair of a fracture and the healing processes involved in the case of an aseptic soft tissue wound. In each instance, delicate collagenous fibrils are

Fig. 1072.

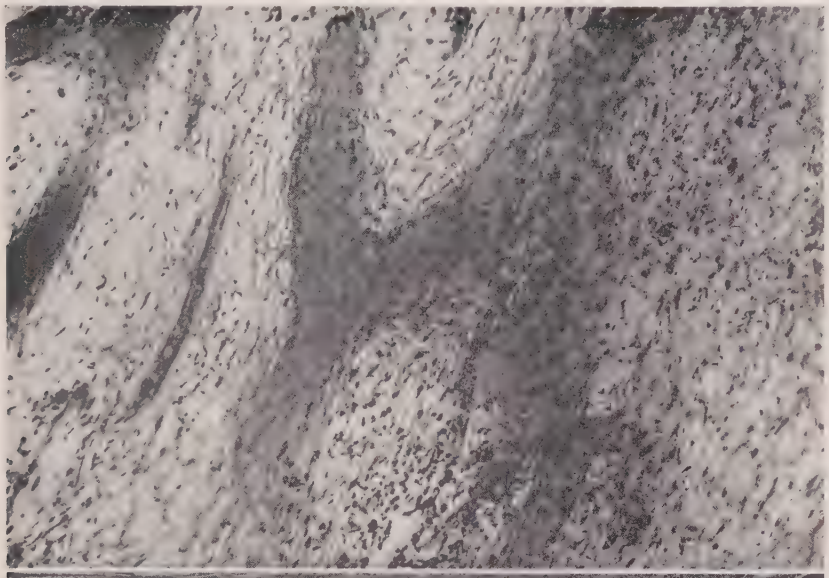


Fig. 1073.

Fig. 1072.—Repair of fracture. Granulation tissue undergoing ossification at the site of a recent fracture of the tibia. This type of bone formation is similar to that observed in normal intramembranous bone growth. (×250.) (After Bennett and Bauer, The Treatment of Fractures, ed. 11, Scudder, W. B. Saunders Co.)

Fig. 1073.—Repair of fracture. Subperiosteal and intermediate callus is evident in this low-power photomicrograph of a healing fracture of the tibia of a young child. (×8.) (After Bennett and Bauer, The Treatment of Fractures, ed. 11, Scudder, W. B. Saunders Co.)

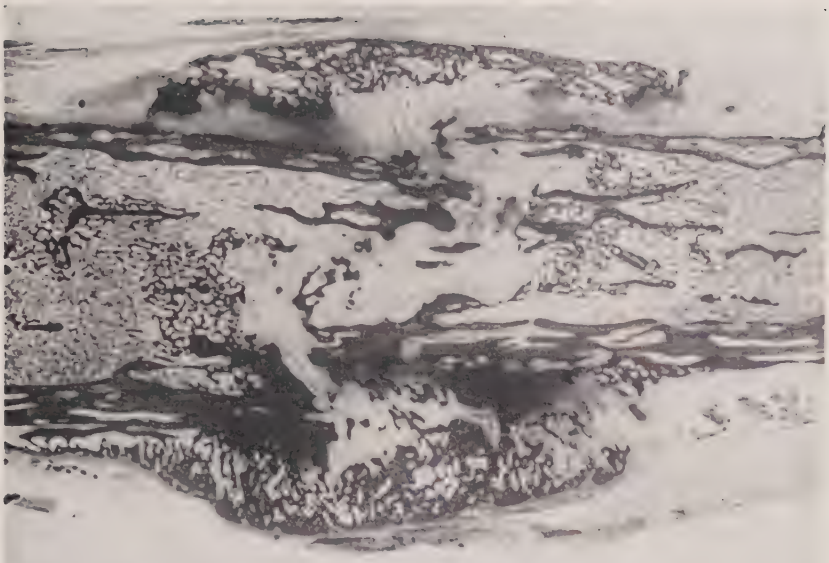
deposited between the proliferating connective tissue cells. However, in the case of a fractured bone, such fibrillar material is soon obscured by the deposition of a homogeneous hyaline matrix (osseomucin) (Fig. 1072). The appearance of this specialized intercellular matrix constitutes the first demonstrable evidence of bone formation.

A further difference between the manner in which bone and soft tissues react to traumatic injury is represented by the extent of regressive change. Owing to the peculiar origin and distribution of the blood supply in the case of bone, one will invariably see evidence of extensive necrosis. Within two or three days after injury such necrosis will be evidenced by empty lacunar spaces in the bone adjacent to the fracture line. Similar changes are apparent in any of the completely detached bone fragments. Microscopic and roentgenologic examinations at a later date reveal marked alterations because bone necrosis involves relatively large areas adjacent to the point of injury. The rate of absorption of such devitalized bone is extremely variable. It is probably caused initially by the local acidity of the medium and subsequently by the action of osteoclasts alone or in conjunction with other processes that are usually designated as humoral in nature.

3. Union by Callus Formation.—By the end of the first week, in most fractures, one can observe the process by which intramembranous bone formation takes place. While new and indistinct bars of homogeneous osteoid matrix are being deposited between the proliferating cells, one notes that the morphology of the connective tissue cells is undergoing modification. Certain of these elongated or branching fibroblastic-appearing cells assume new shapes and become rearranged. They now appear as round or cuboid-shaped cells. They then align themselves in solid rows along one border of each new bar of recently formed matrix and appear to aid in the deposition of additional osseomucin to that recently formed. The morphologic characteristics and obvious activity of these cells enable one to recognize them as osteoblasts. Further, microscopic observation demonstrates that certain of these cells eventually become surrounded by their own secretions, the intercellular substance, and thus become osteocytes. Such cells within lacunar spaces remain even though the bone spicule continues to grow. However, they are never completely cut off from the growing peripheral margins of the trabeculae because each cell develops cytoplasmic processes which maintain communication with similar processes of other cells. In this manner delicate, tortuous channels (canaliculi) are formed. Such canaliculi between lacunar spaces serve as the pathways by which metabolites are exchanged from blood to bone cells in the fully developed osseous tissue.

New osseous tissue, formed in the manner just described, is laid down beneath the detached periosteum to form a tubular sleeve of external callus. It is also deposited in the medullary canal near the ends of the fractured bone. Gradually such osseous tissue grows inward from the periphery of the hematoma and ultimately replaces it (Fig. 1073). In nearly all specimens of fracture repair, one is able to demonstrate areas of recognizable cartilage throughout the callus (Fig. 1074). In the early stages this tissue consists of a structureless mass of large spherical cells separated by homogeneous cartilaginous matrix. Later a more orderly arrangement of such cells takes place, with the formation of imperfectly arranged columns that resemble those of the epiphyseal cartilage plate. The cartilage cells in such areas undergo the same morphologic changes that one observes in normal endochondral ossification. The cells degenerate and the intercellular matrix calcifies. Simultaneously, there is capillary invasion of the degenerating cartilage cells and deposition by osteoblastic cells of osteoid matrix upon the spicules of calcified cartilage. In this manner the cartilaginous portions of the callus are gradually replaced by bone. A satisfactory explanation of the appearance of cartilage in bone repair is not readily apparent. However, the fact that it occurs in larger amounts in fractures where complete immobilization is difficult suggests that repeated stretching and twisting of the yielding callus may determine in part the character and amount of the

Fig. 1074.



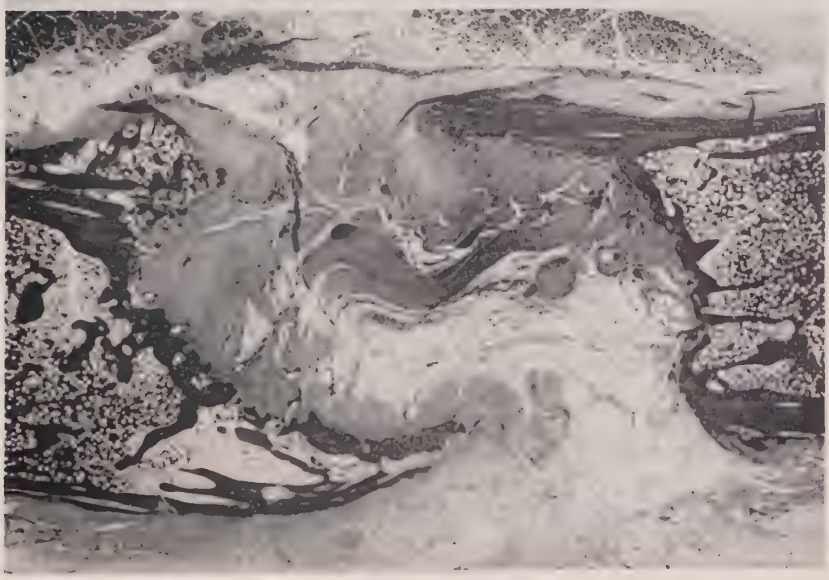


Fig. 1075.

Fig. 1074.—Repair of fracture. Photomicrograph (×8) of a ten-month-old fracture site in a rib of an elderly woman. The interlocking ends of the fractured bone are encased in abundant external and internal callus which is in part cartilaginous and in part bony. Although repair has been slow, it is evident that osseous union would eventually have occurred. The original bone cortex is atrophic. (After Bennett and Bauer, The Treatment of Fractures. ed. 11, Scudder, W. B. Saunders Co.)

Fig. 1075.—Repair of fracture. The fracture site, similar to that shown in Fig. 1074, has resulted in fibrous union, and no evidence of reparative changes remains. The medulla of each fractured bone end is closed by an osseous plate into which the dense connective tissue bundles insert. (×9.)

intercellular substance as well as the morphology and function of the proliferating cells.

During the period in which the above changes are taking place, one may, with appropriate techniques, demonstrate that increasing amounts of mineral salts are being deposited in the intercellular matrix of both the osseous and cartilaginous tissues. The exact mechanism by which this is accomplished is not clearly understood. It seems probable, however, that the bone salts that are dissolved from the fractured bone ends and detached fragments are redeposited. Such solution of bone salts may result initially from increased acidity of the hematoma[22] and later through resorptive changes caused by osteoclastic activity alone or in conjunction with other cellular and humoral processes. Calcium and phosphate are also furnished to the site of repair by the blood. The actual deposition of bone salt is probably governed by many biologic and chemical factors. It is known that osteoblasts and degenerating cartilage cells are responsible for the secretion of the enzyme phosphatase. This enzyme, by breaking down the more complex phosphate compounds, causes a local increase of phosphate ions and in turn a supersaturation of the blood and tissue fluids with calcium and phosphate ions to bring about the deposition of bone salt in a solid form. It has been shown that after the first week in fracture repair the reaction of the medium becomes more alkaline, eventually reaching a pH range in which alkaline phosphatase is capable of reacting.

4. Rearrangement of Callus and Bony Union.—In an ordinary fracture the callus attains its maximum size in two or three weeks. There is a progressive increase in its density as observed by roentgenologic examinations. This is due to the continuous addition of new osseous tissue and the progressively increasing deposition of bone salt.

On microscopic study one observes that the first callus that is laid down is formed largely of trabeculae that radiate transversely from the shaft of the bone. This is the external or subperiosteal callus. In other regions, as for example, between the ends of the fractured bone, the initial callus has little, if any, discernible structure (Fig. 1073). However, within a period of one to two weeks it will be noted that a rapid rearrangement of the newly formed bone is taking place. This is accomplished by resorption of certain portions of the trabeculae that were first formed and by the addition of new bone to other portions of the spicules. It seems evident that this rearrangement is determined largely by the stresses and strains to which the callus is subjected. Concommitantly with the rearrangement of the newly formed bone, one can observe changes that indicate the continued resorption of the original osseous structures and the development of firm attachments between the old and the new bony parts. The amount of osseous tissue comprising a callus gradually diminishes. This process of adaptation continues for many months or years and may, in the more perfect examples of repair, lead to the complete removal of all traces of the injury and the bony overgrowth by which repair was accomplished.

Delayed Union and Nonunion.—There is a wide variation in the time required for complete healing of a fractured bone, and many factors influence the rapidity and perfection with which the repair process is carried out. However, if one eliminates from consideration such factors as interposition of soft tissues between the fractured bone ends, infection, gross disturbances in the nutrition of the individual, and marked impairment of the blood supply to the part, it may be expected that nearly all fractures will heal in a reasonable period of time. There can be little doubt that adequate immobilization is one of the most, if not the most, important factors in promoting rapid and complete union of a fracture. During the stages of granulation tissue growth and early calcification of the callus, any twisting or shearing motion will lead to tissue injury. Continuance of such injury leads to the formation of large amounts of cartilage. In the unfavorable cases the cartilaginous and bony callus is replaced by more yielding fibrous tissue which, upon reaching maturity, will not revert to bone (Fig. 1075). Occasionally a pseudarthrosis results (Fig. 1076).

Bone Graft.—When fibrous union or nearthrosis has developed, it is necessary for the surgeon

to induce the formation of new granulation tissue before bony union can be expected. In the majority of instances a bone graft is inserted at the site of the old fracture. Such a procedure accomplishes a number of things, all of which favor repair. In the first place the operation produces a new injury to bone that will be followed by the growth of new granulation tissue. The implanted graft ordinarily gives support to the fracture line and frequently brings about complete internal fixation. In addition the implanted bone serves as a framework through which the new granulation will grow. It also provides a local source of bone salt that seems to favor satisfactory repair. It has been clearly established that most, if not all, of the engrafted bone becomes devitalized. At most, only the cancellous portions are capable of surviving the injury and interruption of circulation. It is remarkable, therefore, that a bone graft is as valuable as it is known to be in fracture repair. Its function as a lattice or trellis for ingrowth of granulation tissue and its support to the area while old devitalized bone of the graft is being removed and replaced by new bone (creeping substitution) is apparently most important.

Posttraumatic Osteoporosis of Bone.—The atrophy that is usually discernible following a fracture is due in part to disuse. It is probable that local hyperemia is also a factor in bringing about the resorptive changes. A somewhat different form of atrophy is seen in conjunction with certain injuries to the extremities, especially the wrists, ankles, hands, and feet. Roentgenologic evidence of patchy osteoporosis is present. Clinically the amount of swelling and induration of the soft tissues overlying the affected bone may be great and the pain is often severe. The cause of these changes is not known, although favorable results from periarterial sympathectomy has been reported.[23] Sections of excised bony parts may show nothing other than atrophy.

Traumatic Myositis Ossificans.—In distinction to *progressive* myositis ossificans which usually begins in childhood without assignable cause and progresses slowly to a fatal termination, *traumatic* myositis ossificans is a localized lesion which results from single or multiple injuries. Repeated bruising injuries of the adductor or quadriceps muscles of the thigh or single contusions of these and other areas are followed in some instances by inflammatory changes that ossify. The character of the lesion is usually determined by examination of a roentgenogram (Fig. 1077). Microscopic examination reveals, in the early stages, widespread edema and mild inflammation of muscle. In some cases, recent or old hemorrhage is indicated by extravasated corpuscles or hemosiderin pigment. Proliferation of fibroblasts and osteoblasts may be very marked. The exact nature of the lesion is recognized by the presence of osseous tissue (Fig. 1078) which usually resembles callus. Care must be exercised to distinguish myositis ossificans from bone-forming neoplasms (osteogenic sarcoma). The occurrence of such malignant tumors in myositis ossificans has been described.[24] In older lesions there may be little or no residual inflammation and the bone may be dense and heavily calcified.

Traumatic myositis ossificans is usually seen in lesions that arise close to bone, and the bone formation may result from displaced periosteum.

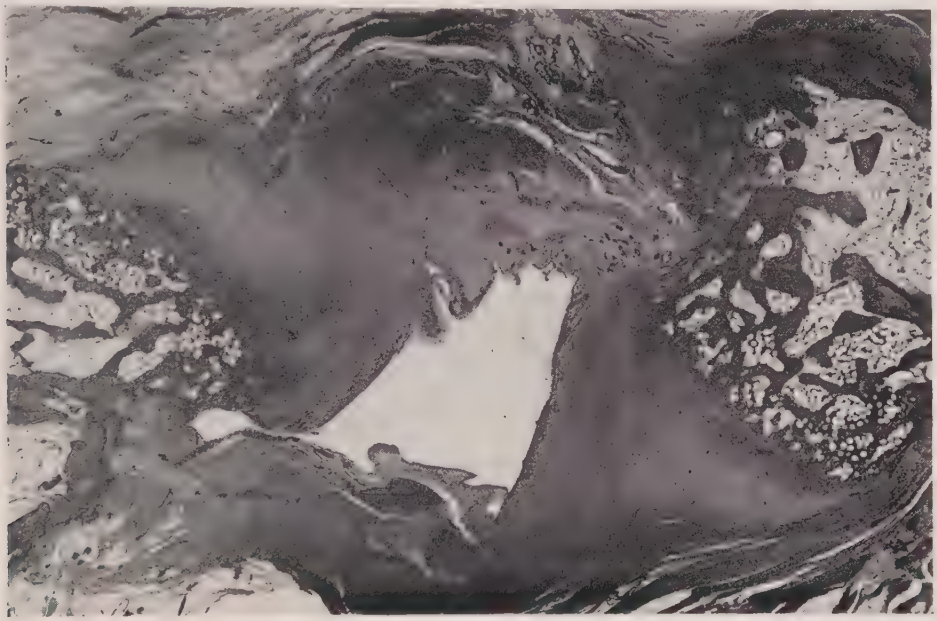


Fig. 1076.—Repair of fracture. In this fracture nearthrosis has resulted. Cartilage covers each fractured bone end and an articular cavity lined by synovial membrane has been formed. (×16.)

It seems probable, however, that undifferentiated fibroblasts, well removed from bony structures, may differentiate into osteoblasts and this may explain the lesions that have no apparent anatomic connection with a skeletal part. The lesion tends to be self-limited although regression may occur slowly. Trauma from repeated biopsy seems to aggravate the lesion, especially in early stages. According to Thorndike,[25] operative removal is indicated only in those cases in which the lesion occurs near a joint, in the origin or the insertion of a muscle, and then only from twelve to twenty-four months after the injury.

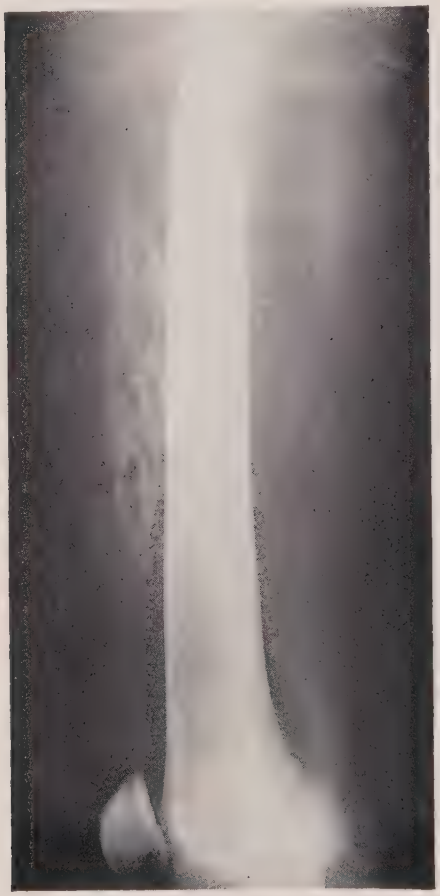


Fig. 1077.—Myositis ossificans. Roentgenogram showing ossification of muscles on the anteromedial aspect of the thigh. (AFIP No. 77648.)

Aseptic Necrosis.—Two types of aseptic bone necrosis may be recognized. One form, such as partial or complete necrosis of the head of the femur, following a subcapital fracture, is clearly related to trauma and probably results from reduction or obliteration of the blood supply. In patients in whom there are multiple fracture lines extending into the joint, bone necrosis with separation of one or more osseous fragments is especially likely to take place. Aseptic necrosis, in the form of bone infarcts, has been observed in caisson disease.[26] Similar infarcts unassociated with a known occupational disease have been described.[27]

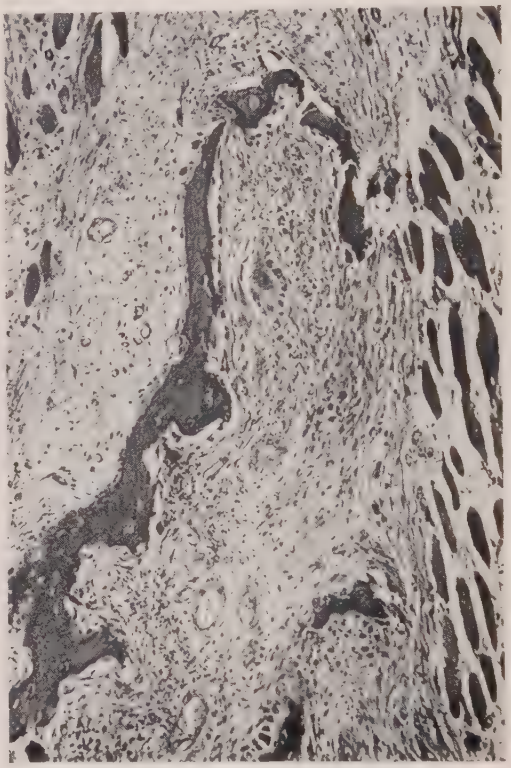


Fig. 1078.—Myositis ossificans. Edema and mild chronic inflammation of the striated muscle which is undergoing ossification are apparent in this reproduction of a section of typical myositis ossificans. (×130.) (AFIP No. 90710.)

The second form, usually referred to as idiopathic aseptic necrosis, occurs most frequently in the epiphyses of growing children. The tibial tubercle **(Osgood-Schlatter's disease)** and femoral head **(Legg-Perthes' disease)** are the foremost sites in the larger bones, whereas the scaphoid, semilunar, and metatarsals are the frequent locations among the smaller bones. These lesions, together with slipped femoral epiphyses, while affecting different skeletal parts, are basically similar and conform to the known picture of bone necrosis caused by ischemia.[28]

The etiology of such lesions remains obscure. Various theories, including low-grade infection, embolic occlusion of vessels, etc., have been suggested but have not been proved. A great deal of clinical evidence has accumulated suggesting that trauma is frequently a predisposing factor or perhaps an actual cause for the ischemia. That ischemia is vitally concerned is suggested by the fact that the bones or epiphyseal portions of the bones that are prone to become involved are largely surrounded by cartilage

and, under normal conditions, have a limited vascular supply.

In the early stages of the process one notes the disappearance of osteocytes from the bony trabeculae and perhaps mild inflammatory changes in the soft tissues. There is little change in architecture, however. The overlying articular cartilage usually remains viable since much of its nourishment is obtained from the synovial fluid. Later, the necrotic bone may crumble and collapse, giving rise to pronounced deformities in the x-ray film.[29] Repair of the lesion results from the ingrowth of bone-forming granulation tissue (creeping substitution). Such reparative phenomena are identical with the responses that lead to the organization and resolution of a bone graft.

Inflammation

Inflammatory lesions of bone (osteomyelitis) may be mild or severe. They may be sharply localized or diffuse throughout an anatomic unit and they may affect principally the periosteum, the cortex, or the marrow tissues in the cancellous portions of a bone. A high proportion of all inflammatory lesions result from the localization of an infectious agent that is readily demonstrable. The responsible bacterium may reach the site of localization by way of the blood stream, by direct extension from a neighboring focus of infection (periapical abscess of a tooth, sinus infection, infected joint or soft tissue abscess), or by a penetrating injury (laceration or compound fracture). Infectious lesions in bone behave quite differently, depending on the characteristics of the causative microorganism, the route by which the infection occurred, and the age of the patient. It is convenient, therefore, to consider inflammation of bone under several well-recognized classes of lesions.

Pyogenic Infections.—Any one of the pathogenic microorganisms may give rise to infections in bone. In osteomyelitis resulting from bacteremia (hematogenous osteomyelitis) the responsible agent is most frequently the staphylococcus. *Staphylococcus aureus* or *albus* may be isolated although the former is more frequent. Streptococci, pneumococci, and other forms of pyogenic bacteria are met with less frequently. In infants under two years of age, streptococcal osteomyelitis is encountered about twice as frequently as osteomyelitis caused by the staphylococcus.[30]

Acute hematogenous osteomyelitis is most common in children and affects in order of frequency the femur, tibia, humerus, and radius. It usually begins in the metaphyseal ends of the diaphyses of these bones. It is probable that the great vascularity of this zone of endochondral ossification is a factor predisposing to localization of bacteria. There is an initial violent, acute, exudative inflammation of the marrow tissues. The lethal effects of the toxins, together with thrombosis and obliteration of vessels from exudate in the bony spaces, lead at once to necrosis of the marrow and osseous parts (Fig. 1079). The process soon spreads through the vascularized channels to reach the external surface of the cortex. Thus, the periosteum is dissected from the cortex (subperiosteal abscess) further impairing the blood supply. Similarly the infection tends to spread elsewhere in the medulla of the bone. In this way a small or large portion of a bone becomes necrotic.

The epiphyseal cartilage, together with the firm and dense periosteal and perichondrial attachments around its margins, seems to offer a certain amount of resistance to the spread of infection, and the epiphysis is not regularly affected, nor is the joint. It should be remembered, however, that both of these structures may become secondarily involved or, less frequently, they may be the sites of primary localization of infection in the skeleton.

In certain instances the infection is localized to a small area where it may entirely resolve or become an abscess encased in a well-defined wall of fibrous or osseous tissue (Brodie's abscess). The periosteum overlying the latter may be irritated sufficiently to cause bone proliferation that results in considerable thickening of the cortex.

The more extensive infections result in necrosis of considerable portions of the involved bone. Subsequently, these devitalized segments become separated from the viable portions (sequestration). The sequestrum appears opaque in the roentgenogram and is frequently surrounded by irregular areas of lessened density (Figs. 1080 and 1081). On gross examination the sequestrum is usually grayish-white in color and has an irregu-

lar surface that is pitted and grooved. It is frequently surrounded by purulent exudate which may be draining from sinuses through the ossifying granulation tissue (involucrum) and overlying soft tissues (Fig. 1082). Such sinus tracts (cloacae) and the walls of the cavities

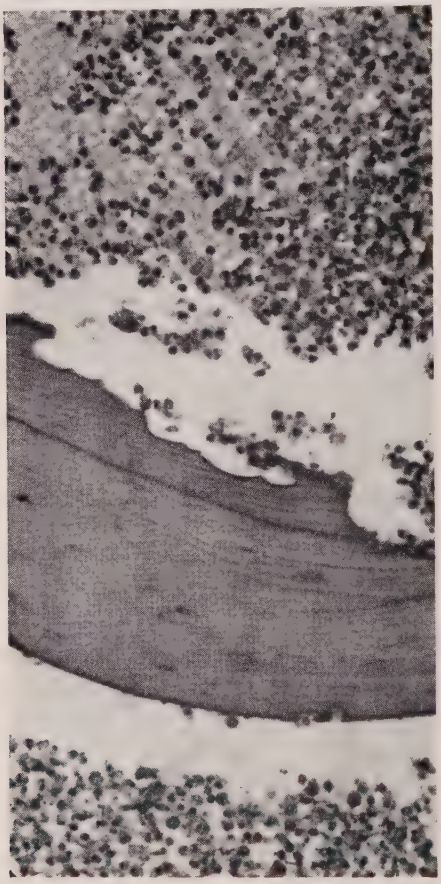


Fig. 1079.—Acute osteomyelitis. The fragment of bone in this photomicrograph contains empty lacunar spaces, and the bony margins are notched and irregular. The soft tissues of the marrow spaces are replaced by purulent exudate. (×265.) (AFIP No. 73820.)

containing sequestra are lined by granulation tissue. In most examples of chronic osteomyelitis one will find areas of acute and subacute inflammation in the cancellous spaces of the necrotic bone that has not completely separated from the viable portions. Hyperemia and active osteoclastic resorption are present in these areas as well as small and large foci of acute inflammation. Such resorptive changes account for the irregular areas of osteoporosis and represent the manner in which the necrotic portions are detached from the living bone.

Occasionally the infectious agent localizes in the periosteum or beneath the periosteal covering of the cortex and spreads only slightly into the interior of bone. In some instances, trauma appears to predispose to these forms of periostitis. They are characterized by painful and tender swelling. If the lesion persists, it will cause bony thickening that is visible in the roentgenogram. Microscopically, in the early cases, one sees hyperemia, marked edema, and polymorphonuclear leukocyte infiltration. Occasionally the reaction achieves the proportions of an abscess and the adjacent bone becomes necrotic. In later stages there is condensation of the cortical bone, and, in most instances, irregular overgrowths of osseous tissue develop beneath the periosteum. Productive lesions of this type are sometimes referred to as Garré's sclerosing osteomyelitis.

Pyogenic microorganisms may enter a bone from a penetrating injury in association with a compound fracture or from the direct extension of a neighboring focus of infection. Although osteomyelitis acquired in this manner may be exceedingly troublesome and difficult to eradicate, it is not likely to produce general disturbances that are as severe as the systemic reactions that regularly accompany hematogenous osteomyelitis.

Tuberculosis.—Tuberculosis of bone is usually caused by hematogenous dissemination of bacilli from an active focus in the lung, kidney, bowel, or lymph nodes. It may occur, however, as the result of direct extension from a caseous focus in soft tissues adjacent to bone. Children are much more frequently affected than adults. In children, the involvement of the long bones usually commences in the metaphyseal ends of the diaphyses. The upper and lower femoral, and upper tibial regions are frequently affected. Infections in these sites may spread, to destroy the epiphysis and to enter the joints (Fig. 1083). In comparison with pyogenic infections, tuberculosis is more likely to extend to involve the epiphysis or to localize initially in this structure. Similarly, on a relative basis of comparison, tuberculosis affects the bodies of the vertebrae (Fig. 1084) more commonly than do pyogenic infections. Tuberculosis of the spinal column is known as *Pott's disease.* The exudate from these lesions may accumulate in the soft tissues, where it excites comparatively little inflammation *(cold abscess).* In some in-

stances the exudate gravitates along the sheath of the psoas muscle *(psoas abscess)*. Such accumulations may extend and cause a fluctuant swelling below Poupart's ligament.

Tuberculous osteomyelitis tends to destroy bone progressively. The caseating granulation tissue spreads through the cancellous tissues, leading to necrosis and fragmentation of bone trabeculae (Fig. 1085). There is little tendency for tuberculous granulation tissue to ossify, and the area of involvement becomes less dense on roentgenologic examination and marked osteoporosis is usually seen on gross inspection. Complete caseation necrosis of all tissues at the site of infection may occur in time. This results in a well-localized tuberculous abscess (Fig. 1086), the wall of which may show miliary and conglomerate tubercles on microscopic examination.

Rapidly spreading tuberculosis with extensive bone necrosis and gross sequestration may occur but is uncommon.

Fig. 1080. Fig. 1081. Fig. 1082.

Figs. 1080 and 1081.—Osteomyelitis. Lateral and anteroposterior roentgenograms of a tibia showing destructive and proliferative changes of long-standing pyogenic osteomyelitis. Sequestrated segments of the original tibial shaft are visible through the shadows cast by the ossified granulation tissue (involucrum).

Fig. 1082.—Osteomyelitis. Photograph of a specimen of bone removed from the tibia illustrated in Figs. 1080 and 1081. Granulation tissue-filled sinus openings are clearly evident on the external surface of the bone. These sinuses formed communications between the skin surfaces and the sequestrum enclosed in the bony cavity.

Syphilis.—Osseous lesions resulting from the *Treponema pallidum* are observed as a part of congenital syphilis or as a manifestation of an acquired infection. In congenital syphilis, the skeletal changes are of two major types; osteochondritis and periostitis. Usually, however, a given bone shows both lesions to a greater or lesser extent. When an affected long bone is split in its longitudinal axis, it is noted that the metaphyseal end of the diaphysis is irregular in outline, grayish-white in color, and frequently contains gritty particles that are yellow or yellowish-gray in color. On microscopic examination one sees fibrosis of the marrow spaces that is accompanied by an infiltration with plasma cells, lymphocytes, and other forms of leukocytes (Fig. 1087). The trabeculae are usually thin and irregularly placed and many of them are fragmented. The growing cartilage is penetrated irregularly by blood vessels that are ensheathed in young connective tissue. The latter is infiltrated with inflammatory cells to some extent. It may be possible to demonstrate spirochetes throughout an area of involvement such as the one demonstrated in Fig. 1087.

Periostitis occurring in congenital syphilis is readily observed in the roentgenogram where one or more shadows paralleling the cortex may be observed. Cross sections through the shaft of such a long bone reveal that excessive and rapid subperiosteal bone overgrowth has occurred (Fig. 1088). The original cortex is usually thin and irregular and the intertrabecular spaces of the recently formed subperiosteal bone are filled with edematous and mildly inflamed connective tissue (Fig. 1088).

The pathologic changes in the bones of infants suffering from congenital syphilis probably result from several factors. Foremost among these is the localization of spirochetes which seem to have the capacity of creating cell and tissue injury and, at the same time, stimulating mesenchymal cells, including osteoblasts, to proliferate excessively. Inflammatory and proliferative changes in blood vessels may give rise to some of the destructive changes that are seen in the ends of the long bones. It is probable that some of the skeletal alterations observed by the pathologist in fatal cases of congenital syphilis are manifestations of general and specific nutritional disturbances.

During the secondary stage of acquired syphilis there may be circumscribed or more or less generalized inflammation of the periosteum. This lesion is accompanied by tenderness and aching pains that are said to be more severe at night. In the early stages of bone involvement, the periosteal tissues are hyperemic and infiltrated with edema fluid. Lymphocytes, plasma cells, and mononuclear leukocytes are

Fig. 1083.

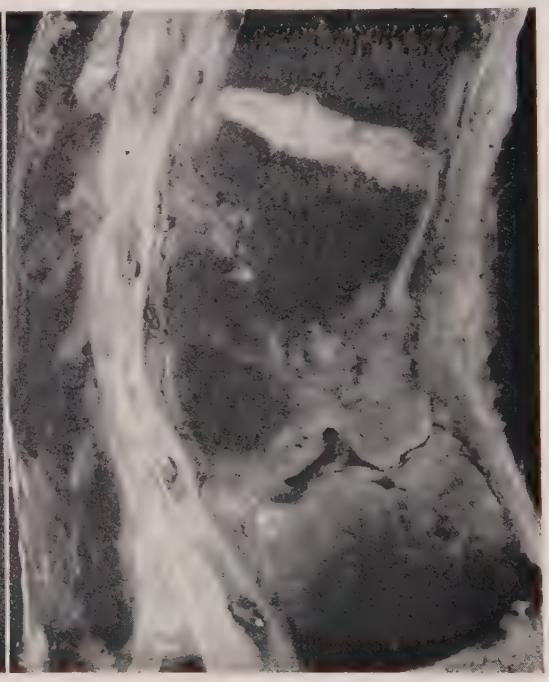


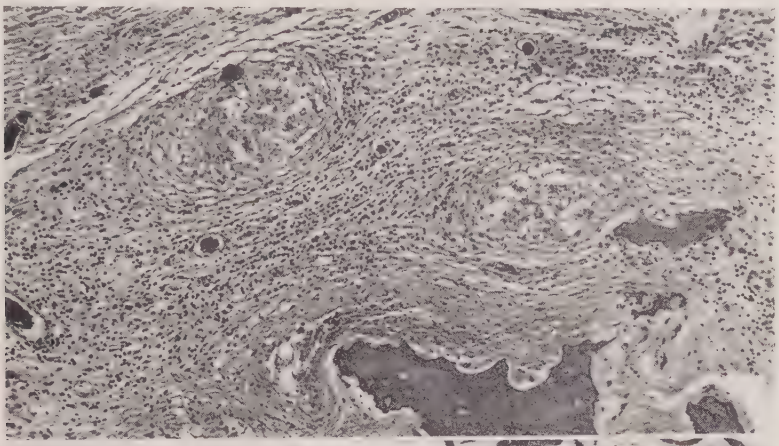
Fig. 1084.

Fig. 1083.—Tuberculosis of the hip joint has resulted in the destruction of most of the femoral caput and acetabular cup. Tuberculous osteomyelitis with the extension of sinus tracts into the adjacent articular capsule and soft tissues is evident on the left-hand side of the photograph.

Fig. 1084.—Tuberculosis. Compression of vertebrae with angulation of the spine has resulted from tuberculous osteomyelitis affecting three vertebral bodies and two intervertebral discs.

present in excessive numbers. The cambium layer of the periosteum is hyperplastic and there may be some new bone formation between the displaced periosteum and the surface of the bone cortex. Such changes include all of the morphologic characteristics of a true periostitis. Later on, there may be extensive subperiosteal bone overgrowth in the form of osteophytes and hyperostoses. These overgrowths may border on destructive lesions that are essentially gummas of bone. The roentgenologic and gross appearances of such lesions may bear distinct resemblances to sclerosing forms of osteogenic sarcomas. The need for a carefully made differential diagnosis in these cases is self-evident. Superficially placed bones, including the anterior surface of the tibia, the clavicle, and the skull, represent the more frequent sites of syphilitic involvement. The lesions that occur in the flat bones of the skull are usually destructive in character and exhibit only slight to moderate degrees of marginal condensation or subperiosteal overgrowth. Despite the destructive nature of the lesions in the skull, it should be emphasized that syphilitic infections of bone induce changes that are basically proliferative in character, whereas tuberculous processes are essentially destructive.

Fig. 1085.



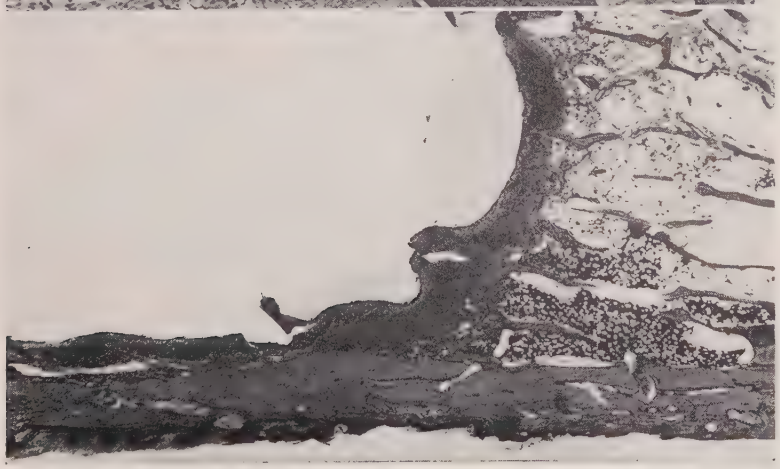


Fig. 1086.

Fig. 1085.—Tuberculous granulation tissue surrounding small spicules of necrotic cancellous bone is illustrated in this reproduction. (×125.) (AFIP No. 73801.)

Fig. 1086.—Tuberculosis. In this section from the upper end of the tibia of an adult man, one notes a cavity that is lined by a narrow zone of tuberculous granulation tissue. In roentgenograms, the lesion resembled a giant-cell tumor. At operation the cavity contained thin yellowish-brown fluid, and fibrin. Note the subperiosteal bone formation overlying the bony wall of the tuberculous abscess. (×10.)

Improvement in diagnostic and treatment methods for syphilis has greatly reduced the incidence of skeletal involvement. This is due to the fact that the bony lesions are among the later manifestations of the disease.

Actinomycosis.—As a result of the tendency for actinomycosis to spread from a pre-existing focus of infection, the ribs, sternum, and

Fig. 1087.

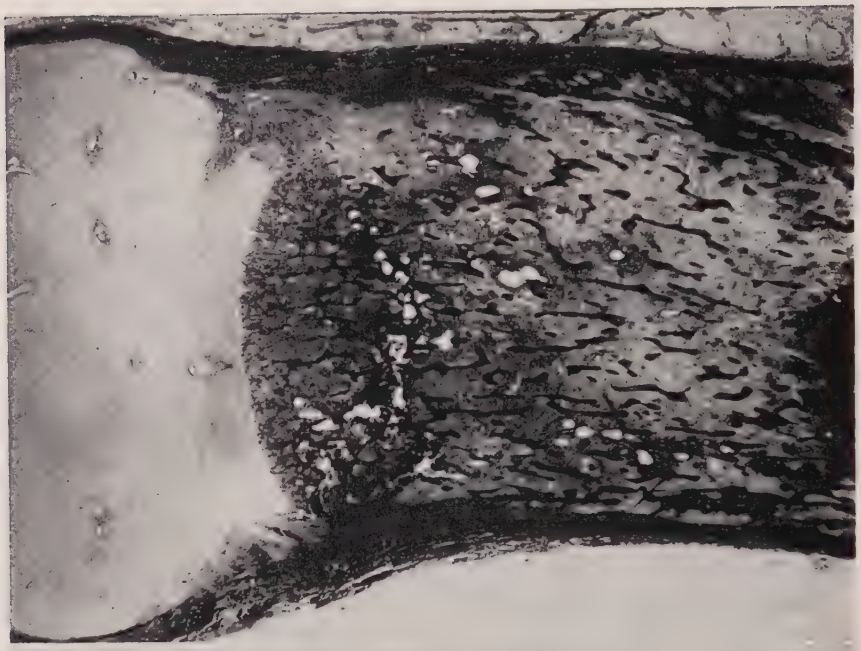


Fig. 1088.

Fig. 1087.—Congenital syphilis. In this longitudinal section of a tibial epiphysis of an infant with congenital syphilis, one notes irregularities in margins of the growth zone, fibrosis of marrow spaces, and subperiosteal bone overgrowth. The combined changes are referred to as syphilitic osteochondritis. (×10.)

Fig. 1088.—Congenital syphilis. This cross section of the lower third of the femoral shaft illustrates the pronounced subperiosteal bone overgrowth of syphilitic periostitis. The connective tissue illustrated in the lightly stained areas of this and the preceding reproduction is edematous and heavily infiltrated with plasma cells, lymphocytes, and other forms of leukocytes. (×10.)

vertebrae may become involved in cases of pulmonary or abdominal infections. Likewise the jaws may become infected by the extension of lesions in the soft tissues in the oral cavity. The bone lesion is essentially one of destruction, and multiple foci of suppuration leading into the sinus tracts are found on gross and microscopic examination.

Blastomycosis.—Blastomycosis of bony structures may arise either from direct extension of established lesions in the soft tissue or from hematogenous dissemination. The former method is more common and occurs not infrequently as a result of dermal infections on the digits. The lesions in bone are destructive in character and resemble tuberculosis on both gross and microscopic examination.

Disorders Resulting From Inadequate or Excessive Amounts of Vitamins

In order that normal development, growth, and maintenance of the skeleton may be assured, the individual must ingest and assimilate adequate amounts of protein, fats, and carbohydrates. In addition, certain chemical agents known as vitamins and certain minerals are specifically required. In several diseases, resulting wholly, or in large part, from inadequate ingestion or utilization of these substances, the predominant and most characteristic lesions are to be observed in the skeleton. This is true particularly when the deficiency occurs in infancy or early childhood.

Scurvy—Ascorbic Acid (Vitamin C) Deficiency.—This disease is known to result from an inadequate supply of ascorbic or cevitamic acid (vitamin C).

It has been known for centuries that prolonged subsistence on diets from which fresh fruits, vegetables, milk, and meat were excluded would result in a disease picture that was characterized by anemia, swelling of the gums, loosening of the teeth, and by hemorrhages into the skin, mucous membranes, periosteum, and joints. Scurvy was therefore regarded as a scourge to sailors. The curative power of fresh fruits and vegetables has also been recognized for a long time. It may seem appropriate, therefore, that ascorbic acid was the first of the vitamins to be prepared synthetically in the laboratory. However, the chemical formula of ascorbic acid was not determined until many years after the essential pathologic features of scurvy in man and animals had been described.[31-33]

These reports, together with more recent detailed studies, have provided a lucid account of the pathologic manifestations of scurvy in all its stages, including repair.[34-36]

Scurvy has been characterized as a condition in which the supporting tissues of the body are unable to produce or to maintain intercellular substances. The intercellular substances so affected include collagen, the basement membranes including the cement substances of capillaries, and the matrices of bone, dentine, and cartilage. Brief reflection on this definition enables one to understand the clinical manifestations of scurvy as well as to predict the predominant sites of pathologic change.

Scurvy is more common in infants and young children during the stages when bone and connective tissues of all types are being formed at a rapid rate. Clinically, there is evidence of anemia and a tendency to bleed spontaneously or from trivial causes. The severely affected child is likely to assume a position of flexion and to lie very still because of the pain that results from any active or passive motion. The pain may be attributed to hemorrhages in muscles, beneath the periosteum, and into joints. In some instances, it is attributable to fractures through the rarefied bone at the metaphyseal ends of the diaphyses of the long bones. The roentgenologic findings are reasonably characteristic. Owing to the generalized osteoporosis, the shafts of the long bones and the bony epiphyses appear less dense than normal and possess a "ground-glass" appearance. The metaphyseal ends of the shafts, including the ribs, are markedly rarefied. Contrasted with this, the zones of provisional calcification are excessively dense. In the long bones this density appears as a transverse line at the zone of junction between the epiphysis and shaft end. In the epiphyses, however, the dense shadow encircles the center of ossification and is referred to as a halo. These zones of relatively increased density are attributable to the heavily calcified and often fragmented spicules of calcified cartilage that are formed during the period of retarded longitudinal growth (Fig. 1089). Displacement of the epiphysis, as the result of fracture and separation, may also be noted in the roentgenogram. Soft tissue swellings from subperiosteal or intra-articular hemorrhage may be apparent. During repair, the extent of the subperiosteal hemorrhage becomes vividly clear since ossification begins peripherally beneath the displaced periosteum.

Pathologic examination of the skeletal parts in fatal cases of scurvy, or of the

bones of experimentally treated guinea pigs, confirms the clinical and roentgenologic manifestations referred to. The bones are porous and there is marked hemorrhage into the muscles, joints, and beneath the periosteum. The entire shaft of a long bone may be encased in a blood clot that lies inside of a displaced periosteal envelope. The periosteal separation is caused by the loosening and disruption of the collagenous attachments (Sharpey's fibrils) from the bone cortex. The epiphyses may be disconnected from the shafts because of fracture through the markedly atrophied metaphyseal zone. Recently acquired soft tissue wounds or bone fractures show little or no evidence of healing. When a costochondral junction or the end of a long bone is sectioned in a longitudinal plane, it is noted that the metaphyseal end of the shaft is exceedingly fragile and that the marrow tissue is pale gray in color or stained from extravasated blood. Instead of the sharp and even translucent blue zone of normal endochondral ossification, the chondral-osseous junction in scurvy is widened, uneven, and frequently concave in outline (Fig. 1089). Fine, granular particles of calcified cartilage that have a yellow color are frequently observed (Fig. 1089). This condensation of calcareous material is responsible for the density observed in the roentgenogram.

Microscopic examination reveals little or no evidence of bone formation either beneath the periosteum or at the margins of the calcified cartilage spicules in the metaphyseal zone. Instead, there is an accumulation of spindle-shaped and branching cells that have the appearance of young fibroblasts. Such cells, embedded in a loosely textured and edematous groundwork, are responsible for the pallor of the marrow tissues near the bone end (Fig. 1089). Evidence that these cells are osteoblasts is provided by noting their activity in repair. In controlled experiments in guinea pigs, these cells will deposit recognizable osseomucin within a period of twenty-four hours after ascorbic acid has been supplied.

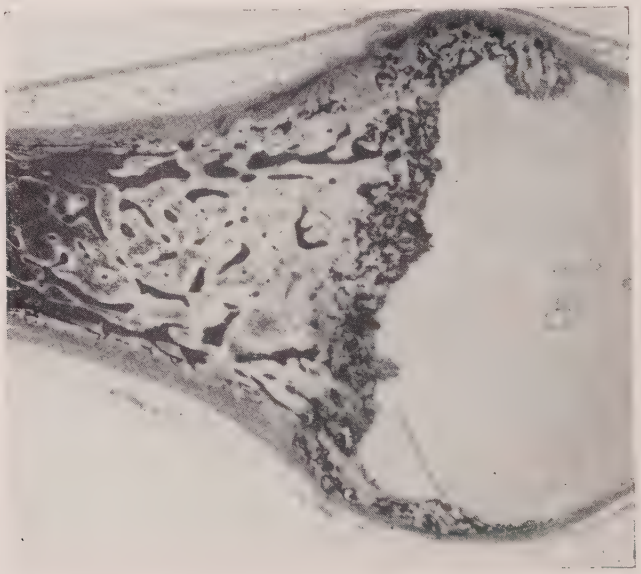


Fig. 1089.—Scurvy. In this costochondral junction one notes the classical features of well-advanced scurvy. The bone shows evidence of osteoporosis and the marrow spaces are filled with loosely textured and edematous connective tissue in which some hemorrhage has occurred. The metaphyseal end of the bone is widened and made up of irregularly arranged spicules of heavily calcified matrix. Growth has apparently been more active at the perichondrial margins of the cartilage, resulting in pronounced cupping. (×10.)

The interesting changes in teeth that are related to impairment in the forma-

tion of dentine and to loosening of the tooth from the alveolar bones have been well studied.[33-37]

Rickets and Osteomalacia—Vitamin D Deficiency.—In his Harvey Lecture on the pathology of rickets, Edwards A. Park[38] reviewed the stages of investigation by which our present knowledge of the pathogenesis and pathology of rickets has been acquired.

Rickets, as well as osteomalacia, its counterpart in adults, has been defined as a derangement of mineral metabolism due to vitamin D deficiency, which is frequently associated with inadequate calcium or phosphorus, or both, in the diet, leading to characteristic osseous changes.[39] Vitamin D does not appear to act directly on bone or on the mechanism by which calcification of bone matrix is accomplished. Instead it seems to exert favorable influences on the economy of calcium and phosphorus. This is believed to be due in part at least to the promotion of their absorption from the intestinal tract.[40] It seems apparent that the pathologic changes of rickets and osteomalacia are dependent upon, and therefore follow, a change in the chemical composition of the blood. In rickets the inorganic phosphorus is usually lowered to a subnormal level, less frequently the calcium is low, and occasionally both of these substances are diminished below normal values. The solubility product which governs the transfer and precipitation of calcium phosphate from the blood into bone and cartilage matrix is therefore lowered below a critical value. Deposition of bone salt becomes irregular and, when the solubility product value is markedly diminished, it no longer takes place. The morphologic counterparts of this fundamental biologic disturbance, in order of their development, are: (a) a failure of calcification of the deepest layer of growing cartilage (provisional zone of calcification); (b) failure of calcification of newly deposited osteoid matrix; (c) deformities resulting either from disturbances in the sequences of endochondral ossification or from bending of the softened bones.

In the majority of instances rickets becomes apparent between the fourth month and the third year of life. However, it may appear at any time up to closure of the epiphyses. In infants the skull shows thickening of the frontal and parietal eminences (bossing) and flattening and thinning of the back of the skull (craniotabes). Thickenings of the costochondral junctions (rachitic rosary) develop and may be associated with a depressed sternum and indentations of the thorax at the level of the insertion of the diaphragm. The epiphyseal ends of the long bones are noticeably enlarged, especially the lower radial, lower femoral, and upper tibial epiphyses. In older children there may be flattening of the feet, anterior bowing of the tibiae, and knock-knee deformity.

Roentgenographic examination reveals widening and thickening of the epiphyseal cartilage plates between poorly calcified bone shafts and bony epiphyses. In some cases there is evidence of bending deformities and incomplete (greenstick) fractures.

In fatal cases examined at autopsy, in addition to the changes already referred to, one may find deformities of the vertebrae and pelvic bones. Pronounced inward projection of the costochondral junctions is observed when the lungs are lifted from the pleural spaces. This is caused by the forces of inspiration upon the softened bone. Sectioning of the bone ends with a knife is often possible. When this is done, one notes that the epiphyseal cartilage plates are widened and thickened and that the line of junction between cartilage and the metaphyseal end of the shaft is no longer regular and sharply demarcated.

The microscopic changes in rickets are of two types. One of these may be seen in any part of the bone, although it is usually most prominent in the cancellous and cortical bone at the ends of the shafts. The bone tissue that was formed and calcified prior to the onset of rickets stains normally. In properly decalcified sections stained with hematoxylin and eosin, this bone takes a reddish-purple stain. In undecalcified tissues it may be shown to contain bone salt. The calcified lamellae are surrounded by zones of homogeneous osteoid matrix which stain vividly pink or red with hematoxylin and eosin, and, in appropriately prepared sections from undecalcified blocks, contain little or no mineral deposit. Varying

degrees of fibrosis are present in the marrow tissues and this may contain poorly arranged trabeculae of uncalcified osteoid. Thus, the osseous changes appear to be the result of the deposition of excessive amounts of uncalcified or poorly calcified matrix. In all probability the bone salt is also withdrawn to a certain extent from the lamellae that were previously formed and calcified. These changes are also apparent in *osteomalacia.*[41]

The other type of change is limited to rickets since it arises from disturbances in the calcification of cartilage matrix and from abnormalities in the growth of cartilage cells. Under low-power magnification one sees a thickened, widened, and markedly uneven epiphyseal cartilage plate that is irregularly penetrated by branching blood vessels from the metaphyseal end of the shaft (Fig. 1090). In the usual example of rickets in the infant or child the histologic picture is too complicated to be readily interpreted. For this reason it is necessary to refer to the progressive changes that occur in rats during the development of rickets and during repair.

The initial morphologic sign of rickets is the partial or complete absence of mineral deposit in the deepest layer of cartilage (provisional zone of calcification). In association with this change the deepest cells in the cartilage columns fail to clear and degenerate and there is no longer a regularly arranged ingrowth of capillaries from the marrow of the shaft. Cartilage cells continue to proliferate, however, and as a result the epiphyseal plate becomes thickened and widened. The cell columns become distorted, and irregular rounded and oval nests of cartilage cells are built up. Blood vessels of small or intermediate size grow in between these clumps of cartilage cells and give off irregular branches. This vascular penetration is most irregular and is attended by the ingrowth of connective tissue from the endosteum. Thus bone matrix, which remains uncalcified, is

Fig. 1090.—Rickets. A greatly widened and thickened epiphyseal cartilage plate is evident in this photomicrograph of the lower femoral epiphysis of a child with advanced rickets. The blood vessel invasion of the cartilage is irregular and a great excess of uncalcified bone matrix has formed. (×10.)

deposited irregularly throughout the distorted epiphyseal plate (Fig. 1090).

Repair in the rachitic rat begins with the deposition of bone salt in the cartilage. At first this is irregularly laid down well in advance of the distorted metaphyseal end of the shaft. Gradually, a new provisional zone of calcification is established, and the orderly sequence of cartilage cell proliferation, maturation, and degeneration is again evident. The excess osteoid, heretofore, uncalcified, is impregnated with bone salt, and subsequent to this it is gradually remodeled by lacunar absorption until the excess bone has been removed.

Effects of Excessive Doses of Vitamin D.—The results of excessive and prolonged administration of vitamin D has been studied in animals, and the unfavorable effects have been noted in man.[42] (See page 417.)

Vitamin A Deficiency.—Renewed interest in the influence of vitamin A upon skeletal growth has occurred in recent years. In rats and certain other animals that have been studied, vitamin A deficiency brings about a suppression of all sequences of growth in the epiphyseal cartilage; the remodeling processes, by which bone is resorbed and rearranged into compact bone, cease. Appositional growth of subperiosteal bone continues, however, until inanition supervenes. These disturbances in bone may result in a disproportionate growth of bone and central nervous system, and thus, by mechanical overcrowding of the brain and spinal cord, account for numerous neurological disturbances.[43]

Effects of Excessive Doses of Vitamin A.—Excessive vitamin A administration leads to an acceleration of the sequences of growth that are retarded by inadequate amounts of the vitamin.[43] (See also page 411.)

Skeletal Changes Associated With Storage of Lipoids

A significant part of the so-called reticulo-endothelial system is embodied in soft tissues of the bony skeleton. Because of this relationship the bones are affected in at least three disorders which may be designated as lipoid storage diseases.

Gaucher's Disease.—In this malady the reticulo-endothelial cells of the spleen, bone marrow, lymph nodes, and liver become hyperplastic and store excessive quantities of a cerebroside, kerasin, or a closely related cerebroglucoside (see also pages 931 and 950).

The outstanding microscopic feature is the accumulation of Gaucher cells—cells that are spherical or oval in shape and measure 20 to 40 microns in diameter (see Figs. 812-815). The light-staining cytoplasm of these cells is abundant. The characteristic lacy or slightly foamy appearance is produced by delicate wavy striations. The Gaucher cells accumulate in clumps of alveolar nests. Their presence in large numbers in bone may lead to diffuse or patchy osteoporosis. In some cases there are deformities of the femoral and humeral heads because of disturbances in endochondral ossification (Fig. 1091). The vertebrae may undergo compression fractures as a result of the osteoporosis.

Niemann-Pick's Disease.—This disorder in lipoid metabolism is a rare and usually rapidly fatal affliction of infancy (see discussion on page 952). Accumulations of lipoid-laden histiocytes in the bone marrow may lead to generalized osteoporosis with circumscribed foci of marked bone resorption.

Lipochondrodystrophy.—(See Gargoylism, page 1194.)

Hand-Schüller-Christian's Syndrome.—This disorder apparently has nothing in common with the three entities mentioned above. As a syndrome the disturbance is characterized by: (a) multiple, sharply circumscribed roentgenographic defects in the skull; (b) exophthalmos, which may be bilateral; (c) diabetes insipidus; and (d) other pituitary signs such as infantilism.

The first reports of this syndrome were those by Hand,[44, 45] (1893 and 1921). Schüller[46] in 1915 described the condition for the second time and attributed the symptoms to pituitary dysfunction. Christian[47, 48] in 1920 interpreted the defects in membranous bones, exophthalmos, and diabetes insipidus as an unusual syndrome of dyspituitarism.

The disorder occurs in children and young adults, and males are affected about twice as frequently as females. The most constant feature of the disease is the presence of one or more areas of bone destruction. These are caused by accumulations of histiocytes that are filled with lipoid. Usually there is some degree of fibrosis, and the lesions often contain significant numbers of polymorphonuclear leukocytes, eosinophiles, plasma cells, and lymphocytes. With increasing age of the lesions, the fibroblasts increase and greater amounts of collagen are laid down. Under the polarizing microscope, the lipoid is seen to be anisotropic in large part, and chemical analysis of the total lesion reveals a high content of cholesterol, cholesterol esters, and neutral fat. These destructive lesions may occur any place in the skeleton, but in the majority of cases the bones of the cranium are affected. When the lesions extend into the soft tissues of the orbit, exophthalmos develops. If the sella turcica is encroached upon, there may be signs of pituitary dysfunction, including diabetes insipidus. In other cases, deafness from involvement of the temporal bone or signs of increased intracranial tension may be noted.

It is apparent, therefore, that the complete clinical picture described by Hand, Schüller, and Christian is dependent upon the proper localization of the underlying xanthomatous lesion. For this reason, the disorder described by these observers should be designated a syndrome and not a disease. Other manifestations of the same fundamental disorder have been described by Snapper,[49] who employs the term *lipoid granulomatosis* of bone. Thannhauser[50] refers to the condition as *osseous xanthomata* and,

in his classification, he includes it among the *primary essential xanthomatoses of the normocholesteremic type.*

Information acquired during the past decade, while still incomplete and inconclusive as to etiology, has raised doubt as to the propriety of grouping the syndrome described by Hand, Schüller, and Christian with Gaucher's disease and Niemann-Pick's disease.[51]

Eosinophilic Granuloma of Bone.—This neoplastic-like lesion is a benign destructive process that begins in the marrow and usually affects but one bone (Fig. 1092). Occasionally there are multiple foci in one or more bones. The condition occurs chiefly in children, but it may affect young adults. Microscopic examination of the soft, friable tissue comprising the lesion shows large numbers of eosinophiles and less numerous mononuclear cells that contain granules, brownish pigment, and lipoid-filled vacuoles (Fig. 1093). Some observers regard this lesion as a stage or a form of Hand-Schüller-Christian's syndrome.[52, 53] Such an interpretation seems unavoidable as the many overlapping manifestations become evident in carefully studied patients.

Letterer-Siwe Disease (Nonlipoid Histiocytosis).—A variety of names, including reticuloendotheliosis, reticulosis, and aleukemic monocytic leukemia, have been used to designate this obscure disorder of the reticulo-endothelial system (see discussion on page 952). In some cases there are focal destructive lesions in bone that bear a considerable resemblance to the lesions of Hand-Schüller-Christian's syndrome, and it is quite likely that the two processes are related.[51, 54] (See page 950.)

Skeletal Changes Related to Dysfunction of Endocrine Glands

Disturbances in the function of the pituitary, thyroid, and parathyroid glands are known to give rise to certain distinctive changes in the skeleton.

Hyperpituitarism.—

GIGANTISM.—Diffuse hyperplasia or adenoma of the acidophilic cells of the anterior lobe of the hypophysis may induce marked symmetrical overgrowth of the skeleton if the lesion develops before the epiphyses have closed. The excessive growth is usually most marked at the time of puberty and may continue on into young adult life because of a concomitant delay in epiphyseal closure. In cases in which the disturbance continues into adult life, acromegalic characteristics may be superimposed upon the gigantism (see also page 978).

ACROMEGALY.—Acromegaly is a chronic disease of adult life that is outwardly characterized by hypertrophic changes in the acral parts.[55] There are thickening and enlargement of the nose, lips, and tongue. The lower jaw is greatly enlarged and projects forward. The hands and feet are increased in their over-all dimensions, especially in width. An increased growth of hair may be noted, especially in the female, in whom masculine traits may develop.

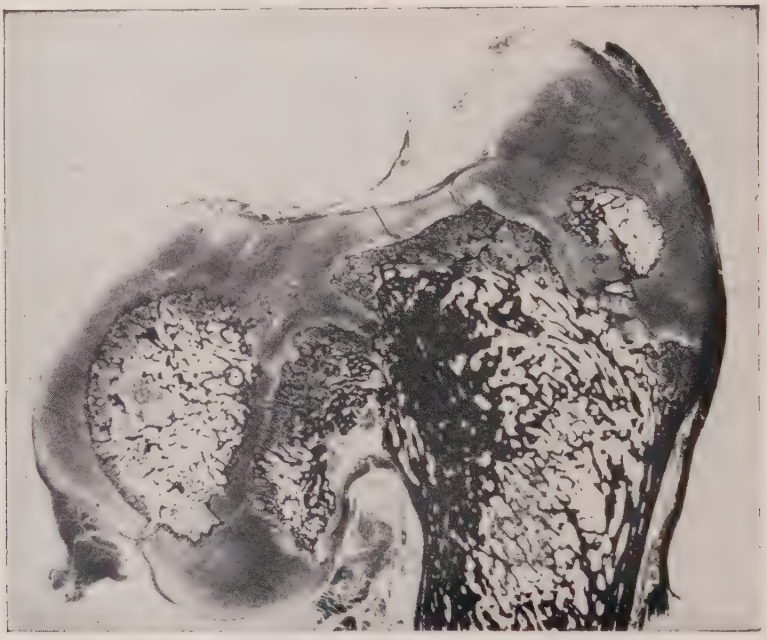


Fig. 1091.—Gaucher's disease. Pronounced deformity of the head and neck of the femur is evident in this specimen from a child with Gaucher's disease. The cancellous spaces are filled with Gaucher's cells.

X-ray films reveal enlargement of the sella turcica. Enlargement of the bones of the skeleton is also evident, especially of the mandible, the thoracic cage, and the bones of the hands and feet. An arrowhead contour may be noted in the terminal phalanges of the fingers.

At autopsy it is noted that there is enlargement of most or all of the internal organs and that, in addition, the connective tissues are hypertrophic. Gross and microscopic examination of the costochondral junctions, vertebral bodies, and articular ends of the bones of the hands and feet reveal osseous overgrowths (Figs. 1094 and 1095). While these enlargements may be due in part to generalized hyperplasia of the connective tissues, including periosteum, there is acceptable microscopic evidence that the process of endochondral ossification is re-established in the ribs, vertebrae, and digits.[56, 57] Since it is known that the mandible continues to grow by endochondral ossification at the condyle, even in the normal mature subject, it is reasonable to assume that the influence of increased growth hormone in the acromegalic subject will be disproportionately great at this site. Such a relationship may explain the pronounced and constant overgrowth of this particular bone in acromegaly.

Cushing's Syndrome.—This disorder is characterized by painful adiposity of the face, neck, and trunk; hirsutism; sexual dystrophy (impotence in males and amenorrhea in females); hypertension; striations in the skin of the abdomen; and osteoporosis that may result in kyphosis, loss of height, and lumbosacral pain (see also pages 983 and 1038).

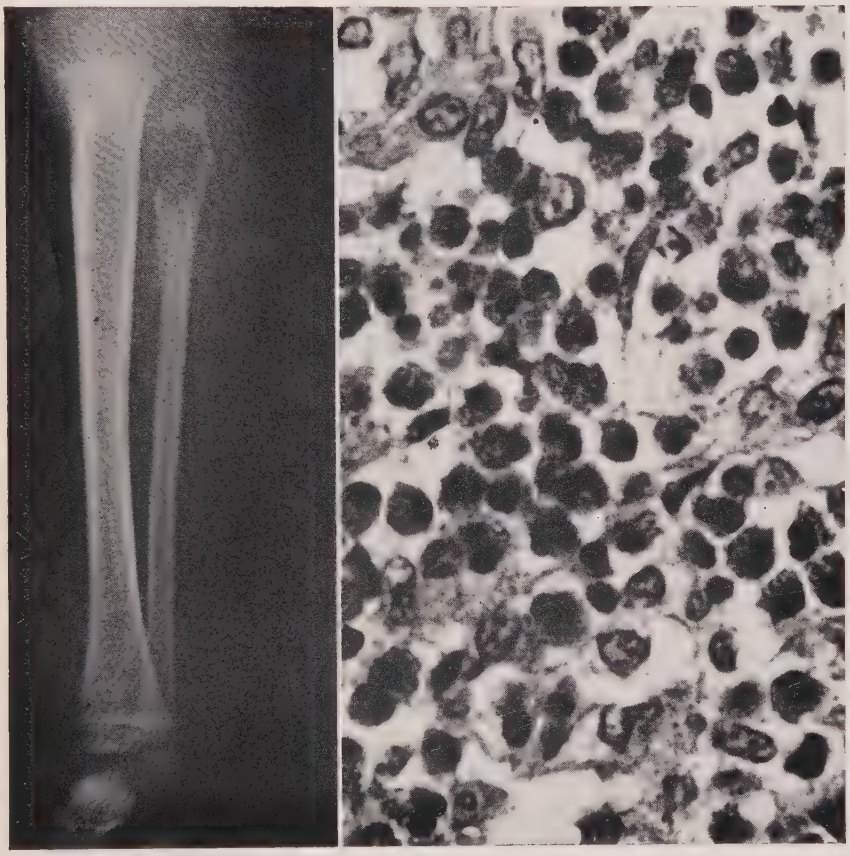


Fig. 1092. Fig. 1093.

Fig. 1092.—Eosinophilic granuloma. A sharply defined destructive lesion may be observed in the upper end of the fibula. The lesion contained soft, friable tissue comprised mainly of eosinophiles and lipoid-laden histiocytes.

Fig. 1093.—Eosinophilic granuloma, showing cytologic features. (×950.)

Hypopituitarism.—

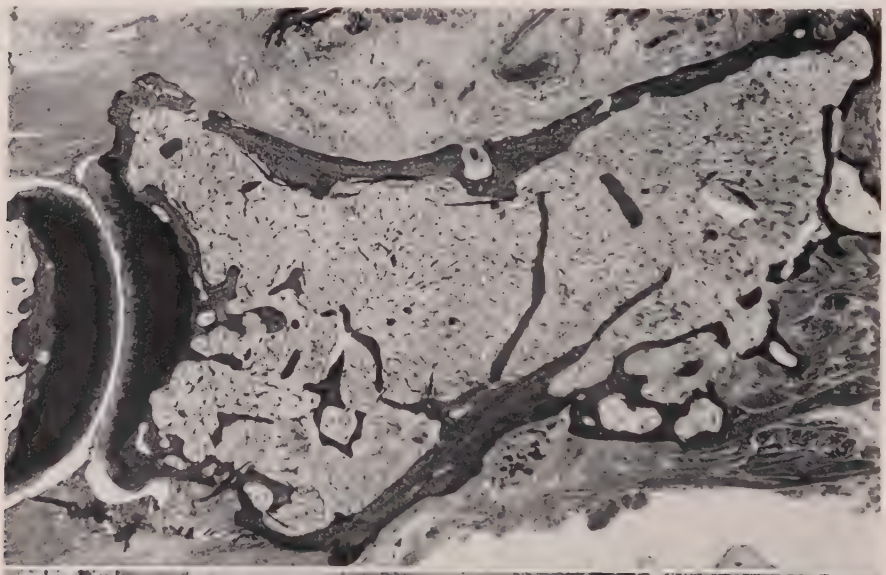
Pituitary Dwarfism.—Pituitary deficiency leading to dwarfism may result from hypoplasia of the anterior lobe or from its destruction by a tumor such as a craniopharyngioma. In dwarfs of this origin, the growth of both cartilage and bone is arrested. The epiphyseal cartilage persists, but a compact layer of bone is formed at the metaphyseal end of the shaft. This separates the diaphysis from the epiphysis, which may remain open for excessively long periods of time. (See also page 978.)

Hyperthyroidism.—In long-standing hyperthyroidism there may be roentgenologic and morphologic evidence of diffuse osteoporosis.[59] The osseous changes are secondary to a marked increase in the excretion of calcium and phosphorus via the kidney and bowel. It is probable that the actual bone change is the result of increased lacunar absorption by osteoclasts. (See also page 998.)

Hypothyroidism.—*Cretinism* results from a diminution or absence of thyroid secretion in childhood. The skeleton grows at a slower rate than normal and the bones may appear excessively dense in the roentgenogram. The epiphyses close at an early age. In addition to retarded growth, the cretin is slow mentally and exhibits a dry, thickened skin, a broad and bloated-appearing face, and a thick-lipped mouth from which the tongue may protrude.

In the adult, a deficiency in thyroid secretion results in *myxedema.* The myxedema patient may show a pronounced diminution in calcium and

Fig. 1094.



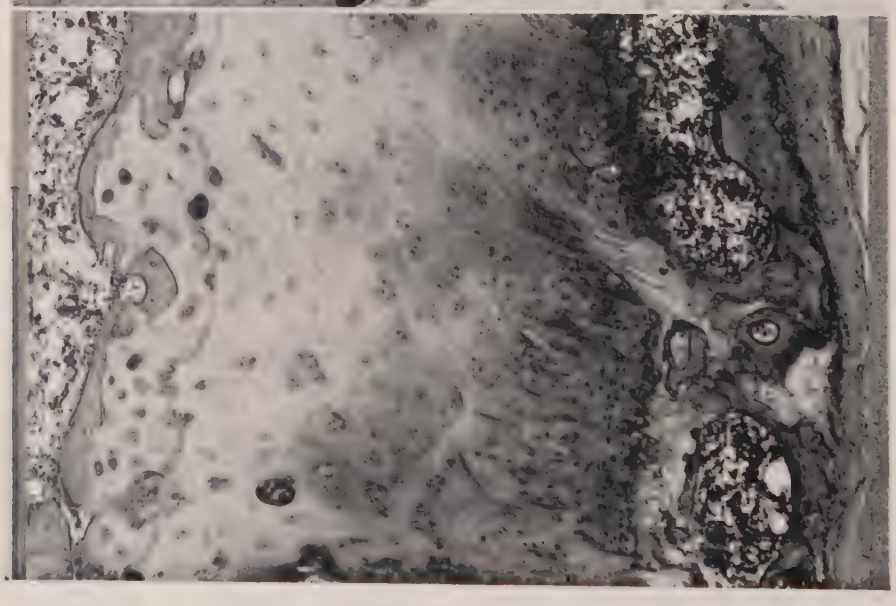


Fig. 1095.

Fig. 1094.—Acromegaly. Bony overgrowth of the terminal phalanx and thickening of the articular cartilage of the terminal interphalangeal joint are illustrated in this photomicrograph. (×10.) (After Waine, Bennett, and Bauer: Am. J. M. Sc. 209: 1945.)

Fig. 1095.—Active endochondral ossification is apparent in this costochondral junction of an elderly man with acromegaly. (After Waine, Bennett, and Bauer: Am. J. M. Sc. 209: 1945.)

phosphorus excretion, and it is possible, in some cases, to demonstrate an increased density of bone by roentgenologic examination. (See also page 1001.)

Hyperparathyroidism.—Increased functional activity of the parathyroid glands may result from either "primary hyperparathyroidism" or "secondary hyperparathyroidism."[60, 61]

"PRIMARY HYPERPARATHYROIDISM."—This term is used to imply that more parathyroid hormone is produced than is needed. The excessive secretion may result from either an adenoma of one or more glands (Fig. 1096), or from diffuse hyperplasia of all of the parathyroid glands.

Under the influence of excess parathormone, a disturbance in calcium and phosphorus metabolism results. This is characterized by an increased excretion of phosphorus and calcium and by a lowering of the serum phosphorus (3.1 mg. or lower) and an elevation of the serum calcium

Fig. 1096.

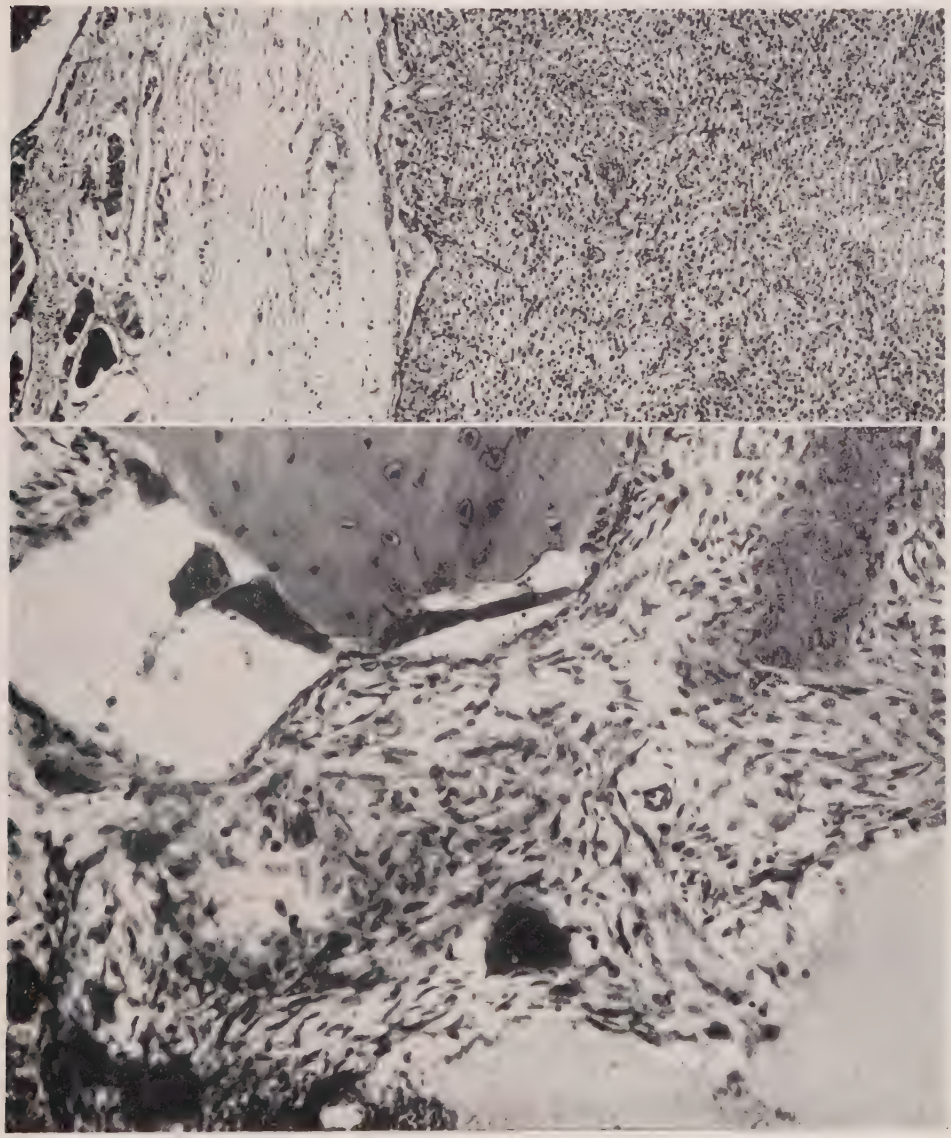


Fig. 1097.

Fig. 1096.—An adenoma of the parathyroid gland is illustrated in this reproduction of a section through the junction of the tumor and the capsule of the thyroid gland.

Fig. 1097.—Resorptive changes in bone, fibrosis of marrow spaces and multiple small cysts may be seen in this reproduction of the biopsy material. Specimens illustrated in Figs. 1096 and 1097 were obtained from the same patient.

(12.5 to 18 mg.). In cases in which this physiologic disturbance is severe and prolonged, osseous changes result.

The skeletal lesions may be slight, consisting only of generalized osteoporosis, or they may be marked, having the characteristics of *osteitis fibrosa cystica generalisata.* The latter is, however, only an exaggeration of the former process and in either case the resorptive changes in bone are probably initiated by the biochemical disturbance.

Microscopic examination of the bones reveals fibrosis of the marrow spaces together with increased lacunar absorption of the lamellae by osteoclasts (Fig. 1097). It is apparent in the sections that both matrix and bone salt are removed simultaneously. There may be small collections of fluid in the fibrous tissues of the marrow (microscopic cysts), or in severely affected bones there may be well-defined cysts that are visible grossly as well as microscopically. In instances in which the disease has been present for a long time, the bones may be deformed as a result of pathologic fractures. Deformity may also result from expansions around cysts and fibrocellular lesions that bear a resemblance to giant cell tumors.

In bone biopsies taken in series beginning at the time of removal of the adenoma, it is apparent that reparative changes may take place rapidly. There is a diminution in the number of osteoclasts and in the cellularity of the fibrous tissue in the marrow spaces within one week after the adenoma has been extirpated. By the end of the second week one sees the deposition of new osseous tissue which calcifies and, after a few months, the bones may return to normal.[62] Well-formed cysts in bone remain unless they are opened or otherwise traumatized. (See also page 1019.)

"SECONDARY HYPERPARATHYROIDISM."—This term has been employed to designate those conditions in which more parathormone is produced than normal but where the excess is needed for some compensatory purpose. The excess parathormone production is usually attended by hyperplasia of all parathyroid glands.

At least two examples of secondary hyperparathyroidism may be cited: rickets or osteomalacia and renal insufficiency. The former needs no further comment at this time.

Secondary hyperparathyroidism associated with renal insufficiency is also spoken of as *renal rickets* or *renal osteitis fibrosa cystica.*[63-65] The renal impairment leads to hyperphosphatemia, acidosis, and hyperplasia of the parathyroid glands. As a result of the latter two changes, the bones undergo pronounced lacunar resorption which is strikingly similar to that seen in primary hyperparathyroidism. In the young subject there may be disturbances in endochondral ossification which, on roentgenologic examination, may suggest rickets. Microscopically, however, there may be little, if any, resemblance to true rickets. (See also page 1024.)

Paget's Disease of Bone (Osteitis Deformans)

This specific skeletal disease entity of older people (40 years of age or older) was described by Sir James Paget in 1876. In the many years that have since elapsed, the disorder has been carefully and thoughtfully studied, and its clinical and pathologic manifestations have been recorded with painstaking care by numerous observers.[61, 66, 67] Despite this amount of sustained attention, it must be admitted that little is known of the cause or essential nature of the disease.

Osteitis deformans, in its fully developed form, is an uncommon disease. However, it is readily recognized. The patient's head is usually enlarged and the presenting complaints often include a statement to the effect that the hat size has been increasing. The weight-bearing portions of the skeleton are usually deformed, and because of this the patient may walk with a waddling gait. In the average example the tibiae show anterior bending, the femurs are bowed outward, and the spinal column is shortened and curved forward. In addition, the roentgenograms reveal that the femoral necks have shifted into a horizontal position in relation to the shafts of these bones. Because of the shortened stature and poor postural alignment, the arms of the patient seem disproportionately long.

The roentgenologic manifestations of Paget's disease are reasonably characteristic. In the early stages the osseous tissues appear excessively porous. Later the affected bones become thickened and dense and the marrow cavities may be partially or completely obliterated. In most examples there is coarsening and interweaving of the trabecular structures (Fig. 1098). A noteworthy roentgenographic feature of Paget's disease is the persistence of normal or near-normal osseous structure in the fibulae, even in those cases where the weight-bearing tibiae are markedly altered. In most cases the arteries in the lower extremities are clearly seen because of excessive calcification.

Many patients complain of tenderness and aching pain in the affected bones, especially on bearing weight. In some instances, however, the affected subject seeks medical care because of the severe pain of recent onset and an attendant swelling of the part. Such symptoms and signs may arise because of the development of a sarcoma in a bone that was

previously affected by Paget's disease (see Fig. 1098).

The frequency with which Paget's disease is followed by sarcoma of bone (approximately one-fourth of the cases) has been commented upon frequently. It is worthy of note that three of the five patients originally described by Paget developed osseous neoplasms. In the author's experience this relationship has been strikingly apparent. The bodies of four persons with known Paget's disease have disclosed at autopsy malignant tumors in the affected skeletal parts. In one of these there were two malignant tumors that appeared to have arisen separately.

Fig. 1098.—Paget's disease. A gross photograph of a slice of an amputated femur. Note the sarcoma arising from bone that bears the characteristic changes of osteitis deformans.

Among the various skeletal diseases there are few that give rise to pathologic changes that are as characteristic as the alterations noted in Paget's disease. The affected skull is greatly thickened in the usual case and the diploë is partially or completely obliterated. Despite the pronounced thickening, the calvaria cuts readily with a saw and it is often possible to break and crumble fragments of the poorly knit bone. When the brain has been removed, it may be noted that the fossae in the base of the cranial vault are shallow and that the bone underlying them is also affected. The external and internal bone surfaces as well as the surfaces made by sectioning are often pink in color from the pronounced vascularity. In some cases, where the process has been present for longer periods, the thickened bone may be excessively dense and hard.

In the long bones, in addition to the changes already referred to, there may be bowing deformities. In some instances cortical fractures are observed. These extend into or through the cortex on the convex surface of the deformed bone. Occasionally, fibrous-tissue-filled clefts are noted on gross examination, and, in some instances, these have undergone cystic changes or show evidence of old hemorrhage.

Long bones that have become affected recently may show sharp lines of demarcation between the diseased portions and the normal cortex (Figs. 1099 and 1100). This feature indicates that Paget's disease begins in a focal area and spreads peripherally until the entire bone has become involved.

The microscopic changes in osteitis deformans are highly characteristic, provided the blocks of tissue are not excessively decalcified. Prolonged treatment with acid destroys the basophilic properties of the cement lines and otherwise obliterates certain marks and patterns that are significant to the morphologist. In properly prepared, hematoxylin-eosin stained sections, one notes a highly characteristic or, in some cases, diagnostic mosaic pattern to the osseous tissues. In long bones this is seen best in sections that are taken crosswise to the long axis, whereas in the skull it is usually well marked in any plane of sectioning. An explanation for this difference may be obtained by noting that the initial destructive process in Paget's disease follows the longitudinally placed Haversian channels (see Fig. 1100) and that for considerable periods of time some parts of the original Haversian lamellae may persist.

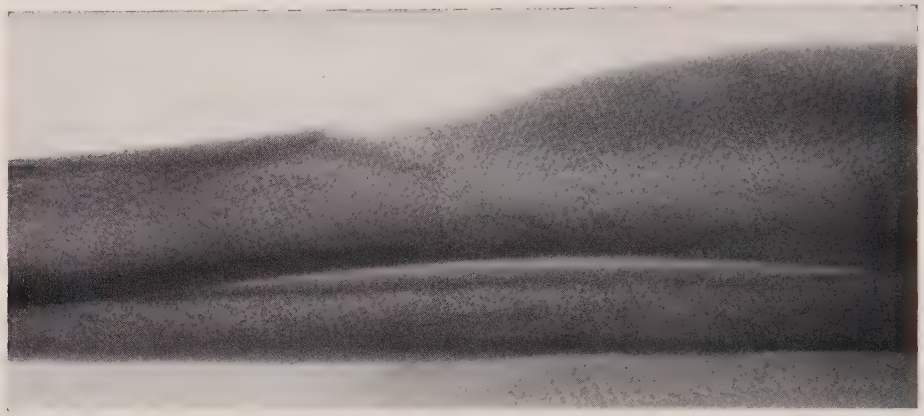


Fig. 1099.

Fig. 1100.

Figs. 1099 and 1100.—Paget's disease. A roentgenogram and photomicrograph of a large celloidin section from corresponding areas reveal widening of the tibial cortex and coarsening of the trabecular structures in a manner characteristic of Paget's disease. Note the sharp boundary between the affected and normal portions of the bone.

The mosaic pattern of Paget's disease may be attributed to two characteristics, the irregular and curved cement lines

within the bony tissues and the irregular notches and depressions on the surface of the spicules. The latter are caused by pronounced osteoclastic absorption (Fig. 1101). These structural features are caused by the simultaneous resorption of old and fully calcified bone and the deposition of new osteoid layers which calcify in a normal fashion. Apparently the resorptive process is carried to a certain point and ceases. In time new bone is formed within this depression and a cement line remains to mark the point of apposition of new bone upon the old. In time, resorptive changes again occur and the architecture of a given area is further disturbed. In all probability this "patchwork" type of bone has a lessened capacity to bear stress and strain and this forms a basis for the ensuing deformity.

In addition to the disturbed architecture of the bony tissue, one notes fibrosis and increased vascularity of the intertrabecular spaces (Fig. 1101).

It would seem appropriate to regard Paget's disease as a disorder of bone maintenance in which there occurs, simultaneously, a pronounced resorptive process and an accelerated formative activity. In early cases the former disturbance overshadows the latter mechanism, whereas the reverse is true in the older examples.

The basis of the relationship between Paget's disease and bone sarcoma has not been established. It seems probable, however, that the long-continued excitation of the bone-forming cells, expressed in unnatural proliferative activity, may lead to unrestrained neoplastic growth.

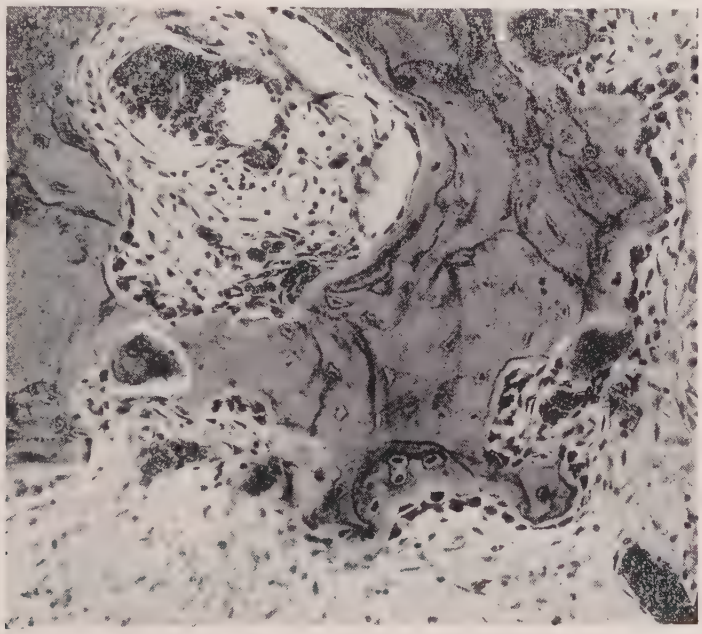


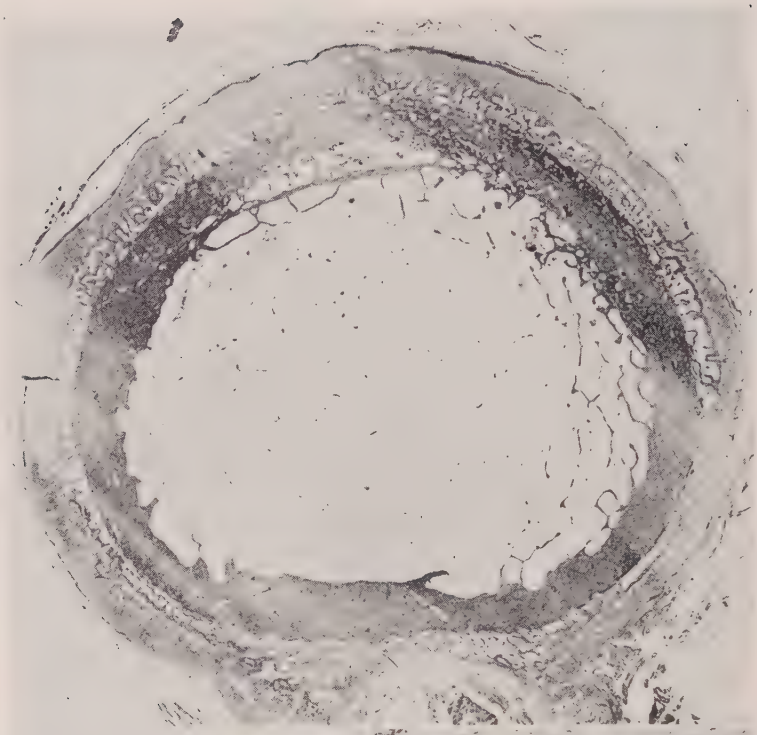
Fig. 1101.—Paget's disease. The mosaic pattern of the diseased bone is caused by the irregular cement lines and scalloped osseous margins, as illustrated in this photomicrograph. The marrow spaces are filled with vascular and loosely textured fibrous tissue. (×180.)

Secondary (Pulmonary) Hypertrophic Osteoarthropathy

In association with congenital heart disease, as well as with certain other intrathoracic lesions affecting the heart, lungs, and mediastinum or the vascular system to the extremities, there may be clubbing of the fingers and toes. Usually the bulbous enlargement of the terminal ends of the digits is accompanied by cyanosis and curving of the nails. Microscopic examination of these tissues is usually disappointing and one must infer that the swelling is caused by hyperemia or soft tissue edema or both. Occasionally small periosteal overgrowths of bone are seen about the terminal phalanges.

Some patients with digital clubbing complain of aches and pains in the small and large joints of the extremities and, less frequently, of bone tenderness. Roentgenologic examination of the extremities of these patients may show subperiosteal bony thickening. Microscopic examination reveals a productive and mildly inflammatory periosteal reaction (Figs. 1102-1104). At times the subperiosteal bone overgrowth is very marked

Fig. 1102.



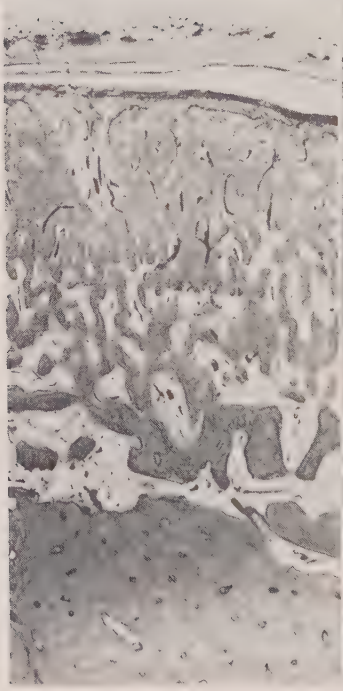


Fig. 1103.

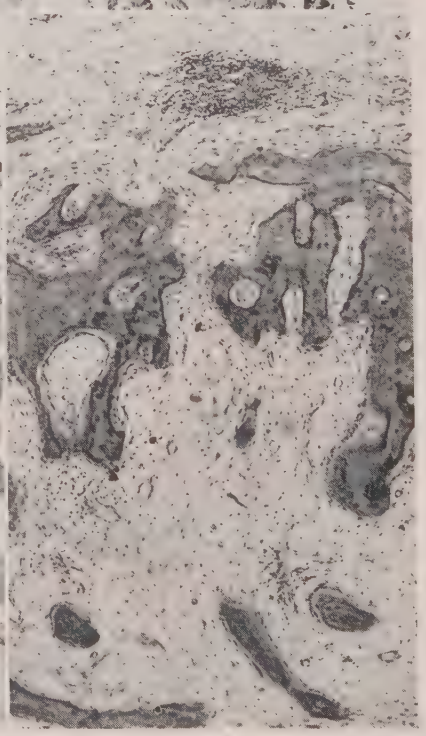


Fig. 1104.

Figs. 1102, 1103, and 1104.—Photomicrographs illustrating the typical changes in secondary osteoarthropathy. Fig. 1102 is a photograph of a complete transection of the femur. Figs. 1103 and 1104 show, in greater detail, the subperiosteal bone overgrowth and the mild inflammatory changes of the lesion.

and consists of more than one layer of added bone that may have resulted from periodic exacerbations (Fig. 1102).[68]

The underlying cause of these changes is not clearly understood. However, it appears likely that any disturbance in circulation may produce the digital clubbing. The hypertrophic osseous changes, however, may require some added "toxic" factor for their development. The latter change is usually, if not always, associated with disease processes in which inflammatory and degenerative changes are superimposed upon disturbances in circulation. Bronchogenic carcinoma, bronchiectasis, and other forms of suppuration in the lungs are among the foremost of the underlying lesions.[69]

Bone Cyst

Solitary bone cyst is a disorder of unknown etiology which usually manifests itself in childhood or adolescence. The distal ends of the shafts of long bones are the commonest sites of occurrence and the upper portion of the humeral shaft is the area of involvement in about half of the cases.[70]

The lesion is usually of moderate or large size when its presence is first detected. Attention is drawn to the lesion in the majority of instances because of pathologic fracture. Occasionally, however, either pain or swelling is noted before the weakened bone is broken.

Anatomically the lesion is comprised of a cyst cavity filled with amber-colored or blood-stained fluid. The external portion of the wall of the cyst is formed of thinned and expanded cortical bone. This is lined, in most specimens, by a smooth, glistening fibrous membrane that is tightly adherent to the bony surfaces. In some examples, however, the cavity contains a considerable amount of tough and edematous connective tissue between the cystic space and the bony wall.

Operative intervention, including curettage and packing of the cavity with bone chips, usually results in obliteration of the cavity. Healing may occur following fracture. The healing of such lesions results from formation of granulation tissue that subsequently ossifies.

Polyostotic Fibrous Dysplasia of Bone

Opinion has varied with respect to nomenclature and interpretation of a number of skeletal disorders whose dominant pathologic manifestations are bone resorption, fibrosis of the marrow spaces, and substitution of poorly formed and unorderly arranged cancellous trabeculae for the original cancellous and cortical bone. In fact there has been a tendency in recent years to group together a number of solitary lesions of bone including unicameral bone cyst, nonosteogenic fibroma of bone[71] and ossifying fibroma of bone, including the variant designated fibrous osteoma of the jaw,[72] as examples of *monostotic fibrous dysplasia* and thus indicate a relationship between these lesions and *polyostotic fibrous dysplasia of bone.*

Information now available suggests that the term fibrous dysplasia should be employed to designate exclusively the disorder described as *osteodystrophy fibrosa* by McCune and Bruch,[73] as *"syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females"* by Albright, Butler, Hampton, and Smith[74] (Albright's syndrome), as *fibrous dysplasia of bone* by Lichtenstein and Jaffe,[75] and more recently as *polyostotic fibrous dysplasia (osteitis fibrosa disseminata)* by Albright and Reifenstein.[61] The propriety of recognizing a *monostotic* form of *fibrous dysplasia* may be questioned, for as Schlumberger[76] has suggested, the monostotic and polyostotic types of bone disease may be unrelated etiologically.

Polyostotic fibrous dysplasia respresents a bizarre syndrome in which any or all of a triad of abnormalities may be present in lesser or greater degree. The triad consists of (a) bone lesions which have a tendency to be unilateral in distribution, (b) nonelevated areas of brown pigmentation of skin (café-au-lait patches) which tend to be on the same side as the bone lesions, and (c) endocrine disturbances affecting growth and development which in young female patients is associated with precocious puberty.

On radiologic examination the skeletal abnormalities are spotty in distribution and vary markedly in appearance. Frequently a single lesion is represented by a fusiform expansion of the shaft of a long bone. The affected part merges imperceptibly into the adjacent normal segments and presents a ground-glass appearance with little or no demarcation between cortex and medulla. Less commonly the osseous lesion has the appearance of a cyst in the roentgenogram but in such instances the margins of the lesion are not sharply drawn. As a result of the resorptive process pathologic fractures are prone to occur and the x-ray film may reveal marked deformities resulting from old or recent injuries.

Gross examination of an involved area of bone reveals widening of the shaft, thinning of the cortex and replacement of the medulla with tough, rubbery connective tissue containing irregularly placed bone spicules. Occasionally cystic spaces are incorporated. Microscopic sections when viewed with low magnification may reveal patterns of bone structure that are highly characteristic (Fig. 1105). The cortex is thin and contains uneven and enlarged haversian canals. The inner portion of the expanded bone is composed of moderately cellular and loosely textured fibrous connective tissue (Fig. 1106) that encloses poorly formed spicules of bone that exhibit both formative and resorptive changes. Usually the irregularly arranged cancellous bone contains numerous individual trabeculae that have curved or sickle shaped configurations (Fig. 1105).

Microscopic sections of the dermal lesions usually show no abnormality other than excessive melanin pigment.

The basis for the endocrine disturbances and an explanation of the different expressions of these disturbances in the two sexes, although subjected to considerable speculation,[61] remain unsolved.

Neoplasms

As we have noted, the fully developed skeleton is formed of highly differentiated forms of mesoblastic tissues including bone, cartilage, and connective tissue. In

its development, primitive mesenchymal tissues are laid down temporarily. These are soon removed and replaced, in the remodeling processes of skeletal growth, by other mesenchymal elements to form the more durable bony and cartilaginous structures of the adult skeleton.

It is necessary to keep these facts before us if we are to understand, even partially, the many varieties of tumors that arise in the osseous parts of the body. In addition, it is necessary to recall that other forms of tissues are incorporated in the developing and mature bony parts. These tissues, which include vascular structures, hematopoietic elements and nerves, also give rise to neoplasms of many kinds.

Numerous attempts have been made to formulate a classification of skeletal system tumors that is sufficiently inclusive to accommodate the various histologic types that are encountered and at the same time restrictive enough to be readily used and understood by the surgeon and pathologist. This problem was reviewed by Ewing[77] (1939), who formulated a revised classification for the Registry of Bone Sarcoma of the American College of Surgeons. Ewing's report includes a discussion of the classification employed by Geschicter and Copeland[78] in 1931.

In the present discussion, a somewhat modified classification is employed (page 1227).

Fibrous Connective Tissue Series.—

FIBROMA.—This sharply delimited, somewhat loculated and often eccentrically placed destructive lesion is seen most frequently in the shafts of the bones of the lower extremities of children.[71] Microscopic examination reveals that the tissue filling the bone defect is composed of fibrous tissue of varying grades of cellularity. In most instances the margin of the tumor is well demarcated from the bony wall but at times extensions of the neoplasm grow peripherally through the marrow spaces. Even when a tumor is

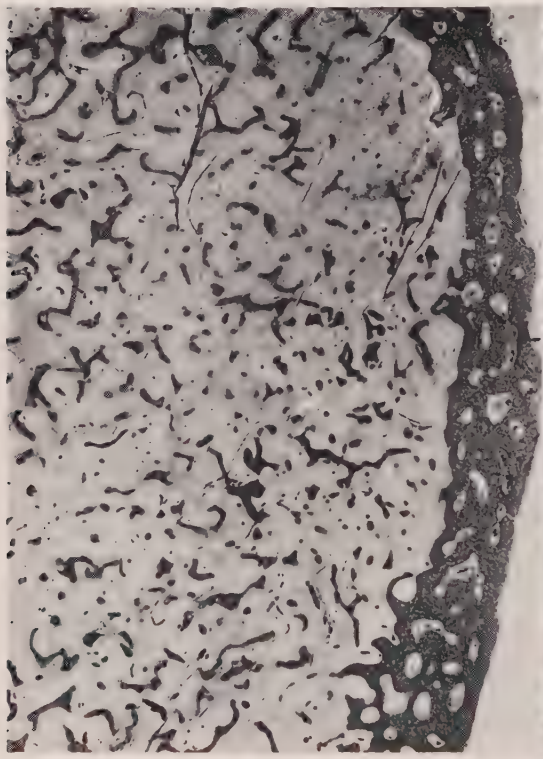


Fig. 1105.

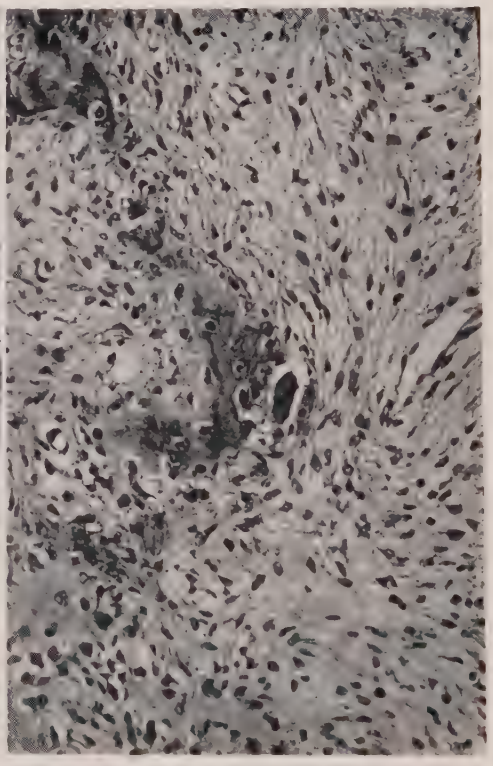


Fig. 1106.

Fig. 1105.—Fibrous dysplasia. In this lesion there is evidence of abundant bone formation (narrow, irregular, and otherwise imperfectly formed spicules). The remainder of the tissue is comprised of moderately cellular and moderately vascular fibrous elements. (×10.)

Fig. 1106.—Fibrous dysplasia. Dense fibrous connective tissue containing occasional osseous spicules or small calcareous particles make up the contents of the destructive lesion. (×183.)

CLASSIFICATION

Type of Tissue Comprising Tumor	Behavior: Benign	Behavior: Malignant
1. Fibrous connective tissue series	Fibroma Ossifying fibroma	Fibrosarcoma
2. Cartilaginous tissue series	Osteochondroma Benign epiphyseal chondroblastoma Chondroma	Chondrosarcoma
3. Osseous (osteogenic*) tissue series	Osteoma Osteoid osteoma	Osteogenic sarcoma (a) Sclerosing (b) Osteolytic
4. Giant cell tumor	Giant cell tumor	Giant cell sarcoma
5. Vascular tissue series	Cavernous angioma Capillary angioma	Angiosarcoma *(malignant angioendothelioma)*
6. Special tumors of marrow (a) Ewing's sarcoma (b) Myeloma		Ewing's sarcoma Multiple (plasma cell) myeloma Solitary myeloma
(c) Reticulum cell sarcoma		Reticulum cell sarcoma
7. Miscellaneous tumors		

*The word *osteogenic* as employed here means "originating in bone" and capable of forming bone.

moderately cellular, possesses numerous mitotic figures, and is poorly encapsulated, its local removal usually results in a cure.

OSSIFYING FIBROMA.—This tumor gives rise to clinical, roentgenologic, and pathologic findings that are similar, except for one detail, to the nonossifying neoplasm just mentioned (Figs. 1107 and 1108). As the name indicates, the mesenchymal cells comprising this tumor possess the capacity to form varying numbers of bony spicules. An identical neoplasm affecting the jaws has been described under the term *fibrous osteoma.*[72]

FIBROSARCOMA.—Malignant neoplasms arising from fibroblasts, although infrequent, may arise in the periosteal coverings of bone or within the cancellous or medullary spaces. The same difficulties which are experienced in distinguishing between benign and malignant tumors of fibroblastic origin arising in the soft tissues of the body are experienced when one is confronted with these tumors in bone. Evidences of rapid growth, invasion, disruption of the bone cortex and histologic qualities of marked cellularity, excessive pleomorphism of cells and numerous mitotic figures, especially the presence of abnormal mitoses, comprise the features that are indicative of malignancy.

Cartilaginous Tissue Series.—Although neoplasms of the chondroma series are listed separately in the classification, it should be noted that they usually arise from chondroblastic tissues within or on the surface of a bone. Occasionally these tumors may arise from mesenchymal cells that differentiate into chondroblasts and in some instances the tumor cells possess the capacity to form both cartilaginous and osseous elements.

OSTEOCHONDROMA.—A synonym for osteochondroma is *cartilaginous exostosis.* In addition the term is sometimes used interchangeably with *osteoma.*

Osteochondromas are benign neoplasms that arise most commonly at or near the ends of long bones (Figs. 1109-1111). They usually develop in children, although they may not produce symptoms or be discovered until adult years. In some instances it can be demonstrated that the outgrowth begins in the periosteal and perichondrial tissues at the metaphyseal end of the shaft in close proximity to the epiphyseal cartilage plate (Fig. 1109). Growth of these tumors occurs in the adjacent connective tissues which perform the function of perichondrium. The new tissue thus formed acquires the gross and microscopic characteristics of hyaline cartilage before it is removed and replaced by bone. The mechanism by which this is accomplished is essentially one of endochondral ossification. (See Figs. 1109, 1110, and 1112.)

The tumor may be a rounded projection (Fig. 1109), a flat mound (Fig. 1110), or have a pedunculated, mushroom configuration (Figs. 1111 and 1112).

These tumors tend to grow slowly and many of them become stationary at the time of cessation of skeletal growth. The cartilaginous cap may entirely disappear,

leaving a cancellous outgrowth of bone (osteoma) as a permanent mark.

Occasionally a bursa forms over the excrescence and this may become inflamed and be attended by pain. In some instances *joint mice* form within the bursal sac.

chondral ossification, *multiple cartilaginous exostoses* may be encountered. A particularly painful form of osteochondroma is the *subungual exostosis* which forms beneath the nail of the fingers and toes, especially the great toe. These lesions may become the sites of infection.

Fig. 1107. Fig. 1108.

Fig. 1107.—Ossifying fibroma. This sharply outlined destructive lesion in the tibia of a child was filled with solid grayish-white tissue in which gritty particles could be detected on section (see Fig. 1108). The cortex was thin and the bone shaft was moderately increased in diameter.

Fig. 1108.—Gross photograph of the sectioned surface of the lesion illustrated in Fig. 1107.

In rare instances chondrosarcomas or osteogenic sarcomas appear to take origin in an osteochondroma. Continued growth of an osteochondroma after the patient becomes an adult is a reason for thorough investigation.

In association with certain congenital and hereditary conditions affecting endo-

Benign Epiphyseal Chondroblastoma.—This tumor, which was formerly regarded as a bizarre chondromatous giant cell tumor, was reinterpreted and given its present name in 1942.[79] The lesion develops in young subjects, most frequently during the second decade. Although the upper end of the humerus is frequently the site of the lesion, any long bone may be affected. Characteristically, the tumor involves both the metaphyseal end of the shaft and the adjacent epiphysis, producing

Fig. 1109.

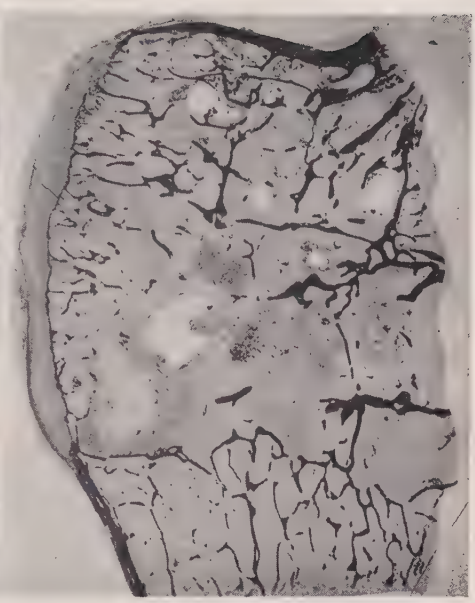


Fig. 1110.

Fig. 1109.—Osteochondroma in an early stage of development in a young child. Section through the junction of the metaphyseal end of the tibia (lower three-fourths of photograph) and the epiphysis (upper right-hand corner). The relation of the tumor to the perichondrium is apparent.

Fig. 1110.—A flat osteochondroma of the upper end of the femur is illustrated in this photomicrograph. Note the perichondrial layer, the growing cartilage, and the irregular trabecular bone that has resulted from imperfect endochondral ossification.

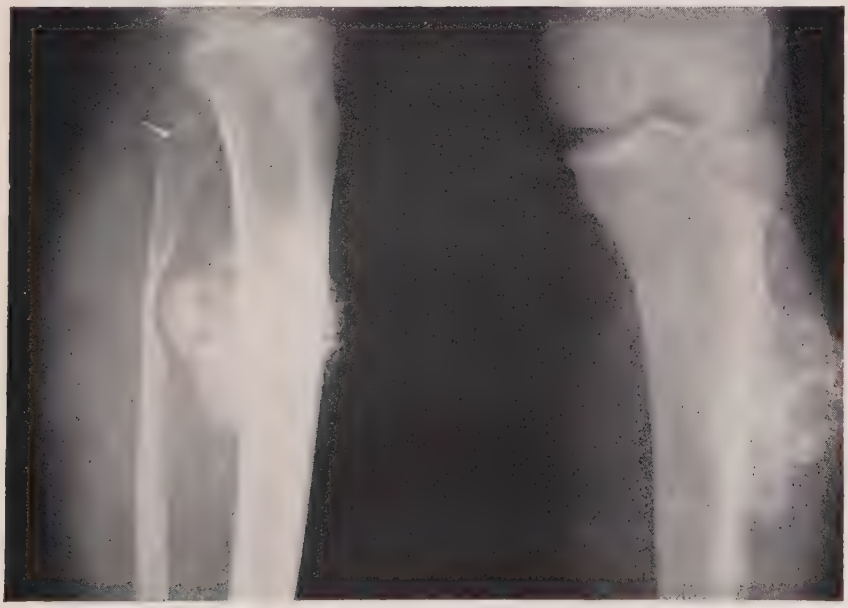


Fig. 1111.—A large, pedunculated osteochondroma of the tibia is illustrated in this roentgenogram. Note that the direction of growth has been away from the epiphyseal end of the shaft. Pressure atrophy of the fibula from contact with the tumor is apparent in the lateral view. (AFIP No. 77515.)

visible resorptive changes which are evident in the x-ray film. Curettings from this lesion consist of tissue fragments resembling cartilage, along with grayish or reddish tissue similar to that of a giant cell tumor. Gritty particles representing calcified bone and cartilage are also recognized. Microscopically, this tumor shows a variety of tissue elements. Some regions are highly cellular and composed of medium-sized round and oval cells. In adjacent areas recognizable spicules of calcified cartilage are identified. Intermingled between these two types of tissues are vascular sinusoids, masses of connective tissue and variable numbers of giant cells. Extravasated blood and hemosiderin pigment are also seen.

Although the benign chondroblastoma may show marked cellularity and be capable of causing considerable destruction of bone, it is known to respond satisfactorily to curettement in most instances. In the occasional case, in which recurrence develops, more radical local removal seems to result in a cure.

Roentgenologic examination shows partial or complete destruction of the involved bone. Frequently the lesion is multiloculated and the margins are usually sharp but regular.

Microscopic examination reveals a tumor composed of nodules of atypical cartilage. The cells have little, if any, pattern of orientation. In the centers of the nodules there is likely to be a preponderance of matrix, and either cystic degeneration or calcification may be noted. The growing margins of the nodules are composed of flattened or oval-shaped cells that merge imperceptibly with the blood-vessel-containing connective tissues that form partitions between the lobular units. Within

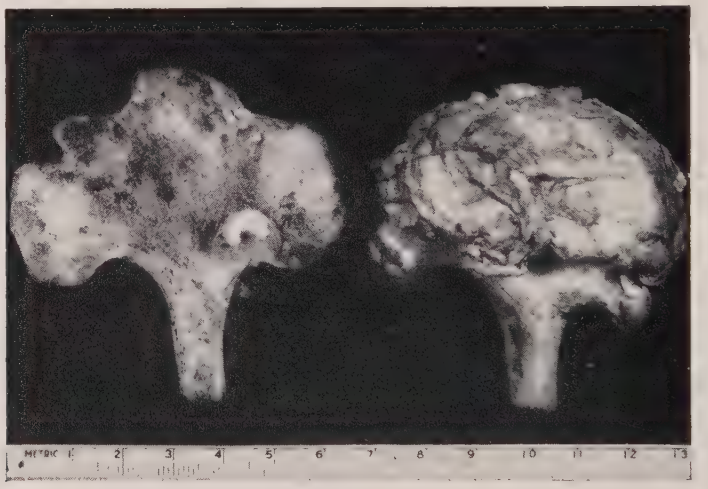


Fig. 1112.—Gross photographic reproductions of a typical mushroom-shaped osteochondroma.

Chondroma.—These tumors are firm, rounded, and lobulated growths of grayish color. They may arise either from the surface of a bone or from its interior. The latter are referred to as enchondromas. The short bones of the hands and feet, the ends of long bones, and the flat bones, including the pelvis, ribs, sternum, and scapulae, are common sites of involvement. On section one sees small and large nodules of grayish-blue tissue that is translucent and resembles normal cartilage. Such nodules are surrounded by connective tissue which may contain blood vessels in moderate numbers. Growth of the tumor can be attributed to the multiplication of the cells that are deeply embedded in these perichondrial layers.

bone, the tumor tissue may be tightly compressed into the cancellous spaces and vascular channels (Fig. 1113). This characteristic is important in explaining the difficulty of eradication of the tumor by curettement.

Chondromas are *benign* neoplasms in the sense that they grow slowly and exhibit histologic evidence of a high degree of differentiation. They differ somewhat from other benign tumors, however, in that they are capable of local invasion and tend to recur following any operative interference short of complete excision of the tumor and all adjacent tissues.

Chondrosarcoma.—The majority of chondrosarcomas arise from pre-existing

chondromatous tumors. This development seems to occur much more frequently in the centrally placed tumors than in chondromas on the surfaces of bone. The transformation appears to be gradual in most instances and it may be easier to determine the change by clinical and roentgenologic study than by histologic examination. Even a large and exceedingly destructive tumor that has spread well beyond the bone in which it arose may reveal microscopic features that differ little, if at all, from the pre-existing tumor tissue examined months or years before. In the usual case, however, careful microscopic study of properly selected blocks will disclose features that indicate malignancy. Increased cellularity, irregular nuclear patterns, and poorly formed intercellular matrix, together with obvious accelerated growth activity at the margins of the individual lobules or nodules are features that usually indicate malignant behavior of the neoplasm.

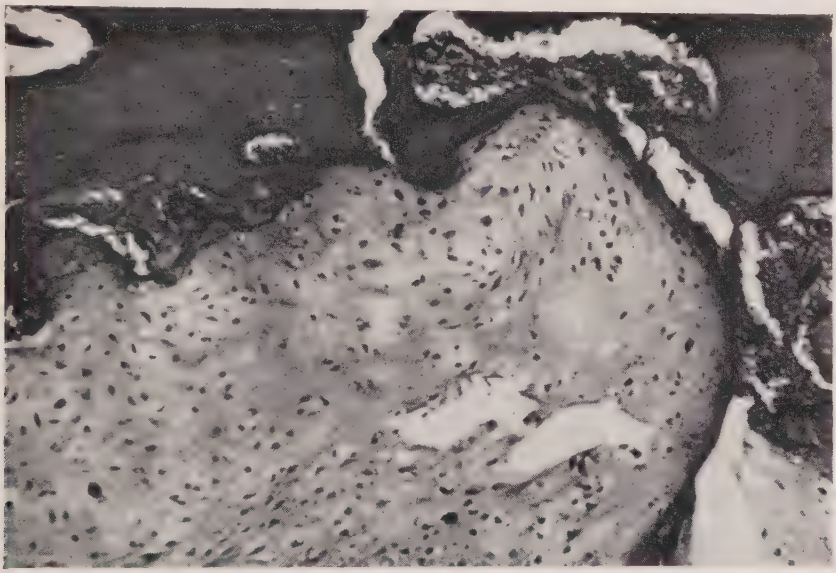


Fig. 1113.—The structural and cytologic features of a typical enchondroma are shown in this reproduction. (×130.) (AFIP No. 90709.)

In sharp contrast to osteogenic sarcoma, chondrosarcoma is pre-eminently a disease of adults, 25 to 50 years of age. The progress of chondrosarcoma is characteristically slower than osteogenic sarcoma and metastasis occurs late in the disease. Secondary nodules almost invariably appear in the lung first, and only rarely are other organs affected. In some instances autopsy reveals a continuous intravascular growth of tumor. This may extend to the right side of the heart or even into the pulmonary arteries.

The known behavior of solid chondromatous tumors as a class is of grave concern to surgeons and pathologists. In many instances an operation, extensive enough to be curative, will result in extreme disability or disfigurement or both. Awareness of this fact, coupled with the knowledge that a lesser operation will at most be followed by slow recurrence, encourages the surgeon to adopt conservative measures. Not infrequently, in these cases, one recurrence follows another until the neoplasm has spread beyond the limits of operability or has invaded the blood vessels and metastasized.

Osseous (Osteogenic) Tissue Series.—

Osteoma.—It is extremely difficult at times to determine whether a given overgrowth of bone is a true benign neoplasm or whether it merely represents the site of a former traumatic injury such as a subperiosteal hematoma or a localized inflammatory process. As we have already noted, some examples of osteomas are the remnants of osteochondromas.

Benign new growths of osseous tissue of either compact or cancellous structure

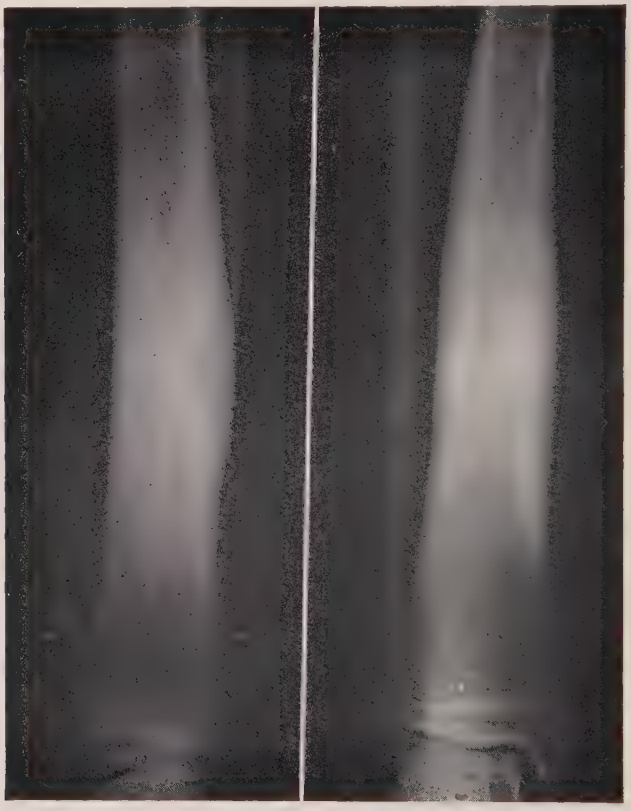
occasionally develop in the bones of the face and skull. Not infrequently these tumors extend into the antrum or other cranial sinuses.

Osteoid Osteoma.—This term was first employed by Jaffe[80] to designate a lesion that was formerly regarded as *chronic bone abscess, osteomyelitis with annular sequestrum,* or *sclerosing nonsuppurative osteomyelitis.* Although some observers have been reluctant to accept Jaffe's contention that the lesion is a neoplasm, few, if any, have doubts that the disorder is an entity.

The condition is most frequently seen in children and young adults, 10 to 25 years in age. Males are more frequently affected than females. The principal symptom is pain, which is persistent but usually not of sufficient intensity to bring the patient under observation until several weeks or months have elapsed after the apparent onset. Physical examination reveals tenderness and there may be slight swelling. Fever is usually absent, and the leukocyte count is generally within normal limits.

The roentgenogram is usually characteristic. The bone for some distance peripheral to the lesion is excessively dense, and, frequently, in a long bone, the cortex is thickened and the shaft is widened (Fig. 1114). Near the center of the hypertrophic bone is a small, sharply circumscribed lesion of relative radiolucency. In the center of this, especially in lesions of considerable duration, is an oval or rounded shadow of varying density.

The pathologic features are equally characteristic, but care must be taken not to overlook the essential lesion. It is perhaps safer to have a roentgenogram made of the specimen and then, using the film as a guide, to section the specimen. Sectioning is made easier if the fixed specimen is first decalcified. Microscopic sections made in this fashion reveal a highly characteristic picture (Fig. 1115).



A. *B.*

Fig. 1114.—Osteoid osteoma. Lateral and anteroposterior roentgenograms (*A* and *B*) showing the typical osteosclerosis associated with osteoid osteoma.

The lesion proper consists of a small spherical nodule of highly vascular connective tissue in which varying amounts of osteoid or fully calcified but irregularly arranged cancellous bone has been deposited (Fig. 1116). Immediately adjacent to the nidus is a zone of porous bone and this is surrounded by the thickened and exceedingly dense bone of the hypertrophied shaft (Fig. 1115).

Excision of the total area or removal of the nidus itself results in a dramatic subsidence of pain. Complete removal probably always results in a cure.

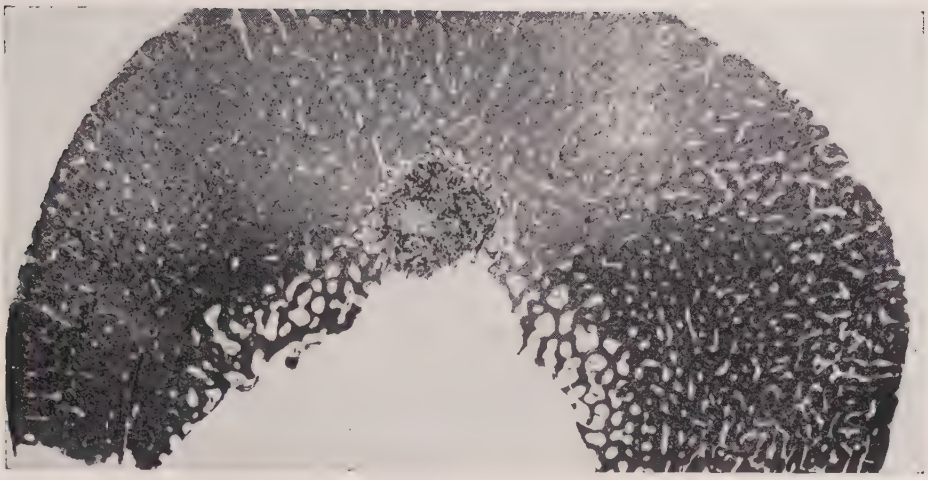
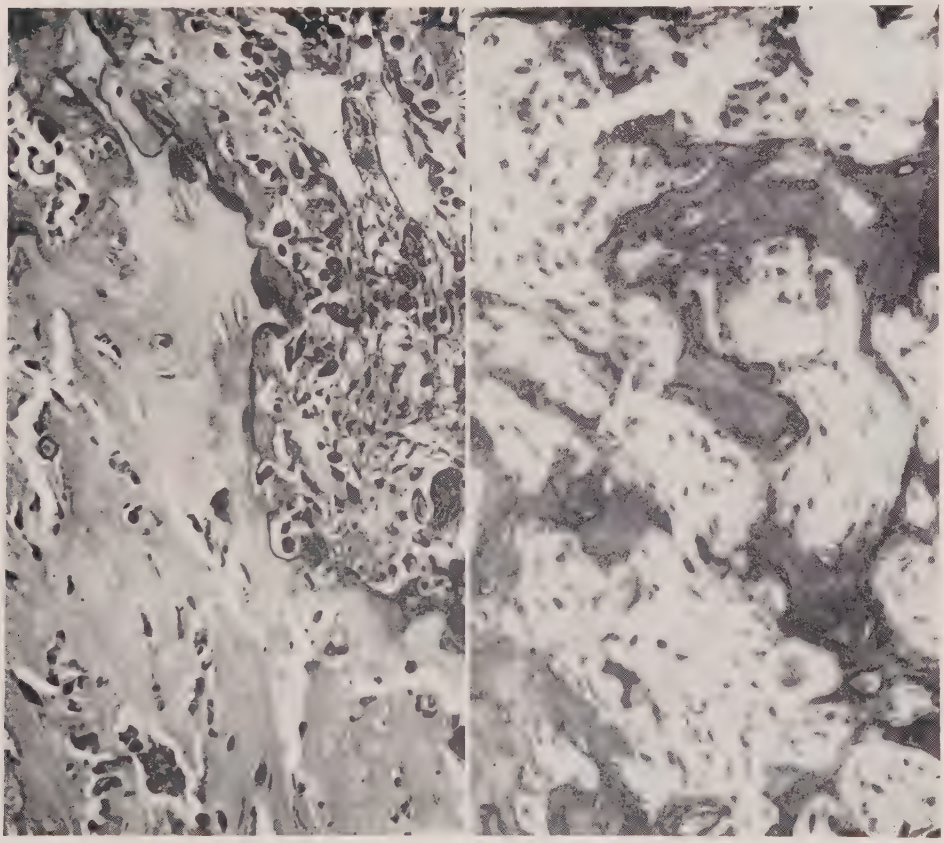


Fig. 1115.—Osteoid osteoma. A photomicrograph of a cross section through the nidus. Note the thickening and condensation of the surrounding cortical bone. Note composition of the osteoid osteoma in Fig. 1116.



A. *B.*

Fig. 1116.—*A* and *B*, Osteoid osteoma. Photomicrographs illustrating abundant osteoid (*A*) and irregular, well-calcified osseous spicules (*B*) that are encased by highly vascular and moderately cellular connective tissue. Osteoclasts are present in moderate numbers. (*A*, ×180.) (*B*, ×250.)

Osteogenic Sarcoma.—The classification stated by Ewing lists six types of osteogenic sarcomas and one of these contains two subgroups. Such a detailed scheme of compartmentalization, while valuable for registry purposes and for specialists in neoplastic disease, is unnecessary and probably impractical for the purposes of the student of medicine.

Osteogenic sarcoma is the most common primary malignant neoplasm of bone. Like hematogenous osteomyelitis, it arises most commonly in the metaphyseal ends of the shafts of long bones, particularly the lower end of the femur, the upper end of the tibia, and the upper end of the humerus. Occasionally the neoplasm arises in the middle portion of the shaft of a long bone. The disease is seen most frequently in children and young adults. About 75 per cent of the tumors occur in patients between 10 and 25 years of age and males are affected about twice as often as females. Many tumors are noticed soon after

Fig. 1117.

Fig. 1118.

Fig. 1117.—Osteogenic sarcoma. Roentgenogram of a midsagittal slice of a femur undergoing replacement by a sclerosing osteogenic sarcoma. Note the condensation and loss of architectural design of the affected segment of femur and the marked osseous tissue growth subperiosteally.

Fig. 1118.—Osteogenic sarcoma. The gross appearance of the sectioned surface of the sarcoma illustrated in Fig. 1117 is reproduced in this photograph.

trauma, but it is usually impossible, in a given case, to prove an etiological relationship.

Deposition of radium in the human skeleton, acquired in the luminous paint and dial industry and by other methods, is known to cause injury to the bone and bone marrow. This is followed in some cases by osteogenic sarcoma. These changes, including the production of osteogenic sarcomas, have been studied in the rat.[81] (See also page 178.)

exceedingly difficult, therefore, to determine the precise point of origin. In all likelihood the neoplasms are derived from either the bone-forming cells within the cancellous spaces of the shaft or from the periosteal layer. It is uncertain which is more common.

The roentgenologic and pathologic features of osteogenic sarcomas are variable and depend to a large extent on the amount of bone that is produced in a particular tumor. In this regard, there

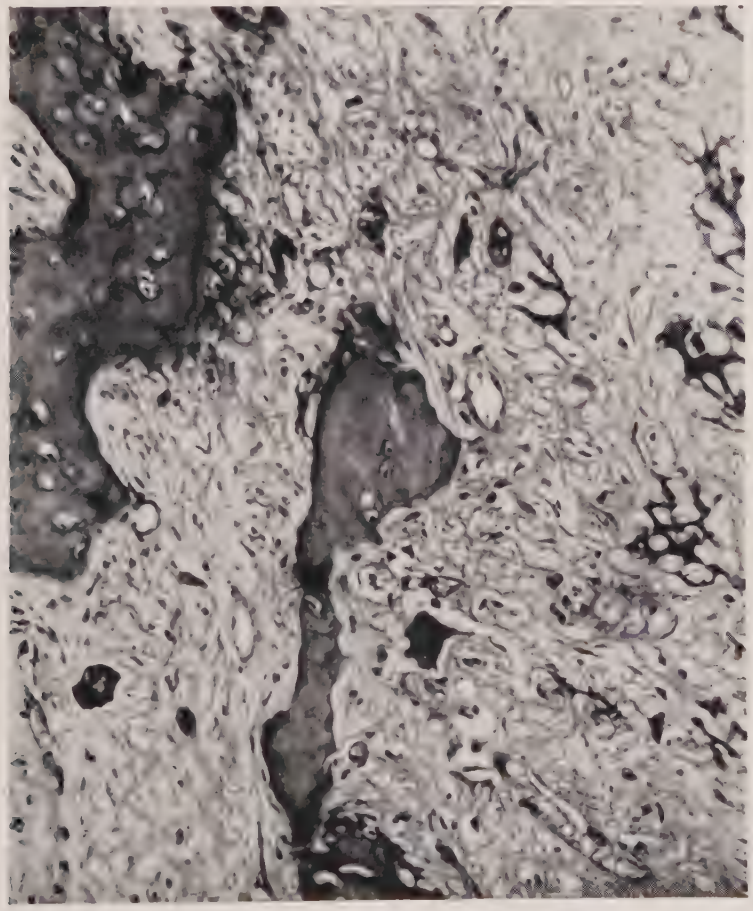


Fig. 1119.—Osteogenic sarcoma. The bizarre cellular pattern and irregular ossification of a sclerosing osteogenic sarcoma are illustrated in this photomicrograph (×230). (AFIP No. 63769.)

By the time an osteogenic sarcoma is recognized and submitted for examination it is seen to involve the interior of bone, to have extended through the cortex, and to have caused an elevation of the periosteum for some distance along the shaft (Figs. 1117 and 1118). It is

are two main types: (a) a tumor that produces a great deal of osteoid matrix which calcifies—**sclerosing osteogenic sarcoma** (Figs. 1117-1119); and (b) a tumor, usually of exceedingly rapid growth rate, that produces little or no recognizable bone—**osteolytic osteogenic sarcoma**

(Figs. 1120-1122). Highly vascular neoplasms—**telangiectatic osteogenic sarcomas**—are likewise destructive in character, as are the tumors, irrespective of growth rate, that are composed of fibrous tissue elements.

The typical sclerosing osteogenic sarcoma shows, on roentgenographic examination, a condensation of the original bone and loss of its normal architecture. The cortex on one or both sides is irregular in outline and the normal markings are obliterated. Extending outward at right angles from the cortex beneath the displaced periosteum is a fringelike density that is referred to as "ray" formation. These linear markings are attributable to calcified trabeculae within the neoplasm (Fig. 1117). When such a specimen is sawed in its longitudinal axis, one sees tumor tissue of grayish-white color. At the periphery it is usually cellular and friable, in contrast to the densely calcified portion that lies nearest to the shaft. The original cancellous bone of the shaft end is converted into exceedingly dense ivory-like bone. An interesting detail may be noted at the upper extremity of the tumor where the periosteum has been recently separated from the cortex, producing a characteristic triangle (Codman's triangle). At the lower extremity, the tumor usually extends to, but not beyond, the attachment of the periosteum to the perichondrial margin of the epiphyseal cartilage plate (Fig. 1118). The latter structure apparently resists the spread of the neoplasm for a time, but in numerous instances the bony epiphysis is invaded by the time the extremity is removed.

In the so-called lytic or osteolytic osteogenic sarcoma, the roentgenologic picture is less characteristic. Usually there is evidence of partial or total destruction of the original bone in an area of variable size. The margins of the lesion are usually irregular in outline. There may be a soft tissue shadow from the extension of the tumor into the extraosseous tissues. (Fig. 1120.) Examination of the cut surface of such a tumor reveals a sharply outlined but irregular area of bone destruction. Filling the bony cavity is a mass of cellular and friable tissue that is pinkish-gray in color. In numerous examples, one will note red areas caused by hemorrhage or yellowish foci attributable to necrosis. (Fig. 1121.) Small amounts of calcified bone may be present. Microscopically such lesions are usually highly cellular and show little or no osteoid matrix between cells. Tumor giant cells and numerous bizarre mitotic figures are often present in large numbers. (Fig. 1122.)

Occasionally one encounters tumors that fail to conform to either the sclerosing or destructive (lytic) types just mentioned. One such variant is a tumor that is comprised in part of cartilage and in part of bone (Figs. 1123-1125). Other atypical forms include a certain amount of myxomatous tissue. It is because of these transitions that the older literature made reference in the form of prefixes to "myxo-," "fibro-," "chondro-," "osteoid-," and "osteo-" sarcomas. Not uncommonly two or more such prefixes were employed in an effort to characterize a single tumor.

Osteogenic sarcoma is a tumor that leads to a fatal termination in a high percentage of instances, irrespective of the form of treatment employed. In published accounts, the five-year survival rates range from 10 to 30 per cent.

Metastasis takes place chiefly by way of the blood stream, and the initial site of secondary growth is usually the lung. Not infrequently the liver, heart, and other organs are invaded by the time the disease has run its course. Metastases in distant bones are seldom observed.

Giant Cell Tumor.—Few if any neoplasms, regardless of site of occurrence, have given rise to as much divergence of opinion as has the giant cell tumor of bone. The causes for disagreement are many, but foremost among them is the dissimilarity in concept of what properly constitutes a *giant cell tumor*. Some authors have elected to be all-inclusive and, in order to designate the particular type of lesion under consideration at the moment, have referred to *variants* of one sort or another (fibrocystic variant, chondromatous variant, xanthomatous variant, malignant variant, etc.) as contrasted against a *typical* giant cell tumor. In opposition to this view, some observers have restricted the use of the term, giant cell tumor, to examples of the *typical* neoplasm with the conviction that the *atypical* lesions are either unrelated neoplasms or nonneoplastic, reactive processes.

The truth of the matter has not yet become evident—in fact, it seems doubtful that the problem will be settled to everyone's satisfaction for some time to come.

The distinctive giant cell tumor behaves as a neoplasm that is usually, but not necessarily, benign in its subsequent behavior. The lesion characteristically occurs in the ends of long bones of young adults in whom the epiphyses have closed. The lower end of the femur and the upper end of the tibia are the commonest sites, but the tumor may occur in ends of any of the long bones, especially the lower extremity of the radius or in a few flat bones.

Fig. 1120. Fig. 1121.

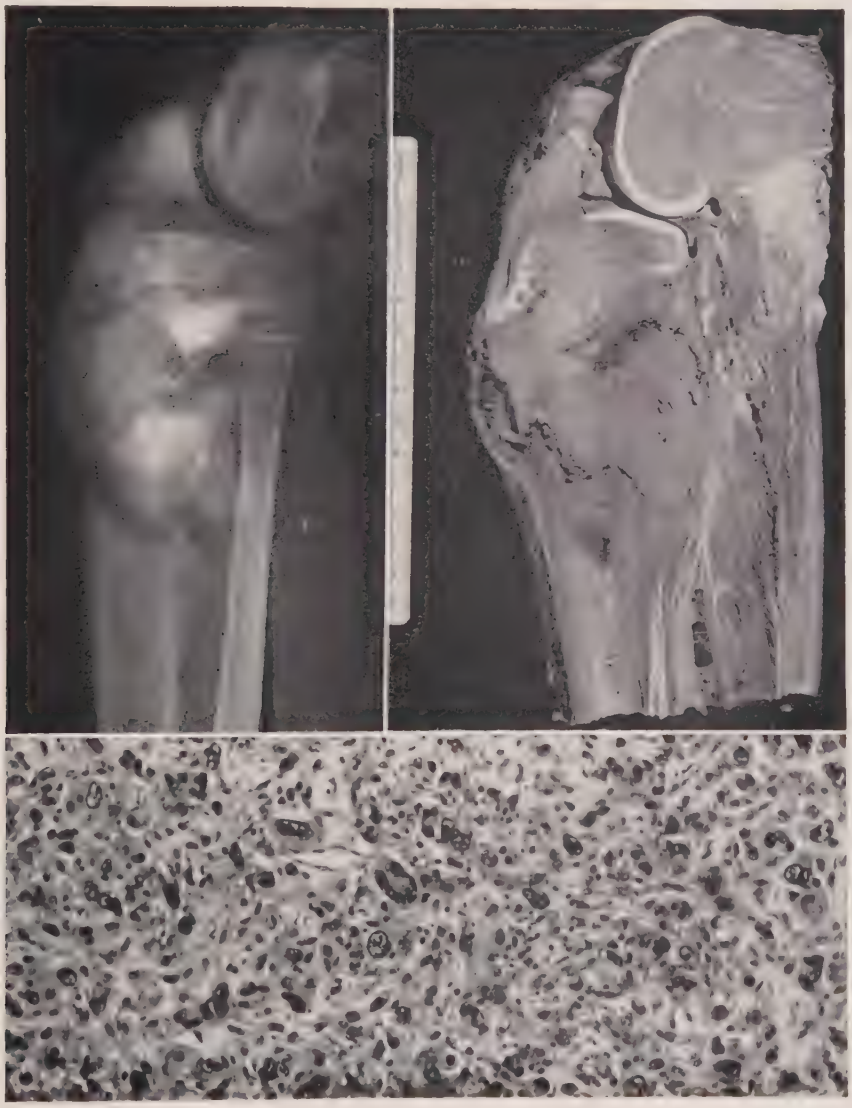


Fig. 1122.

Figs. 1120 and 1121.—Osteogenic sarcoma. Roentgenogram and gross photograph illustrating a destructive and rapidly growing sarcoma of the tibia which has resulted in a pathologic fracture.

Fig. 1122.—Osteogenic sarcoma. Marked variation in the size and shape of cells, bizarre mitoses, and little or no evidence of bone matrix formation are noteworthy features in this reproduction of a lytic form of osteogenic sarcoma. (×165.) (AFIP No. 73613.)

Pain that is especially severe on weight-bearing and motion is usually the first symptom. Later there may be noticeable swelling. In some instances a pathologic fracture causes the patient to seek medical attention.

The radiographic appearance is frequently but not always characteristic. In early cases the roentgenogram reveals a sharply outlined and usually single area of complete bone destruction. Such a lesion is generally in one of the condyles. In older lesions the destructive process may have extended to involve the entire bone end. When this has occurred, there is usually a noticeable expansion, and the peripheral margins of the tumor are indicated by a thin and discontinuous bony shell formed beneath the displaced periosteum. The "cystic" lesion may consist of a single space or have a multiloculated appearance. In either case, the relationship of the expanded area to the shaft of the bone is not unlike a soap bubble being inflated from a straw. A fracture through such a lesion may introduce bizarre features from telescoping and from repair. (Fig. 1126.)

Fig. 1123.

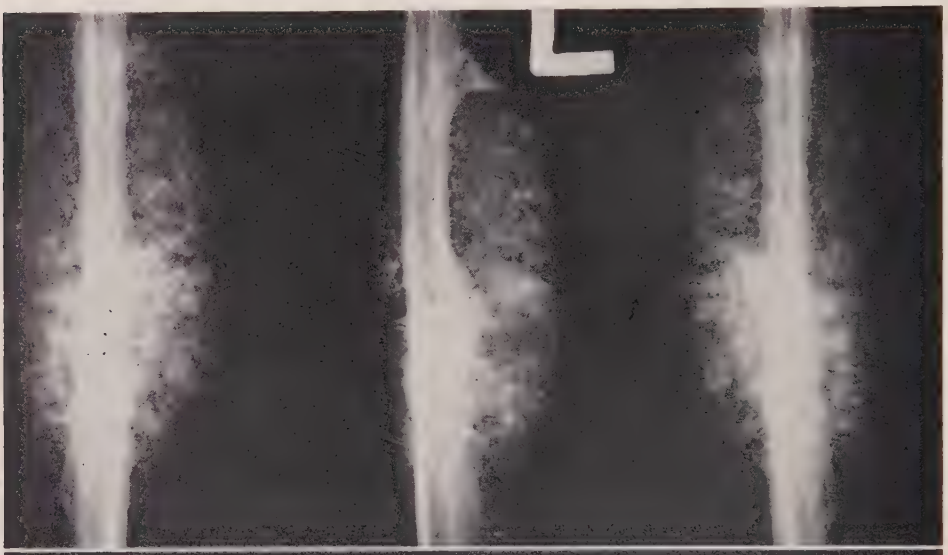


Fig. 1124.

Fig. 1123.—Roentgenograms of a sclerosing osteogenic sarcoma of the fibula. The tumor was slowly growing. It was made up of both osseous and cartilaginous tissues. (See Fig. 1125.)

Fig. 1124.—Gross photograph of the specimen illustrated in Fig. 1123. (Courtesy Dr. F. Chandler.)

The gross specimen shows a sharply delineated expansion at the junction of

the tumor and the shaft. The expanded portion is partially or completely encased in a thin shell of bone which may be readily indented by pressure and easily cut with a knife or scissors. When the specimen has been divided in its long axis, it is noted that there is a sharp line of demarcation between the marrow of the bone medulla and the tumor tissue filling the expanded end of the bone. The neoplasm may extend to the undersurface of the articular cartilage. The neoplastic tissue is firm and friable. It is grayish in color, with either a pinkish or brownish tint. Focal areas of degeneration of yellow-brown color and hemorrhagic areas of red or dark-brown color, depending on the age of the hemorrhage, are usually present. In addition, there may be linear bands of fibrous tissue or stellate scars where necrotic tumor tissue has been replaced.

Microscopic examination shows a highly characteristic pattern (Fig. 1127). The most distinctive feature is the presence of large numbers of giant cells. These contain many even-sized, oval nuclei (twenty to one hundred in a sectioned cell surface) that are crowded together near the center of the cell. These have prominent nuclear membranes and each contains a single nucleolus. In between the giant cells is a well-vascularized and cellular "stroma" that is comprised of spindle and oval-shaped cells. A few mitotic figures may be found in these cells and, in some instances, they may be numerous. Some observers have laid great stress on the cellularity of the "stroma," the number of plump, rounded cells and the number of mitotic figures, believing these details provide an index to the probable behavior of the tumor. On this basis a system of classification into three grades has been suggested.[82] These authors hold that grade III tumors possess malignant properties either inherent in the tumor from its beginning or acquired through successive recurrences of tumors originally belonging to grades I or II.

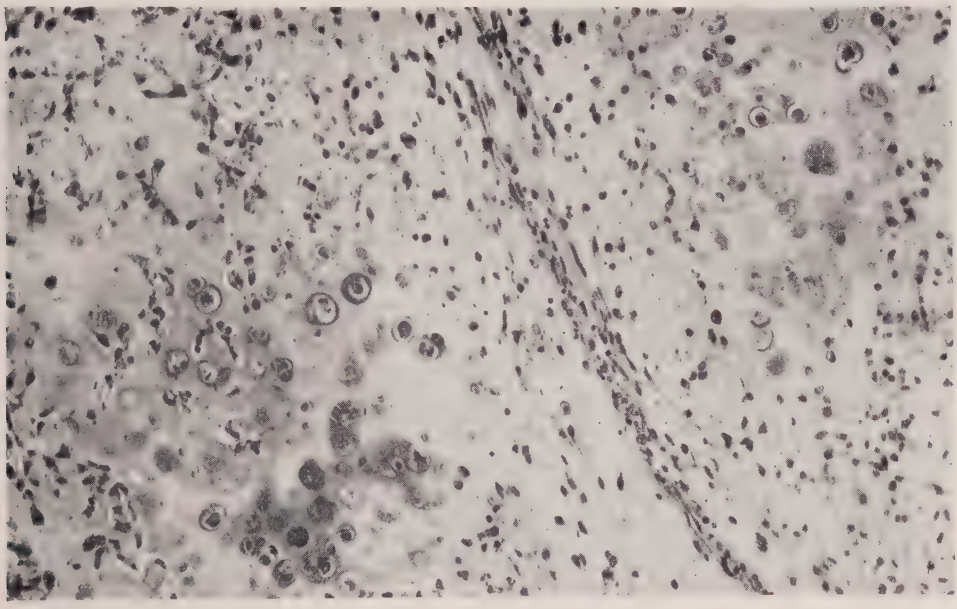


Fig. 1125.—Imperfectly formed bone and cartilage make up this malignant tumor. The histologic features portrayed here are similar to those seen in the tumor illustrated in Figs. 1123 and 1124. (×170.) (AFIP No. 66706.)

Giant Cell Sarcoma.—Occasional neoplasms, possessing most of the histologic features of the giant cell tumor, either have from their inception or acquire subsequently the clinical and pathologic features of malignancy. Such tumors are rapidly growing and excessively destructive and show a capacity to break out of the bony shell and invade adjacent soft tissues. In some instances the process of invasion includes the entrance of tumor tissue into vascular channels,

and distant metastases thus may be established. On microscopic examination tumors having these qualities are usually highly cellular and show numerous mitotic figures including atypical mitoses. The giant cells are likely to vary in size and shape and in the number and size of the nuclei.

Fig. 1126.—Giant cell tumor. In this reproduction one notes a multicystic lesion which has destroyed both condyles of the femur. A pathologic fracture with resultant collapse of the lesion is evident. (AFIP No. 70987.)

Giant cell tumors when possessing the recognizable features of malignancy should be designated as *giant cell sarcoma* and treated by whatever means required to completely remove the lesion.

Vascular Tissue Series.—

ANGIOMAS.—Benign angiomas are occasionally observed in the skeleton, especially the vertebrae, where they ordinarily cause no symptoms. They may be sharply circumscribed or spread diffusely through the bone. The former is accompanied by a focal area of bone destruction, whereas the latter may give rise to coarsened trabeculation and increased porosity in the x-ray film. These features probably are due to the increased size of the haversian channels in the compact bone and to the anastomoses of the vascular channels.

ANGIOSARCOMA.—Malignant hemangioendotheliomas of bone are seldom encountered. The bone may be partially destroyed in a progressive manner over a wide area or completely and rapidly removed in a well-circumscribed focus. The author observed one lesion of the latter variety in a patient with Paget's disease of bone. Grossly, these tumors may be cellular and friable and gray in color or, because of the high degree of vascularity, they may be red in color and ooze blood when sectioned. The histologic characteristics are no different from like tumors in extraosseous tissues.

Special Tumors of Marrow.—

EWING'S SARCOMA.—This malignant neoplasm which arises in bone was differentiated from osteogenic sarcoma and established as an entity by James

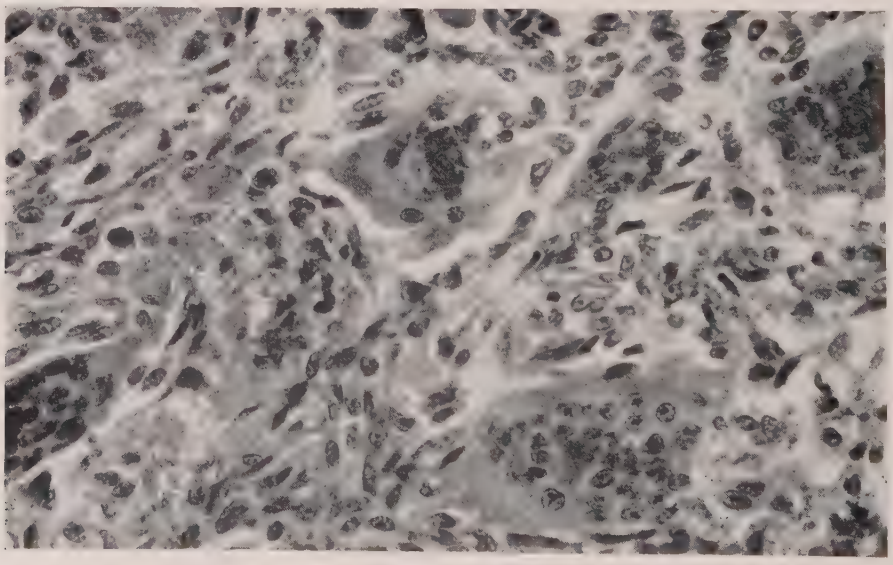


Fig. 1127.—Giant cell tumor. Photomicrograph illustrating the typical cytologic and structural features of a benign giant cell tumor of bone. (×765.) (AFIP No. 63505.)

Ewing,[83-85] whose name it bears. It is probable that the tumor represents the "small round-cell sarcoma" of earlier writers. Ewing regarded it as a myeloma derived from endothelium—**endothelial myeloma.**

Soon after Ewing's sarcoma was established as an entity, the material from the Registry of Bone Sarcoma of the American College of Surgeons was thoroughly reviewed by Connor[86] and again by Kolodny.[87] Among the 650 tumors then registered, forty typical and ten questionable examples of this lesion were found.[87]

Although there is general agreement on the specificity of this variety of neoplasm, Ewing's concept of the histogenesis has been questioned. Evidence purporting to show that the tumor arises from the reticulo-endothelial system and that the tumor cells possess the capacity to differentiate into plasma cells, lymphocytes, or other cell types has been presented.[88] A similar opinion has been expressed recently by Lichtenstein and Jaffe,[89] who hold that the tumor is an entity, primary in bone but possessing no bone-forming capacity, and that it is probably derived from the reticular tissue of the marrow.

Ewing's sarcoma is usually seen in children and young adults, 10 to 25 years of age. Since this is the exact age period in which the incidence of osteogenic sarcoma is highest, difficulty is often experienced in distinguishing between the two tumors before operation. The neoplasm, while not rare, is much less frequent than osteogenic sarcoma.

In the usual case, the patient complains of pain in the affected area. Swelling may or may not be present. The patient may have a slight elevation in body temperature, and the leukocyte count may be slightly or moderately elevated. These signs and symptoms may lead to an erroneous diagnosis of osteomyelitis of low-grade character. Roentgenographic examination of the entire skeleton at the time of admission of the patient usually reveals but one bone lesion. This consists of a certain amount of destruction of the original bone and, provided the lesion is in the shaft of a long bone, there is frequently a series of layers of new subperiosteal bone. (Fig. 1128.) This "onion-skin" appearance is not observed as frequently in Ewing's sarcoma as the literature suggests, and it should be noted that a similar appearance may result from other conditions. In most patients, the original lesion is followed, after a period of weeks or months, by the appearance in the roentgenogram of other foci of tumor.

The disease may begin in any bone. However, in the majority of instances the shafts of the long tubular bones and the bones of the pelvis are affected first.

When the bone that is affected by the tumor is split in its long axis, it is noted that the original bone is porous and that small and large portions have been resorbed. Recognizable tumor tissue is found beneath the displaced periosteum and in the irregular cavities within the bone. This is white or gray-white in color and exceedingly soft and friable. Areas of hemorrhage and necrosis may be evident. The new bone, observed in the roentgenogram, is also evident on gross inspection. This is most prominent beneath the periosteum and microscopically it is apparent that its formation has resulted from the stimulation of the periosteal cells and not from any bone-forming potentiality of the tumor cells themselves. The tumor tissue as viewed microscopically consists of broad or narrow sheets of small round cells growing between partitions of well-vascularized connective tissue. (Fig. 1129.) Little cytoplasm is evident, but the nuclei are relatively large and of round or oval contour. Mitotic figures are numerous but tumor giant cells as well as other pleomorphic forms are uncommon.

As the disease progresses, the other bones of the skeleton become involved and metastasis to the lungs occurs. At autopsy there may be metastases in other organs. While it is true that Ewing's sarcoma is radiosensitive, radiation therapy either alone or combined with surgical removal of the affected part seldom effects a cure.

Multiple Myeloma.—Myeloma is a tumor of bone that characteristically affects multiple sites by the time it is recognized. The tumor cells arise from bone marrow constituents and may bear resemblances to plasma cells, lymphocytes, or to cells of either the myeloid or erythroid elements. In a high percentage of instances, however, the tumor cells reproduce the nuclear and cytoplasmic characteristics of the plasma cell, and the disease is generally referred to as *multiple myeloma* or *plasma cell myeloma.* (See discussion also on page 908, and Figs. 796 and 797.)

This malignant disease of the skeleton is attended by symptoms of pain, anemia, weight loss, weakness, and fractures of bones, particularly the bodies of the

vertebrae. Occasionally the myeloma cells gain entrance into the circulating blood and may be identified in the blood smears. They are frequently recognized in samples of sternal marrow. The disorder is one of adult life and more than three-fourths of the patients are between 40 and 70 years in age. Men are affected about twice as frequently as women.

sharp borders ("punched-out areas") and are unaccompanied by proliferative reactions at their margins unless a fracture has occurred. Even in the presence of a pathologic fracture the formative process may be feeble and unapparent in the roentgenogram.

Sections through the affected bones reveal small and large areas of sharply

Fig. 1128.

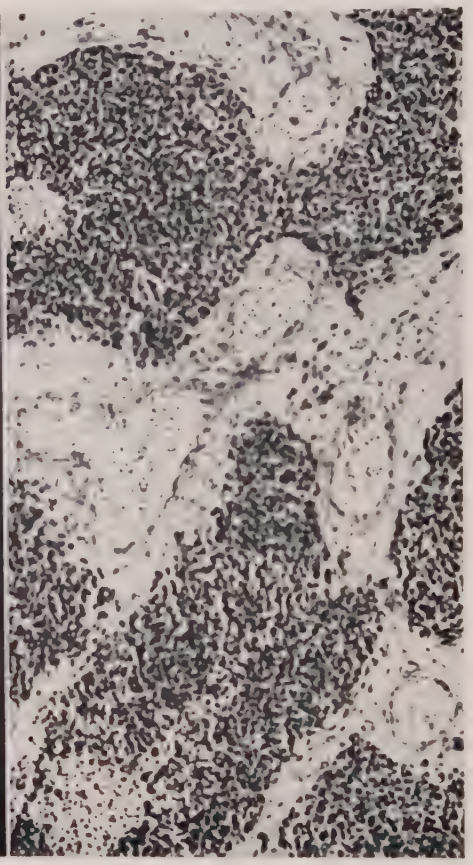


Fig. 1129.

Fig. 1128.—Ewing's sarcoma. Roentgenogram showing the more characteristic features of Ewing's sarcoma of bone. One should note the irregular areas of osteoporosis and osteosclerosis, the loss of bone architecture, and the multilayered periosteal new bone formation.

Fig. 1129.—Ewing's sarcoma. Closely packed small round cells make up the substance of this tumor. Note the loosely textured connective tissue containing numerous blood vessels which forms partitions between the masses of tumor cells. (×160.) (AFIP No. 73775.)

Hyperproteinemia, due to increased globulin, may be demonstrated in about 70 per cent of the patients, and Bence-Jones protein appears in the urine during the course of the disease in a slightly higher percentage of instances.

Roentgenologic examination reveals multiple, small and large areas of bone destruction (Fig. 1130). These have

outlined bone destruction. These areas are occupied by soft, friable, and exceedingly cellular tumor tissue that is pinkish-gray in color or distinctly red because of hemorrhage (Fig. 1130). Microscopically the tumor nodules are composed of closely packed cells of characteristic type (Fig. 1131). The majority of cells are oval in shape and consist of

Fig. 1130.—Multiple myeloma. Roentgenogram and gross photograph of a hemisection of a femur showing extensive bone destruction caused by multiple myeloma. The reddish-gray masses of tumor cells are clearly shown in this gross photograph. Note the absence of any reactive bone formation.

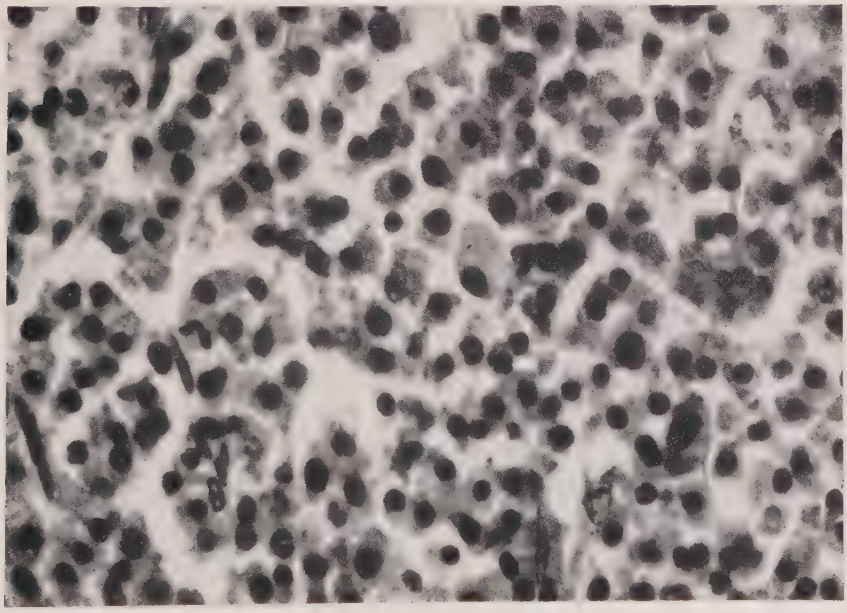


Fig. 1131.—Multiple myeloma. Closely packed tumor cells resembling plasma cells are illustrated in this photomicrograph of a section of multiple myeloma.

fairly abundant cytoplasm of lavender tint and an eccentrically placed, rounded nucleus. The latter cell part is stained heavily, but in most instances there are peripherally placed clumps of chromatin that give it a "clock-faced" appearance. Some variation in size and shape of the cells is frequently noted and, in some examples of the tumor, the degree of pleomorphism may be moderately prominent. In these specimens, multinucleated cells may be numerous.

Multiple myeloma runs a fatal course in several months to a few years. Death may result from inanition, infection, or from the renal changes that are frequently associated with the disease. Postmortem examination reveals widespread destruction of the skeleton. In addition, if renal impairment has occurred, there are interesting changes in the kidneys (Fig. 474, page 589). Occasionally there is amyloid deposit in the organs and tissues, or there may be evidences of pathologic calcification. Rarely there may be myeloma cell infiltration in the organs and lymph nodes.

Solitary Myeloma.—A few reports have appeared of single tumors in bone that have the cytologic characteristics of myeloma.[90] Following local removal, there may be no apparent tendency toward generalization. It is uncertain whether *solitary myeloma,* sometimes referred to as *solitary plasmacytoma,* is a distinct entity or a localized stage of multiple myeloma. An equally rare tumor of similar appearance and behavior occurs in the lymphoid tissues of the tonsils or soft palate and in the floor of the mouth.[91]

Reticulum Cell Sarcoma.—In 1939, Parker and Jackson[92] drew attention to an uncommon primary tumor of bone which they named *reticulum cell sarcoma.* The tumor occurs principally in the long bones. Roentgenologically there is uneven destruction of bone, causing osteoporosis and loss of normal architecture. Microscopically, the tumor resembles the reticulum cell sarcoma of lymphoid tissues. It has been observed that the affected patients may remain in good health, even when the tumor has reached a large size, and that metastasis is slow to occur. This latter feature and the known radiosensitivity of the tumor cells probably accounts for the comparatively good results from combined radiation and surgical treatment. Radiation therapy alone is apparently inadequate to control this distinctive neoplasm.[93]

Miscellaneous Tumors.—

Liposarcoma.—One of the rarest varieties of tumors of skeletal tissues is the liposarcoma.[94, 95] When inspected grossly, the tumor tissue is pale yellow in color and soft in consistency. Multiple tumors in bone including the skull may be recognized. It is not certain whether these are separate primary neoplasms or metastases; if the latter, a tendency for early metastasis to bone must be assigned to this neoplasm. Microscopically the cells are large and pale and their cytoplasm contains abundant amounts of finely divided particles of fat that may be stained in a characteristic manner. The cells show considerable pleomorphism and may be arranged in alveolar groups.

Adamantinoma.—Adamantinomas occur in three positions in relation to bone. The commonest site is the jaw.[96] The base of the skull in relationship to the craniopharyngeal pouch is the second most frequent area of involvement.[97] The tibia is the only other area of origin that justifies comment.[98]

Adamantinoma of the tibia is an exceedingly rare neoplasm. It is essentially benign although it possesses the ability to invade locally and to recur following incomplete removal. In the roentgenogram there is usually a multiloculated area of complete bone destruction. Grossly, in these areas, one finds a dense grayish tissue that is sharply demarcated from the osseous parts. (Fig. 1132.) Microscopically, the lesion resembles the better-known adamantinoma of the jaw in all essential respects (Fig. 1133).

This astonishing condition probably results from embryonic ectodermal rests. It has been suggested that the influence of growth of the periosteal and osseous tissues may account for the special morphologic pattern of the epithelial growth.[98]

Chordoma.—This rare neoplasm arises from remnants of the notochord and invades the bones at the base of the skull or near the coccyx. Infrequently it may arise in other regions of the vertebral column. Although locally invasive and prone to recurrence, it rarely metastasizes. Grossly the tumor is firm and elastic, much like a chondroma. Some examples, however, have a mucinous quality and are soft in consistency. Microscopically the tumor shows cords and sheets of cells that are oval or globular in shape and have clear cytoplasm. These are surrounded by a homogeneous and pale-staining mucoid matrix. These features often give rise to a resemblance to colloid carcinoma, from which the tumor must be distinguished. (See also page 1292, and Fig. 1200.)

Metastatic Tumors in Bone.—The skeleton is a frequent site of metastasis for carcinomas primary in the prostate, breast, kidney, stomach, lung, and thyroid. Cancers arising in other organs, including the body and cervix of the uterus, adrenal, bladder, and testicle may also spread to bone. Melanomas sometimes give rise to extensive skeletal involvement.

In order of frequency, the bones most commonly involved are: the spine, pelvis, femur, skull, ribs, and humerus. Metastases to the bones of the forearm, wrist, and hand, and to the bones of the leg, ankle, and foot are of infrequent occurrence.[99]

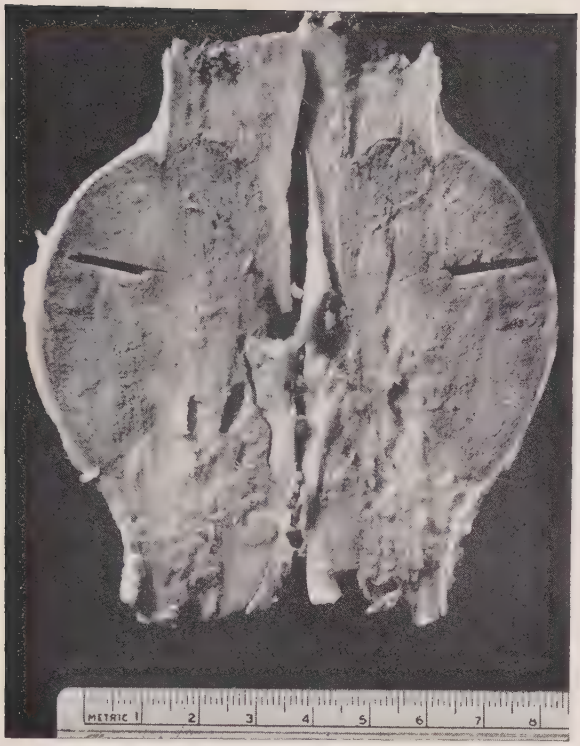


Fig. 1132.—Adamantinoma. A large solitary tumor mass in the midportion of the tibia has led to sharply defined bone destruction. The neoplasm was dense, but moderately cellular and friable, and on section revealed the typical features of an adamantinoma. (See Fig. 1133.)

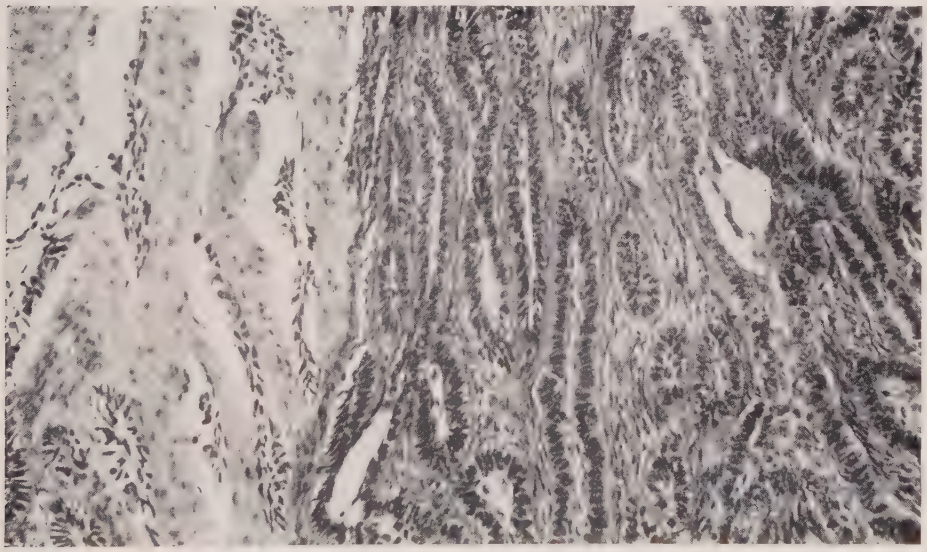
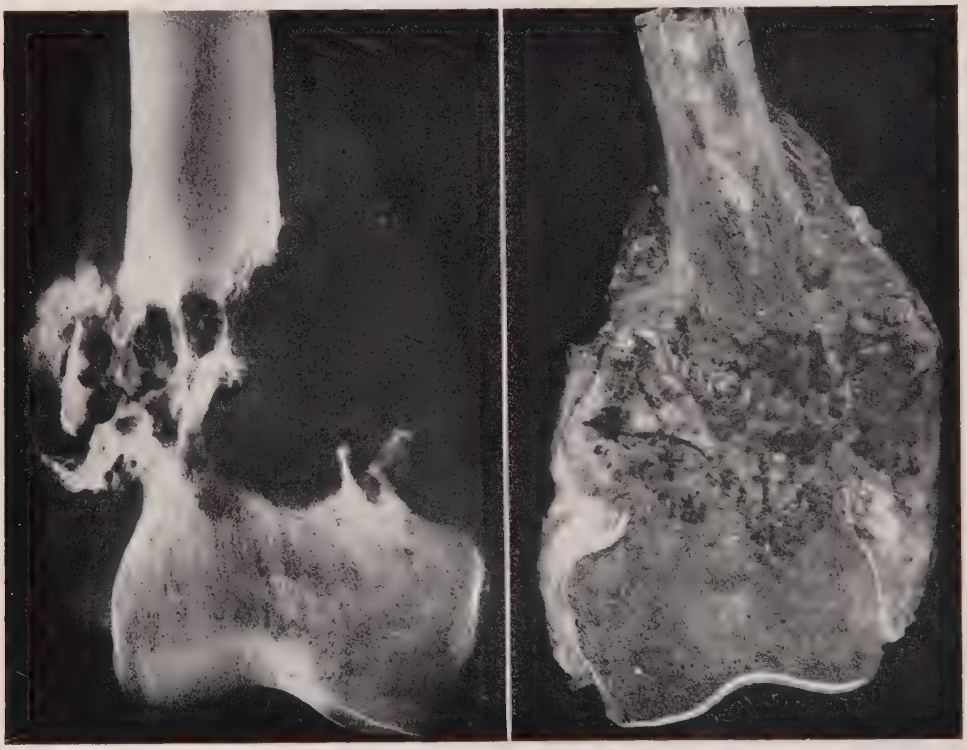


Fig. 1133.—Adamantinoma. Photomicrograph showing the alveolar arrangement of tall cylindrical cells with centrally placed fusiform and oval cells. Invasion of bone is evident at the left-hand margin of the reproduction. Section was prepared from tumor shown in Fig. 1132. (×145.)

With the exception of carcinoma of the prostate, where the metastases usually give rise to a condensation of bone, the areas of skeletal invasion by malignant neoplasms are characteristically destructive. In individual cases, however, the opposite effects may be noted and a carcinoma of the breast or stomach occasionally may give rise to formative or *osteoplastic* metastases, whereas carcinoma of the prostate sometimes induces destructive or *osteolytic* lesions.



A. *B.*

Fig. 1134.—*A* and *B*, Carcinoma of kidney (hypernephroma) metastasis. Roentgenogram and gross photograph of a slice of left femur showing a large destructive lesion with pathologic fracture. A similar metastatic lesion was present in the upper third of the right humerus.

Neuroblastomas may cause excessive bone formation on the cranial surfaces and along the long bones. Metastases from adenocarcinomas of the kidney (hypernephromas) usually result in large destructive lesions in one or two bones. (Fig. 1134.) Because of the pronounced vascularity, these tumors may pulsate and give rise to an audible bruit.

The routes by which metastasis to bone occurs are: (a) the blood vessels, (b) lymph vessels, and (c) direct extension from the primary neoplasm or from its established metastases. Extension along perineural lymphatics in cancers of the prostate is frequent.

The association of elevated serum acid phosphatase with skeletal involvement in carcinoma of the prostate is an interesting biologic phenomenon as well as a recognized aid in diagnosis.

Pathologic fractures may be the first indication that metastasis to bone has taken place. Less often it may constitute the first evidence of the primary disease. In late cases, pathologic fractures of the affected bones may add greatly to the discomfort of the patient.

Skeletal metastases, when demonstrated in any given patient, are obviously of great importance in determining prognosis and in guiding treatment. In general, the consequences of such lesions to the patient are pain that is frequently intolerable and disability to the point of complete invalidism until the disease has terminated fatally.

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Chapter 43

THE JOINTS

Granville A. Bennett

The term joint disease covers a wide range of disorders that frequently have nothing in common except involvement of the specialized tissues that comprise the articulations. Therefore, before describing the pathologic changes that are associated with any particular infirmity, it is necessary to recall the outstanding anatomic and physiologic characteristics of these tissues.

ANATOMY AND PHYSIOLOGY OF JOINTS

Most articulations are simple in structure. They are comprised of two or more opposing cartilage-covered bone ends, joined by a flexible tube of dense connective tissue, the articular capsule. An intimal layer of varying microscopic structure lines the capsule. This is referred to as the synovia or synovial membrane. Within this enclosed space is a small quantity of clear, viscid synovial fluid.

Adjacent to the joints are similar tissue components such as fascial layers, tendons, tendon sheaths, and bursae. Not only are these structures of great importance in the normal mechanical functions of the joint, but in the majority of articular diseases they are either primarily or secondarily affected.

Articular Cartilage.—The hyaline cartilage covering the bone ends at the articulations is an elastic, avascular, and cell-poor tissue. Its chief, if not sole, source of nourishment is the synovial fluid contained within the articular cavity. Compared with other connective tissues articular cartilage has relatively little capacity for regeneration and repair following injury. Since articular cartilage is the recipient of most of the mechanical shocks and stresses that are exerted upon the skeleton, it is apparent that the maintenance of an entirely smooth articular surface, so essential to normal function, is constantly endangered. It has been clearly shown that articular cartilage is readily damaged by a wide variety of toxic agents, by acute injuries, and also by minor and repeated traumas that are incident to everyday activities.

Synovial Membrane.—On both embryologic and histologic evidence, the intimal layer of the articular capsule is to be regarded as connective tissue that has undergone certain modifications in functional and structural characteristics. In contrast to cartilage it has a marked capacity for regeneration. Experiments on animals indicate that repair is complete in thirty to one hundred days after synovectomy.[1, 2]

The synovial intima varies from dense fibrous connective tissue that is partially lined by inconspicuous flattened cells to a membrane comprised of many layers of round, oval, or cubical cells that are supported by loosely textured and highly vascular connective tissue. These latter areas contain recesses or crypts as well as permanently formed papillary projections called villi.

Among the known functions of synovial membrane are the formation of synovial mucin and the regulation of the passage of materials between the blood, lymph, and synovial fluid.[3] Foreign materials of colloidal or particulate nature are transferred across this membrane for removal from the joint. In the case of continuous or intermittent bleeding into the articular cavity there may be extensive deposits of hemosiderin in phagocytic cells in the subsynovial tissues or in the synovial lining cells. Lipoids may also accumulate in these tissues under certain abnormal circumstances. In contrast to the membranes lining certain other body cavities, synovial membrane has a markedly greater permeability.[4-6]

Joint Capsule.—The articular capsule is comprised of dense fibrous tissue, reinforced by tendons, muscles, and fascial layers. Its chief function appears to be the binding together of the bone ends entering into the articulation. In close proximity to the capsule or extending between its layers are tendon sheaths and bursal spaces that are lined by membranes which are similar in structure and function to the synovia of the joint proper.

Synovial Fluid.—The normal joint contains a small quantity of cell-poor, clear, pale yellow, viscid liquid. It is possible to aspirate 0.45 c.c. (average) of fluid from the normal adult human knee.[7] In such fluid the total nucleated cells average 63 per cubic millimeter of which 63 per cent are mononuclear phagocytes, 24 per cent lymphocytes, 6.5 per cent polymorphonuclear leukocytes, 4.3 per cent synovial cells, and 2.2 per cent unidentified cells. The relative viscosity is 150 at 25° C. The average total albumin and globulin content is 1.72 Gm. per 100 c.c. and the average mucin content is 0.85 Gm. per 100 c.c.[8] The distribution of nonelectrolytes and electrolytes between the blood serum and the synovial fluid is in accord with the concept that synovial fluid is a dialysate of blood plasma containing albumin, globulin, and mucin. The mucin is probably elaborated by functionally specialized cells in the synovial tissues.

Changes in the amount and appearance of synovial fluid and in its physical and chemical characteristics occur rapidly as a result of injury or disease and such alterations may be of aid in diagnosis and treatment.[9, 10]

The joints are anatomically and functionally adapted to permit easy motion within a certain range. They are, however, so constituted that the cartilage surfaces and the synovial tissues are subjected to frequent injuries of mechanical, toxic, and metabolic nature. In the case of cartilage, such injuries are not well tolerated because of certain inherent biologic characteristics which limit its ability to regenerate. The articular surfaces are prone, therefore, to undergo important regressive changes solely from physiologic aging and the wear and tear of daily use.[11] Such alterations may be greatly accelerated because of deleterious agents, single or repeated trauma, or as the result of deranged mechanics from faulty posture or disturbed locomotion.

DISEASES OF JOINTS

Incidence

Since ancient skeletons of man and animals that have been obtained from widely separated geographic locations bear unmistakable marks of certain forms of arthritis and other diseases that are prevalent today, it may be concluded that articular disorders are among the oldest and most widely prevalent infirmities.[11-13]

A survey conducted by the United States Public Health Service in 1938 gives a good index to the great social and economic importance of joint disease in modern times. It was estimated that the number of persons disabled annually by rheumatic disorders exceeds those affected by tuberculosis and diabetes in a ratio of ten to one and cancer and other tumors in a ratio of seven to one. The number of cases of "rheumatism" (including arthritis, gout, lumbago, neuralgia, etc.) in the United States in 1937 was calculated to be 6,850,000.

Classification

The most prevalent and disabling infirmities affecting the articulations of the body are the various forms of chronic deforming arthritis. However, since almost all known diseases can and occasionally do give rise to manifestations of joint disease, it is proper to indicate in tabular form the conditions that will be discussed in the following sections of this chapter. It should be emphasized that a truly satisfactory classification must await more precise information concerning the etiology and pathogenesis of these various abnormal states.

Classification

1. Arthritis caused by known infectious agents.
2. Arthritis associated with rheumatic fever.
3. Rheumatoid arthritis.
4. Degenerative joint disease.
5. Arthritis caused by trauma.
6. Arthritis associated with gout.
7. Arthritis of neuropathic origin (Charcot joint).
8. Miscellaneous forms:
   a. Systemic diseases with which arthritis is frequently associated.
   b. Local disorders affecting articular tissues.
9. Neoplasms of articular tissues.

Arthritis

Arthritis Caused by Known Infectious Agents.—Compared with arthritis of unknown etiology, the incidence of specific infections of joints is low. However, it should be remembered that one of the possible complications of any infectious disease is the localization of the responsible microorganism in one or more of the joints. Although any pathogenic microorganism may produce a joint infection, the more important forms of arthritis of this category are those that are caused by the gonococcus, streptococcus, staphylococcus, pneumococcus, and tubercle bacillus. These infectious agents may reach an articulation by way of the blood stream, the lymphatic vessels, or by direct implantation of the microorganism either from a perforating injury or the extension of an infectious lesion from the neighboring bony or soft tissues into the articular cavity.

It has been adequately demonstrated experimentally that the synovial tissues are especially susceptible to the localization of organisms when a bacteriemia has been induced.

Gonococcal Arthritis.—Before chemotherapy, involvement of the joints occurred in 2 to 5 per cent of the persons who developed gonorrheal infections.[13, 14] The knees, ankles, wrists, fingers, shoulders, and toes, in that order of frequency, are sites that are commonly affected.

The arthritis usually begins in from one to three weeks following the onset of the underlying disease. Less frequently the joint lesion develops many weeks or months later. In approximately 80 per cent of cases, the arthritis is polyarticular at the onset. In the majority, however, the signs and symptoms of joint inflammation promptly

subside in all but one or two of the joints. The affected articulation becomes swollen, red, and tender. There is pronounced pain on motion and movements are markedly restricted. The joint space becomes distended with inflammatory exudate. Fever ranging up to 104° F. and a moderate leukocytosis are frequently observed. The sedimentation rate is rapid.

Examination of the joint fluid reveals a great increase in the number of nucleated cells, polymorphonuclear leukocytes predominating. Cell counts range as high as 250,000 cells per cubic millimeter. Gonococci may be demonstrated in smears in some cases. Positive cultures are obtained in approximately 25 per cent. Another diagnostic aid is the gonococcus complement fixation test of blood (positive in approximately 80 per cent of the cases).

The extent of the inflammatory change within the joint and the degree of destruction of the articular tissues are variable and may range from a moderate synovitis that heals without residual stiffness or deformity, to a purulent arthritis that is accompanied by destruction of the articular cartilage and synovial tissue. The latter types of lesion may give rise to a permanent deformity and occasionally to bony ankylosis.

Arthritis Caused by Other Pyogenic Microorganisms.—Streptococci, staphylococci, pneumococci, and other pathogenic microorganisms may localize in the synovial tissues from the blood or reach the joint by direct extension from an adjacent focus of infection. The reaction, although often more violent and destructive, is similar to that produced by the gonococcus. The synovial tissues become hyperemic and edematous and there is an effusion of fluid into the joint. Soon the articular fluid is rich in leukocytes and fibrin, and if the articular cavity is opened it will be seen that the synovial surfaces are covered with fibrinopurulent exudate. The articular cartilage becomes yellow-gray in color and nonglistening. It is rapidly undermined at the perichondrial margins, and large or small portions of the cartilage may become detached from the underlying cancellous bone. The degree of stiffness and deformity ensuing will depend upon the extent to which the cartilage and synovial tissues were damaged. Healing occurs by granulation tissue formation and subsequent cicatrization. There is little or no regeneration of the injured cartilage and bony ankylosis is not uncommon.

Tuberculosis.—While almost invariably resulting from the localization of organisms disseminated via the blood stream, tuberculous arthritis may be either primary in the synovial membrane or secondary to a focus of tuberculous osteomyelitis in close proximity to the articulation. In the knee in adults, initial involvement of the synovial tissues is much more frequently observed, whereas in children the involvement of the joint is usually secondary to a focus in the adjacent bone end. Such a focus usually arises from localization of the infection in the metaphyseal end of the shaft, and the joint is invaded either by a spread of the infection through the soft tissue or through the epiphysis. Regardless of the point of origin, the end result of a tuberculous infection of a joint is likely to be the same. Generally, however, the progress is more protracted in infections arising in the synovial tissues.

The synovial membrane becomes hyperemic, edematous, and redundant. Its surface is obscured by grayish-yellow exudate. Occasionally tubercles can be recognized if care is used in inspecting the exposed surfaces. However, there is greater likelihood of recognizing caseating lesions on surfaces made by slicing into the synovial tissues. In some cases the articular lining is totally replaced by abundant shaggy fibrinous exudate and shreds of necrotic tissue, and occasionally the joint space will contain grayish-white bodies the size and shape of melon seeds (joint mice). The amount of fluid contained in the joint is variable, but as a rule only a small to moderate amount of turbid liquid containing shreds and flakes of fibrin is evacuated when the joint is opened. Occasionally an excessive quantity of relatively clear fluid distends the joint (tuberculous hydrops). The changes observed in the articular cartilage depend to a considerable extent on the duration of the infection. The cartilage is attacked either from the articular surface or from the cancellous bone spaces in the epiphysis. In many instances both surfaces are affected simultaneously. In early cases the cartilage may show no change other than a loss of its smooth glistening luster. This may be accompanied by the extension of tuberculous granulation tissue from the perichondrial margins onto the articular surfaces. In more severely affected joints the cartilage is loosened from the underlying bone and in some instances it disappears, leaving an uneven granular base of necrotic bone and exudate.

In microscopic sections the loosened fragments of cartilage show faintly stained matrix devoid of cartilage cells. The affected osseous tissue reveals areas of bone necrosis surrounded by tuberculous granulation tissue in which many tubercles are usually apparent. The necrotic bone trabeculae undergo fragmentation and gradual resorption (caries). Extensive sequestration is uncommon. Sections of the synovial membrane usually reveal a thick surface layer of exudate with underlying caseation necrosis. Beneath this, recognizable miliary and conglomerate tubercles are usually present in abundance.

The course of tuberculous arthritis is variable. If the infection is confined to the synovial tissues the lesion may heal with limited disability. More frequently, however, the cartilage covering of the bone ends is destroyed and the adjacent bone is affected. In these cases, healing, if successfully accomplished, results in either fibrous or bony ankylosis of the joint.

Syphilis.—The frequency with which the joint structures are involved in syphilis has not been determined. It is known, however, that arthritis may occur in either the congenital or acquired forms of the disease.

a. Congenital Syphilis: Varying degrees of involvement of the articular capsules and epiphyses may be noted in conjunction with the characteristic changes represented by osteochondritis and periostitis. Such an affection leads to pain, tenderness, and swelling of the joint. Microscopically, these articulations show hyperemia, edema, lymphoid and plasma cell in-

filtration, and proliferation of fibroblasts. In addition, there may be small areas of necrosis in the cartilage, bone, or capsular tissues.

In older children showing manifestations of congenital syphilis, there sometimes develops a peculiar form of arthritis known as Clutton's joints. One or both knees may be affected and occasionally some other joint is involved. The affected joint, while rarely painful, is swollen and lax and contains an excessive amount of fluid. The synovial tissues are thickened and appear soft and gelatinous. Microscopically, there is edema and a diffuse and focalized infiltration with lymphocytes and plasma cells. Gummatous lesions may be present in some of the specimens.

b. Acquired Syphilis: During the early stages of an acquired infection the joints may be painful and tender. Stiffness is also a complaint. While pathologic investigations are notably lacking, it seems probable that these symptoms of acute arthritis result from the same inflammatory and vascular lesions that give rise to such visible lesions as the skin rash and mucous patches. In the usual case, the joint pain subsides without giving rise to lesions that are detectable on physical examination. Occasionally, however, the joint swells and evidence of an effusion can be elicited. The knee joint is the articulation that is most frequently affected and the involvement is commonly bilateral.

In later stages of syphilis the joints may be the site of gumma formation or of a diffuse nonspecific chronic synovitis that is associated with moderate or marked grades of effusion. Gummatous lesions, when they occur, may be limited to the synovial tissues or they may be more extensive and involve the adjacent ligaments as well as the articular cartilage and adjacent bone.

Arthritis Associated With Rheumatic Fever.—Rheumatic fever is a disease of unknown etiology, characterized in most instances by fever, migratory arthritis of short duration, and cardiac damage. Since in more than half of the patients the onset of rheumatic fever is preceded by streptococcus infections in the throat or tonsils or by other infections of the lungs or upper respiratory passages, it is generally believed that infection is the actual cause of the disease or, at least, an important predisposing factor. (See discussion on page 452.)

Acute arthritis, usually migratory in nature, is among the more frequent manifestations of rheumatic fever. Although any joint in the body may be affected, the larger articulations are most often involved. In children the ankles, knees, and wrists are the common sites.[15]

All of the usual signs of acute inflammation such as pain, tenderness, swelling, heat, and local redness are evident in an affected joint. In addition to soft tissue swelling of the articular and periarticular tissues there is usually a transudation of fluid into the joint space. The synovial fluid is frequently turbid and contains increased nucleated cells, ranging up to 30,000 per cubic millimeter or higher. Polymorphonuclear leukocytes may comprise 90 per cent or more of the total in early cases. Cultures are consistently negative.

Although few pathologic investigations have been conducted on articular tissues in the early stages of the arthritis, there is some evidence to indicate that there is marked hyperemia, edema, and leukocytic infiltration of the synovial tissues. Fibrinoid swelling of collagen like that seen in the subcutaneous nodule may also be present.[16] Actual suppuration does not occur and necrosis of tissue is apparently minimal.

In the great majority of patients the arthritis subsides after a few days and complete restoration of joint function is the rule. Occasionally, however, residual pain and stiffness of continuous or intermittent character persists. In some of these cases mild to moderate degrees of chronic inflammation of the synovial and subsynovial tissues have been found when the joints were examined. Diffuse infiltration of lymphocytes, plasma cells, and mononuclear leukocytes is the most frequent change in these cases. There is rarely, if ever, any evidence of pannus.[17] In about 20 per cent of rheumatic fever patients, one will find small subcutaneous nodules in the soft tissues overlying bony prominences and usually near the joints. The regions of the olecranon process and patella are the most common sites. On microscopic examination these nodules show "fibrinoid" degeneration with latticing of the collagen and a mild to moderate grade of inflammatory cell infiltration. The lesions are usually poorly demarcated from the surrounding tissues and seldom show evidence of complete necrosis of the affected connective tissue. Occasionally, small focal areas of necrosis of collagen surrounded by mononuclear cell infiltration are observed. Such lesions may resemble the myocardial Aschoff nodule. Although the pathologic features of these nodules are qualitatively similar to those observed in the subcuta-

neous nodule of rheumatoid arthritis, it is usually possible to distinguish between the two lesions.[18]

Rheumatoid Arthritis.—The common synonyms for rheumatoid arthritis are atrophic arthritis and proliferative arthritis. In children the disease is frequently referred to as **Still's disease.**[19] When the sole or predominant involvement is located in the spine, sacroiliac, and hip joints, the disease is referred to as **Strümpell-Marie spondylitis.**

Before considering the clinical, roentgenologic, and pathologic findings of rheumatoid arthritis, it is appropriate to describe briefly two disorders which, although bearing different names, are believed by most physicians to be forms of rheumatoid arthritis. The first of these is Still's disease. This term came into common usage when Still separated juvenile rheumatoid arthritis into two groups, the first of which was like that seen in adults. The patients in the second group showed similar lesions in joints but, in addition, exhibited manifestations of splenomegaly, lymphadenopathy, and sometimes adhesive pericarditis. Present-day awareness that lymphadenopathy and splenomegaly occur in adults, although less commonly than in children, has caused most clinicians and pathologists to reject the concept of a separate disease entity.[20] The second affection is frequently designated *Felty's syndrome.*[21] The rheumatoid arthritis, in this instance, is accompanied by leukopenia and enlargement of the spleen and liver. The spleen may be infiltrated with plasma cells and show a striking phagocytic activity in the reticular elements. Most clinicians specializing in the study and management of arthritis patients believe that these associated disturbances do not justify a separate designation, and the term Felty's syndrome is used less frequently than formerly.

Rheumatoid arthritis is a systemic disease[22] of unknown etiology characterized by a chronic and progressive inflammatory involvement of the articulations and by atrophy and rarefaction of the bones and muscles.

Although the disease affects persons of all ages, it occurs most frequently in the early decades of adult life. Approximately 80 per cent of the cases commence between the ages of 20 and 50 years. Women are affected two to three times oftener than men. In Strümpell-Marie spondylitis, however, women are rarely affected.

Fig. 1135. Fig. 1136.

Fig. 1135.—Rheumatoid arthritis. Diffuse lymphocytic and plasma cell infiltration in the subsynovial layer of a tendon sheath, from a patient with long-standing rheumatoid arthritis.

Fig. 1136.—Rheumatoid arthritis. Chronic inflammation in a tendon near its insertion into bone. The patient had widespread and advanced rheumatoid arthritis.

There may be prodromal manifestations such as slight fever, loss of weight, fatigue, and increased sweating of the hands and feet. The onset of the disease, while usually insidious, may be abrupt and violent.

In the majority of patients, joint involvement is polyarticular, tends to be bilateral, and is somewhat symmetrical in distribution. Early in the disease there is pain, swelling, and stiffness of the joints. Slight redness and warmth may also be present and the soft tissues about the articulations are thickened. This swelling, in combination with muscular atrophy,

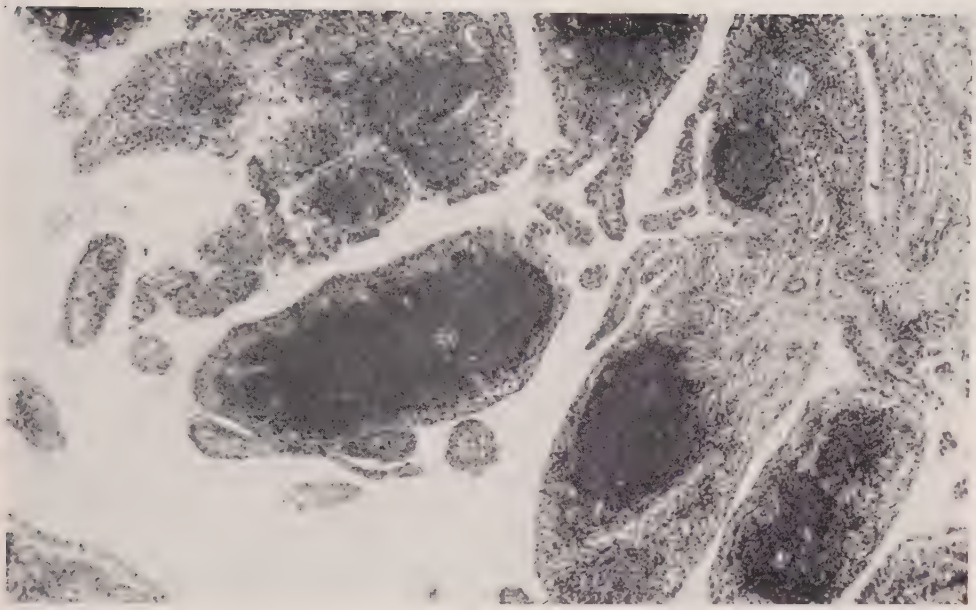


Fig. 1137.—Rheumatoid arthritis. Marked hypertrophy of synovial villi and extensive chronic inflammation of the subsynovial tissues are illustrated in this photomicrograph of tissue removed from the knee of a patient with rheumatoid arthritis. The focal accumulation of lymphocytes is a common feature of the disease.

Fig. 1138.—Rheumatoid arthritis in an early stage. The articular cartilage on the lower half of the photomicrograph is being replaced by ingrowing granulation tissue from the perichondrial margin.

gives rise to fusiform or spindle-shaped digits.

One of the striking features of the disease is the pronounced tendency for exacerbations and remissions. Remissions occur irregularly and may last for months or years at a time.

Microscopic examination of specimens of articular tissues excised in the early stages of the disease reveals hyperemia, edema, and inflammation in the synovial and subsynovial layers. The near-by tendons and tendon sheaths are frequently affected in a similar manner (Figs. 1135 and 1136). At first the inflammatory cell infiltration, consisting of lymphoid cells, plasma cells, and mononuclear and polymorphonuclear leukocytes, is diffuse and evenly distributed. Later, focal collections of lymphocytes appear and germinal

Fig. 1139.—Rheumatoid arthritis in an early stage of fibrous ankylosis. Granulation tissue projecting inward from the margin of an interphalangeal joint has formed an adhesion across the joint space. Nearly all of the articular cartilage has disappeared beneath the pannus which is clearly shown in the lower half of the photograph.

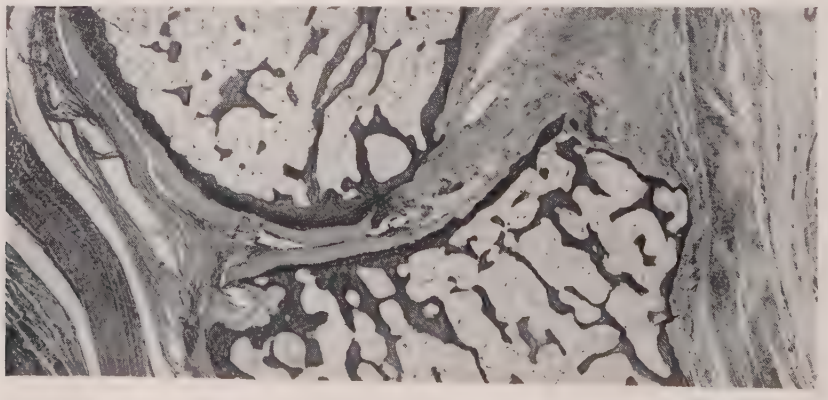
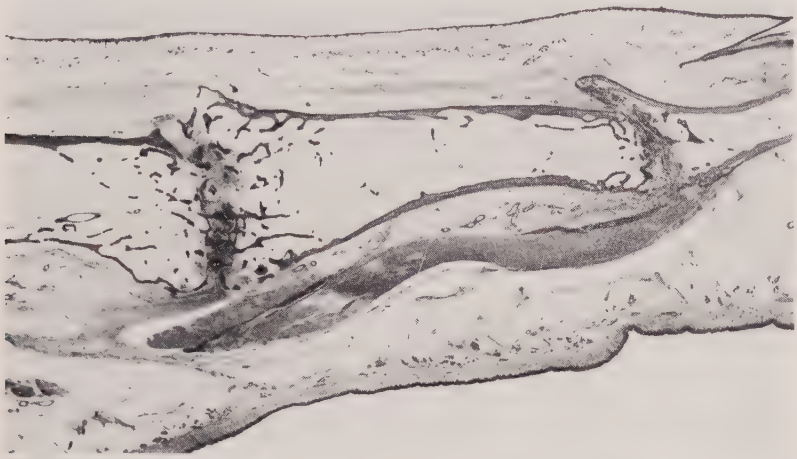


Fig. 1140.—Most of the salient features of rheumatoid arthritis are illustrated in this low-power photomicrograph of an interphalangeal joint. In addition to bone atrophy and partial subluxation, the articular cartilage is thinned and pitted and overgrown with pannus. Also, the joint space in the right half of the reproduction is obliterated by dense fibrous adhesions.

follicles may develop in the greatly enlarged and lengthened synovial villi (Fig. 1137). It is worthy of note that even in the early stages of involvement there is little evidence of tissue necrosis, and suppuration does not occur.

the result of similar changes on the two opposing joint surfaces, fibrous adhesions are formed (fibrous ankylosis) (Figs. 1139 and 1140). In time the articular cartilage may be completely destroyed (Fig. 1141). This may be followed by ossification of the

Fig. 1141.



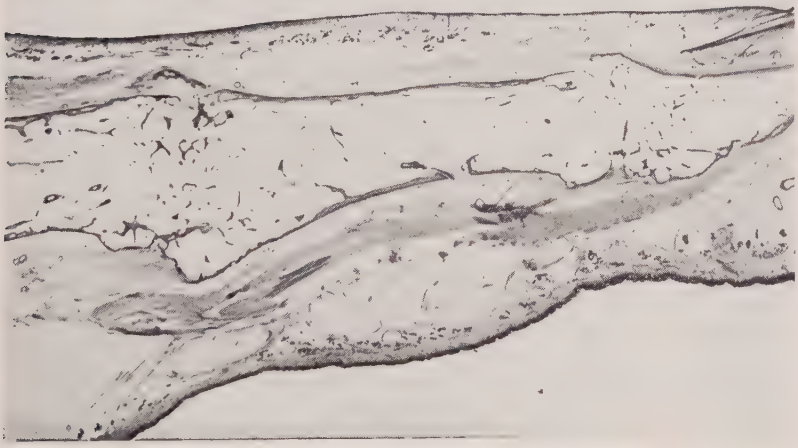


Fig. 1142.

Figs. 1141 and 1142.—Midline longitudinal sections of the second and fourth digits are reproduced in these figures. Atrophy of the osseous and dermal tissues is evident in both photographs. Active chronic inflammation is shown in the middle and terminal interphalangeal joints in Fig. 1141. All other joints have been destroyed and bony ankylosis is evident.

As the arthritis progresses, granulation tissue grows from the synovial tissues at the perichondrial margins to cover the articular cartilage surfaces (pannus). Concomitantly the cartilage is invaded and replaced by well-vascularized connective tissue showing moderate to marked degrees of chronic inflammation (Fig. 1138). As

granulation tissue leading to bony ankylosis (Fig. 1142).

In many instances the deformity is increased by subluxation of the joint.

As a result of these various changes the joints become permanently stiffened. In addition they may become markedly twisted and contracted (Fig. 1143).

One of the early and constant changes in rheumatoid arthritis is atrophy of bone (Figs. 1141 and 1142). Although this striking feature of the disease frequently appears early, it is believed to result chiefly from disuse of the part. Pronounced atrophy of muscle and skin is also observed in most patients who have had the disease for any considerable period.

Chronic inflammatory changes resulting, in some instances, in well-circumscribed nodules ("nodulous rheumarthritic perineuritis") have been observed in the sheaths of peripheral nerves of patients suffering from rheumatoid arthritis.[23] Similar inflammatory and nodular lesions occur in the muscular tissues of the body.[24]

Fig. 1143.—Deformed and stiffened hands of chronic rheumatoid arthritis. Note the evidence of muscular atrophy and the smooth glossy skin.

Fig. 1144.

Fig. 1145.

Fig. 1144.—A large subcutaneous nodule over the olecranon process is evident in this photograph.

Fig. 1145.—Subcutaneous nodules having the typical morphologic features of the nodule of rheumatoid arthritis are illustrated in this photograph of the tendo achilles areas.

Photographs of a patient with rheumatoid arthritis. (Courtesy Dr. F. A. Chandler.)

In all probability the most characteristic single lesion associated with rheumatoid arthritis is the *subcutaneous nodule* (Figs. 1144-1146).[18] These firm swellings appear over bony prominences, especially the

olecranon process, in approximately 20 per cent of the patients having the disease.

Such lesions are firm and rubbery in consistency and range from a few millimeters to three or four centimeters in size. On section they appear grayish in color and frequently embody one or several areas of yellowish-gray necrotic substance. Frequently there are slitlike clefts in the necrotic centers and occasionally the interior of the lesion undergoes cystic degeneration. Microscopically the zones of necrosis appear sharply outlined and are bounded by proliferating cells that are regularly oriented (palisading) (Fig. 1146). The surrounding connective tissue is diffusely or focally infiltrated with lymphocytes and plasma cells. In its entirety this lesion resembles a gumma to a considerable extent. The observed pathologic changes suggest that this lesion would be incapable of rapid resolution. Such a supposition is apparently justified since it is known that the subcutaneous nodule of rheumatoid arthritis, once it has formed, is likely to persist for months or even years; this known behavior is unlike that of the nodules appearing in rheumatic fever. In the latter condition the subcutaneous nodules tend to appear in crops and to resolve and disappear in from a few days to a few weeks.

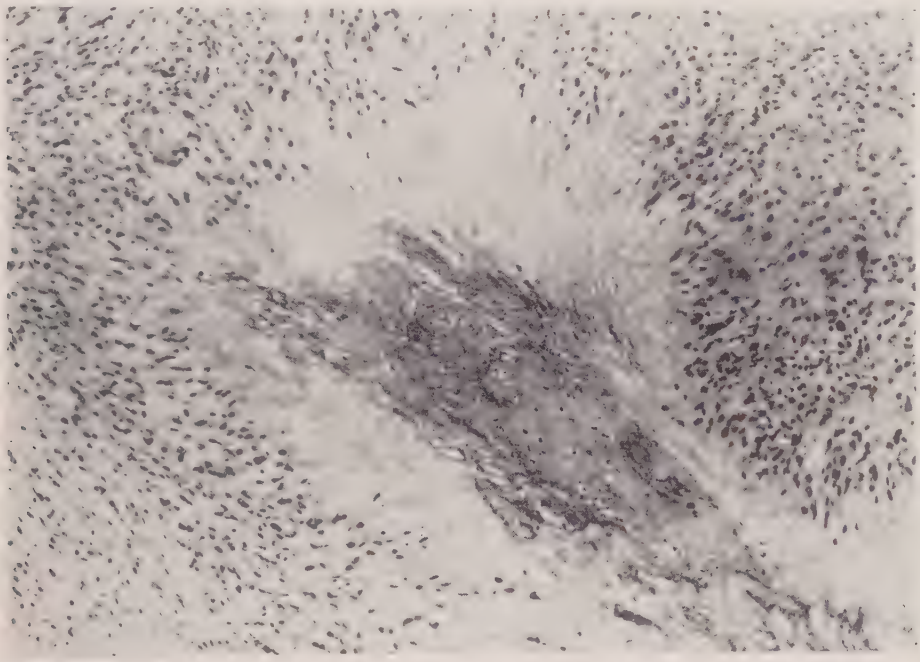


Fig. 1146.—Subcutaneous nodule of rheumatoid arthritis. A portion of a necrotic focus surrounded by palisades of proliferating cells. (×200.) (AFIP No. 73941.)

Remarkable progress has been made in recent years in the study and management of rheumatoid arthritis. This gain may be attributed in large part to the discovery of cortisone and ACTH and the use of these substances on patients affected with rheumatoid arthritis.[25, 26] Induction of dramatic remissions in the disease has been observed clinically. Also evidence has been obtained that administration of these hormones may induce prompt resolution of inflammatory changes in articular tissues. It has not been established, however, that the subcutaneous nodules are affected by the hormones.

Because of certain similarities in the clinical and pathologic manifestations of rheumatic fever, rheumatoid arthritis, periarteritis nodosa, disseminated lupus erythematosus, and scleroderma, it has become increasingly popular in recent times to refer to these disorders as *collagen* or *connective tissue* diseases or, employing a less specific designation, as *group* diseases.

Among the varied morphologic features of these disorders, the most impressive single histologic change that would seem to relate one disease to another is fibrinoid degeneration. The favorable influence of cortisone and ACTH on all of the disorders of the so-called collagen disease group also may imply a relationship between the several entities.

Fig. 1147.—Irregular thinning, softening, and fraying of articular cartilage over the patella, patellar surface of the femur, and the medial condyle of the femur are shown in this reproduction. Marginal lipping is most marked along the border of the medial condyle of the femur. Early erosion of the cartilage of the condyles of the tibia exposed through the somewhat frayed menisci is also seen. The synovial tissues appear normal. These changes are all indicative of an early stage of degenerative joint disease.

Among the more obscure rheumatic conditions are two: (a) *periarticular fibrositis* and (b) *intermittent hydroarthrosis*. These are commented on in this section because their etiology and pathogenesis have not been established and their position in a logical classification cannot be determined on the basis of present information.

Periarticular Fibrositis.—The term fibrositis has been employed to designate a variety of imperfectly understood clinical manifestations of a "rheumatic" nature in which it is assumed that the fibrous tissues of the various parts of the body are involved in an inflammatory reaction of a particular nature. Among clinicians there is no unanimity as to what constitutes a condition of fibrosis. Indeed, the existence of an entity of this type is questioned by some experienced observers.

Histologic studies on excised tissue specimens have not aided materially in proving or disproving the existence of a disease entity that may properly be designated fibrositis. Reported findings have varied from accounts of nonspecific acute or chronic inflammation to descriptions of granulomatous nodular lesions. Not infrequently there are no microscopic changes to explain the stiffness, soreness, or aching pains that are usually more pronounced upon awakening or following periods of inactivity.

Intermittent Hydroarthrosis.—This condition is among the more uncommon disorders of articular structures. Although trauma, infections, allergic factors, and angioneurosis have been accused, the etiology of this condition remains obscure.

The condition usually affects but one joint, the knee. Occasionally it is bilateral and less commonly some other articulation is affected. The syndrome is characterized by periodic and recurrent effusions into the joint. Such swellings usually persist for several days and recur at intervals varying from days to a month or more. The effusion is seldom attended by much pain, tenderness, or by signs of inflammation. Little is known of the pathogenesis or pathology of the condition. In some instances, patients believed to have this syndrome develop, at a later date, the signs and symptoms of rheumatoid arthritis.

Degenerative Joint Disease.—This exceedingly prevalent articular disorder is frequently referred to by such terms as degenerative arthritis, hypertrophic arthritis, osteoarthritis, and chronic senescent arthritis.

Joint changes characterizing this infirmity develop to some degree in all persons beyond the third or fourth decade of life.[11] Symptoms and physical signs of *arthritis* may or may not be present in joints showing even well-marked gross and microscopic evidence of disease. Likewise, since the primary pathologic lesion is confined to articular cartilage, there are no early changes that are visible in the x-ray film.

Large weight-bearing joints (knees, hips, and spine) are usually the first to become affected. The portions of the articular surfaces that are subjected to the greatest stress are the first to show regressive changes. In the knee the most vulnerable areas are the weight-bearing portions of the femoral condyles, the patel-

lar groove of the femur, and those portions of the tibial condyles that are exposed to pressure and friction through the openings in the menisci (Fig. 1147). Of the small joints, the terminal phalangeal articulations of the fingers are the ones that are most commonly altered (Heberden's nodes).

undergoes regressive changes that progress continuously but at varying rates throughout the life of the individual. Grossly the cartilage is likely to become yellowish in color and less elastic than normal. The surface shows irregular depressions, pits, and linear grooves. Fragments become detached from its surface. Microscopically

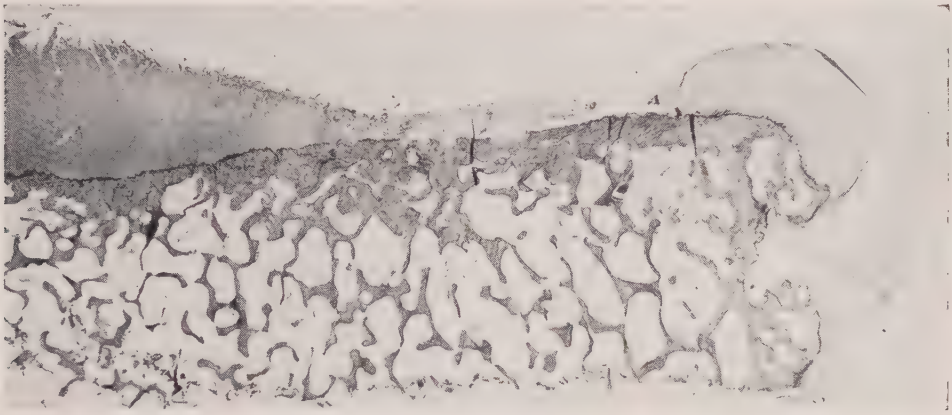


Fig. 1148.—Degenerative joint disease. The articular cartilage of this patellar surface of the femur shows pronounced degeneration. Fibrillation and splitting of the matrix is present. Fragmentation and detachment of cartilage is evident toward the right side of the illustration where the subchondral bone has been denuded. (×10.) (AFIP No. 67996.)

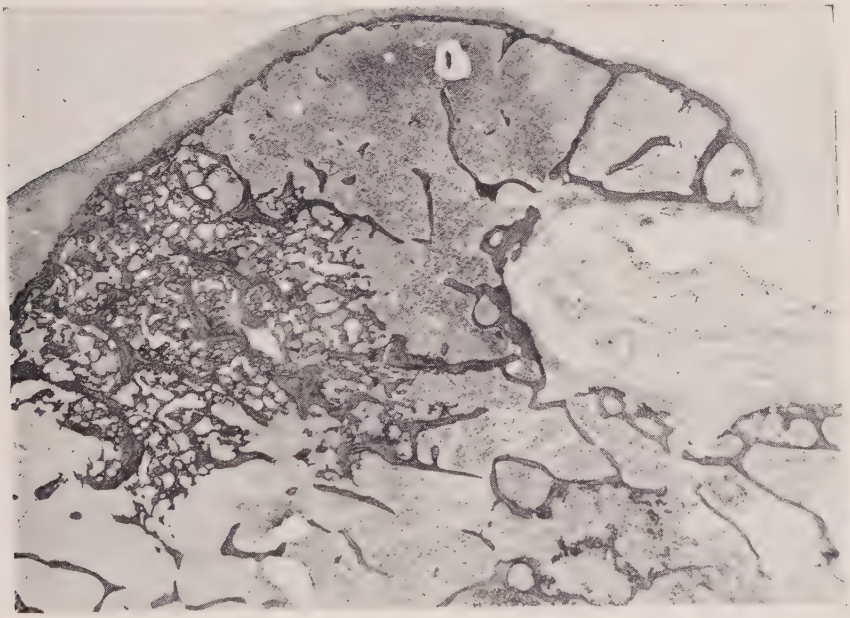


Fig. 1149.—Extensive marginal lipping. (×10.) (AFIP No. 67998.)

Gross and microscopic study of all stages of the disease indicates that beginning in early adult life the articular cartilage

at this stage, the homogeneous quality of the matrix is lost and the ground substance fibrillated and split in a vertical plane.

Reduction in the thickness of the cartilage in some areas may also be apparent.

In more advanced lesions the cartilage appears softened and mossy. Marked thinning to a degree that can be designated erosions will be observed, and, finally, in specimens showing marked changes, no cartilage will remain on areas of small or large size. The denuded bone is characteristically dense, polished, and in some instances grooved in the direction corresponding to the motion of the joint. These increasing gross changes have their microscopic counterpart. The softened cartilage shows fibrillation and fraying of the matrix and clustering of the cartilage cells (Fig. 1148). The process of disintegration progresses from the surface of the cartilage downward. When the subchondral bone plate has been exposed, fragments of cartilage loosen and are cast off. Under the stimulation of pressure and friction the exposed bone becomes more and more solid (eburnation).

It is evident that while these degenerative changes are taking place in the articular cartilage, the perichondrial tissues at the articular margins are proliferating and giving rise to new cartilage that is in turn being replaced by bone. The cause of this excessive marginal growth (lipping) is not entirely understood. It is known, however, that the tissues giving rise to it are less highly specialized and more adequately nourished than is the hyaline cartilage of the articular surface. Thus, the perichondrial tissues are probably more capable of responding to the stimulus of tension incurred in joint motion. Such stimulation no doubt increases as the articular surfaces become misshapen and the mode of locomotion becomes disordered. Irrespective of its cause, marginal lipping constitutes the most readily visible roentgenographic change and, in addition, is one of the most striking gross and microscopic features of the disease. Grossly the perichondrial margins are elevated and overhanging. When viewed from the side they appear somewhat scalloped. Microscopically they project outward from the articular surface as rounded or beaklike osteophytes (Fig. 1149).

Such projecting margins may become detached or broken from the bone end. In such instances they give rise to loose bodies that may be impinged between the bone ends and cause sudden locking with attendant pain and in some instances effusion of fluid into the joint.

The synovial membrane frequently remains normal until the deterioration of the cartilage and the hypertrophic changes in the perichondrial margins have become marked. In late stages of degenerative joint disease, the synovial membrane loses its elasticity and becomes progressively more villous in character. Unless acutely injured from trauma or other causes, the synovial tissues remain free of significant inflammatory reaction.

Proliferation of synovial or perichondrial tissues resulting in recognizable pannus is almost never seen and it is exceedingly doubtful that uncomplicated degenerative joint disease leads to ankylosis.

This form of arthritis is not accompanied by evidence of any related systemic disease. Fever, leukocytosis, anemia, and weight loss do not occur as a part of the clinical syndrome.

A great mass of evidence has been assembled in recent years in support of two fundamental pathogenetic concepts in relation to degenerative joint disease. The first of these is the disadvantageous biologic position of articular cartilage with regard to its nutrition and ability to repair itself. The second concerns the role of mechanical stress and strain incident to everyday use in promoting attrition changes in cartilage. If these considerations are valid, it seems certain that extensive degenerative changes will result from the occasional traumatic shocks to which a joint is subjected. In fact, no sharp distinction can be made between degenerative joint disease and the second form of traumatic arthritis that is discussed in the section to follow.

Arthritis Caused by Trauma.—Injuries of the joints resulting from trauma are of two main types: (a) the acute injuries that are usually produced by the application of a single strong physical force, and (b) chronic injuries that follow minor and frequently repeated traumas. However, acute injuries frequently lead to disturbances in the anatomy and physiology of the articulation and thus induce chronic and, at times, progressive articular disease.

Acute Injuries Resulting From Direct Physical Injury.—Any one of the component

parts of a joint may be injured by physical force, particularly if the stress is applied suddenly. According to Moritz[27] if a joint is twisted, hyperextended, hyperflexed, or otherwise forced to move beyond the limits permitted by the elasticity of its ligaments, a sprain, subluxation, or dislocation occurs. Such injuries represent varying degrees of a single type of damage. Thus, as the result of a twist, blow, or fall, the synovial tissues, the ligaments, or capsule may be stretched, lacerated, or ruptured. In the knee, menisci may be displaced, detached, or torn. The articular cartilage may be compressed, split, or detached from the underlying bone. With greater violence, the joint may be dislocated or the bones may be fractured.

The signs and symptoms of acute traumatic arthritis vary with the location and extent of the injury. In the least severe there may be only transitory pain and tenderness, with or without an effusion into the joint space. Most lesions of this type heal promptly leaving no residual disability. It is noteworthy, however, that the articular cartilage may be damaged without giving rise to signs or symptoms commensurate with the importance of the lesion. The absence of signs is due to the fact that hyaline cartilage is nonvascular and has no nerve supply. Healing occurs slowly if at all, owing to the limited regenerative capacity of this tissue. An indication of the importance of traumatic injury of cartilage was obtained in a study of a series of knee joints obtained from persons who had denied having had any signs or symptoms referable to their articulations. Examination of these specimens frequently revealed fissures and clefts in the cartilage that were believed to be of traumatic origin. It seemed certain that many of these lesions represented an early stage in the development of more extensive degenerative lesions.

In patients in whom the injury has been more severe, producing contusions or tears in the synovial tissues and intra-articular ligaments, there will usually be greater disability and more pain, and in most instances there will be a bloody effusion.

Injuries that include severe lacerations of the ligaments and articular capsules may be associated with dislocation of the bone ends. In these more severely damaged joints there may be permanent weakening and instability as well as predisposition to recurrent dislocation.

In the knee joint, a meniscus may be buckled, displaced, detached, or lacerated. Injuries to this structure are followed in many instances by persistent stiffness of the joint or by recurrent "locking" as the lax or displaced semilunar cartilage is impinged between the articular surfaces of the tibia and femur.

Fractures of the cartilaginous and bony components of the articulations almost invariably cause intra-articular bleeding. Usually the extravasated blood is completely absorbed, but in some instances the blood clot organizes, with the production of fibrous adhesions across the joint space. Portions of bone that are completely detached by the fracture become necrotic although the articular cartilage survives. These detached portions of cartilage and bone remain in the joint as loose bodies ("joint mice") and may give rise to pain or cause recurrent locking of the joint. Malalignment of the fracture fragments may cause an uneven joint surface that predisposes to excessive wear and tear. Degenerative changes are thus accelerated and chronic arthritis of varying degrees may result.

Chronic Injuries That Result From Minor and Frequently Repeated Trauma.—The injuries within this category are of many kinds and grades of severity. They include injuries incurred in the daily activities of a normal person, traumas sustained in recreational or occupational pursuits, and mechanical-functional disturbances induced by obesity, abnormal posture, disturbed locomotion, and skeletal deformities.[28]

The articular changes produced are varied both in kind and extent of involvement. In some instances the lesions are found in the periarticular structures, including ligaments, tendon sheaths, or bursae. More frequently the joint proper is the site of involvement. Effusions of fluid into the bursae, tendon sheaths, or articular cavities occasionally occur. Loose bodies may be present within distended bursal or synovial cavities. Occasionally calcification will be found in tendons or bursal walls. Such changes are especially common in the region of the shoulder.[29] The arthritic changes within the joint are most frequently those of degenerative joint disease with or without secondary hypertrophic changes. There may be low or moderate grades of inflammation in the synovial tissues.

Arthritis Associated With Gout.—Gout has been defined as an hereditary and constitutional disease, pre-eminently of men, occurring at any age and in most instances characterized by recurrent acute arthritis.[30]

From 2 to 5 per cent of chronic joint disease is represented by gouty arthritis.[31] The onset of the acute arthritis of gout is usually sudden and attended by severe pain. The affected joint rapidly becomes swollen, tender, red, and warm to the touch. The metatarsal phalangeal joints are particularly likely to be involved, and, in approximately 50 per cent of the cases, the first metatarsal phalangeal joint is among the articulations first affected. In some instances, particularly in young subjects, the arthritis may shift from one joint to another. Usually the initial or early attacks are of short duration, lasting from a few days to a few weeks. Recurrence at variable intervals is the rule, and, eventually, because of the deposits of urates, the arthritis becomes chronic. In such cases the articular cartilage is the site of the most marked urate deposition. Urate deposits may also occur in the synovial tissues and in the subchondral bone. In rare instances these changes may result in widespread ankylosis.[32]

The articular tissues are progressively destroyed by the increasing amount of urates that are deposited and by the chronic inflammatory and foreign body reaction that accompanies their deposition. The destruction of bone leads to subchondral rarefied lesions (punched-out defects) in the x-ray films. Later the tophi may extend to cause complete destruction of the articulation and lead to subcutaneous deposits of sodium urate that erode through the

covering skin to permit the extrusion of chalky-white, crystalline material from an ulcerated lesion.

The predilection of the urates for cartilaginous tissues probably explains the early development of the arthritis as well as the later appearance of the characteristic tophi in the ears.

The most significant laboratory findings in gout are the elevation of serum uric acid values (usually above 6 mg. per cent) and a diminished renal excretion of uric acid. Because of these observations it is believed by some that the fundamental metabolic disturbance in gout is related to the mechanism of uric acid disposal (see also page 77).

Arthritis of Neuropathic Origin (Charcot Joint).— Patients with certain types of spinal cord lesions, caused in most instances by syphilis or syringomyelia, are prone to develop an exceedingly destructive type of joint lesion known as a Charcot joint. Approximately 5 to 10 per cent of tabetic patients and 25 per cent of those with syringomyelia are so affected.[13] Usually only one joint is involved. In the tabetic, the knee, hip, or ankle is the common site, whereas in syringomyelia the articulations of the upper extremity are more likely to be affected. Joint lesions of similar character occur in patients afflicted with leprosy. In these instances the arthropathy is secondary to peripheral nerve changes.

The articular lesion begins with cartilage destruction and rapidly extends to involve the subchondral bone. In the early stages there is swelling of the joint with, in most instances, a pronounced effusion. Later, as the bone ends undergo disintegration, calcification and ossification take place irregularly in the articular capsule. In the late stages the joints become lax and misshapen. Despite the pronounced swelling and deformity that is evident, the Charcot joint is usually painless and nontender.

Miscellaneous Forms of Joint Disease

In addition to the forms of acute and chronic arthritis that have been described in the previous sections, there is a large variety of articular disorders, usually of dissimilar nature, that may be grouped into two main classes as follows: (a) systemic diseases with which arthritis is frequently associated, and (b) local disorders affecting articular tissues.

Systemic Diseases With Which Arthritis Is Frequently Associated.—The more important diseases in this category are *acromegaly, hemophilia, purpura, psoriasis, Raynaud's disease, Reiter's syndrome, secondary (pulmonary) osteoarthropathy, serum sickness,* and the so-called collagen diseases including *disseminated lupus erythematosus, periarteritis nodosa,* and *scleroderma.*

The pathologic changes observed in the majority of these diseases have been discussed elsewhere in the text. In instances where this is true it is appropriate to draw attention only to the manner in which the manifestations of arthritis arise in conjunction with the underlying disease process.

For the most part, in these conditions, the signs of articular involvement result from the presence in the joint tissues of the anatomic lesions or specific functional disturbances that produce the particular morbid changes elsewhere in the body. Thus, in *periarteritis nodosa* the manifestations of arthritis are caused by the occurrence of the characteristic vascular lesions in the synovial and capsular tissues. Similar relationships probably hold for *Raynaud's disease* and *dermatomyositis.* In scleroderma and disseminated lupus erythematosus the underlying pathologic changes seem to reside in the connective tissue structures of the body, including the articular tissue, and there is some evidence[33] that the articular lesions of disseminated lupus may embody a certain degree of specificity.

In *acromegaly,* as is noted elsewhere, two mechanisms appear to be operative in causing increased joint lesions of a degenerative nature. One of these has to do with the increase in body size with an associated loss of muscular tone and of sound mechanics of locomotion. The other involves the apparent reactivation of cartilage growth and ossification which may hasten the rate of articular cartilage degeneration. The articular lesions observed in the acromegalic subject are essentially like those of degenerative joint disease although the secondary hypertrophic changes may be more pronounced.[34]

The joint changes associated with *secondary (pulmonary) hypertrophic osteoarthropathy* are quite clearly the result of an extension of the characteristic mild inflammatory and proliferative periosteal reaction to the regions where the articular capsules insert into the bone coverings. In addition, in some cases at least, there is seen a mild synovitis that may well result from the same physiologic disturbances that cause the osseous lesions.

The joint disorders that accompany *hemophilia* and, less frequently, *purpura* are dependent upon the repeated hemorrhages that occur into the joint space and into the synovial and capsular tissues. The resulting pathologic changes may vary from the presence of clotted blood within the joint to marked thickening of the synovial tissues and even pronounced cartilage destruction and ankylosis of the joint. These changes appear to result from the vascular endothelial cell and fibroblastic proliferation that occurs in the process of organization of blood clot. As a rule, the synovial tissues are heavily stained with pigments derived from the destruction of hemoglobin.

Reiter's syndrome, of unknown etiology, consists of urethritis, conjunctivitis, and arthritis. The urethritis is usually associated with purulent discharge and there may be a co-existing cystitis. The conjunctivitis results in purulent exudation and may be followed by keratitis or iritis. Articular involvement of the knee, ankle, hip, and small joints of the hands and feet forms the other component of the syndrome. There is usually polyarticular involvement, and although the joints may be swollen and painful and show diffuse acute inflammatory changes in the synovial tissues during the acute stages

of the disease, there is little if any residual stiffness, and ankylosis does not occur. The disease is usually recovered from within a period of a few weeks.[13]

Psoriasis is known to be accompanied by arthritis with sufficient frequency to leave no doubt that some inherent relationship exists between the two conditions. The incidence of psoriasis in patients with rheumatoid arthritis ranges from 2.6 per cent to 4 per cent.[35, 36] Although the terminal interphalangeal joints are particularly prone to early and extensive involvement in the arthritis that accompanies psoriasis, the gross and microscopic features of the arthritis are usually indistinguishable from those of rheumatoid arthritis.[37]

fied by the "housemaid's knee" where the prepatellar bursa becomes enlarged and painful as the result of crawling on floors and stairs and closing drawers and doors with the knee. Such injuries may also cause degenerative and hypertrophic changes in the joint proper.

Bursal cysts that are connected with the knee joint are not uncommon (Fig. 1150). In some instances the openings connecting the cysts with the articular cavity are long and tortuous. Not infrequently the opening becomes obliterated by cicatrization. These examples of bursal cysts are usually referred to as **Baker's cysts** although Baker's original papers[38] described cystic lesions in association with a variety of pathologic conditions of dissimilar causation.

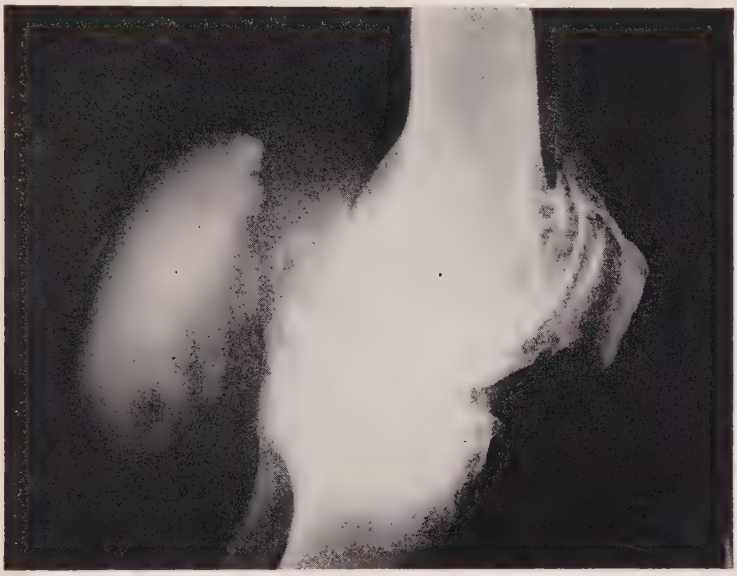


Fig. 1150.—Bursal cyst in the popliteal space filled with sodium iodide. The knee shows well-marked hypertrophic changes, typifying advanced degenerative joint disease.

Local Disorders Affecting Articular Tissues.—

Aseptic Necrosis of Bone.—Descriptions of the various bone lesions that may be designated as aseptic necrosis are presented on page 1204. It may be noted here that in certain locations, especially the hip, the deformities resulting from aseptic necrosis may be followed by progressive deterioration of the joint. The resulting lesion is similar to or identical with other forms of degenerative arthritis.

Bursitis and Bursal Cysts.—When it is recalled that a bursa is a synovial membrane-lined sac either communicating with or placed near a joint, it may be expected that it will be vulnerable to the same injurants that affect an articulation.

The common lesions are those resulting from trauma or infection.

Traumatic bursitis may result from a single injury such as a blow upon the elbow (olecranon bursa) or the knee (prepatellar bursa). More commonly, however, it is the repeated injuries from excessive pressure or bruises that initiate the inflammatory changes. This is well exempli-

When an excised bursal cyst is examined, it is found to have a dense fibrous wall of variable thickness. The enclosed cavity is often divided partially or completely into two or more chambers by fibrous septa that project inwardly from the cyst wall. The cavity contains fluid that may be either clear or turbid and of either watery or mucinous character. At times the fluid is stained with blood pigments. Not infrequently the cavities contain "melon seed" bodies similar to those found in articular chambers (Fig. 1151). The origin of these bodies from small excrescences on the cyst wall or the tips of fringe-like villi projecting into the cavity is clearly apparent in many instances. The linings of the cysts vary from smooth, glistening surfaces to nodular and villous membranes. Microscopically, apparent synovial membranes may be present but more frequently the cyst space is lined by dense fibrous connective tissue that contains focal and diffuse infiltrations of lymphocytes and hemosiderin-laden phagocytes.

Purulent inflammation of bursal cavities may result from the localization of pathogenic

microorganisms. This may follow penetrating injuries, extension of infection from an adjacent cellulitis or abscess or from the localization of organisms circulating in the blood.

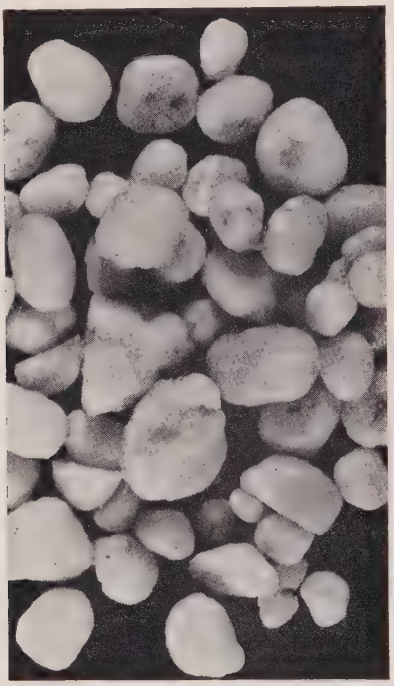


Fig. 1151.—Joint mice removed from a shoulder joint. The synovial membrane was studded with small nodules comprised of dense fibrous tissue and cartilage. Detachment of these tissue excrescences was the apparent source of the loose bodies.

Cysts of the Semilunar Cartilage.—These lesions are usually a semicystic enlargement, of rubbery consistency, located in the lateral meniscus near its anterior insertion. When incised, they contain a number of indistinct locules that are filled with mucinous or gelatinous fluid. Microscopic sections may reveal bits of synovial tissue lining portions of the more distinct cavities and there is usually evidence of diffuse fraying of the fibrocartilage of the meniscus. The latter change probably results from the extravasation of mucin-containing fluid into the interstices of the dense and relatively acellular connective tissue of the preexisting semilunar cartilage.

These lesions have much in common with ganglions of tendon sheath origin and are probably formed in a similar manner. Two possibilities have been suggested to explain their development. One explanation is that the lesion represents a mucinous degeneration of fibrocartilage. The other holds that synovial membrane extensions into fibrocartilage become segregated and distended into cystic cavities by the secretion of mucin-containing fluid.

Dupuytren's Contracture.—This is an affection of the palmar fascia of either or both hands that leads to permanent flexion contracture of one or more fingers. In the usual order of frequency the fifth, fourth, and third digits are involved. The condition is usually unattended by symptoms of pain and tenderness. It occurs most frequently in males and in approximately half of the patients it is bilateral. In addition to thickening, stiffening, and shortening of the fascial tissues, there may be a certain amount of nodularity. Microscopically the lesion shows an active proliferation of fibroblasts in the fascial layer with fibrous replacement of the adjacent fat and disappearance of the skin appendages in the overlying dermis. Inflammatory changes are either nonexistent or minimal. The cause of the condition is unknown but occupational and hereditary factors seem to be important in some instances.

Ganglion.—One of the familiar cystic or semicystic lesions of synovial membrane origin is the *ganglion*. This swelling is most frequently observed on the ventral or dorsal surfaces of the wrist, but it also occurs over the dorsum of the foot, adjacent to the ankle, or in close proximity to the knee. Occasionally the lesion is a well-defined synovial membrane-lined cyst which may or may not have a detectable pedicle attachment to a synovial sheath or joint capsule. Such cysts are filled with clear mucinous fluid and it is presumed that they represent herniations of synovial membranes through a tendon sheath or the articular capsule of the joint. In many instances the excised swelling is a poorly defined mass of mucin-filled connective tissue, in which no synovial membrane is demonstrable. Still other lesions contain small fragments of recognizable synovial tissue incorporated in a loosely textured and edematous connective tissue mass.

It appears probable that these lesions may result from: (a) herniation of the synovial lining of a tendon sheath or articular cavity, (b) displacement of synovial tissues into the fibrous connective tissue near tendon sheaths or articular capsules, or (c) by extravasation of synovial fluid with subsequent mucinous degeneration of the connective tissues near articular structures.

Protrusion of Intervertebral Discs.—Herniation of an intervertebral disc, has been shown to be an important cause of pain in the lumbar region or pain radiating downward along the sciatic nerve (sciatica). Trauma, especially from lifting or sudden exertion, is believed to be the initial cause in most instances. Furthermore, it is likely that the degree of protrusion is influenced by flexion and hyperextension of the spine. The discs of the lumbar region, particularly the one between the third and fourth vertebral bodies, are most frequently affected. The rounded protrusion exerts pressure upon the spinal cord or one of its branches. Microscopically the herniated disc tissue is composed of loosely arranged and relatively acellular tissue similar to the nucleus pulposus from which it originates.[39]

Osteochondritis Dissecans.—This condition is one in which there is a segregation or detachment of a fragment of articular cartilage or cartilage and underlying cancellous bone. The lesion is seen most frequently in the knee, particularly on the internal condyle of the femur. Less commonly, the elbow, hip, or shoulder is affected. Such lesions are productive of moderate discomfort that may be

associated with an effusion into the joint. If the altered segment of cartilage is completely separated, it serves as a loose body and may cause sudden locking of the joint.

The etiology of osteochondritis dissecans has not been clearly established. Traumatic injury is clearly implicated in some instances but in other cases it is presumed that the lesion results from aseptic necrosis of the subjacent bony tissue.

On microscopic examination the articular cartilage covering the detached segment is usually viable but shows vertical clefts and varying degrees of fibrillation of the matrix. There is also clustering of the enclosed cartilage cells. The bony tissue, in a completely detached segment, is necrotic. In a lesion that is only partially separated, there may be irregular areas of bone necrosis. The surface of the concavity from which the lesion has separated is usually covered by fibrous tissue that is only moderately vascular. Signs of inflammation are minimal and consist of slight to moderate accumulations of lymphocytes.

In exceptional cases of osteochondritis dissecans, cystic lesions have been demonstrated in the subjacent bone.[40]

OSTEOCHONDROMATOSIS.—This relatively uncommon articular disorder may occur as an isolated lesion or in conjunction with other forms of joint disease, particularly degenerative joint disease. It is characterized by the development, in the synovial tissues, of small or large numbers of cartilaginous nodules which tend to undergo secondary ossification. Many of the nodules become detached and float free in the joint fluid where they may continue to grow. When the joint is opened, dozens or even hundreds of flat or rounded cartilaginous bodies escape in the excess fluid that is contained in such a joint. Inspection of the synovial lining of the joint reveals similar translucent masses of cartilage projecting from the surface or hanging from narrow pedicles into the joint space.

The cause of the lesion is not known. It can perhaps best be regarded as ectopic cartilage and bone growth that is possible since all articular components are derived from the same embryologic tissues. In most instances the lesion develops gradually and without known antecedent injury. Occasionally, however, trauma appears to be a precipitating factor of causation.

NEOPLASMS OF JOINTS, BURSAE, TENDONS, AND TENDON SHEATHS

Any of the tissue components of the articulations including bursae, tendons, and tendon sheaths may give rise to benign or malignant neoplasms. Thus, among the benign tumors one will occasionally encounter *chondromas, osteochondromas, myxomas, angiomas, fibromas,* and *lipomas.* These neoplasms and the malignant tumors derived from corresponding cell types are no different from tumors of the same histologic composition that are seen elsewhere in the body. However, because of the anatomic and functional peculiarities of the joint structures, such tumors may give rise to signs and symptoms at a relatively early stage in their development. Pain on motion of the joint, limitation of range of joint motion, and effusion into the joint space may direct attention to the presence of the tumor.

Of particular importance in this section of the text are the neoplasms whose origin and behavior are determined by the presence of specialized synovial lining cells in the articulations, bursae, and tendon sheaths. Such tumors may be considered in two main classes: (a) giant cell tumors of tendon sheaths (*benign synoviomas*), and (b) malignant tumors of synovial cell origin *(synovial sarcoma).*

Giant Cell Tumors of Tendon Sheath Origin (Benign Synoviomas).—These neoplasms occur in close proximity to the tendons of the fingers, wrists, ankles, feet, and knees. Less frequently, they arise from the articular capsules or tendon sheaths in other portions of the body. Such tumors grow slowly with compression and displacement of the adjacent tissues. Where the tendons and other tissues are firmly anchored in bone, the tumors may cause surface erosions or deep rounded depressions in the bone cortex. These bony changes are the result of pressure atrophy. In some examples the neoplastic tissue is compressed between two or more tendons and tightly adherent to all adjacent structures. These anatomic relationships, when encountered, increase the difficulty of complete surgical removal, and the recurrence rate is much higher than it is in instances where the tumor pushes out from a tendon into the subcutaneous tissues.

The gross appearances of these tumors vary within wide limits. The neoplasms range in size from a few millimeters in greatest diameter to several centimeters. Those that have been cleanly enucleated have a dense fibrous covering formed of the compressed surrounding tissues. They are firm and only slightly elastic. Sectioning reveals a dense and inelastic tissue that is gray in color. In many instances, yellowish areas or streaks are

noted. The yellow color is proportional to the amount of lipoid that is contained within histocytic cells within the tumor. It is because of the yellow color that some of these lesions have been designated as xanthomas or xanthofibromas.

Examination of the microscopic sections reveals cellular and structural features that are highly characteristic in the majority of tumors (Figs. 1152 and 1153). The giant cells from which the tumor derives its name may be numerous or few in number. They contain many small oval nuclei that are usually crowded together in one portion of the cell. The cytoplasm may be scant or abundant and the configuration of the cells is equally variable (see Fig. 1152). The remaining portions of the tumor are comprised of small oval or spindle-shaped cells and irregularly placed bundles of connective tissue. The ratio, one to the other, of these elements is exceedingly variable within the same and different tumors. Some neoplasms are highly cellular and show active cell proliferation. Others are dense and fibrous and contain few cellular elements. An average tumor is portrayed in Fig. 1152. The number of lipoid-laden phagocytes seen in these tumors is also variable. Some tumors are comprised chiefly of such cells, while other tumors contain only scattered foam cells or small aggregates similar to those illustrated in Fig. 1153.

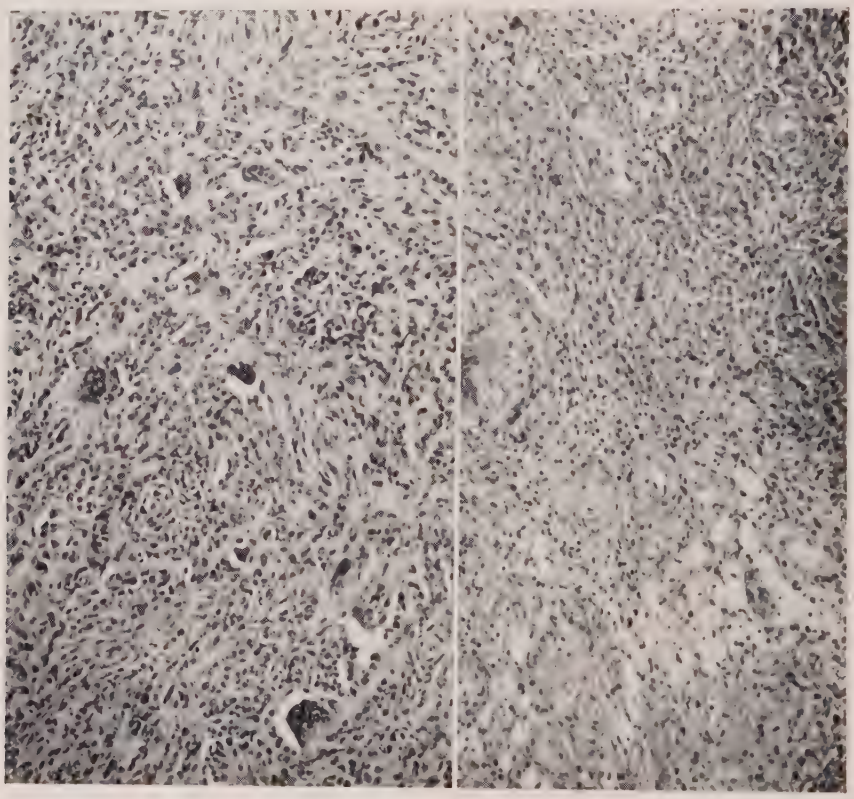


Fig. 1152. Fig. 1153.

Fig. 1152.—The typical histologic features of a giant-cell tumor of tendon sheath origin (*benign synovioma*) are illustrated in this photomicrograph. (×130.) (AFIP No. 90662.)

Fig. 1153.—A giant cell tumor of tendon sheath origin containing many lipoid-laden cells. (×130.) (AFIP No. 82251.)

Careful study of these tumors reveals irregular, slitlike cavities that are lined by oval or flattened cells. Occasionally one notes that small tufts of these cells project into the cavities (Fig. 1152). It is probable that these structural features are related to the inherent propensities

of synovial lining cells from which these tumors are probably derived. When the cellularity of these tumors is great and the tendency for cleft formation and tufting is highly developed, it may be difficult to distinguish sharply between this neoplasm and the malignant neoplasm of synovial membrane origin that is known as synovial sarcoma.

Synovial Sarcoma.—The term synovioma was suggested in 1927 by Smith[43] to designate a group of malignant tumors that are believed to arise from the cells lining synovial cavities in any part of the body. In a recent review of the literature Haagensen and Stout[44] found descriptions of 95 cases which they considered to be acceptable examples of synovial sarcoma, which with nine additional tumors from their own material, formed a total of 104 examples. A review of the specimens submitted to the Army Institute of Pathology for interpretation during the years of World War II revealed 32 examples of synovial sarcoma.[45]

Fig. 1154.

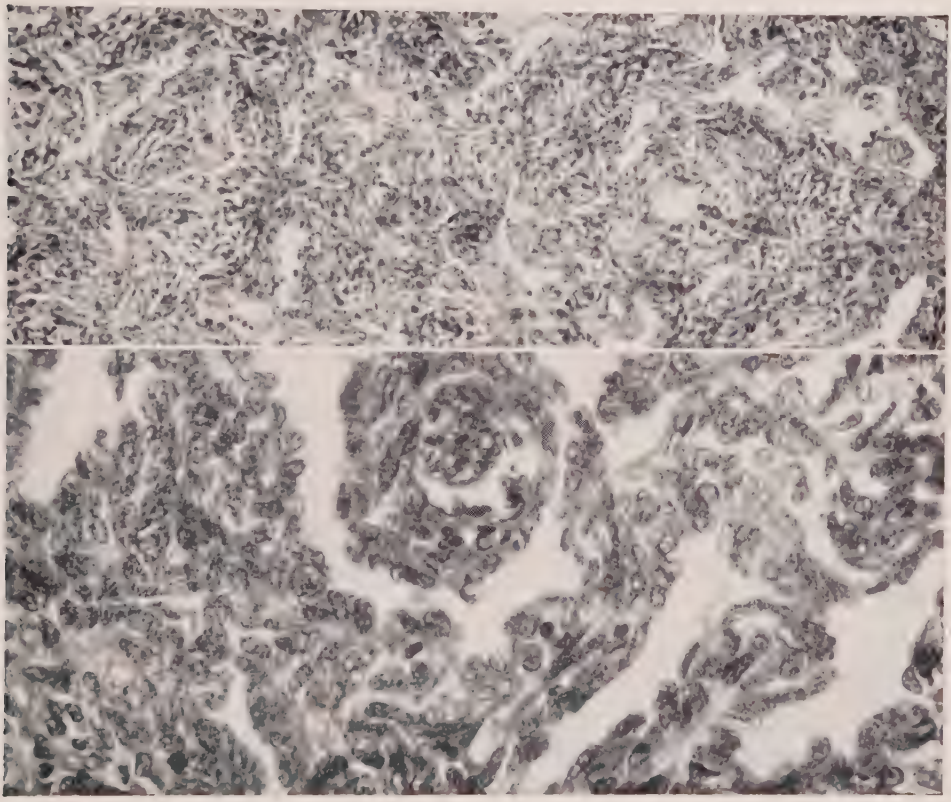


Fig. 1155.

Fig. 1154.—Malignant tumor of synovial membrane origin (synovial sarcoma), showing characteristic structure. (AFIP No. 90623.)

Fig. 1155.—Higher power photomicrograph of synovial sarcoma. (×550.) (AFIP No. 90623.)

In addition to the giant cell tumor of tendon sheath origin, one occasionally encounters tumorlike overgrowths within the knee that vary from simple inflammatory hyperplasia of the synovia to complex masses of granulation tissue containing giant cells, lipoid-laden phagocytes, and blood pigment. It is difficult to determine in some instances whether the lesion is of inflammatory character or whether it represents a true benign neoplasm.[41] The term **pigmented villonodular synovitis** has been suggested to designate synovial membrane lesions having these variable characteristics.[42]

These tumors seldom develop within the cavities of joints and for this reason

their derivation from synovial tissues may not be suspected until they are examined microscopically. The sites of most frequent occurrence are the regions of the knee and the lower segment of Hunter's canal. Less frequently they are encountered in other portions of the body where synovial tissues of joints, bursae, or tendon sheaths are known to exist.

On gross examination the tumors are variable in size, texture, and appearance. Usually they are sharply circumscribed and give the appearance of being partially or completely encapsulated. The compressed and attenuated adjacent tissues form a pseudocapsule that accounts for this appearance. In the process of removal it is frequently noted that the tumor is attached at one or more points to tendons or tendon sheaths. Various colors and densities are noted on sectioning the neoplasms. Some are firm in texture and moderately fibrous but more frequently they are spongy and friable. Pinkish-gray areas of viable tumor tissue are frequently interspersed with yellow areas caused by necrosis and brown or red portions that have resulted from old or recent hemorrhage. Occasionally small or large areas of calcification are encountered on sectioning. Such calcification may be noted in the x-ray film prior to removal of the tumor.

The microscopic appearances of these tumors are dependent on three basic morphologic patterns that are developed with varying degrees of clarity in any single tumor. These patterns are believed to represent expressions of the functional and morphologic characters of synovial tissues in general.

One pattern is represented by the formation of tissue spaces which vary from slitlike clefts to well-defined gland-like spaces containing serous or mucinous fluid. The second major design is the formation of cell tufts. This feature varies from compact groups of oval or polygonal cells segregated in solid portions of the tumor tissue to papillary projections extending into clefts and gland-like spaces. The third architectural design that is noted in the more highly characteristic tumor is the reproduction of epithelium-like cells upon a supporting stroma of compact tissue formed of elongated cells with small dark nuclei. (Figs. 1154 and 1155.)

Extensions of tumor tissue into vascular channels may be noted and examination of the margins of the tumor mass will usually reveal invasion of the adjacent tissues in one or more areas. Mitotic figures are usually seen in moderate or large numbers. It seems doubtful, however, that their frequency gives any reliable index to the degree of malignancy of the neoplasm.

Experience has clearly demonstrated that the fatality rate of this group of tumors is high, although in many instances the initial lesion may have been present for several months prior to its surgical removal. In the series of 104 cases tabulated by Haagensen and Stout,[44] only three patients were alive and free of metastases five years after treatment was begun. It is possible that this high mortality rate might be reduced if more radical surgical treatment was generally adopted in the early stages of development of a given tumor. It is clearly evident, however, that these neoplasms are among the most highly malignant of all mesenchymal tumors. Radiation therapy has little beneficial effect upon either the primary tumor or its metastases. Metastases develop in the lungs, lymph nodes, and other organs including the heart and brain. The distinctive morphologic features of the primary tumor are usually perceptible in the metastases.

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Chapter 44

THE NERVOUS SYSTEM

JEFF MINCKLER

In common with other organ systems the brain, spinal cord, and peripheral nerves and their membranes are susceptible to malformation, degeneration, neoplasia, infection, toxemia, and trauma. Recognition of certain peculiarities in the morphology of the nervous system assists greatly in understanding the pathogenesis of these disabilities. In recounting the particular points of anatomy with direct bearing on pathologic problems it is convenient to describe them under the headings: (1) gross anatomy and topography, (2) vasculature, and (3) ventriculomeningeal system.

Gross Anatomy and Topography

The subdivisions of the brain, viewed medially, are indicated in Fig. 1156. The hemispheres of the cerebrum exhibit a somewhat indistinct lobation, as shown in lateral view in Fig. 1157. Further anatomicophysiologic grouping of nervous structures is apparent in a coronal section of the brain (Fig. 1158), and in a transverse section of the cord (Fig. 1159). These subdivisions not only serve the purpose of descriptive localization but also connote embryogenic and physiologic distinctness. Because of regional differences in function, pathologic processes, particularly focal ones, are reflected in rather specific clinical behavior patterns. These behavior patterns are dependent not only on the localization of the lesion but on the nature of the process as well—whether irritative or obliterative, acute or chronic, tractile or expansive. In localizing a lesion pathologically, transverse sections of the brain stem including cerebellum and coronal sections of the forebrain expose most disorders and leave the tissue in admirable shape for microscopic preparations. In addition, by arranging the grossly cut pieces of brain in a sequential pattern, the location, relationships, and course of a lesion will be amenable to photographic display or to checking on previously prepared mimeographed outlines of cerebral levels. Such a display is illustrated in Figs. 1160 and 1161 which show the gross brain and successive sections of a brain from a case of extensive cystic degeneration following trauma. The topography of the dura has several features of major importance. The veins (sinuses) are discussed below. The falx (Fig. 1162) and the tentorium with its aperture (Fig. 1163) are extremely important septa and limit excursions of brain

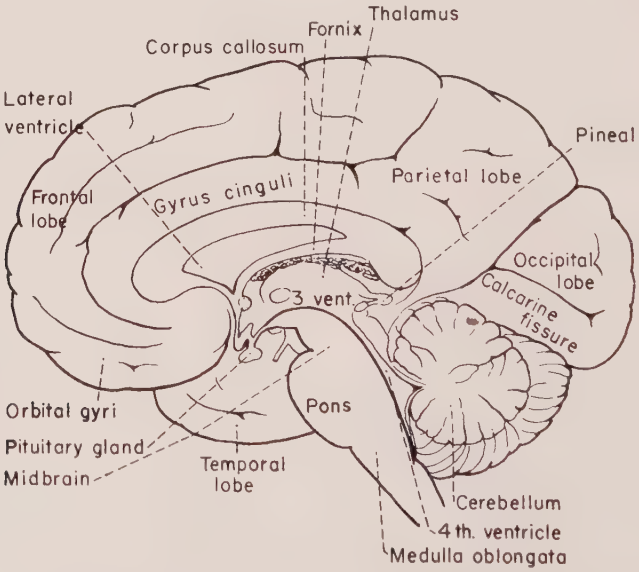


Fig. 1156.—Diagram of medial view of cerebral hemisphere and brain stem.

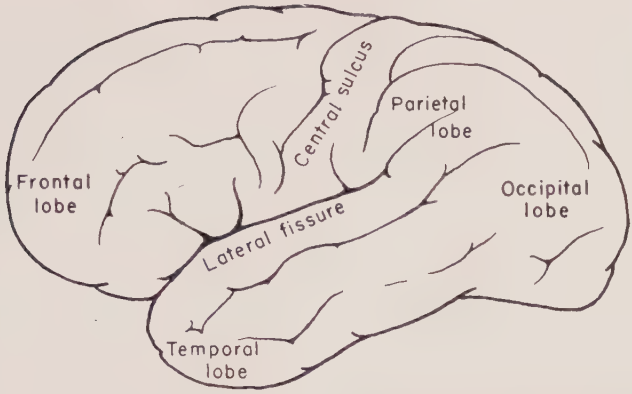


Fig. 1157.—Diagram of lateral view of cerebral hemisphere.

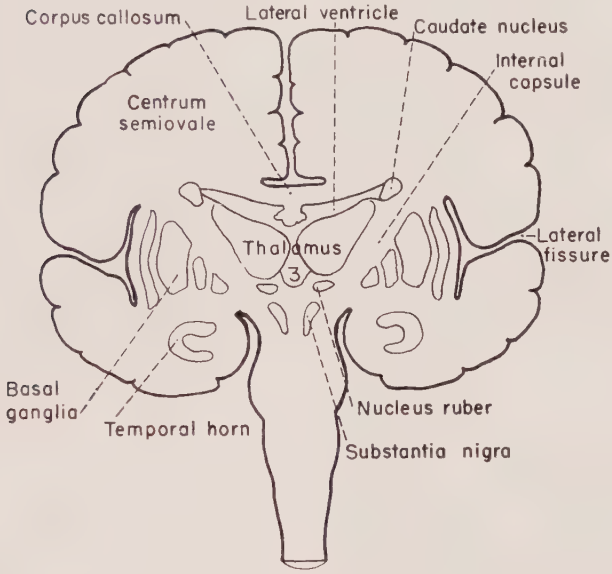


Fig. 1158.—Diagram of coronal section of brain and brain stem showing major topography.

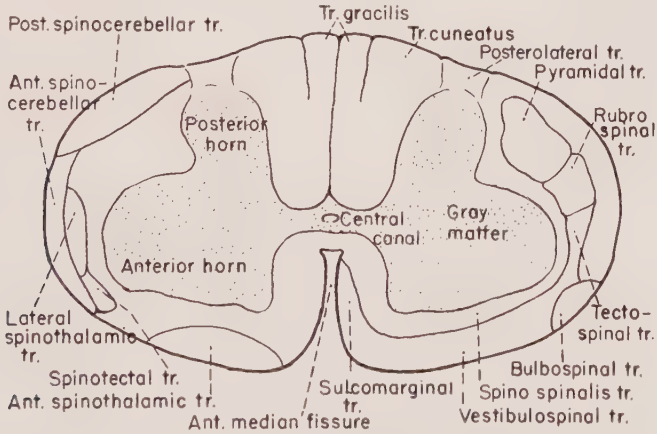


Fig. 1159.—Diagram of cross section of spinal cord showing descending pathways on the right and ascending pathways on the left.

substance within the cranial vault. With serious changes in pressure and shifting of cranial contents these dural folds and rims impinge upon the brain, leaving indentations (Fig. 1213). Recall particularly the apertures (tentorial aperture and foramen magnum) which represent the "give" points which are important in elevated intracranial tension.

Vasculature

Arterial.—The arterial vasculature of the dural meninges of the brain is provided from three principal sources: (1) anterior, from ethmoidal branches and the intracranial portion

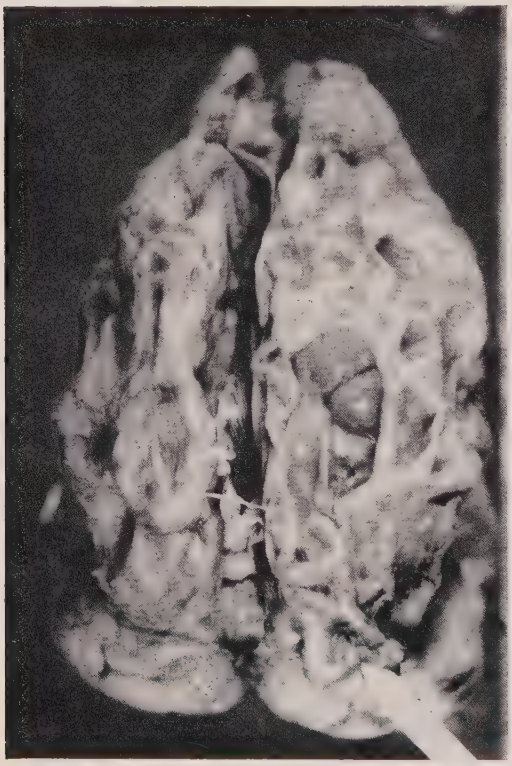


Fig. 1160.—Gross neonatal brain showing pronounced cystic change and shrinkage. This is presumed to be antenatal trauma on a vascular basis and is duplicated in postnatal severe trauma. The arrow points to a patch of preserved gyri.

of the internal carotid arteries; (2) middle, from the internal maxillary arteries; and (3) posterior, from the occipital and vertebral arteries. The most important is the middle meningeal artery which passes through the foramen spinosum and is distributed to almost all the lateral and vertex areas of the dura. The vessels course in the outer layer of the dura and, projecting from the external surface, are embedded in the inner table of the skull. This relationship makes them particularly liable to traumatic injury. Bleeding from these vessels is epidural in position. The arterial supply to the spinal dura is through the spinal rami of the intercostal and lumbar arteries.

The arterial supply to the central nervous system arises through three main channels: (1) internal carotid arteries, (2) vertebral arteries, and (3) radicular arteries. The internal carotid arteries branch to form the middle and anterior cerebral arteries. The vertebral vessels fuse to form the basilar which branches dichotomously into the two posterior cerebral arteries. A branch from the posterior cerebral artery (posterior communicating) connects with the internal carotid on each side, and a communication between the anterior cerebrals (anterior communicating) completes the arterial circle of Willis. The complex basilar artery and the arterial circle and the roots of their branches comprises the *basal vasculature* of the brain (Fig. 1164). The brain stem from lower midbrain to medulla and including cerebellum are supplied from branches of the basilar and vertebral arteries. Posterior and anterior branches from the vertebral arteries provide posterior and anterior spinal arteries. These, together with radicular arteries, complete the arterial supply to the spinal cord. The distribution of the principal arteries is important in understanding embolic phenomena, including abscess spread, tumor metastasis, arterial occlusive disease, hemorrhage, and the transmission of arterial pressure to cerebral vasculature. The problem of congenital basal aneurysm also has an important relationship to the branching patterns of the basal vessels (page 1331).

Venous.—The dural sinuses (Fig. 1162) are the major conduits for blood passing from the brain. The immediate drainage of brain substance is via (1) superficial and (2) internal cerebral veins. The superficial cerebral veins empty into the dural sinuses at numerous but rather specific points (Fig. 1162). It should be noted that venous anastomoses are abundant and bring practically all cortical areas into possible relationship with focal sinus lesions. Because of the existence of ischemia, obstruc-

Table XIX
Emissary Veins

VEIN	COMMUNICATION
1. Frontal	Nasal mucous membrane to superior sagittal sinus
2. Ethmoidal	Nasal mucous membrane to superior sagittal sinus
3. Mastoid	Postauricular and occipital regions to transverse sinus
4. Parietal	Scalp to superior sagittal sinus
5. Condyloid	Deep veins of neck to transverse sinus
6. Hypoglossal	Deep veins of neck to occipital sinus
7. Ophthalmic	Face and orbit to cavernous sinus
8. Pharyngeal	Pharyngeal and pterygoid plexuses to cavernous sinus
9. Diploic	Establish numerous connections between intracranial sinuses and supraorbital, deep temporal, posterior temporal, and occipital veins.

tion to venous drainage of the brain may induce infarction. In addition, septic material may be spread widely by reversal of venous flow. The venous drainage of the spinal cord is into the epidural venous plexus. This plexus communicates with the vertebral venous plexus, described as highly important in metastatic conduction.[1] By experimental methods it is almost impossible to arrest completely the venous flow from the head region by compression of the neck.[2] It seems apparent that collateral channels for returning blood from the brain are commodious particularly within the vertebral canal. Thus the surgeon can approach the jugular system almost with impunity.

An important venous system prominent in conveying infections to the dural sinuses is the emissary complex. The emissary veins and their connections are summarized in Table XIX.

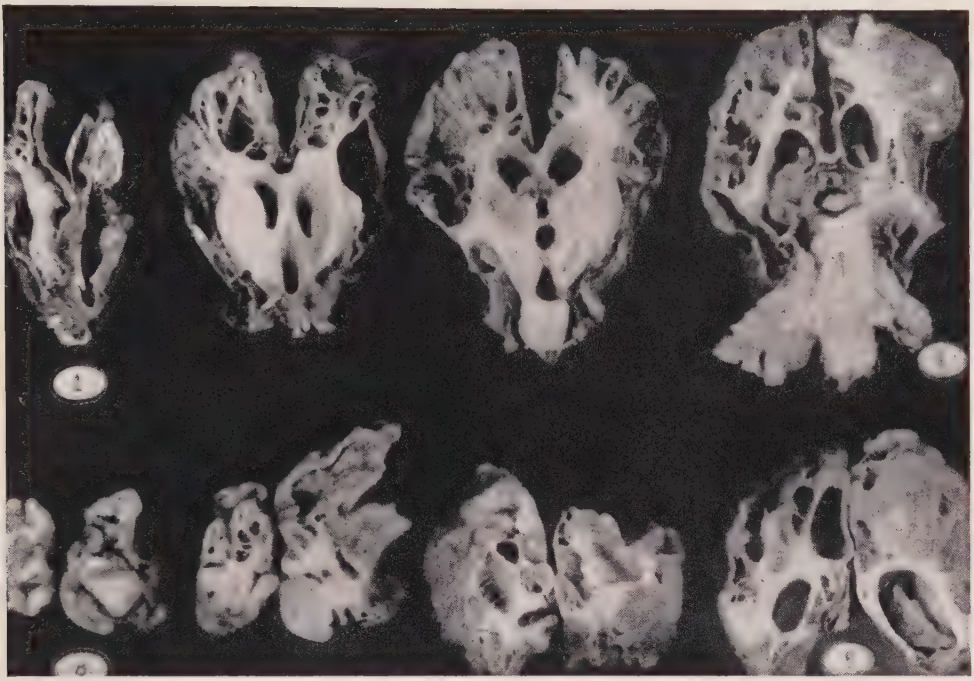


Fig. 1161.—Consecutive gross coronal sections of forebrain and stem shown in Fig. 1160. The pictorial record has many advantages in preserving the topography of the lesions.

Ventriculomeningeal System

Since the introduction of air studies in localizing intracranial lesions, the roentgenographic morphology of the ventriculomeningeal spaces has become extremely important. A lateral tracing of the ventricular system and its topography is shown in Fig. 1163. Space-occupying lesions characteristically distort the normal pattern of the ventricular shadows, depending on their location. Since Dandy's experimental block procedures[3] it has been accepted that the flow of cerebrospinal fluid is as follows: lateral ventricles, interventricular foramina, third ventricle, cerebral aqueduct, fourth ventricle, foramina of Luschka and Magendie, subarachnoid space. The course of the fluid in the subarachnoid spaces is, in general, directed

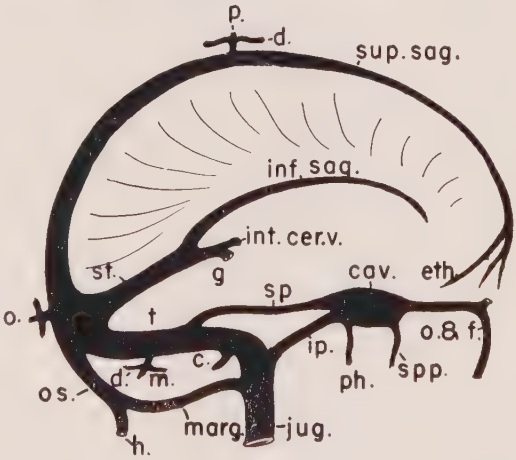


Fig. 1162.—Diagram of dural venous vasculature: *p*, parietal emissary; *d*, diploic vein; *sup. sag.*, superior sagittal sinus; *inf. sag.*, inferior sagittal sinus; *int. cer. v.*, internal cerebral veins; *g*, great vein of Galen; *st.*, straight sinus; *o*, occipital emissary; *t*, transverse sinus; *sp*, superior petrosal sinus; *cav*, cavernous sinus; *eth*, ethmoidal emissary; *o* and *f*, ophthalmic and facial emissary; *spp*, sphenoparietal sinus; *ph*, pharyngeal emissary; *ip*, inferior petrosal sinus; *jug*, jugular vein; *c*, condyloid emissary; *marg*, marginal sinus; *m*, mastoid emissary; *h*, hypoglossal emissary; *os*, occipital sinus.

toward the vertex, where some 95 per cent of its volume is emptied into dural sinuses and lacunae through the arachnoidal granulations. The remainder is absorbed into veins of the sinus terminalis, dural sinuses at the exit of spinal nerves, and probably directly into subarachnoid vessels. In this flow, which is undoubtedly irregular, the spinal subarachnoid space and the cisternae are traversed. The cisternae are represented by enlarged regions of the subarachnoid space and include the following: (1) c. cerebellomedullaris (magna), between cerebellum and medulla into which the foramen of Magendie empties; (2) c. pontis,

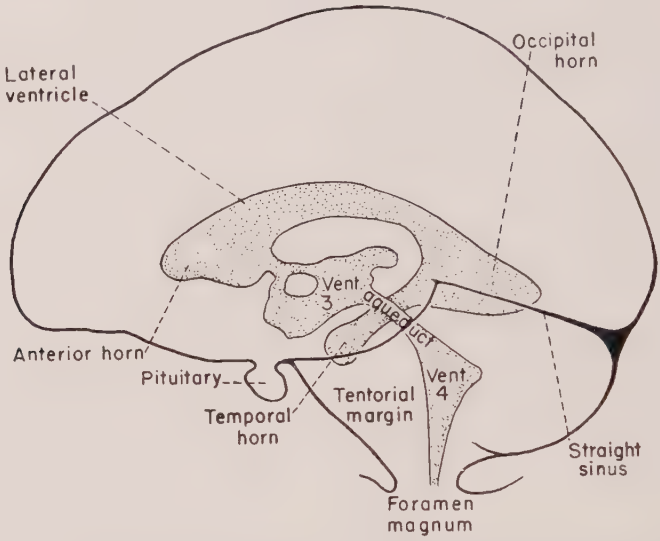


Fig. 1163.—Line tracing from radiograph of cerebrum showing topography of ventricular system in relationship to skull and tentorium with its aperture. Note particularly the subdivision of the intracranial vault into supra- and infratentorial spaces.

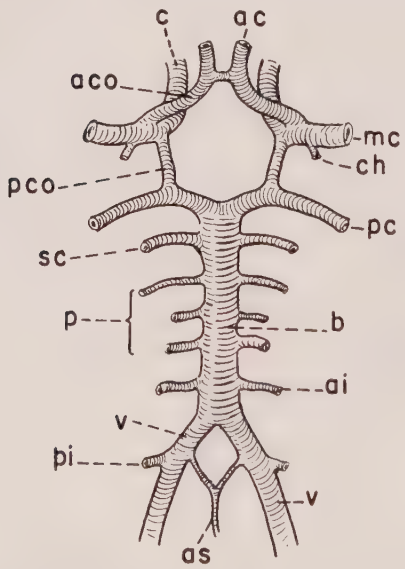


Fig. 1164.—Diagram of basal vessels of brain; *ac,* anterior cerebral artery; *aco,* anterior communicating artery; *c,* internal carotid artery; *mc,* middle cerebral artery; *ch,* anterior choroidal artery; *pco,* posterior communicating artery; *pc,* posterior cerebral artery; *sc,* superior cerebellar artery; *p,* pontine arteries; *bas,* basilar artery; *ai,* anterior inferior cerebellar artery; *v,* vertebral arteries; *pi,* posterior inferior cerebellar artery; *as,* anterior spinal artery.

lying over the ventral and inferior surface of the pons and in the angle between the cerebellum and pons and receiving fluid from the foramina of Luschka; (3) c. superius, lying over the roof of the midbrain below the pineal gland; (4) c. venae magnae cerebri (of Galen), lying around the vein of Galen and extending into the transverse fissure overlying the third ventricle; (5) c. basalis, including the area around the optic chiasma (c. chiasmatis), the region below the floor of the third ventricle and around the infundibulum, the interpeduncular fossa and its recesses (c. interpeduncularis); and (6) c. Sylvii, in the lateral fissure of the cerebrum (Fig. 1163). The importance of the tentorial aperture as a constricted channel (Fig. 1163) is illustrated in many pathologic conditions. (See hydrocephalus, page 1277, meningitis, page 1325, intracranial tension, page 1337.) The subarachnoid space continues along the cranial and spinal nerves for varying distances. Most important in this connection is the sheath of the optic nerve and its role in papilledema (page 1338).

Subdural and epidural spaces are notable pathologically as limiting fascial planes in hemorrhage and infection (see page 1336 and Figs. 1240 and 1241).

Embryogenesis and Growth of the Nervous System

The nervous system arises from a linear midline ectodermal plate which by expansive

growth forms a groove. Continued lateral growth approximates the sides of the groove and eventual dorsal fusion establishes the medullary tube. By expanding growth and complex folding at the cephalic extremity, the mature brain is evolved. This fusion and expansion of parts of the primordial nervous structure is paralleled by growth and fusion of the surrounding bony structure. Faulty growth and fusion are manifest in a variety of anomalies which, for recognition, require information of the normal course of events particularly in two categories: (1) time of closure of fontanels and arches; (2) growth of nervous structures as revealed in age-weight relationships. The time of closure of fontanels and arches are illustrated in Figs. 1165 and 1166, adapted from Scammon.[4] Brain and spinal cord weights and dimensions are summarized in Table XX, after Scammon.[4]

TABLE XX

WEIGHTS OF PARTS OF THE CENTRAL NERVOUS SYSTEM (AFTER SCAMMON[4])

	AVERAGE WEIGHT IN GRAMS	
	NEWBORN	ADULT
Brain	350	1,350
Cerebrum	325	1,185
Cerebellum	20	140
Brain stem	5	25
Spinal cord	3.5	30
Meninges	22	65

Gross Developmental and Congenital Disorders

Related to faulty closure of the bony structures housing the medullary tube are numerous developmental disorders which vary primarily in degree of involvement (Figs. 1167-1174). **Rachischisis** (Fig. 1167) is a failure of formation of the dorsal arch throughout the length of the vertebral column, with exposure of the unclosed neural groove. **Myelocele** is similar to rachischisis except that part of the dorsal arch (usually the thoracic portion) is formed. The spinal cord may be wholly or partially formed as a medullary tube. **Meningocele** (Fig. 1168) is a leptomeningeal protrusion through a local defect in bone and dura with the leptomeninx underlying the skin. This may occur in the vertebral column or skull. **Meningomyelocele** (Fig. 1169) is similar to meningocele with the inclusion of spinal cord tissue in the protruding part. If brain is the part involved, the condition is called **encephalocele.** Syringomyelocele (Fig. 1170) is similar to meningomyelocele but with the addition of a marked distention of the central canal. **Spina bifida occulta** is a congenital local dorsal arch defect (usually lumbar or sacral), in which the gap is filled with connective tissue to which the cord membranes are attached. With unequal growth of cord and vertebral column, tension of the cord may result in neurological signs. This condition yields to surgical treatment. Occult spina bifida with no neurological disability is a very common incidental radiologic finding.

Malformations may primarily involve brain tissue (Figs. 1171-1174). **Anencephaly** is the condition wherein the forebrain and calvaria are absent. Often there are marked pathologic changes elsewhere, such as atrophy of adrenal

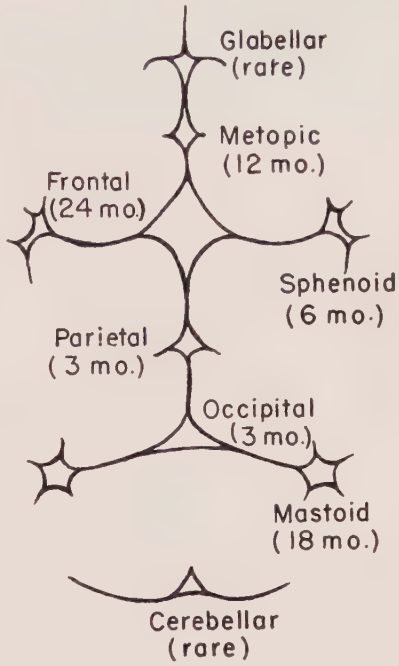


Fig. 1165.—Composite diagram of vertex view of infant skull showing fontanels and time of normal closure. (After Scammon.)

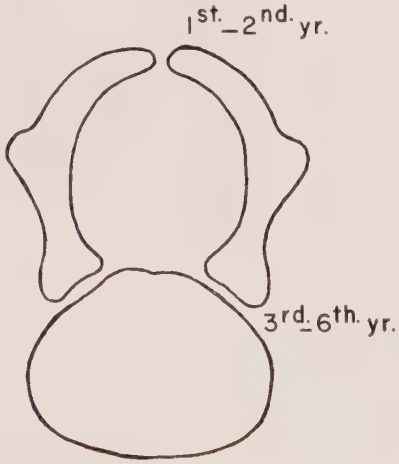


Fig. 1166.—Diagram of vertebra showing main fusion points and times of closure.

glands. It probably is due to defective organization in primordial tissues. **Porencephaly** (Figs. 1174, 1175) is an abnormal cavitation within the brain substance, with the cavities usually communicating with both ventricles and subarachnoid space. The cause has been at-

tributed to maldevelopment with agenesia, to arterial occlusion, to subacute encephalitis, and to phlebothrombosis and phlebostasis associated with hydrocephalus.[5] *Traumatic* porencephaly is represented by a communicating hemorrhagic lesion between meningeal spaces and ventricles (Fig. 1238). Occasionally a patient will survive and a cystic discolored communication remain. A communicating fatal hemorrhage of this type is not unusual in aneurysmal rupture of basal vessels and is seen occasionally in cerebral hemorrhage related to arteriosclerosis and hypertensive heart disease. Unusually large gyri are called **macrogyri,** unusually small ones, **microgyri** (Fig. 1225). Disturbances in brain volume are said to exist when brain weight in the adult varies beyond certain extremes. With an average weight around 1,350 grams, it is not uncommon to encounter brains weighing as little as 1,000 or as much as 1,700 grams. **Microcephaly** is the term applied to very small brains, **macrocephaly** to very large brains. Each condition is often associated with hydrocephalus. **Oxycephaly** is a condition in which a tower-shaped skull is associated with premature synostosis of cranial sutures. Mental deficiency, papilledema, and, eventually, blindness result from disproportionate growth of the brain in the deformed skull.

Arnold-Chiari malformation represents a complex bony defect including fusion of the atlas and occiput with shortening of the upper cervical canal, posterior displacement of the odontoid process, and a funnel-shaped posterior fossa with a short basi-occipital shelf. The defect encourages herniation of cerebellar and medullary parts with a resultant distortion giving rise to obstruction of cerebrospinal fluid flow at the fourth ventricle outlets. The malformation is, thus, commonly associated with hydrocephalus. Spina bifida is a frequent accompanying defect.

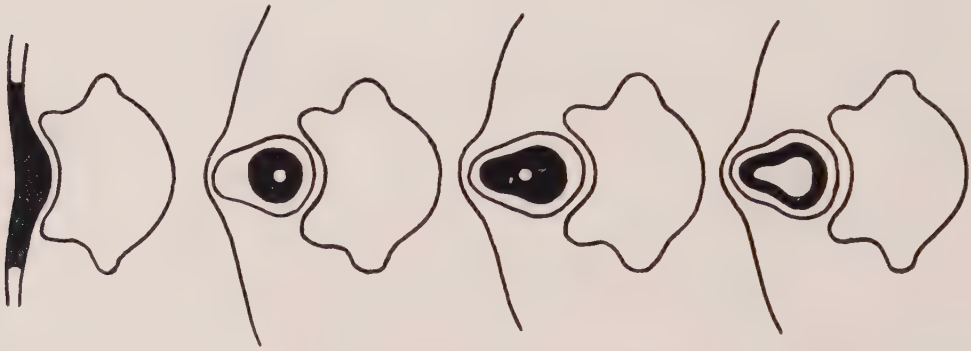


Fig. 1167. Fig. 1168. Fig. 1169. Fig. 1170.

Fig. 1167.—Diagram of cross section of vertebral column and medullary plate (black) in rachischisis.

Fig. 1168.—Diagram of dorsal aspect of body in spinal meningocele. The hernia includes only meninges. The medullary tube (black) remains in position.

Fig. 1169.—Diagram showing herniation of medullary tissue in meningomyelocele.

Fig. 1170.—Diagram showing dilatation of central canal in syringomeningomyelocele.

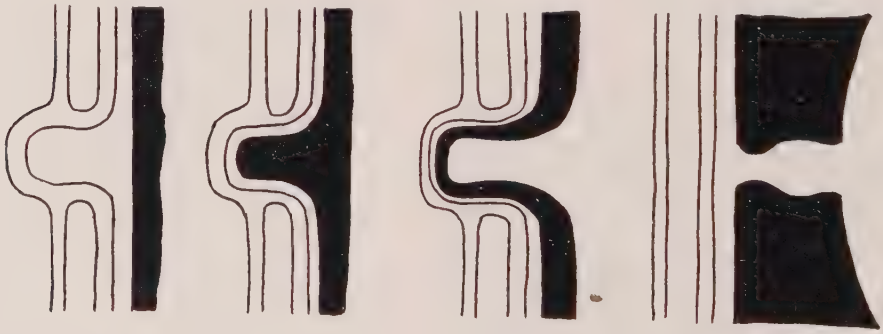


Fig. 1171. Fig. 1172. Fig. 1173. Fig. 1174.

Fig. 1171.—Diagram showing herniation of meninges in cerebral meningocele.

Fig. 1172.—Diagram showing herniation of cerebral substance (black) in encephalocele.

Fig. 1173.—Diagram showing dilatation of ventricle with inclusion of thin-walled cerebral tissue in hernia in syringoencephalocele.

Fig. 1174.—Diagram showing cavitation in cerebral substance communicating between ventricle and meningeal spaces in porencephaly.

Platybasia refers to occipitalization of the atlas associated with deformity of the foramen magnum. The odontoid process commonly bears on the brain stem which may excite an arachnoidal response tending to interfere with the flow of cerebrospinal fluid. **Hydromyelia,** distention of the central canal of the spinal cord, may be present in the region due to distortion from the defect.

Congenital hydrocephalus is the condition of an abnormal amount of intracranial cerebrospinal fluid present at, or shortly after, the time of birth. Several descriptive terms are applied to the condition depending upon gross variations. **External hydrocephalus** describes the condition wherein most of the fluid accumulates over the surface of the brain. **Internal hydrocephalus** exists when the ventricular system is distended. **Hydromicrocephaly** refers to the condition of small head, early closure of fontanels and sutures, with a concomitant hydrocephalus, usually both external and internal. Examples of this condition are the "pinheads" of circus fame. **Hydranencephaly** exists when the forebrain is represented only by a thin membranous sac filled with water. The head size may be normal with the fontanels closing appropriately.[6] In **hydromacrocephaly** the head is enlarged, with fontanels and sutures wide open. The ventricular system is dilated, sometimes to a volume of several liters. Often the chambers are confluent. Considerable brain tissue often persists in the outer shell. These cases represent the condition most often referred to as hydrocephalus. **Communicating hydrocephalus** exists when abnormally increased fluid is present, although the connections between the ventricular system and the subarachnoid space are patent.

Theoretically, the production of hydrocephalus can be brought about in three ways: (1) by overproduction of fluid, (2) by obstruction to its flow, and (3) by interference with its absorption into the venous system.

(1) The production of cerebrospinal fluid fluctuates with venous pressure. Hence, an obstruction to venous return from the choroid plexus might well cause excessive production of fluid. This situation may be found with tentorial tears in the newborn, where blood accumulates in the superior cistern and around the vein of Galen. Intracranial hemorrhage of this type is often associated with increased intracranial tension and, at autopsy, an incipient hydrocephalus can be demonstrated. However, the extravasated blood and the resultant arachnoidal reaction may operate to obstruct the flow of fluid through the aperture of the tentorium cerebelli in the subarachnoid space. The condition would then represent an obstructive type of communicating hydrocephalus. Exuberant growth or cysts of choroid plexus are commonly found associated with infantile hydrocephalus, but probably are not causative.

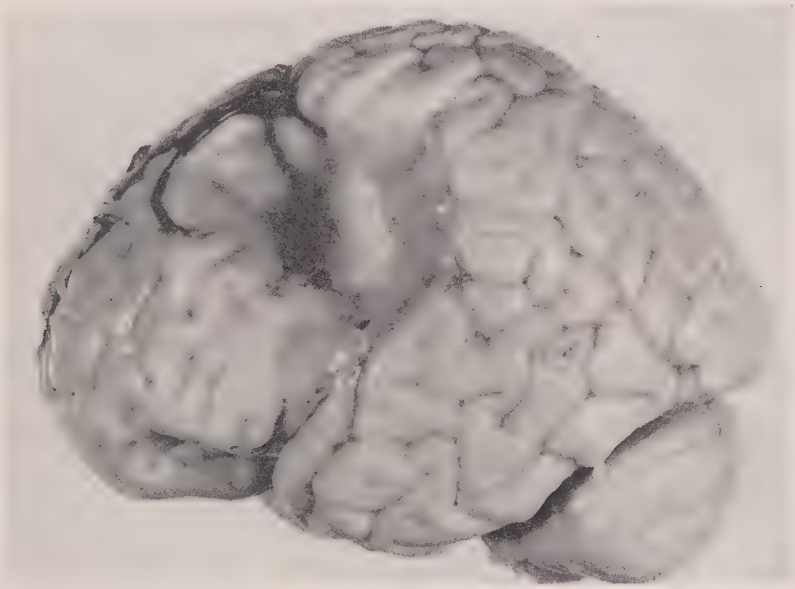


Fig. 1175.—Porencephaly with massive meningo-ventricular communication bridged externally by arachnoidal membrane. The lesion demonstrated is bilateral and symmetrical.

(2) Obstruction to the flow of cerebrospinal fluid is noted commonly in the following locations: (a) interventricular foramina (of Monro), (b) cerebral aqueduct (of Sylvius), (c) apertures of the fourth ventricle (of Magendie and Luschka), and (d) in the subarachnoid space at the constricted tentorial aperture (Fig. 1163). The etiology of the obstruction is often obscure, but there have been noted *congenital atresia* of the cerebral aqueduct, *occluding tumors* of the aqueduct in infants,[7] and *ependymitis* with inflammatory changes producing obstruction, particularly at the interventricular foramina and in the aqueduct of Sylvius. Recently, *toxoplasma* has

been incriminated as an inciting organism.[8] The infection is thought to be transmitted in utero since the defect produced often can be allocated to early pregnancy by the stage of development of certain structures. *Arachnitis* from meningeal infection may obstruct cerebrospinal fluid flow by exuberant fibrous proliferations over the foramina of Luschka and Magendie and in the interpeduncular and superior cisterns at the tentorial aperture. This condition has been found in infants but is probably more important in generating adult hydrocephalus. A marked arachnoidal thickening and fibrosis can result from subarachnoidal hemorrhage.

(3) Interference with absorption of cerebrospinal fluid may occur from destruction of arachnoid granulations by meningitis. This mechanism of development of hydrocephalus also occurs in expanding central lesions of the brain which, by compressing the brain against the skull, obliterate the subarachnoid space over the vertex (see page 1338).

Histologic Elements of the Nervous System and Their Reactions

Ten fundamental tissues (notochord, ependyma, choroid plexus, neuroglia, neurones, meninges, sheath and capsule cells, vasculature, microglia, and cerebrospinal fluid) constitute the adult nervous system and its principal supporting structures. The alterations in these tissues beyond the limits of anatomicophysiologic variability provide the subject matter for histopathology of the nervous system.

1. **Notochordal Tissue.**—The notochord is an embryonic axial rod which lies ventral to the neuraxis and around which the vertebrae and intervertebral discs develop. While the continuity of the structure is broken in development, fragments remain as "chordal rests" in the adult most commonly in the following places: (a) along the clivus, (b) in the hypophyseal fossa, (c) deep to the posterior wall of the pharynx, (d) in the dens, (e) in the nuclei pulposi of the intervertebral discs, and (f) in the sacrum. The most frequently encountered chordal rest appears as a soft mucoid projecting nodule on the clivus, which may be a centimeter or so in diameter, and which projects into the interpeduncular fossa. Histologically, the tissue simulates closely the appearance of fat. The cell nuclei are, however, central in position, and finely fibrillated or mucinous precipitate in the stroma appears in abundance. Large vacuolated (physaliferous) cells in a mucinous matrix characterize the microscopic appearance. The pathologic changes involving notochordal tissue include neoplasia (chordoma, see page 1292), and ruptured intervertebral disc (page 1336).

2. **Ependyma.**—Epithelial cells line all the cavities of the nervous system and continue in modified form over the choroid plexus tufts. These ependymal cells vary markedly in shape but are most commonly cuboidal or columnar. Each possesses a peripheral process extending into the medullary substance and a cilium projecting into the ventricle. While cilia are inconstant in sections of adult ependyma, very often intracytoplasmic pieces of cilia (blepharoplasts) can be identified. These are helpful in identifying tumors as ependymal in origin. The peripheral processes form a thin fibrillar network immediately beneath the ependyma, the subependymal glial layer, which is usually cell-free and undoubtedly includes an admixture of glial fibers from intramedullary neuroglia.

The more common reactions associated with ependymal tissue include proliferation, subependymal gliosis, and inflammation. *Proliferation* (Fig. 1176), manifested by reduplication to several layers of cells, may appear as an aging process. This is common in lower levels of the spinal cord, sometimes to such an extent that the central canal appears obliterated. Similar proliferations appear in the medullary substance at the junction of the roof and floor of the fourth ventricle and at the superolateral aspects of the lateral ventricles. *Subependymal gliosis* appears as a thickening and sclerosis of the subependymal glial layer. The condition is presumed to be a residual of toxemia or inflammation and occasionally takes the form of nodular glial projections covered by flattened ependymal cells (nodular ependymitis). *Inflammation* (ependymitis) is seen in septic conditions of the ventricles and as a result of irritation of the lining cells by other agents, such as toxoplasma (see page 1321). The subependymal layer is swollen and infiltrated with neutrophilic leukocytes, and the lining cells are reduplicated, festooned, swollen, or eroded.

3. **Choroid Plexus.**—The choroid plexus may be regarded as a pia-ependymal membrane invaginated by subarachnoidal vasculature. The ependymal epithelium with a thin fibrous substrate is disposed in foliated or villous pattern with a highly vascular core composed of loose trabecular tissue resembling arachnoid. Alterations in the choroid plexus are common but usually are unimportant. Most often encountered are *cyst formation,* the thin-walled translucent cysts appearing most frequently at the confluent part of the lateral ventricles; *concretions* (brain sand), amorphous firm bodies sometimes quite numerous; and sclerosis, a *fibrosis* of the choroid core.

4. **Neuroglia.**—The intramedullary supporting glial cells are astrocytes and oligodendroglia. In sections stained by hematoxylin and eosin they must be differentiated by nuclear configuration. The nucleus of the astrocyte is large, oval, pale and vesicular, with chromatin material deposited in small dustlike particles on a fine linin net. The nuclei of the oligodendroglia are about one-third smaller, more rounded, and stain darkly, with clumped chromatin masses (Fig. 1177). Special stains show that the astrocytes possess sucker-foot attachments to blood vessels and a great many fibrillar processes (Fig. 1178). The oligodendroglia have but few processes. Astrocytes appear in greater number in gray matter than in white. Oligodendroglia are equally numerous in both gray and white matter, forming the "satellite cells" of the neurones and the "interfascicular supporting cells" of the central nerve fibers.

Astrocytes may undergo either regressive or reactive changes. Regressive changes are most commonly seen as degenerative processes in tumor cells, or in severe toxemia, and are manifested by shrinkage and gemistocytosis. *Shrink-*

age is identified by pyknosis of the nucleus with fragmentation and extrusion. In *gemistocyte formation* the cells swell and the cytoplasm becomes stainable by routine methods (Fig. 1179). The distal parts of the cell processes fragment and disappear while the roots become faintly visible. The nuclei are eccentric and may be multiple. These cells are often referred to as "fat-astrocytes." Reactive changes in astrocytes are represented by *proliferation,* an increase in number by mitotic division; by *gliosis,* a production of glial fibrils forming a dense fibrous network and entering into repair phenomena (Fig. 1180), and by *swelling,* the visible cytoplasm increasing and varying up to the formation of "giant" astrocytes.

Oligodendroglia present three common reactive changes. *Acute swelling* and *vacuolation* (Fig. 1181) are nonspecific alterations which may occur as an agonal phenomenon. *Proliferation,* or an increase in number, is seen in toxic or inflammatory conditions. *Satellitosis* (Fig. 1182) is an increase in the number of oligodendroglia neighboring a nerve cell body, and is seen in certain toxic states. It has been referred to as incidental to neuronophagia (see page 1281). It may, however, represent an independent toxic response.

There are many alterations in the nervous system in which the parent reacting element is obscure, but in which glial cells may take part. *Glial nodes* (Fig. 1183) are nests of proliferated glial cells, and are particularly prominent in

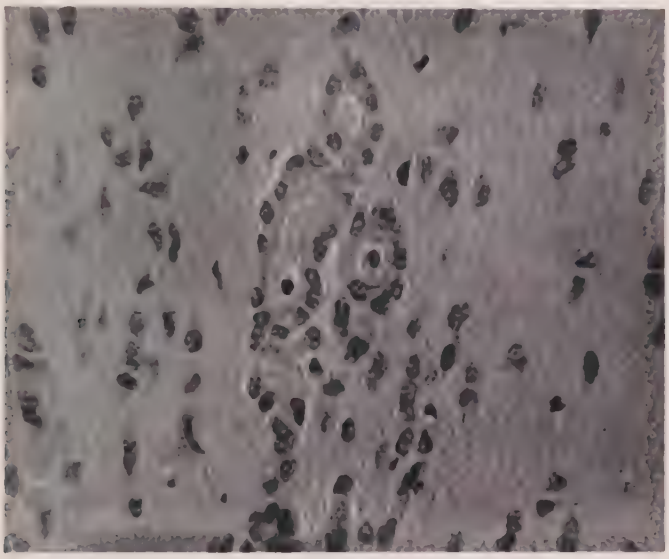


Fig. 1176.—Ependymal proliferation and inclusions.

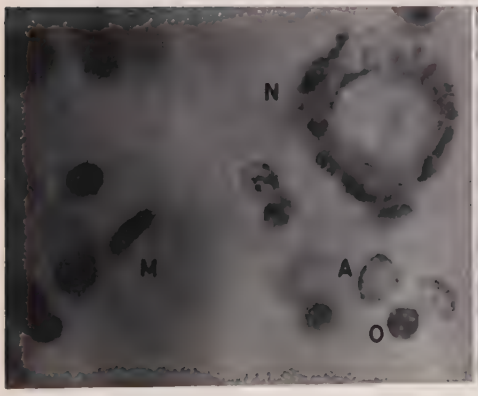


Fig. 1177.

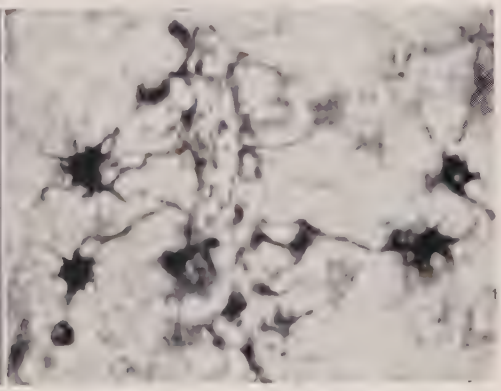


Fig. 1178.

Fig. 1177.—Comparative nuclear structure of *N,* nerve cell; *A,* astrocyte; *O,* oligodendroglia; and *M,* microglia.

Fig. 1178.—Astrocytes showing sucker-foot attachments to blood vessel.

rickettsial encephalitides. As they are often aggregated close to vessels and house intracellular organisms, the cells may be derived from perithelial cells of vascular adventitia. *Glial placques* (Alzheimer) are sclerotic nodules representing focal repair efforts. They may contain glial fibers and cells with an admixture of fragmented nerve fibers. *Corpora amylacea* (Fig. 1184) are concentric hyaline bodies of disputed origin. They are common after 40 years of age and often are conspicuous in premature senility. They stain with iodine but contain neither amyloid nor fat. They resemble corpora amylacea of the prostate or the lung.

microns[9] possess a fatty covering, the myelin sheath. In the central nervous system this sheath is limited externally by the network of fibrillar processes of supporting cells (oligodendroglia). In peripheral nerves the myelin is encased in a wrapping supplied by sheath cells (Schwann). Each sheath cell has distinctly marked linear limits which form a constriction (node of Ranvier) around the axis cylinder, at which point the myelin layer is obliterated. The axis cylinders terminate in buttonlike knobs (boutons) (Fig. 1188) which provide the contact points at the synapse,[10, 11] or in special peripheral structures in muscle or gland.

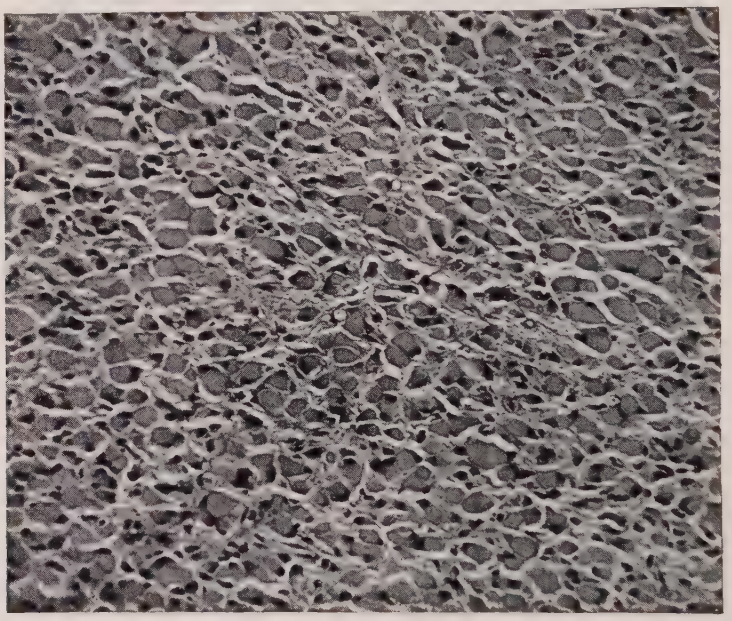


Fig. 1179.—Gemistocytes in gemistocytic astrocytoma. (From Anderson, Synopsis of Pathology, The C. V. Mosby Co.)

5. **Neuron.**—The neurons are the functional units of the nervous system and by their interrelationships provide the physical basis for nervous activity. Each consists of a cell body and its processes (Fig. 1177). Microscopically, the best criterion for identification is the nucleus. It is large, round, vesicular and contains a large nucleolus. The nuclear membrane is distinct. The cytoplasm contains varying amounts and patterns of basophilic material known as Nissl substance. Special stains enable identification of neurofibrils which traverse the cell body and continue into the processes. The shape of the cell body varies greatly; it may be multi- or unipolar and the size ranges from a diameter of a few microns to over 100, depending on location and function. From the cell bodies arise a varying number of processes, some of which (dendrites) serve to fix the cell body and provide receptive surfaces for synaptic contact. The axone is the process over which a nervous impulse is conveyed to an adjacent neuron or to an end organ. Those axones (axis cylinders) attaining a diameter greater than 1.5

Changes in the Body of the Nerve Cells.—The complex nature of the neurone and the distances over which the processes spread make difficult the interpretation of alteration in its parts. The common reactions of the *cell body* are shrinkage, swelling, vacuolation, pigment changes, and chromatolysis. *Shrinkage* (Fig. 1185) is indicated by marked irregularity in the shape of the cell, pyknosis of the nucleus, clumping and condensation of Nissl substance, and sclerosis or contortion of processes. Shrunken cells are common in senility and other cerebral atrophies, and also may appear in chronic infections. *Swelling* of nerve cells clouds the irregular surface contour. The cytoplasm stains faintly, the processes fragment, and the cell may be evident in outline only. This change, apparently reversible, occurs in acute toxic states and mild infections. It is the most prominent change in tetanus. *Vacuolation* (Fig. 1186) of nerve cells occurs in toxic states. The appearance of light brown or yellow pigment in a perinuclear position or in cytoplasmic blotches is observed commonly and is referred to as *pigment degeneration* (Fig. 1187). This degenerative

process should not be confused with the normal pigment in cells of certain locations (locus caeruleus and substantia nigra). In **chromatolysis** (Fig. 1185) the Nissl substance becomes fine, dispersed, peripheralized or loses its staining properties altogether. The nucleus of the involved cell is eccentric in position. Because this change is believed to be a specific retrograde response to axone injury, it has been widely used to identify the nuclear or ganglionic origin of damaged fiber bundles in the central and peripheral nervous systems.

of poliomyelitis. A mass of macrophages may be seen occupying the position of, or within, a nerve cell body. In satellitosis, on the other hand, the cells are seen around but not within the nerve cell body. The phagocytic cells may be mononuclears from the blood, microglia, or possibly oligodendroglia.

CHANGES IN AXIS CYLINDERS.—The reactions of the axis cylinder to injury include changes in the neuraxis, alterations at the synapse or end organ, and neuroma formation. By coating the argyrophilic neurofibrillar structure with reduced

Fig. 1180. Fig. 1181.

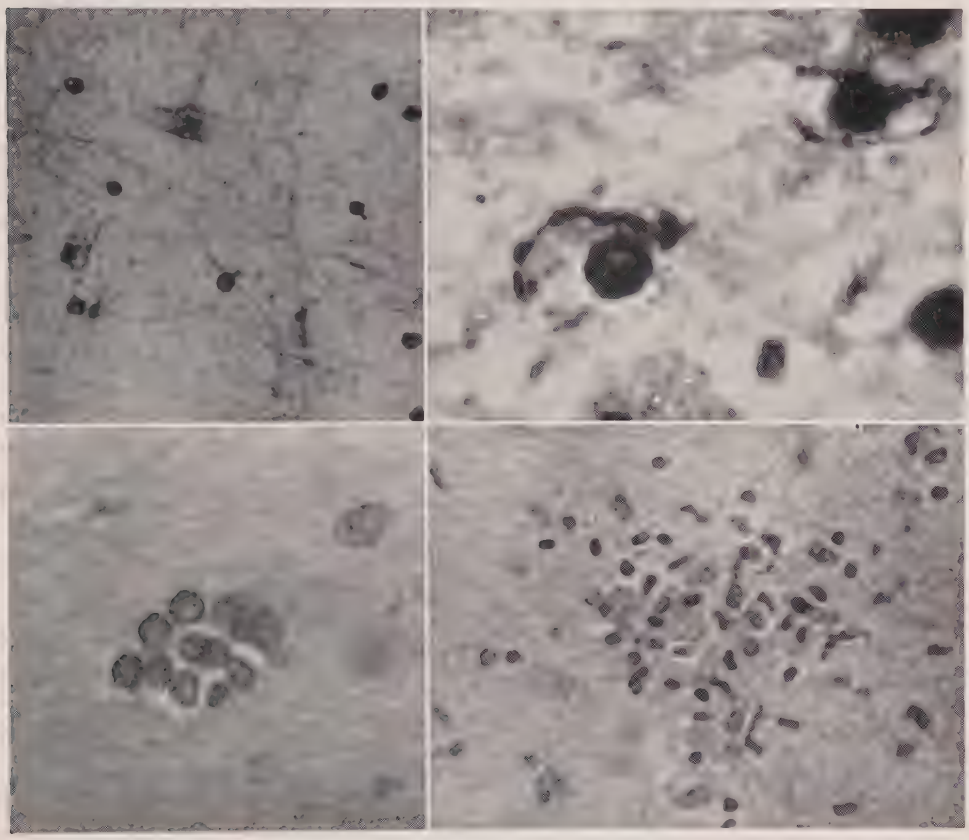


Fig. 1182. Fig. 1183.

Fig. 1180.—Gliosis. This refers to the fibrillar substance produced by the cells and frequently exists without prominent astrocytic proliferation.

Fig. 1181.—Oligodendroglial swelling.

Fig. 1182.—Satellitosis.

Fig. 1183.—Glial node.

Disappearance of nerve cells is accomplished through liquefaction necrosis or neuronophagia. *Liquefaction* occurs as a rapid lysis in the end stage of irreversible reactions. *Neuronophagia* involves reaction of macrophages as well as nerve cells. Phagocytosis of nerve cells is common only in inflammatory diseases and is conspicuous only when the death of the cells is brought about by an intracellular agent. It is the characteristic lesion

silver salts, the morphology of the axis cylinder and its terminal boutons is seen to vary under pathologic influence. The neuraxis may swell in irregular nodules or fragment and become granular. The synaptic change may be a loss of structure, or accentuation by beading and reduplication of terminal bulbs[11] (Fig. 1188). The diffuse encephalomyelitides induce the most profound synaptic changes. In peripheral nerves the end

organs undergo dissolution following severe damage to the nerve.[12] Neuroma formation occurs as a regrowth reaction to traumatic interruption of nerve fibers. The neuroma is a tangle of regrowing neurofibrils, each spearheaded by a bulbous expansion, the growth cone. Neuromas may develop along the trunk of a nerve at a point of trauma or at the extremity of an amputated stump. The microscopic appearance is complicated by growth of fibrous tissue or by sheath cell proliferation. In a traumatic neuroma of some duration, these supporting elements remain and the argyrophilic substance of the neuraxes disappears (see Tumors of the Nervous System, page 1306).

MYELIN DEGENERATION.—The loss of myelin substance (demyelination) is a prominent pathologic change in both central and peripheral nervous systems. In considering demyelination as an index of injury it is essential to remember that most fibers normally possess no myelin. This fatty substance, a complex of at least four lipoids, is deposited around fibers of both central and peripheral neuraxes. Injury to the cell body or axis cylinder causes a degeneration of the myelin, or its dissolution may appear spontaneously without apparent nerve injury. Demonstration of the demyelination depends principally upon the use of three staining procedures. The *Weigert* technique (Fig. 1189) stains normal myelin blue or black.

Fig. 1184. Fig. 1185. Fig. 1187.

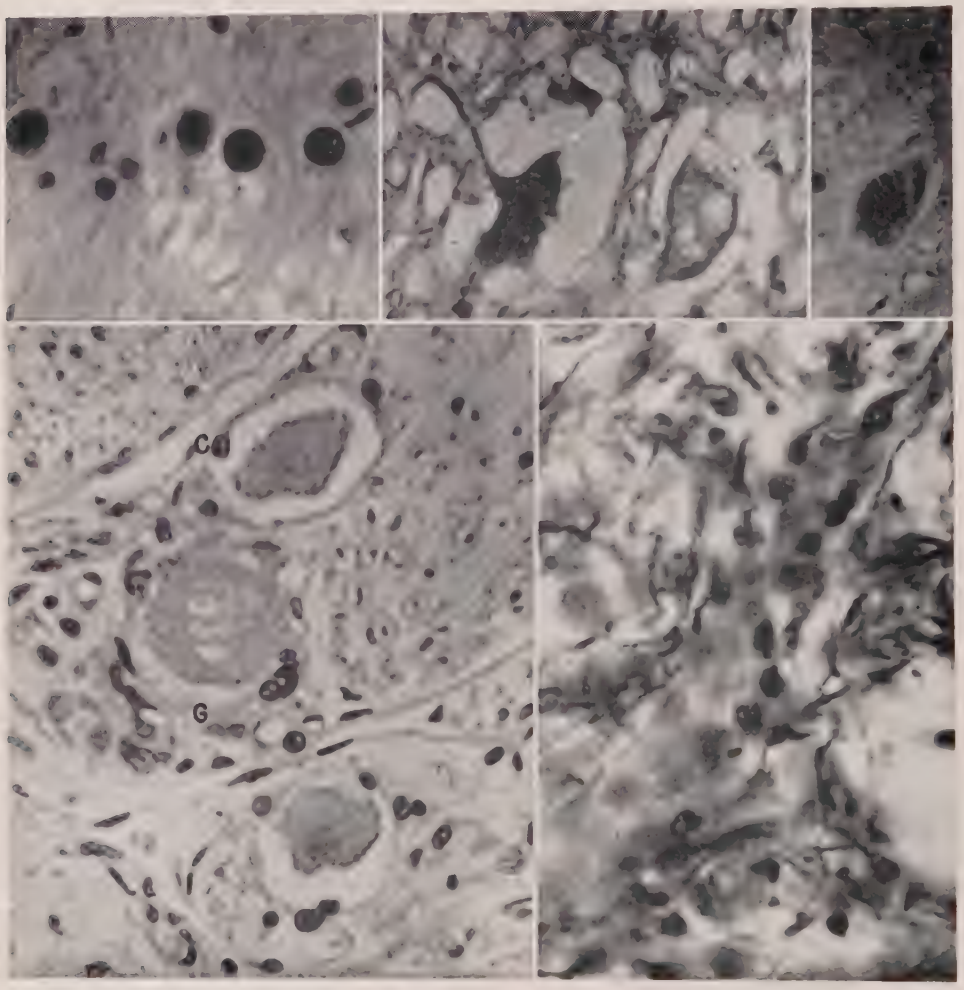


Fig. 1186. Fig. 1188.

Fig. 1184.—Corpora amylacea.
Fig. 1185.—Nerve cell shrinkage and vacuolation with sclerosis of the ground substance.
Fig. 1186.—Vacuolation and chromatolysis of autonomic ganglion cells, *g; c,* capsule cell.
Fig. 1187.—Pigment degeneration in a nerve cell.
Fig. 1188.—Swelling and granulation in central nerve endings (boutons) adjacent to a dendritic root.

Demyelinated areas do not stain and hence are identifiable by contrast. This procedure is applicable to normal tissue and to old degenerations. The *Marchi* technique (Fig. 1190) stains the altered lipoids of degenerating myelin directly, so that this procedure demonstrates active degeneration. *Osmic acid* will blacken normal myelin. Used principally in peripheral nerve study, the failure to take osmic acid implies loss or absence of myelin (compare Figs. 1189 and 1190, 1191 and 1192).

The demyelinating process and accompanying changes occurring secondary to trauma or interruption of peripheral nerves is called **Wallerian degeneration.** This proceeds in both distal and proximal directions from the point of injury. Proximally, the observable alterations in the myelin are generally stopped at the next node of Ranvier. The node probably plays no role in this arrest since the same limitation of retrograde change is seen in the central nervous system. Proliferation of neurofibrils proximal to the injury occurs within a few hours. Distally, the axis cylinders become granular and fragment, and the myelin undergoes dissolution and forms fat droplets. The products of degeneration are removed mainly by macrophages in a few weeks. Simultaneously, regenerative changes occur. The sheath cells (neurolemma, Schwann) proliferate, enlarge, and migrate from both proximal and distal stumps into the defect, bridging it and providing cytoplasmic channels for the regrowing neurofibrils from the proximal stump. The endoneurial connective tissue persists, reinforcing the neurolemmal cells. Regrowth may be inhibited by scar tissue and by poor apposition of the stumps. Regrowing neurofibrils will progress at the rate of 0.25 mm. per day through the scar and 3 to 4 mm. per day through the peripheral stump.[13] Slowly, certain of the regrown fibrils enlarge within the Schwann cells and accumulate a myelin sheath. The original status of an individual myelinated peripheral nerve fiber is reestablished in nine to twelve months. The complete restitution of all fibers of a peripheral nerve probably does not occur.[14, 15, 16]

In the central nervous system there is a somewhat different process of demyelination. The sheath cells are represented here by oligodendroglia which lack the remarkable regenerative properties of the former. Central nerve cell processes may be as inherently capable of regrowth as peripheral cells, but only those which possess a neurilemmal sheath are able to be restored. Consequently, functional repair of interrupted central neuraxes does not occur, although abortive neurofibrillar attempts at regrowth are constantly observed.[14, 17, 18, 19] Hence, disruption of nerve tissue with accompanying demyelination in the central nervous system is an irreversible reaction. In the area of injury or softening where a large amount of myelin is broken down, the degenerating fatty products are removed by macrophages (microglia). The degeneration of myelin progresses distally from the point of injury. The myelin appears in droplet form and acquires staining reactions which imply chemical alteration. The droplets will, however, remain in position for months, or even years, and mark the degenerating tract (Fig. 1190). Proximally (toward the cell body) the process may progress for a short distance but ordinarily it is insignificant.

Fig. 1189.

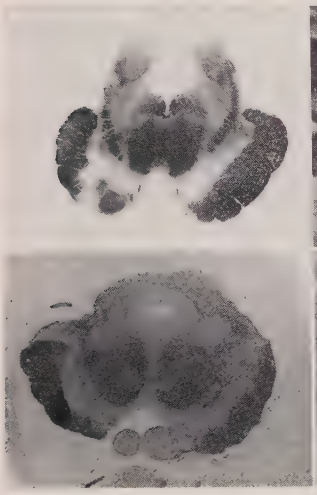
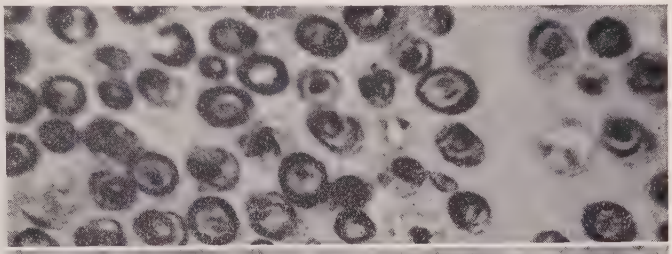


Fig. 1191.



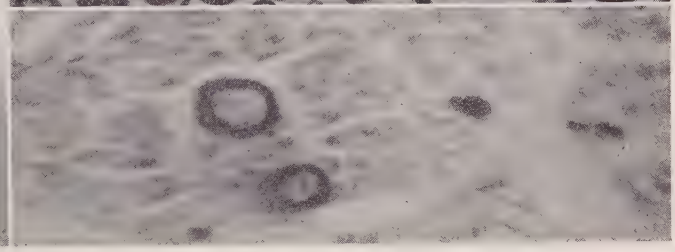


Fig. 1190.

Fig. 1192.

Fig. 1189.—Weigert section of midbrain showing demyelinated tract in the cerebral peduncle.
Fig. 1190.—Marchi section at a slightly higher level than Fig. 1189.
Fig. 1191.—Normal peripheral nerve—myelin stain.
Fig. 1192.—Degenerated peripheral nerve—myelin stain.

A second type of demyelination occurs in the central nervous system without identifiable cause (see Demyelinating Diseases, page 1319 and Fig. 1228).

6. **Sheath and Capsule Cells.**—A membranous covering for peripheral nerve cell bodies and neuraxes is provided by capsule and sheath cells. Microscopically, their nuclei appear as rounded forms satellite to ganglion cells and as elongate structures along peripheral nerves (Fig. 1186). The sheath cells form cylindrical tubes threaded by a neuraxis and separated from it by a concentric sheath of myelin. When myelin is absent the neuraxis is covered intimately by a thin-walled sheath cell. Applied to the outside of Schwann sheaths are the collagenous elements of the endoneurium. The reactions to which sheath and capsule cells are subject are, principally, *hypertrophy* and *proliferation* and these occur prominently in repair of peripheral nerves.

cells are occasionally encountered buried in the dura. These are *arachnoidal rests. Melanoblasts* can be identified in the basal meninges of the brain and in the fissures of the cord. The common reactions of the meninges to injury include *production of macrophages,* and *false dura formation.* The macrophages are derived from meningothelium or fixed histiocytes, or both, and appear in great number in inflammatory conditions (Fig. 1193). False dura formation amounts to a rapid repair process in which a coagulum forms, later to be invaded by fibroblastic cells. This occurs when dural continuity is interrupted in walling off hemorrhage.

8. **Vasculature and Related Structures.**—Intimal, medial, and adventitial changes in cerebral vessels are similar to those occurring elsewhere. There are, however, several peculiarities in cerebral vasculature which play prominent roles in reactive phenomena. Vessels less than 70 microns in diameter contain little or no

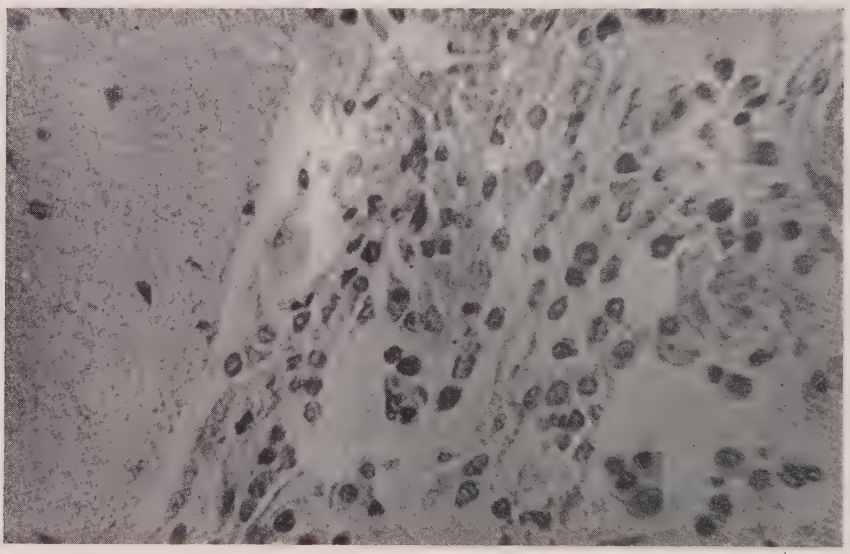


Fig. 1193.—Meningothelial reaction with free-lying meningothelial cells in the leptomeningeal spaces.

7. **Meninges.**—The coverings of the central nervous system include the dura (pachymeninx) and the pia-arachnoid (leptomeninx). The dura is adherent to the cranial persiosteum (external layer of dura) but is separated widely from the periosteum of the vertebral canal. The pia follows the surface of the brain closely and is separated from the arachnoid, which is in apposition with the dura, by the subarachnoid space. The space contains cerebrospinal fluid and is bridged by a spongy network of filaments, the *arachnoid trabeculae.* The principal histologic element of all membranes is collagenous tissue. Elastic fibers appear in the pia-arachnoid and in the innermost layer of the dura. Flattened mesothelial cells *(meningothelium)* line the subarachnoid and subdural spaces and cover the arachnoid trabeculae. In addition to the lining cells, fibroblasts and fixed histiocytes are identifiable in the membranes. Nests of epithelium-like

muscle in the media after 40 years of age.[20] In passing through the subarachnoid space the vessels acquire a meningothelial sheath, and in penetrating to an intramedullary position, carry a second outer sheath derived from the pia lining. These concentric wrappings establish a *perivascular space* (of Virchow-Robin) which is continuous with perineuronal and interstitial spaces in the central nervous system. This space is the morphological basis for the reaction of *perivascular infiltration or cuffing* (Fig. 1194). Drainage from the interstitial spaces of the medullary substance passes through the Virchow-Robin channels and in so doing may load the space with inflammatory cells or products of degeneration. In addition, exudate reaches the perivascular space through the vessel wall. Vascular adventitial elements provide the parent tissue which reacts to form an abscess wall in response to invasion by certain bacteria.[21] Cere-

bral vessels are also peculiarly susceptible to pseudocalcification identified by blue-staining amorphous droplets of unidentified nature appearing in the vessel walls (Fig. 1198).

widely throughout the nervous system in postnatal life. Normally, they appear to be at rest (fixed), in which form only the nucleus is evident in ordinary sections (Fig. 1177). Compared

Fig. 1194.—Perivascular infiltration. (See also Fig. 38, page 38.)

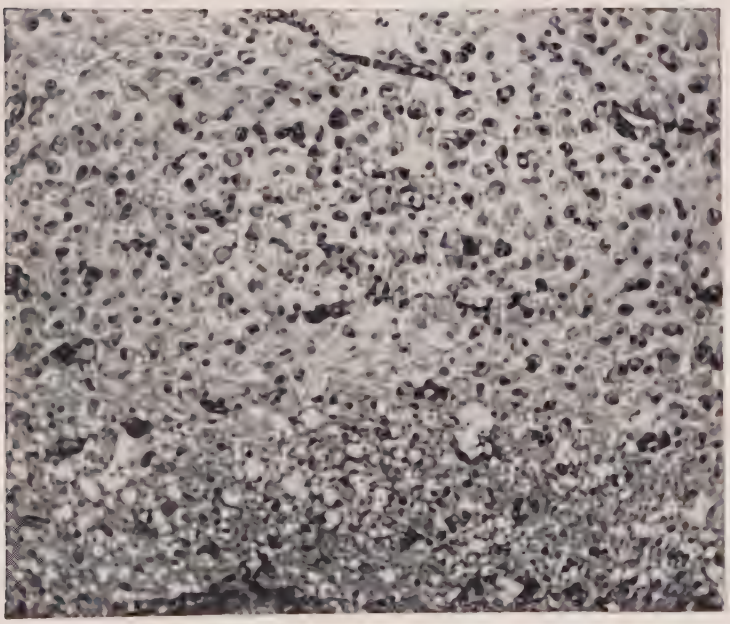


Fig. 1195.—Fat-granule cell reaction in cerebral infarct. (From Anderson, Synopsis of Pathology.)

9. **Microglia (Mesoglia).**—Microglial cells are believed to be mesodermal elements derived from perivascular tissues and are distributed

to the neuroglia, the microglial nucleus is small, very compact, and may be irregular in shape (round, elongate, or curved). The scanty cyto-

plasm and thin branching processes require special staining to be demonstrated. These cells respond to the products of myelin degeneration. In this *fat-granule cell* reaction, the cell processes are pulled in and the nucleus elongates, becoming bipolar. This *rod cell* migrates to the site of injury, where the nucleus becomes rounded and lighter staining. As fat products are engulfed, the cytoplasm becomes globular and the nucleus eccentric (Fig. 1195). These fat-laden macrophages (fat-granule cells, compound granular corpuscles) often migrate into the perivascular spaces. They are the characteristic cells in an area of cerebral softening. Rod cells are conspicuous in the cortex in paresis.

10. **The Cerebrospinal Fluid.**—The cerebrospinal fluid forms a circulatory system peculiar to nervous tissue, perhaps taking the place of the absent lymphatics. The fluid is formed from blood by the choroid plexus of the cerebral ventricles, probably by a process of dialysis, though there may be an active secretory mechanism as well. The cerebrospinal fluid reflects by its changes many important disease processes. Normally, the volume is about 125 c.c. It is clear, colorless, has a specific gravity of 1.006 to 1.009 and contains fewer than 12 cells (mononuclears) per cubic millimeter after 12 years of age. In infants there may be 20 to 30 cells per cubic millimeter. In disease, there may be color changes due to fresh hemorrhage, or xanthochromia, a yellowish tinge derived probably from hemoglobin and implying stasis following hemorrhage. The cell content may be altered both in number and character, and chemical and serologic changes occur which are valuable aids in diagnosis. The most striking change involving cerebrospinal fluid is the mechanical effect resulting from obstruction to its flow (see page 1227). Unusual accumulation of interstitial fluid in the nervous tissues is, as elsewhere, edema which presents a characteristic microscopic appearance (Fig. 1198).

Histogenesis of Nervous and Allied Tissues

The interrelationships of the various tissues contributing to the nervous system and its supporting structures are displayed in the schema, Table XXI. Early in embryonic life five fundamental tissues differentiate to provide the stem cells for the adult structure. These include: (1) notochord, (2) medulloepithelium, (3) neural crest tissue, (4) mesoderm, and (5) neuroskeletal intertissue.

1. *Notochordal tissue* remains as chordal rests in the positions described on page 1292. The cells apparently do not differentiate further.

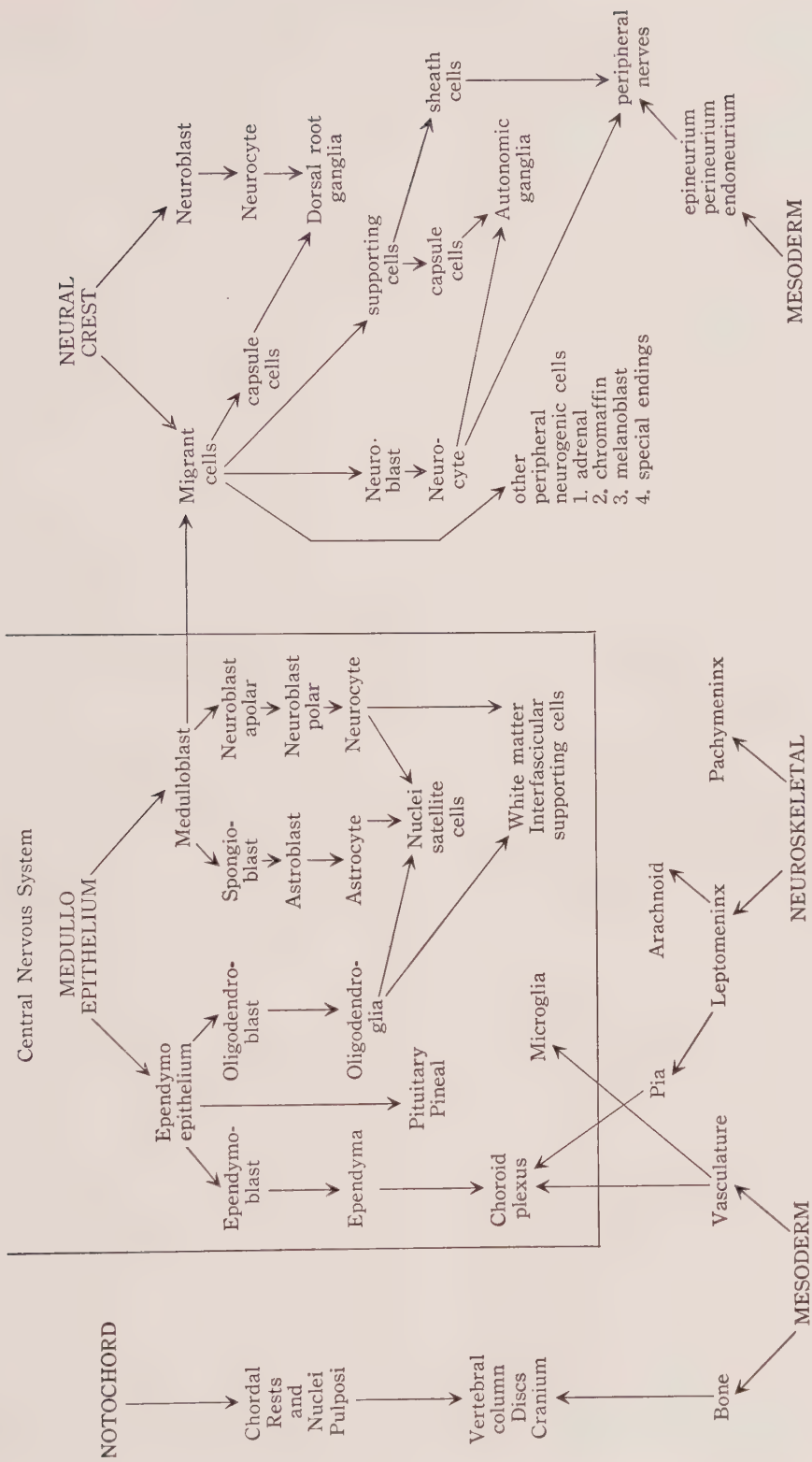
2. *Medulloepithelium* arises as an infolding of the dorsal ectoderm and gives rise to cells providing both neurofunctional and supporting structures. Posterior pituitary and pineal parenchyma arise, probably, as direct differentials of this primitive tissue. Those cells remaining as lining elements for the medullary tube are designated *ependymoepithelium* and those migrating into the medullary substance *medulloblasts*. *Spongioblasts* retain fibrillar attachments to the limiting membranes. These fibrillar spongioblasts and processes eventually are retracted and further modified in progressing into the astrocyte series. The medulloblasts are presumed to occur as process-free migrant cells.[22] According to Kernohan and Kernohan[23] (see schema) the *ependymoepithelium* differentiates in two directions leading eventually to the formation of (a) mature ependymal cells which are retained as ventricular and choroid plexus lining cells and (b) mature oligodendroglia which are intramedullary supporting structures. The latter take up positions as satellites to nerve cell bodies and as interfascicular supporting elements along the axis cylinders. The *medulloblasts* are presumed to differentiate within the medullary substance to (a) *spongioblasts* and (b) *neuroblasts*. With the advent of vasculature the spongioblasts contribute the astroblasts by attaching to vessel walls by means of sucker foot processes. These elements mature into astrocytes which are the dominant supporting elements in the gray matter. The neuroblasts, by maturation consisting of enlarging and elaborating processes, become mature neurocytes and aggregate in nuclear masses in the central nervous system. The migrant neuroblast (medulloblast equivalent) appears to spearhead the outgrowth along peripheral nerve paths. This takes place in two ways: (1) clusters of neuroblasts send processes out the nerve buds to establish the mature final-common-path cells; (2) migrant whole-cells move with the growing nerve bud which are thought to act as the stem cells for (a) peripheral neurocytes (ganglion cells), (b) sheath and capsule cells for peripheral nerves and ganglia, and (c) for special peripheral neurogenic tissues including adrenal, chromaffin, melanoblastic, and specialized nerve-ending structures. (See Table XXI.)

3. *Neural crests* arise either as buds from dorsal ectoderm, as extensions of medulloepithelium, or as derivatives of both. In general, neural crest tissue is thought capable of differentiating into both ganglion cells and peripheral supporting elements. In this capacity neural crest cells may contribute to the migrant elements described above as derivatives of the central medulloblast.[24] There is general agreement that dorsal root ganglion cells and their capsules are derived locally from neural crest stem cells.

4. *Mesoderm* is regarded as the source of the fibrous wrapping of peripheral nerves exclusive of the sheath and capsule cells (endoneurium, perineurium, epineurium). The vasculature of the nervous system and the bone contributing to the formation of the vertebral column and cranium are also mesodermal in origin. In addition, the microglial elements stem from perivascular structures and migrate into the nervous system postnatally providing a store of resting cells with the potentiality of macrophage formation.[25] They arise in special regions as "fountains" of migrant cells and become widely distributed. The perivascular connective tissue provides reactive elements which play a prominent role in limiting bacterial infections.

5. *Neuroskeletal intertissue* refers to the embryonic tissue lying between the medullary tube and its bony covering. From it arise the meninges. Because of the complex histology of the tumors arising from the meninges the histogenesis of the tissue is of much interest. Harvey and Burr[26] describe it as ectodermal in origin,

TABLE XXI



The schema of histogenesis is based on Kernohan's concept of the interrelationships of the gliomata. The cells differentiating in, and remaining in, the central nervous system are blocked off by the heavy broken line. Note particularly the migrant cell which leaves the medullary tube and serves as a stem cell for the various peripheral neurogenic tissues.

and this conception lends itself well to the general epithelial nature of the tumors (see below). The neuroskeletal intertissue differentiates into an outer layer, the future dura, and an inner layer, the leptomeninx. The latter, with the advent of cerebrospinal fluid, is laminated into an inner *pia* and outer *arachnoid*.[27] These two lamina are connected by *arachnoid trabeculae* which bridge the subarachnoid space forming a spongy network. The inner surface of the dura, the outer surface of the pia, and all intervening spaces (subdural, subarachnoid) are lined with meningothelial cells.

Histologic Organization of the Nervous System

The establishment in normal order of an histology as complex as that of the nervous system might be expected to be a surprising event.

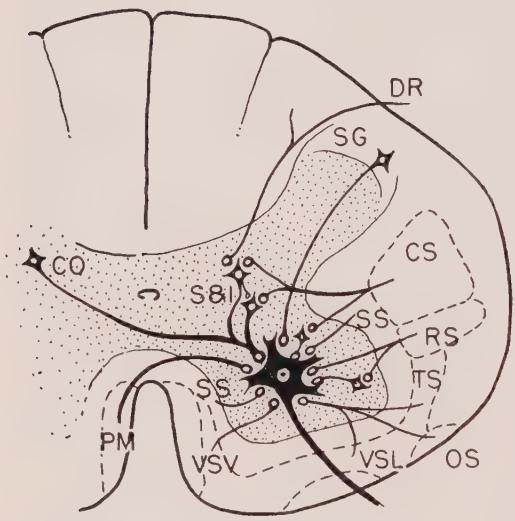


Fig. 1196.—Diagram of the final-common-path-cell complex in the spinal cord. Known tracts bearing directly on this cell include: spinospinalis, *SS;* rubrospinal, *RS;* tectospinal, *TS;* olivospinal, *OS;* vestibulospinal, *VSL* and *VSV;* commissural, *CO;* premotor, *PM;* sensory and internuncial pools in the central gray matter, *S & I;* possibly substantia gelatinosa, *SG*. Dorsal root fibers, *DR*, and corticospinal fibers, *CS*, probably transmit their impulses to the final-common-path through internuncial pools.

Actually the reverse is true, and faulty histogenesis (see Hamartial Diseases, below) is fortunately rather rare. Organization depends presumably on (1) an inherent capability of the cell to differentiate to predestined adult stature and (2) on the influence of other tissues in directing the course of development (organizers). The histologic organization within the nervous system exhibits an evident functional alignment. Cells subserving special functions aggregate in columns and their axones course in common fascicles (Fig. 1159). Cerebral localization of areas by function is well established, and, going farther, the cells in each of these areas laminate in anatomico-physiologic separateness. The mechanisms involved in this organization are being gradually clarified through study of physiologic embryology.[28-32] For application to the present study it is essential to recall (1) that the nervous system is fundamentally organized as a receptor-integrator-effector complex and that (2) each of these components retains both anatomic and physiologic separateness. Reduced to diagrammatic simplicity the nervous system may then be represented by afferent components bearing on an integrator complex which in turn bears on the effector. As an illustration (Fig. 1196) the final-common-path cell is ultimately brought into relationship with numerous known, and probably many unknown, integrators, and these in turn with afferents and other complex chains of internuncial elements. It is evident that the contiguous, rather than continuous, disposition of the elements lends itself to erasure of parts without greatly affecting the morphologic complex. If the descending paths are removed, the internuncial pools and the final common path remain intact. Similarly, if the internuncial pools, or parts of them, or the final path cells are removed, the other elements need not be affected morphologically. In the same way, it is presumed that remaining elements retain their function. Pathologically, any of the organizational components, or even parts of each component, may be affected separately or in combination. These involvements are referred to as abiotrophies and for descriptive convenience are grouped as dysplasias (see page 1275), productive malformations (hamartias), neoplastic diseases, and degenerative malformations.

Hamartial Diseases of the Nervous System

Hamartial diseases are those identified by embryonic tissue defects supposedly representing deficient organizing influence. While the basic mechanisms are evasive, the terminal maldevelopment or misuse of tissue is apparent and characterizes the disease. These faults in histogenesis or organization are distinguished here from the grosser malformations reflected in absence of parts, faulty closures, embryonic infarctions, and obstructions (see page 1275). Likewise, in view of the productive nature of the lesions, these defects are separable from degenerative diseases (page 1313) in which the basic directive deficiency is similar but is reflected in collapse of previously sustained parts. Since hamartias represent embryonic tissue defects which may form tumefactions, they are less easily dissociated from the category of neoplasm. Their behavior is, however, distinctive and they lack the property of limitless growth. Most important among hamartial diseases are heterotopias, syringomyelia and syringobulbia, tuberous sclerosis, vascular malformation, and multiple neurofibromatosis. It is apparent from the names that the dominance in malformation may appear in any of several fundamental tissues.

Heterotopia.—Heterotopias are normally developing histologic elements in abnormal positions and are regarded as stemming from defective or arrested migration. Not infrequently, clusters of nerve cells are encountered

in the white substance of the brain. Ganglion cells appear frequently along nerve fibers, particularly in the autonomic chains. Fragments of ependymal and ependymal-lined tubular structures often appear in the brain substance separated from the ventricular system (Fig. 1176). These are common at points where the ependymal lining is folded back on itself. Residuals of the external granular layer in the cerebellum are not uncommon and may be related to the occurrence of medulloblastomas in children.[33] Arachnoidal rests are regarded as displaced meningeothelial nests within dura. These, too, may be the anlage of neoplastic transformation. Heterotopic glial tissue in the nose has been described.[34]

Syringomyelia and Syringobulbia.—With the expansion of the spinal medullary tube to adult proportions the region of the central canal and dorsal median septum exhibit the least extensive differentiation. It is presumed that these locations are most susceptible to malformation particularly of axial or midline type. A gliosis of ependymal or glial cell origin represents the early phase of the lesion eventuating in syringomyelia. Progression is slow and irregular, beginning, usually, in the cervical segments and spreading longitudinally. The process may begin in dorsal median septum or incorporate the central canal.[35, 36] In any transverse level the gliosing process may extend laterally, involving both white and gray matter. With involvement of vasculature, cystic degeneration and liquefaction occur establishing the fluid-containing cysts (Fig. 1197). A true lining membrane is seldom demonstrable microscopically. Damage to nervous structure is wrought both by pressure and encroachment. The classical disorder, brought about by destruction of the white commissural bands in the cord, is loss of the senses of pain and temperature with sparing of those of touch and pressure through the levels involved. Other axial malformations (spinal muscle defects, scoliosis) often occur with syringomyelia.

Fig. 1197.—Syringomyelia.

Tuberous Sclerosis.—Tuberous sclerosis is a disease of many parts ordinarily dominated by involvement of the central nervous system. Often associated are hamartomas of the kidney and adenoma sebaceum of the skin, and less frequently tumors of heart, lens, and skin.[37, 38] Clinically, there is mental deficiency, usually epileptiform seizures, and often a familial history. The symptoms appear a few months to several years after birth and exhibit a slow progression. There is great variability in the appearance of the brains at autopsy. The characteristic gross change is a nodular firm whitish expansion of a gyrus, or similar multiple lesions. Similar nodular lesions, rubbery in consistency on gross section, may project into the ventricles. Microscopically the lesions consist principally of massive glial scar tissue. Abnormally large glial and nerve cells, often of bizarre pattern, occur both in the definitive lesions and in the outlying brain substance. There may be extensive demyelination from involvement of the gyri by the tumefactions.

Vascular Malformation.—Vascular malformations involving the nervous system are many and varied. *Telangiectasis* refers to focal vascular distention most common in the brain stem. The lesions are similar to telangiectasis of mucous membrane or skin and may be multiple (Osler's disease). Ordinarily, single lesions are not recognized clinically and are incidental observations at autopsy. Microscopically there are well-formed small vessels separated by glial interstitial tissue.[39, 40] Vascular cephalic nevi associated with calcified and ferruginized deposits in cerebral and meningeal vasculature constitute *Sturge-Weber-Dimitri's* disease. The mineralized deposits are visible roentgenographically as sinuous shadows. Concurrent vascular malformations in the oral submucosa, eye, nose, and throat also are present.[41]

Angiomas (hamartomas) are defective vascular complexes which vary greatly in their gross disposition and clinical behavior. They are

space-occupying lesions, probably by expansion of the vessel walls rather than by new growth. The defective vessels may be venous or arterial, and Turner and Kernohan[40] describe arterio-venous types. Grossly, the lesions vary from aneurysmal dilatations and simple varices to massive tangles of tortuous vessels which may occupy a large part of a cerebral hemisphere. Microscopically the vascular walls are poorly formed and in an intramedullary position are separated by glial stroma. In tumors of long standing, there may be thickening of the elastica and calcium or pseudocalciform deposition (Figs. 1198, 1199). Angiomatosis of the retina (von Hippel's disease) in combination with visceral and cerebellar angiomata comprise the complex known as Lindau's disease (see vascular neoplasms, page 547).

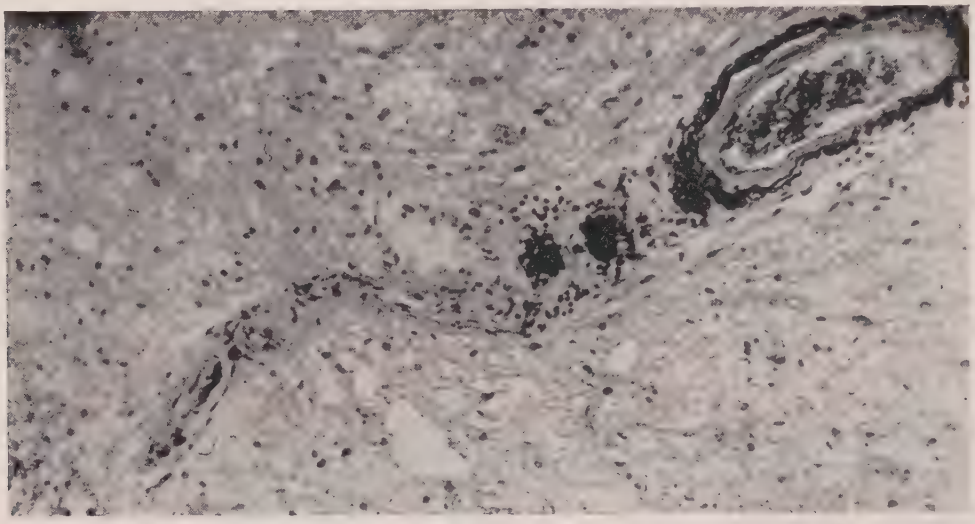


Fig. 1198.—Mineralization of degenerating vascular wall. The deposit simulates calcification but does not stain specifically—hence, "pseudocalcification." The surrounding disruption of tissue is characteristic of edema with interstitial fluid pools and vacuoles.

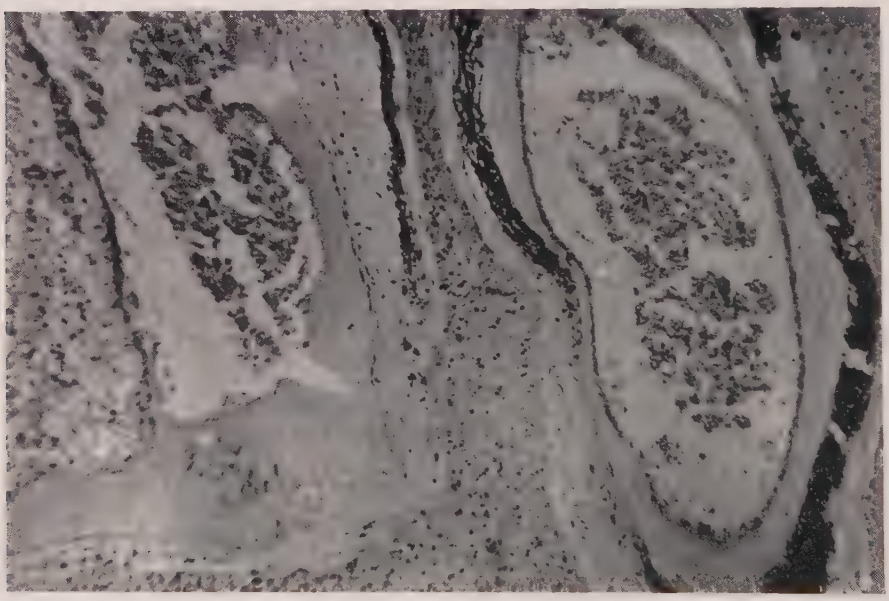


Fig. 1199.—Calcific deposit in the thickened wall of angiomatous vessels. Note intervening nervous tissue between vessels.

Multiple Neurofibromatosis (von Recklinghausen's Disease).—Multiple nodular pigmented

peripheral nerve tumors often in segmental disposition and associated with nevi and other malformations represent another type of disseminated hamartia[37] (see peripheral nerve tumors, page 1302).

Tumors of the Nervous System

Tumors of the nervous system have long been regarded as singularly unpleasant and are frequently described as invariably malignant clinically, regardless of their biologic character. This distinction between clinical and histologic malignancy was unimportant, except academically, until the tumors were made accessible through neurosurgical procedures in the last few decades. At present, some 70 per cent of patients presenting space-occupying masses of the central nervous system can expect relief through neurosurgical or radiological therapy—a record comparing favorably with that of management of tumors in any other organ system. This alone will justify attempts at classifying brain tumors and estimating their malignancy and dictates the necessity of improving and simplifying the categories in the interest of usefulness. Of the many groups of tumors in, and allied to, the nervous system those which are primary neurogenic in origin, and which occur within the central nervous system, have been the most troublesome to classify. Tumors arising in peripheral nervous structures, in membranes, bone, vasculature, glands, embryonic vestiges, and notochordal tissue within and near the central nervous system can be arranged in satisfactory order on which there is general agreement (see groups I, and III to VIII below). The primary intramedullary neurogenic tumors (group II, below), however, remain less well understood. Consequently, the proper classification of these tumors awaits clarification of the histogenesis of the elements involved. Bailey and Cushing[22] contributed enormously to the understanding of these tumors and established the principal features of their classification. The Kernohans' modification[23] is incorporated in the comprehensive histogenetic pattern outlined in Table XXI, page 1287.

Special mention is required in connection with descriptive terms for the primary intramedullary neurogenic tumors outlined as group II in the classification below. The "classical" term for each tumor in the subgroups is listed as the main designation. The grade of malignancy for the astrocytoma[42] and ependymoma[43] groups provides a simplified means of designating a tumor in each of the two categories. This grading system is apparently less applicable to the oligodendroglial group[44] and probably to the nerve cell tumor group.[42-45] The standard for grading is that commonly employed for malignancies in other tissue systems[46]: thus, astrocytoma, grade 1, grade 2, etc. While there is some objection to using the same term for a benign and a malignant tumor, the system offers simplicity and prognostic significance, features of real value in this confused area of neuropathology.

Classification of Tumors of the Nervous System

I. Chordoma
II. Primary intramedullary neurogenic tumors
  A. Gliomas (supporting cell tumors)
    1. Ependymoma group (Ependymoma, grades 1 to 4)
      a. Colloid cyst
      b. Papilloma choroideum
      c. Myxopapillary ependymoma
      d. Epithelial ependymoma
      e. Cellular ependymoma
      f. Ependymoblastoma
      g. Medulloepithelioma
    2. Oligodendroglioma group
      a. Oligodendroglioma
      b. Oligodendroblastoma
    3. Astrocytoma group (Astrocytoma, grades 1 to 4)
      a. Pilocytic astrocytoma
        (1) Localized
        (2) Diffuse
      b. Gemistocytic astrocytoma
      c. Malignant astrocytoma
      d. Astroblastoma
      e. Spongioblastoma
      f. Glioblastoma multiforme
    4. Pinealoma
    5. Medulloblastoma
  B. Nerve cell tumors
    1. Neurocytoma
    2. Neuroblastoma
    3. Retinoblastoma
III. Primary extramedullary neurogenic tumors
  A. Supporting cell tumors
    1. Neurofibroma
    2. Perineuronal fibroblastoma
    3. Neurinoma (Schwannoma)
    4. Acoustic neurinoma
    5. Multiple neurofibromatosis (von Recklinghausen)
    6. Neurofibrosarcoma (neurogenic sarcoma)

B. Tumors of peripheral nerve cells and their processes
1. Ganglioneuroma
2. Traumatic neuroma
3. Plexiform neuroma
4. Myelinic neuroma
5. Neuroblastoma (including sympathicoblastoma)

C. Miscellaneous peripheral neurogenic tumors
1. Melanoma
2. Carcinoid
3. Pheochromocytoma (paraganglioma, chromaffinoma)
4. Carotid body tumor

IV. Meningiomas
A. Meningothelial meningioma
B. Fibroblastic meningioma
C. Psammoma
D. Metaplastic meningioma
1. Osteoblastic
2. Chondromatous
3. Lipomatous

E. Malignant meningioma
1. Fibrosarcoma
2. Diffuse sarcomatosis
3. Meningiomatosis
4. Gliomatosis
5. Melanoma

V. Tumors of cerebral vascular and perivascular structures
A. Tumors of blood vessels
1. Telangiectasia
2. Angioma
3. Hemangioma
a. Capillary
b. Cavernous
4. Hemangioendothelioma
5. Hemangioblastoma
6. Hemangiosarcoma

B. Mesodermal supporting tissue tumors
1. Perithelioma
2. Perivascular (perithelial) sarcoma
3. Fibrosarcoma
4. Microglioblastoma
5. Reticulum cell sarcoma
6. Lymphoblastoma

VI. Mixed tumors
A. Epidermoid cyst (cholesteatoma, pearly tumor)
B. Dermoid cyst
C. Teratoma
D. Craniopharyngioma
1. Rathke pouch cyst
2. Adamantinoma

VII. Hypophyseal tumors
A. Adenoma
1. Chromophobe
2. Acidophile
3. Basophile

B. Infundibuloma

VIII. Metastatic tumors

Statistical data regarding incidence, age of occurrence, common distribution, and general statement of malignancy and radiosensitivity of the more common tumors are presented in Table XXII. These data are summarized principally from the statements of Cushing,[47] Adson,[48] Baker,[49] Walshe,[50] and Dyke and Davidoff.[51]

The general statement of obscure etiology applies to tumors of the nervous system as well as to tumors of other organ systems (see page 428). Brain tumors are not infrequently related in their clinical appearance to trauma. There is no evidence, however, that a causal relationship exists. The tendency of many tumors to be announced by a bleeding episode may account for the sudden onset often associated with trauma however trivial. Tumors of the central nervous system bring about damage primarily by space occupation. With rare exceptions the tumors do not metastasize.

I. Chordoma. Neoplasia of chordal rest tissue is a relatively rare occurrence. The commonest sites are basisphenoid and sacrococcygeal (88 per cent, Horwitz[52]). Rarely, the tumors are intraspinal[53] and, of these, most are extradural. Ordinarily, these tumors are extraspinal in position and, according to Horwitz, have their origin in vertebral, rather than disc, vestiges. Grossly, the tumor is expansive and has a tendency to invade or incorporate bone. The consistency is soft with a mucinous appearance. Histologically, there is great variability with epithelioid to sarcomatoid general architecture. The characteristic cell is the large vacuolated or physaliferous cell which dominates the picture in the usual tumor (Fig. 1200). Fletcher et al.[54] list the specific characteristics as follows: (1) formation of intra- and extracellular mucus, (2) physaliferous cells, (3) lobular arrangement of cells, (4) vacuolation of nuclei, (5) resemblance to nucleus pulposus. The usual criteria of anaplasia (hyperchromatism, mitotic figures, bizarre nuclear patterns, invasiveness) indicate rapid growth and high malignancy.[55] However, for the most part (85 per cent), chordomas grow slowly, but recurrence is the rule due to inaccessibility.

II. Primary Intramedullary Neurogenic Tumors.

A. Gliomas.

1. *Ependymoma Group.* Ependymomas are slowly growing tumors derived from the ependymal lining cells of the ventricles and central canal. A close relative of these cells is the secretory epithelium of the choroid plexus, and tumors of this derivation are included with the ependymomas. In addition, certain characteristics of colloid cysts make pos-

TABLE XXII

STATISTICS—INTRACRANIAL TUMORS

(After Cushing,[47] Adson,[48] Baker,[49] Walshe,[50] Dyke and Davidoff[51])

TUMOR	INCIDENCE (%)	COMMON AGE OF OCCURRENCE	COMMON DISTRIBUTION	MALIGNANCY	OPERABILITY	RADIOSENSITIVITY
Chordoma	1	Adult	Clivus, vertebrae	Variable, usually slowly growing	Complete removal seldom possible; recur	Variable
Glioma	44					
Astrocytoma	13	Children and adults	Cerebrum of adults, cerebellar hemisphere of children	Slowly growing	Often can be excised	Possibly slightly sensitive
Glioblastoma multiforme	11	Middle age	Cerebral hemispheres	Extremely malignant	Inoperable	Slight or none
Medulloblastoma	5	Children	Midline of cerebellum	Highly malignant	Inoperable	Highly sensitive transiently
Ependymoma	4	Children and adults	Ventricular spaces, especially 4th, spinal cord	Often slowly growing but malignant by position	Usually inoperable	Probably sensitive
Oligodendroglioma	3	Adults	Cerebral hemispheres	Slowly growing	Often inaccessible and not wholly removable	None
Astroblastoma	2	Adults	Cerebral hemispheres	Malignant	Inoperable	Possibly sensitive
Spongioblastoma	1	Young adults	Optic chiasm, brain stem	Slowly growing	Usually inoperable	Probably sensitive
Others	5					
Neurinoma	10	Middle age	Eighth nerve, cerebellopontine angle	Benign	Good	None
Meningioma	15	Children and adults	Along sagittal sinus, parietal meninges, olfactory groove, sphenoidal ridge, tuberculum sellae	Benign	Good	None
Mesodermal	4					
Vascular	3	Often congenital	Lateral surface of cerebellum, cerebellar hemisphere	Benign	Usually inoperable	Variable
Stromal	1	Adult	Cerebral hemispheres	Malignant	Recur	None
Mixed	5					
Dermoid, epidermoid	1	Young adults	Midline base	Benign	Frequently excisable	None
Craniopharyngioma	4	Children and young adults	Sella turcica, 3rd ventricle	Benign	Usually not removable; drainage only	Probably affected by x-ray
Hypophyseal	16	Children and adults	Hypophysis	Benign	Partial removal	Sensitive
Metastatic	3	Past middle age	Usually multiple	Malignant	Rarely excision yields symptomatic relief	Variable, often transient relief from x-ray
Granuloma	2	Any age	Meninges, base, hemispheres, occipital lobes	Inflammatory	Surgery often excites spread	None

sible the inclusion of these tumors with the ependymoma group (see below). While ependymomas may appear in any of the craniospinal cavities (Fig. 1201), they are most common in the fourth ventricle and along the thoracic cord. They are also described as occurring in the hollow of the sacrum.[23] Not infrequently the tumor mass may be lodged within intramedullary substance as a distinctly demarcated tumor and the lining origin obscured. This is explained by the incorporation of primitive ependymal cells at some distance from the lining membrane in the process of organization of the central canal. Adapted from Kernohan and Kernohan,[23] ependymomas may be classified as follows: (a) Colloid cyst, (b) papilloma choroideum, (c) myxopapillary ependymoma, (d) epithelial ependymoma, (e) cellular ependymoma, (f) ependymoblastoma, (g) medul-

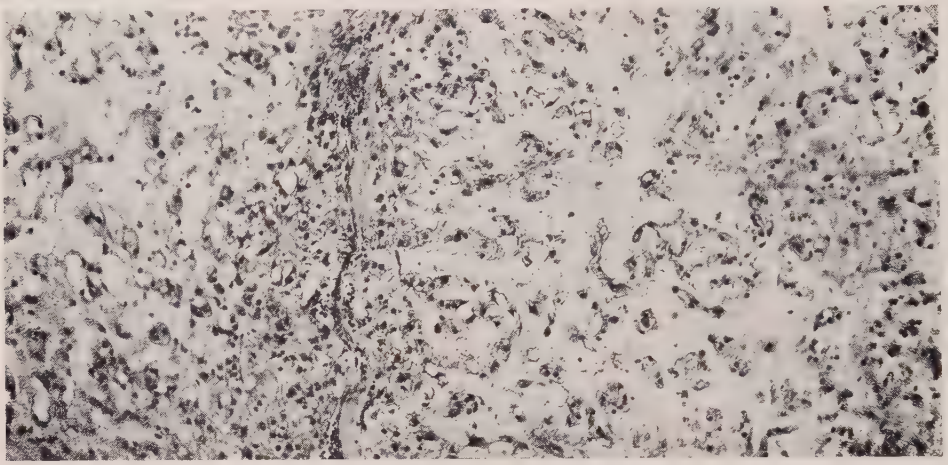


Fig. 1200.—Chordoma. Note the mucoid character of the tumor and the bubblelike physaliferous cells.

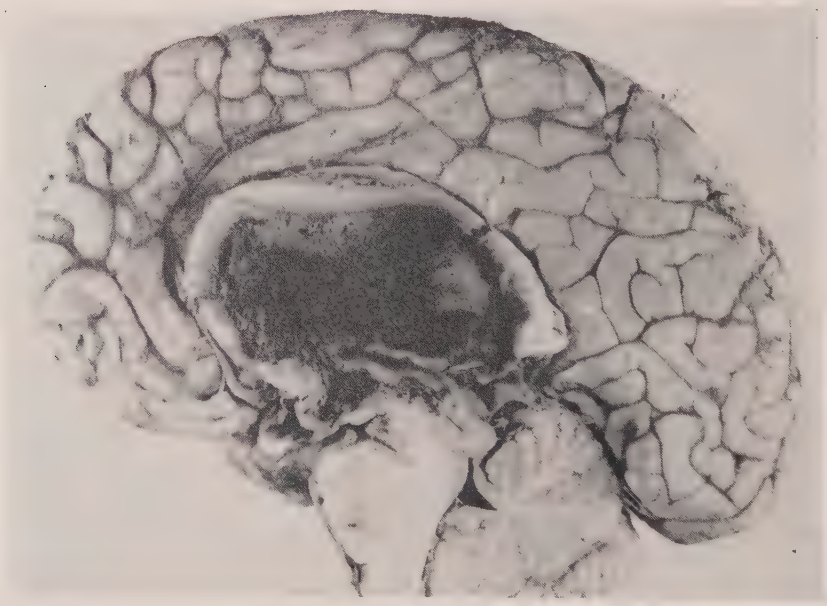


Fig. 1201.—Massive hemorrhagic ependymoma filling the third ventricle and extending into adjacent brain substance.

loepithelioma. More recently, it has been suggested that all ependymomas be classed according to degree of anaplasia and recorded as ependymoma, grades 1 to 4.[43, 45]

The cysts are thin-walled and are filled with gelatinous material which is rubbery in consistency after fixation. The lining consists of cuboidal or low columnar epithelium of the general character of choroid lining cells, including occasional cilia. The question of derivation is reviewed by Zimmerman and German.[56] The possibility that these tumors arise from paraphyseal tissue is suggested by their position of attachment to the velum interpositum behind the fifth ven-

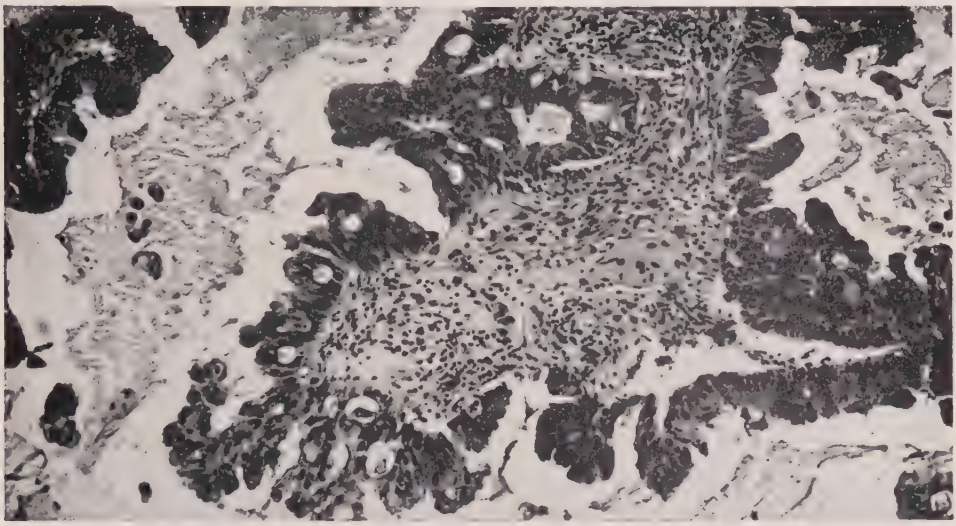


Fig. 1202.—Papilloma choroideum.

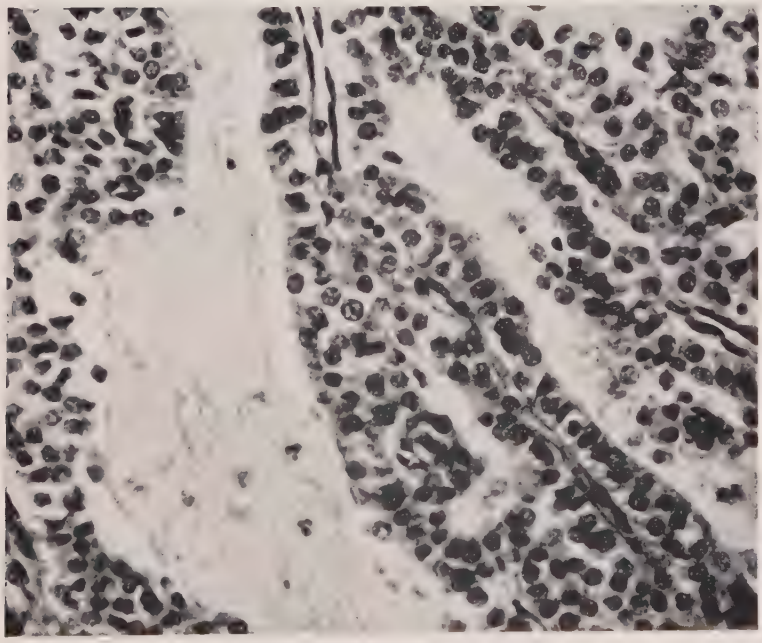


Fig. 1203.—Papillary ependymoma.

a. *Colloid cysts.* Colloid cysts occur in the third ventricle with attachments to choroid plexus or to ependyma near the foramina of Monroe or at the posterior aspect of the fifth ventricle.

tricle. Histologically, the lining cells and vascular supporting tissue suggest choroid plexus. The presence of cilia and the frequent attachment to ependyma are utilized in relating the cysts to ependymal origin. Since choroid plexus papillomas are closely allied to ependymomas, it seems reasonable to include these and colloid cysts in one group.

Colloid cysts are slow growing and are histologically benign. By position in the third ventricle the onset of symptoms may be abrupt due to blockage of the interventricular foramina. Because of the mobility of the tumors the symptom complex includes recurring bouts of ventricular blockage often relieved by change of position.

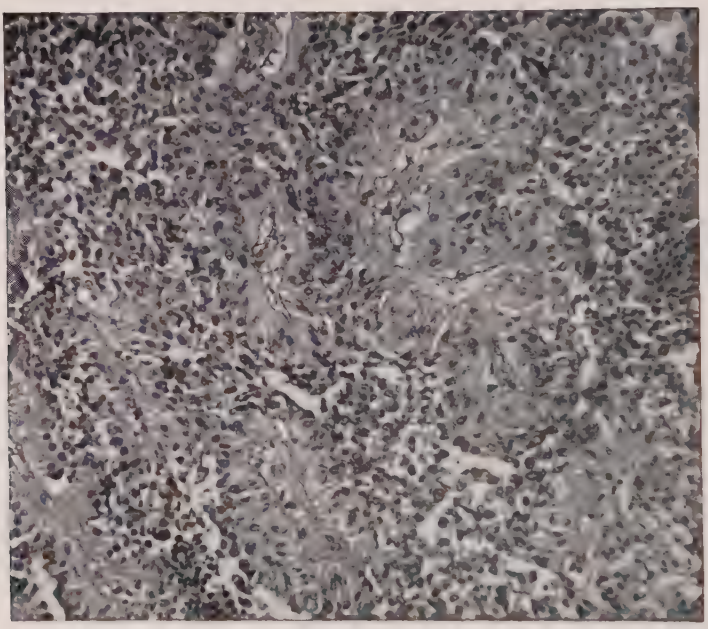


Fig. 1204.—Epithelial ependymoma. (From Anderson, Synopsis of Pathology.)

b. *Papilloma choroideum.* The lining cells of the choroid plexus differentiate from ependyma, and together with the pia-vascular core provide the structural makeup of papilloma choroideum. These tumors occur as papillary masses projecting into the ventricles and attached to choroid plexus or its base at the ependymal junction. The epithelium is tall columnar and is dotted by large mucoid droplets which appear as vacuoles in section. The papillary cores simulate closely those of normal choroid plexus tufts with a highly vascular loose connective tissue (Fig. 1202).

c. *Myxopapillary ependymoma* (papillary ependymoma). These tumors are papillary masses resembling papillomas of the choroid plexus both grossly and microscopically. The epithelial cells are more cuboidal than columnar and do not contain the large vacuoles or mucous droplets (Fig. 1203). The papillary cores are dense and exhibit myxomatous degeneration. Ordinarily blepharoplasts can be demonstrated in the epithelial cytoplasm.

d. *Epithelial ependymoma.* Epithelial ependymomas are so designated because of the incorporation in the tumor of numerous epithelial structures resembling central canals. The ependymal cells do not contain mucus or vacuoles. Blepharoplasts can usually be demonstrated (Fig. 1204).

e. *Cellular ependymoma.* Areas of great cellularity with formation of pseudorosettes appear frequently in most types of ependymomas. In the absence of dominance of the histologic picture by definitive epithelial structures as described above, the tumors are most difficult to classify. The histology is one of great cellularity broken by pseudorosettes with faintly fibrillar processes radiating from a central point sometimes marked by an eosin-staining body. The cells and processes are refractory to the usual glial stains.

f. *Ependymoblastoma.* Ependymoblastomas are rapidly growing malignant tumors showing mitotic figures, occasional giant cells, and great cellularity in a histologic field similar to that of cellular ependymoma. This picture may be evident as an alteration in recurring ependymomas, and may be regarded as indicating increasing malignancy.

g. *Medulloepithelioma.* Medulloepitheliomas are rare, highly malignant tumors developing from primitive neuroepithelium in the midbrain of children. The formations simulate, histologically, the primitive medullary canal with internal and external limiting membranes defining the rows or channels of columnar cells. Histogenetically, this represents an extremely

primitive tissue with potential to differentiate in directions other than to ependyma. Because of microscopic similarities, however, it seems appropriate to include them with the ependymoma group (ependymoma, grade 4).[45]

2. *Oligodendroglioma Group.* a. Oligodendrogliomas are slowly growing tumors most often encountered in the cerebral hemispheres of adults. Grossly, they are well demarcated, grayish-pink in color, and often cystic. Calcium deposits are frequent and often permit the tumor to be located by x-ray. Histologically, oligodendrogliomas are highly cellular with small, darkly staining, round nuclei surrounded by clear zones or halos (Fig. 1205). Kernohan and Kernohan[23] suggest that these tumors are derivatives of a common stem cell with ependymomas and find the two histologic types often together in the same tumor.

b. *Oligodendroblastomas* are malignant variants in which the nuclei are larger, the cytoplasm stains with routine methods, and mitotic figures of bizarre character appear.[44]

3. *Astrocytoma Group.* Astrocytomas are the commonest of the gliomas and occur most often in the cerebral hemispheres (temporal lobe) of adults and in the cerebellar hemispheres of children. The tumors are indistinctly demarcated grossly, with the margin blending gradually with brain substance. They are gray in color, firm in consistency, and often exhibit the brownish pigmentation of old hemorrhage. Frequently they are cystic, particularly in the cerebellar hemispheres, where the solid tumor remains only as a mural nodule. Histologically, astrocytomas are subgrouped as pilocytic and gemistocytic types. On the basis of anaplasticity, all astrocytomas, including astroblastomas, spongioblastomas, and glioblastomas, may be designated grades 1 to 4[42, 45] without indication of histologic subtype.

a. *Pilocytic astrocytomas* are made up of well-differentiated astrocytes with demonstrable processes forming a dense fibrillated stroma. The cytoplasm of the tumor cells is more often evident in routine stains than is the cytoplasm of normal astrocytes. In the diffuse type the picture is that of normal-appearing nerve cells separated by bulky and dense astrocytic fibrillar stroma. Special stains reveal both protoplasmic and fibrillar astrocytes in the network. Occasional gemistocytes usually occur in these tumors (Fig. 1206). There seems to be a gradient as to demarcation among these tumors, all showing a relatively benign histologic cell pattern. On the one hand are fairly well defined tumefactions contrasting in color and consistency with the brain substance. At the other extreme of morphologic variance the *diffuse pilocytic astrocytoma* presents on gross sectioning no demarcation (Fig. 1207). Such a tumor shows a general enlargement of the hemisphere with extending enlargement into the stem. Histologically, the tumor tissue is mixed with well preserved nervous tissue including cell bodies. These tumors simulate the microscopic architecture of the peripheral ganglioneuroma. They are associated with a relatively long clinical course (2 to 3 years).

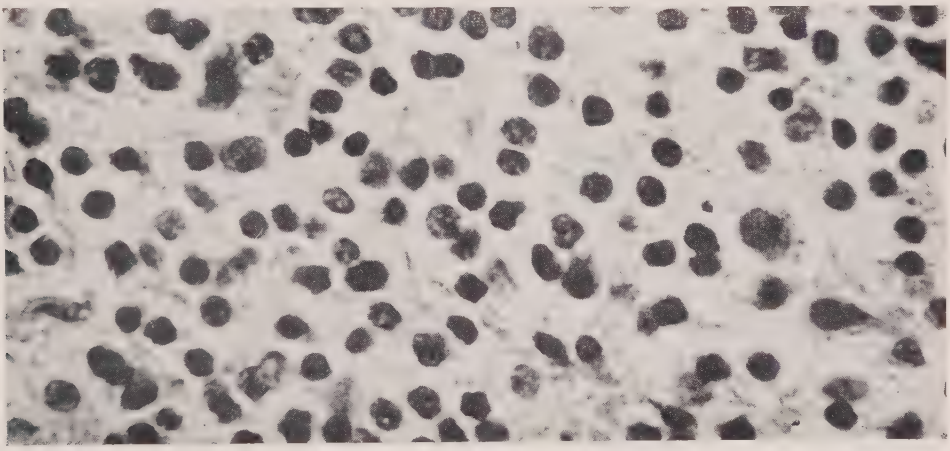


Fig. 1205.—Oligodendroglioma.

b. *Gemistocytic astrocytoma* refers to tumors dominated by gemistocytes histologically. These appear as greatly swollen astrocytes with eccentric nuclei and short, often fragmented processes (Fig. 1179). These are presumed to be

degenerating forms and appear, as well, in malignant astrocytoma and in glioblastoma multiforme.

c. *Malignant astrocytoma.* While the eventual outcome of astrocytoma is such as to classify them as "clinically" malignant, their histologic make up is characteristically benign (Fig. 1206). That the microscopic appearance changes through successive resections to one of frank histologic malignancy is well recognized. Rarely, the eventual tumor has the make-up of glioblastoma multiforme. More commonly, the malignant variant is distinctive enough to retain the appellation of astrocytoma. All the standard criteria of malignancy are apparent, including clinical course. The histologic features of glioblastoma multiforme are, however, wanting.

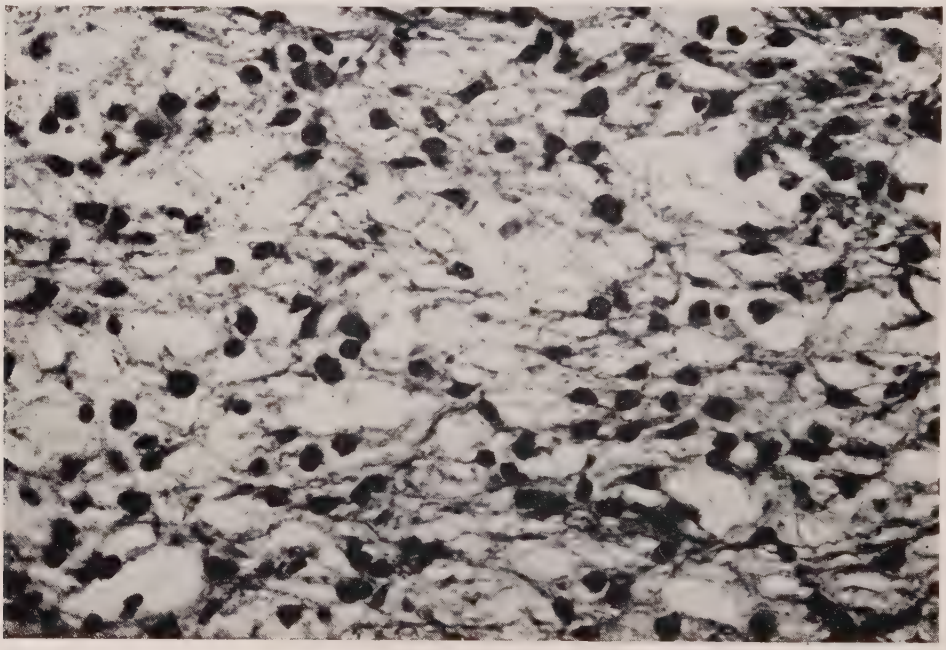


Fig. 1206.—Astrocytoma.

d. *Astroblastoma.* Astroblastomas are relatively rare tumors of the cerebral hemispheres of adults. Grossly they are expansive and unencapsulated. Frequently they are hemorrhagic and degenerated centrally, and occasionally exhibit multiple small cystic areas on gross section. Microscopically they show widely degenerated fields interrupted by thickened vasculature around which the astroblasts are disposed in radial pattern. The cells, individually, are large and polyhedral with large nuclei containing somewhat denser chromatin than astrocytes. By special staining it is apparent that the radiation pattern around blood vessels is imparted by filamentous sucker foot attachments extending between the astroblast cell body and the vessel wall. Astroblastomas give a less favorable prognosis than astrocytomas.

e. *Spongioblastoma* (spongioblastoma polare). Spongioblastomas are slowly growing tumors with a predilection for cerebrum in adults and pons in children. Grossly they are soft, expansive, and poorly delineated. Histologically, they have a striking resemblance to neurofibromas (central neurinoma), and may occur as part of the complex in multiple neurofibromatosis.[57] The characteristic cell is spindle in shape with either a single polar process (unipolare) or bipolar processes. The cells are disposed in interlacing bundles but fail to show palisading of the nuclei. Spongioblastomas are clinically malignant and are almost wholly inaccessible surgically due to location. As in the case of astrocytomas there is marked variation in histologic appearance and degree of anaplasticity. Some are quite fibrous generally, others highly cellular with abundant signs of malignancy. Spongioblastic areas appear in glioblastomas (multiforme) as well as in the malignant variants of astrocytomas. The interrelationships of these three tumors are undoubtedly close.[45] They possess, however, topographic, microscopic, and clinical distinctness enough to merit discussion as separate entities.

f. *Glioblastoma multiforme* (spongioblastoma multiforme). Glioblastoma multiforme is the most malignant of all brain

tumors and represents some 30 per cent of all gliomas, being second in occurrence to astrocytomas. They occur most commonly in the cerebral hemispheres of middle-aged adults. They are markedly expansile and infiltrative and exhibit ill-defined borders on gross section. Usually at the time of death they attain a diameter over 5 cm. and involve a large part of a hemisphere with infiltration across the midline through the corpus callosum. There is marked distortion of the ventricular spaces. The gross appearance varies greatly, but most tumors are irregular in outline, are diffusely hemorrhagic and discolored with alternating yellowish, brown, and reddish-gray patches (Fig. 1208). Microscopically, the multiform pattern characterizes the tumor. Diffuse necrosis in large patches is common. Perhaps the most common cell is the spongioblast with scattered astrocytes often of gemistocytic type and other more primitive cells. Several cell patterns can usually be identified, although recognition of all is not necessary for diagnosis. Giant cells are

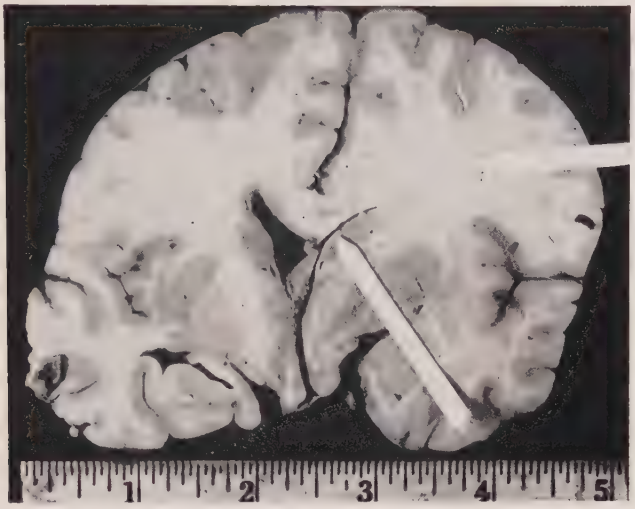


Fig. 1207.—Diffuse pilocytic astrocytoma. Note absence of demarcation, generalized swelling of hemisphere, and shift with obliteration of ventricle.

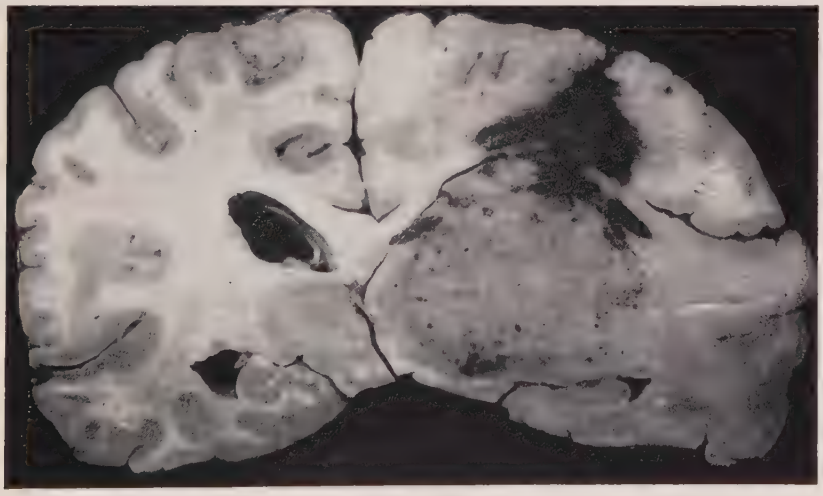


Fig. 1208.—Glioblastoma multiforme with residual wound from biopsy procedure. (See also Fig. 325.)

common. These are multinucleated and often show very bizarre mitotic figures. Search will usually reveal eosin-staining irregular large cells exhibiting karyorrhexic nuclear fragments with no remaining nuclear membrane. Commonly there are numerous necrotic zones surrounded by laminae of small dark-stained glial nuclei in pseudopalisade pattern. One striking characteristic is the appearance of marked hyperplasia and hypertrophy of vascular endothelium. Often the vessel lumina appear to be obliterated. The frequent necrosis of glioblastomas is attributed to these vascular occlusions (Figs. 1209 and 1210).

On the basis of histologic malignancy, these are grade 4 astrocytomas.[42]

4. *Pinealoma.* On a topographic basis only, all tumors arising in the pineal region have been called pinealomas. Because, however, several types of tumors (gliomas, sarcomas, teratomas) are known to arise in this region, a histologic diagnosis is required and the term, pinealoma, is restricted to those tumors which can be recognized as pineal tissue derivatives.[58, 59] The characteristic picture is a mosaic of islands of large light-staining cells set in a background of dark-staining small cells (Fig. 864, page 992). The proportion and disposition of the two types of cells varies greatly, and often the mosaic pattern is evasive. Grossly, there is great variability in size and disposition. Situated at the apex of the tentorial aperture, the tumors expand anteriorly into the third ventricle or posteriorly through the tentorial aperture to overlie the midbrain. In general they are believed to exert pressure damage only to thalamus or midbrain, although the possibility of endocrine effect is often quoted from associated precocious puberty in children (see page 992). In a review of 58 cases, Russel and Sachs[59] find approximately one-half the cases occurring between the ages of 15 and 25 years and predominantly in males (88 per cent). The tumors grow rapidly, most patients presenting symptoms of less than one year's duration. The prognosis for surgical or radiologic relief is poor.

5. *Medulloblastoma.* Medulloblastomas are highly malignant tumors of the cerebellum of children and young adults. According to Raaf and Kernohan[33] they represent neoplasia of residua of the external granular layer of the cerebellum. Closely allied tumors (neuroblastomas, tumors of peripheral migrant cells, page 1039) necessitate insertion of the medulloblast as a link in the histogenetic schema (page 1287), but, as a source of tumor development, these cells appear to restrict their primary activity to the midline of the cerebellum. They do, however, metastasize by implantation along the cerebrospinal fluid channels and may come to involve almost the entire meningeal space, including spinal.[60] Grossly, the tumors are expansive and extend into the fourth ventricle producing early blocking and signs of intracranial hypertension. Curiously they often appear distinctly encapsulated and can be shelled out surgically. Recurrence is, however, an absolute rule. The tumors extend also by implantations apparently by contact through free flowing in the meningeal spaces. In this capacity they are similar to retinoblastomas (see below). Grossly the primary tumors are pinkish-gray in color and firm in consistency and the secondary nodules and plates are tough and elastic. Microscopically, the type cell is pear-shaped with a stubby cone of cytoplasm to one side of a compact nucleus. Many fields show clusters of these cells disposed in irregular arcs sometimes completed as rosettes without lumina (pseudorosettes) (Fig. 1211). Neuroblasts and spongioblasts are often identified among the cells of the tumor. Medulloblastomas are strikingly radiosensitive.[51, 61]

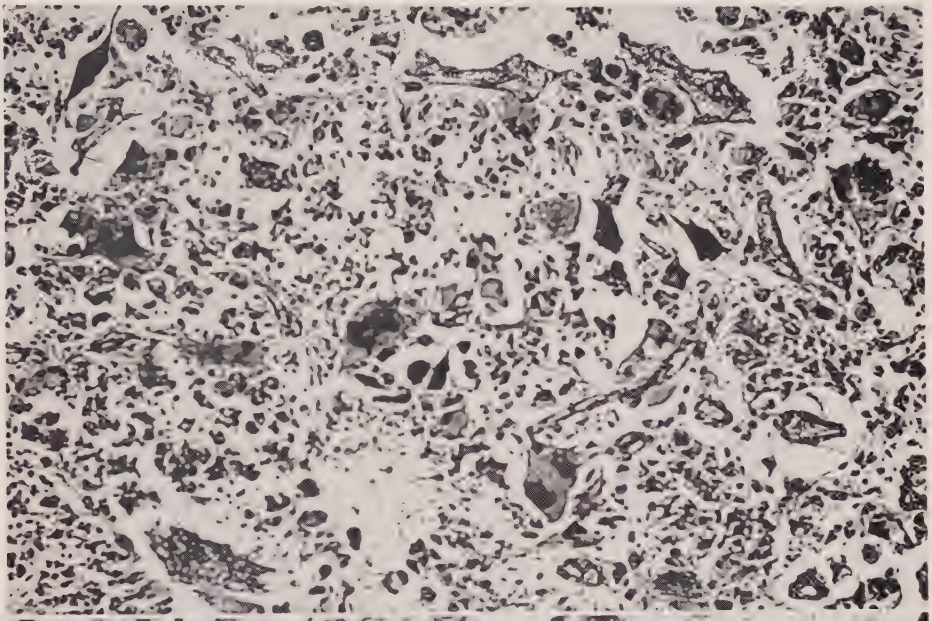
B. **Nerve Cell Tumors.**

1. *Neurocytoma* (ganglioneuroma, ganglioglioma). Central neurocytomas are extremely rare tumors characterized by the appearance of well-developed neurocytes in a glial stroma having a morphology similar to that of a spongioblastoma. Identification of Nissl substance and the nuclear characteristics of nerve cells is necessary for diagnosis. The tumors grow slowly and are poorly demarcated grossly. Their counterpart in the peripheral nervous system is ganglioneuroma.

2. *Neuroblastoma.* Neuroblastomas are rare tumors of the central nervous system. Identification depends upon the appearance of neuroblasts in section. These cells exhibit the large vesicular nucleus of the neurocyte but have little demonstrable cytoplasm and no Nissl substance. Histogenetically they are closely related to medulloblastomas and behave in a similar manner biologically. Neuroblastomas are far more common as a retinal tumor (retinoblastoma) and as a tumor of peripheral neuroblastic migrant cells (see page 1039).

3. *Retinoblastoma* (neuroepithelioma of retina). Retinoblastomas are tumors of infancy and childhood which arise from retinal neuroblasts (see page 730). These tumors resemble medulloblastomas in behavior and are peculiar in their ability to metastasize by migration in the optic vaginal spaces to the meningeal spaces. Histo-

Fig. 1209.



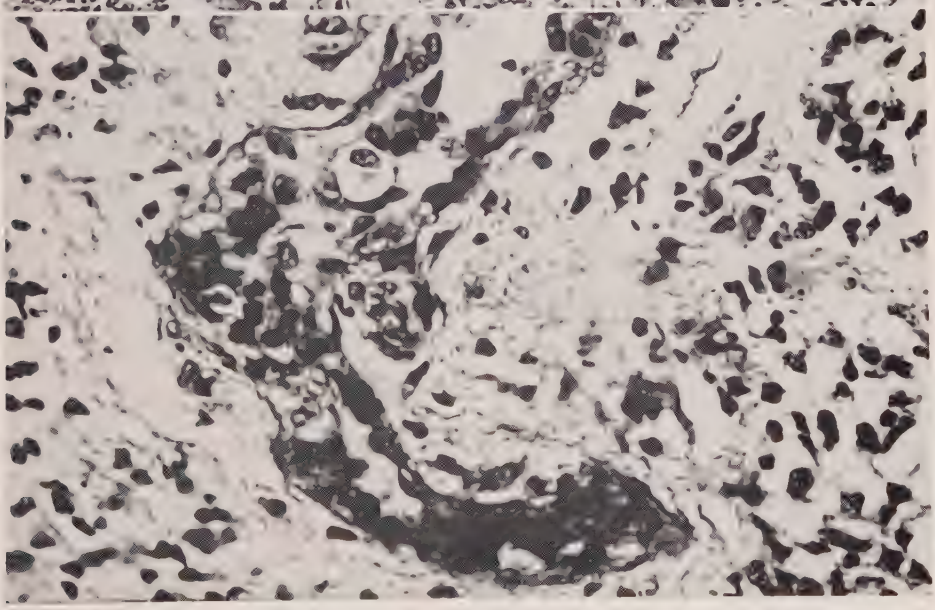


Fig. 1210.

Fig. 1209.—Glioblastoma multiforme showing multiform histologic architecture.
Fig. 1210.—Glioblastoma multiforme showing vascular endothelial proliferation.

logically the type cell is rounded with little cytoplasm and a large, pale-staining nucleus. A common variant is the occurrence of true rosettes (neuroepithelioma) of single cells which may dominate some areas of sections of the tumor. (See Figs. 637-639.)

III. Primary Extramedullary Neurogenic Tumors.

Primary extramedullary neurogenic tumors include, principally, two groups: those stemming from supporting cells and those arising from nerve cells or their processes. In addition, there are several peripheral neurogenic tumors whose origins are controversial. The supporting cells available as a source of tumor formation include the sheath cells of Schwann and the connective tissue cells making up the endo-, peri-, and epineurium. The nerve cell parts appearing in neoplastic processes include the cell body, axis cylinders, myelin sheaths, and nerve endings. In general, the tumors are designated according to the dominant tissue apparent in section. Very often it is difficult to determine the exact nature of the parent tissue; e.g., whether neurolemmal or endoneurial. There are, however, certain morphologic differences, histologic, gross, or topographic, which warrant subdivision for descriptive purposes. The demonstration of the production in vitro of collagen and reticulin by Schwann cells suggests that all the histologic types, including the so-called fibroblastoma, may be Schwannian in origin.[62]

A. Supporting Cell Tumors.

1. *Neurofibroma.* Neurofibromas are common benign tumors appearing in subcutaneous tissue, along peripheral nerves, and at the neuromedullary junctions. As special variants they occur commonly enough to merit separate description (see *2, 3, 4, 5,* and *6,* below). In the skin, neurofibromas occur as nodules which may be single or multiple. Along peripheral nerves they appear as fusiform swellings or eccentric pedunculated masses of varying size up to many centimeters in diameter. At the neuromedullary junction, neurofibromas may be located wholly intradurally, both intra- and extradurally, wholly extradurally, or as *dumbbell tumors* with the central mass within the vertebral canal connected by a shaft of tumor tissue passing through an intervertebral foramen to the peripheral mass in a paravertebral position. Grossly the tumors are gray or grayish-brown in color and are firm in consistency. Cyst formation, particularly in those tumors within the craniovertebral canal, is not uncommon. Microscopically there is great variation in makeup, ac-

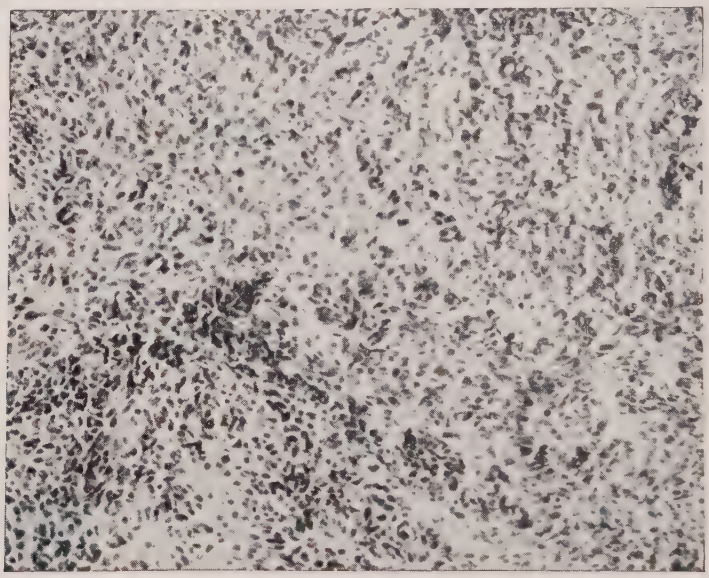


Fig. 1211.—Medulloblastoma. (From Anderson, Synopsis of Pathology.)

counting for the numerous subtypes. The tumor most readily recognized as neurofibroma is made up of interlacing strands of elongate cells resembling a cellular fibroma except for the absence or dearth of collagen in the stroma.

2. *Perineuronal fibroblastoma* is the term applied to these tumors when collagenous tissue dominates the histologic field. These may be fundamentally fibroblastomas, may represent fibroblastic replacement of original neurogenic tissue, or may represent a natural product of Schwann cell tumor.[62]

3. *Neurinoma* (neurilemoma, Schwannoma). Neurinomas are regarded as tumors of Schwann cells, are invariably benign, and present a characteristic histologic makeup. These, again, should probably be regarded as variants of neurofibromas with dominance of Schwann cells and little collagen formation. Microscopically, the characteristic feature is an interlacing network of wavy flowing streams of cells in which the nuclei palisade prominently. The vasculature often exhibits hyaline thickening and there are often large areas of loose reticular tissue in which fat-laden foam cells can be identified. There are usually numerous small degenerated areas in which small cysts occur and there is often patchy pigmentation of blood origin (Fig. 1212).

4. *Acoustic neurinoma.* Acoustic neurinomas are benign expansive tumors of the eighth cranial nerve (Fig. 1213). They are thought to arise from Schwann cells within the internal auditory canal and expand centrally to occupy the cerebellopontine angle. The eighth nerve, and frequently the seventh, loses its identity within the tumor or its capsule. Occasionally, the seventh nerve can be freed over the surface of the mass and spared in its surgical removal. These tumors present the microscopic picture described above for neurinomas.

5. *Multiple neurofibromatosis* (von Recklinghausen). Neurofibromatosis occurs as a disseminated process manifest as multiple pigmented skin tumors associated with nevi and often disposed in segmental pattern. The tumor development may be remarkably widespread including both somatic and autonomic elements and not uncommonly the central nervous system. Grossly the nerve tumors are firm and nodular. Histologically, great variation occurs and representative areas of each type of neurofibroma can usually be demonstrated. In general, however, the tumors are more fibroblastic and it has been suggested that there is a fundamental defect in mesodermal makeup which may be one of many parts of von Recklinghausen's disease. For reasons that are obscure, neurofibromas of this disease complex are prone to become malignant and often recur after partial removal. It is not unusual for efforts at surgical removal to incite malignant transformation of other associated tumors.[63, 64]

6. *Neurofibrosarcoma* (neurogenic sarcoma). Malignant neurofibromas occur most commonly along the trunks of large peripheral nerves or retroperitoneally in a paravertebral position although the tumors have been described in a wide variety of locations. In general they behave in a somewhat more benign manner than fibrosarcomas, being characterized by local recurrences after surgical removal with eventual extensive invasion and metastases. Microscopically they are highly cellular and markedly fasciculated. Ewing[65] described three types which reflect a significant gradient of malignancy: (a) Sclerosing neurofibrosarcoma is slowly growing, locally infiltrating, and shows relatively few cells microscopically with a dense fibrous stroma. These tumors recur locally. (b) Spindle cell neurofibrosarcoma is highly cellular and markedly fasciculated with spindle-shaped cells in tightly packed bundles which interlace. The stroma is finely fibrillated. There may be patches of fat or embryonic fat cells and there may be extensive mucinous degeneration. (c) In a cellular anaplastic type the fibrillar material is extremely scanty. There is a tendency toward an epithelioid character which suggests the possibility of neuroblastomatous or neuroepitheliomatous origin.[66]

B. **Tumors of Peripheral Nerve Cells and Their Processes.**

1. *Ganglioneuroma.* Ganglioneuromas are slowly growing tumors appearing anywhere in the body but more commonly along the paravertebral line in thorax or abdomen. They exhibit no distinguishing gross features, the characterizing morphology being the occurrence of ganglion cells histologically. The ganglion cells vary greatly in stage of development and are embedded in a

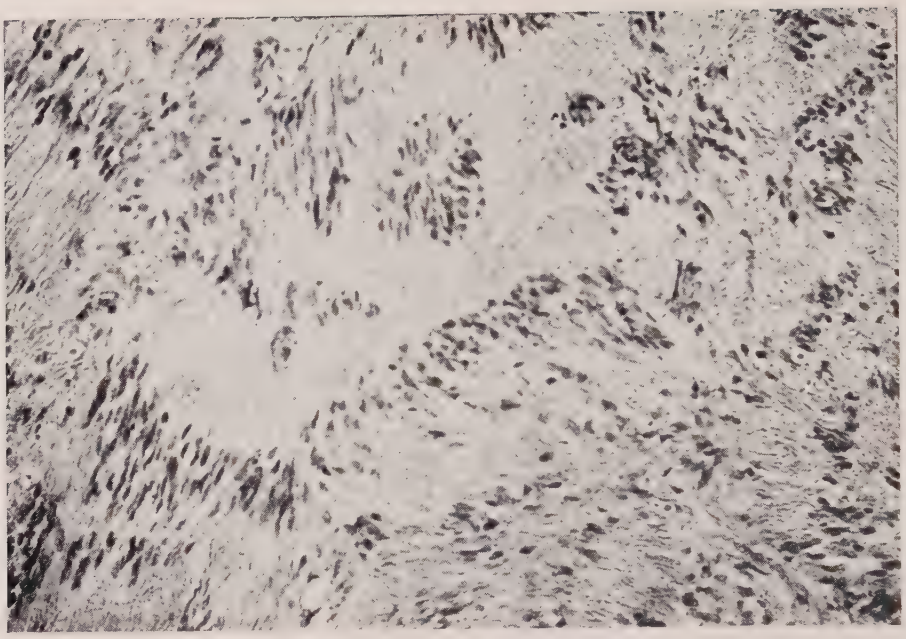


Fig. 1212.—Acoustic neurinoma.

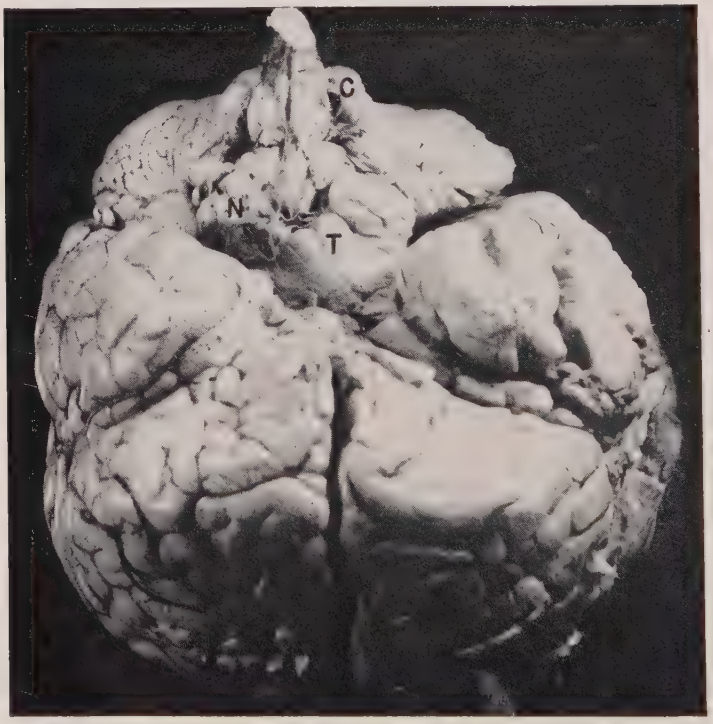


Fig. 1213.—Acoustic neurinoma, *N*, in cerebellopontine angle. Note the "coning" of the cerebellar tonsils, *C*, and the marked defect of the temporal lobe *T*, resulting from pressure through the tentorial aperture.

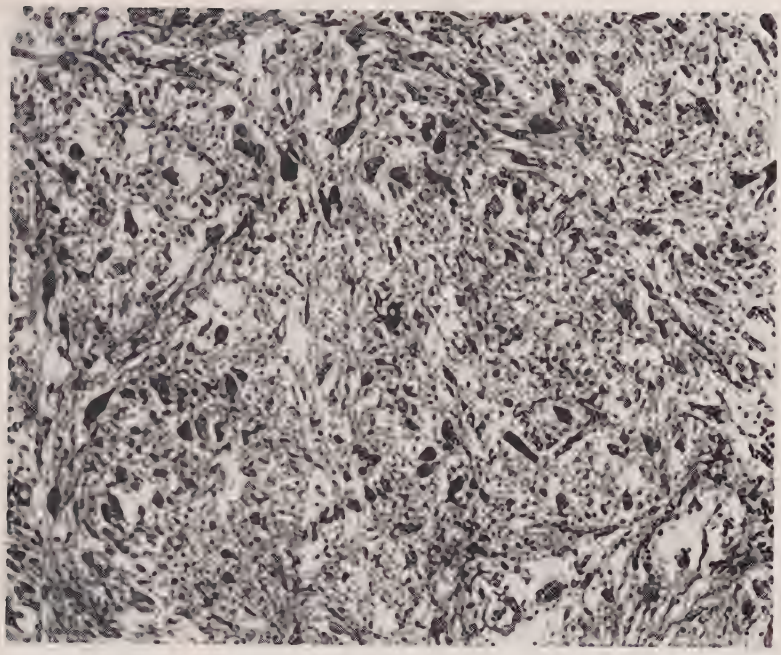


Fig 1214.—Ganglioneuroma.

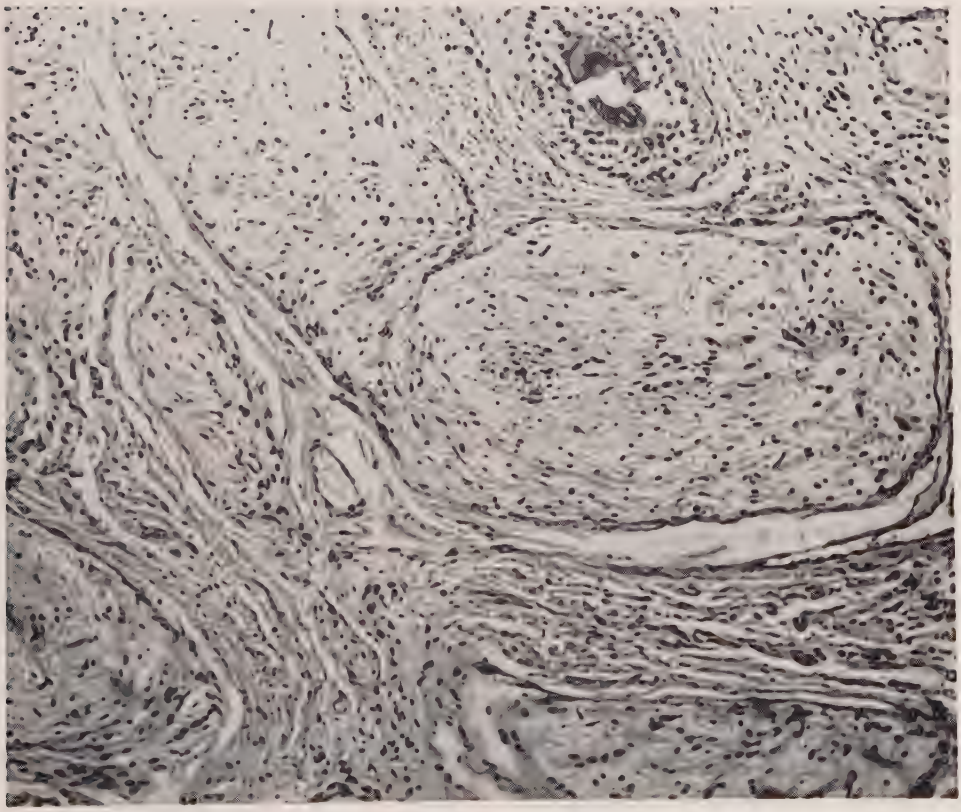


Fig. 1215.—Plexiform neuroma of skin.

fibrous stroma of Schwann cells (Fig. 1214). Malignant change is uncommon but does occur.[67]

2. *Traumatic neuroma* is incited by trauma to a nerve trunk, most commonly amputation (amputation neuroma). Initially there is a growth response of neurofibrils (page 1282) together with proliferation of Schwann cells. Eventually the Schwannian tumor dominates the picture and this is often replaced by collagen and connective tissue.

3. *Plexiform neuroma* is a tangle of well-differentiated hypertrophied peripheral nerve filaments, resembling grossly a tangle of spaghetti. The mass often produces marked deformity, especially prominent in involvement of the facial nerves. Microscopically, numerous well-differentiated nerve bundles including all adult parts with areas of degeneration and atrophy appear in the section (Fig. 1215). For the most part the individual fascicle is edematous and mucoid and shows rather poor preservation of nerve filaments. Occasionally, however, the nerves are exceedingly well preserved. This is well seen in the neuromatosis in an obliterative appendix or, rarely, in the dermal layer of a painful nipple. Plexiform neuromas may be localized to an area (facial gigantism), to an organ (stomach, urinary bladder), or may be disseminated and attached as soft tumors to peripheral nerves. As true neuromatous (nerve) structures they appear to be distinct from neurofibromas (neurinomas). The exact relationship between disseminated neuromas and disseminated neurofibromatosis of von Recklinghausen is obscure. Compare the histologic features in Figs. 1212 and 1215. In spite of such striking histologic diversity and obvious difference in lineage, such tumors are commonly described as variants of the same order of lesion.

4. *Myelinic neuroma* applies to gigantic retroperitoneal neuromas in which there is massive production of myelin. Occasional areas of normal-appearing nerve fibers can be identified. Grossly and microscopically a whorled pattern may be evident. The tumors exhibit a benign behavior.

5. *Neuroblastoma.* An important group of tumors (neuroblastoma, sympathicoblastoma, sympathicogonioma) appear as malignant representatives of cell lines leading from the migrant "blast" cells to peripheral nervous elements, particularly sympathetic ganglia, paraganglia, and adrenal medulla. The best differentiated of the allied tumors in the group is the ganglioneuroma described above. Neuroblastomas are typically retroperitoneal or adrenal masses of large size occurring in infants. They grow rapidly and metastasize in remarkably widespread and frequently bizarre pattern. The liver may be almost wholly replaced by such a tumor. Commonly a metastasis to bone may signal the clinical aspects of the disease. The metastatic lesions in long bones give rise to a characteristic "onion-skin" layering recognizable in the x-ray. Metastases in flat bones produce vertical periosteal spines. These features as well as massive metastases to bone in addition to identification of adrenal neuroblastomas in cases of Ewing's sarcoma tend to cloud the distinctions between these disease entities (see Willis[68]).

C. **Miscellaneous Peripheral Neurogenic Tumors.** A rather large and important group of tumors of debated origin occur in many peripheral structures. There is considerable evidence that many of these are neurogenic. They are, however, more appropriately described elsewhere: see Melanoma, page 1165; Carcinoid, page 792; Pheochromocytoma, page 1040; Carotid body tumor, page 757.

IV. Meningioma.

Most statistical reviews place meningioma second in numerical importance among intracranial tumors, exceeded only by the gliomata (Table XXII, page 1293). Estimates vary from 15 to 25 per cent. Meningiomas occur most commonly in middle age and are rare in children.[69] Predilection of the tumors for certain sites is well recognized and is reviewed in detail in Cushing and Eisenhardt's comprehensive treatise.[70] The dominant sites include: (a) parasagittal, (b) over the free convexity, and (c) sphenoidal ridge. Less frequently, meningiomas occur in the olfactory grooves, posterior fossa, and in a suprasellar position. One-fourth of 557 intraspinal neoplasms in the Mayo Clinic series[71] were meningiomas. They are also described as occurring in choroid plexus, in the orbit, Gasserian ganglion, and in numerous scattered intracranial locations not specifically designated above.

Meningiomas vary greatly in gross appearance, but are usually nodular, encapsulated, soft in consistency, and gray in color (Fig. 1216). They are usually quite vascular and may contain bone, cartilage, or calcified bodies which can be detected on section. A striking feature of intracranial meningiomas is the tendency to hyperostosis. Not infrequently there will be a conical mass of bone projecting into the tumor from the pressure surface on the cranial vault or base. This characteristic is rare in intraspinal meningiomas (Brown[71]). The histologic classification of meningiomas is clouded by the uncertain origin of the meningeal cells—whether mesodermal (Weed[27]) or epiblastic (Harvey and Burr[26]). In a measure the controversy is avoided by the noncommittal term "meningioma" (rather than meningeal fibroblastoma, etc.) and by regarding the source as neuroskeletal intertissue. In this way it is permissible to subgroup all tumors arising in meninges as a topographic, rather than a histogenic, entity.

The subdivisions find some utility in guides for identification. Cushing and Eisenhardt present nine types of meningiomas each with two to four variants. This classification may be simplified to introductory stature (see Brown[71]) as follows: (1) meningothelial type, (2) fibroblastic type, (3) psammomatous type, (4) metaplastic type (osteoblastic, chondromatous, lipomatous, melanotic), and (5) malignant type. Over 90 per cent of meningiomas will fall in types 1, 2, and 3. There are, in addition, tumors of vascular origin which are not infrequently meningeal in position. Topographically, these may be termed angioblastic meningiomas. Since, however, the parent tissue is well established, it seems more appropriate to discuss them with other intracranial angiomas.

Fibroblastic Meningioma. The fields in this variety of tumor are dominated by interlacing strands of fibroblastic elements in which reticulin and collagenous fibers can be demonstrated by special stains. Nests of meningothelial cells are incorporated in the masses of fusiform cells (Fig. 1218). The nuclei of the elongate cells may be palisaded, resembling neurofibroma. The tumors contain relatively few vessels and show no evidence of rapid growth.

Psammomatous Meningioma (Psammoma). Hyalinized or calcified laminated bodies may be demonstrable in any meningioma. In psammomas these bodies dominate the histologic picture (Fig. 1219). Psammoma bodies result from degenerative changes either in a vessel or a meningothelial nest, with ultimate hyalinization and calcium deposition. Because of the calcification, psammomas are roentgenographically visible.

Metaplastic Meningioma. Whether meningothelial tissue actually undergoes metaplasia to become bone, cartilage, or fat-forming tissue is controversial. The periosteal nature of the outer layer of cranial dura carries the implication of bone-forming potentiality. In any event, *osteoblastic meningioma,* quite distinct from hyperostosis, is described. Similarly, *chondroblastic meningioma* with areas of cartilage formation, and *lipomatous meningioma* with well-differentiated fat cells appear as rare variants.

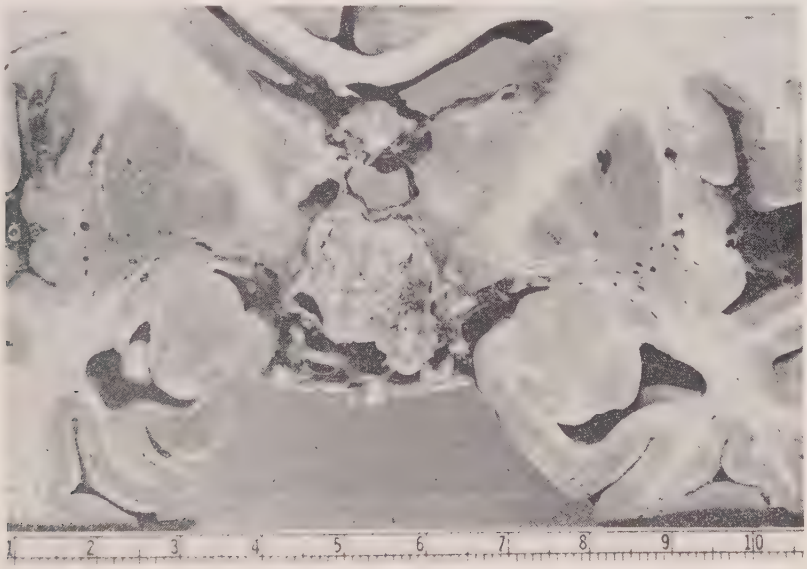
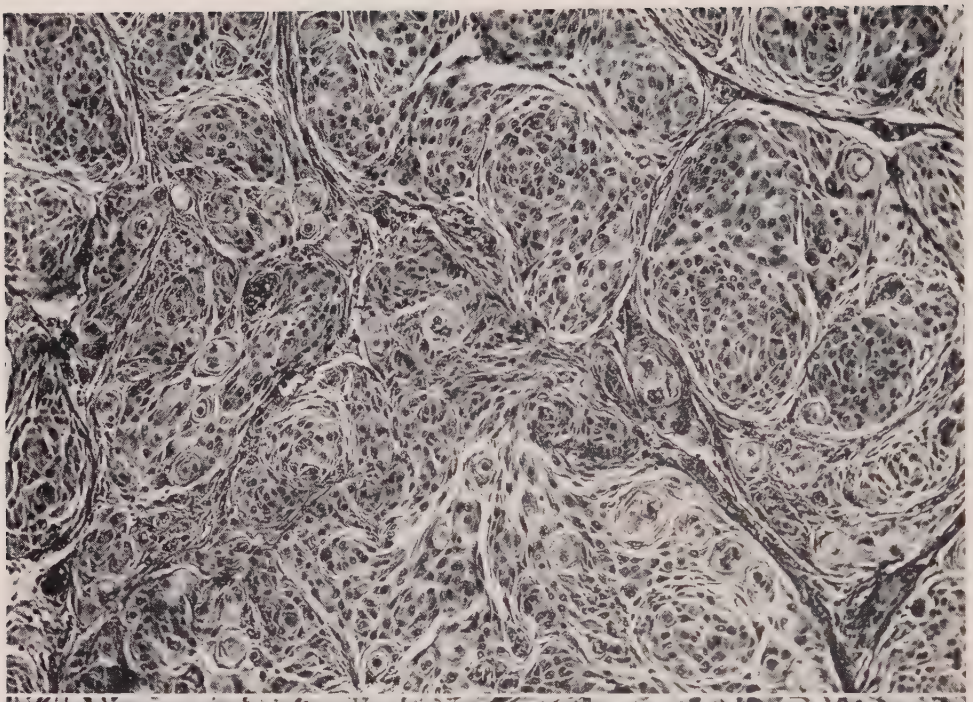


Fig. 1216.—Meningioma compressing the floor of the third ventricle.

Meningothelial Meningioma (Meningothelioma). These are the commonest of the meningiomas and are thought to represent neoplasia of arachnoid lining cells. Histologically, meningotheliomas are made up of large cells with indistinct cell boundaries disposed in nests, sheets, or alveoli. Often the alveolar nests give the impression of a concentric laminated disposition suggesting a whorl. Frequently the meningothelial nests are separated by interlacing or stream patterns of elongate or flattened cells suggesting fibroblastic elements (Fig. 1217). Special stains, however, fail to demonstrate reticulin or collagen in these fusiform elements. Sections of this variety of meningioma may contain scattered psammoma bodies.

Malignant Meningioma. Rarely, meningiomas show the usual criteria of malignant change yet retaining recognizable meningeal parent tissue. More commonly, tumors of *fibrosarcoma* type arising in meninges are encountered. These are made up of round or spindle-shaped cells, show abundant mitoses, and may even metastasize.[72] The origin of the tumor is attributed both to leptomeninx and to stromal elements which have

Fig. 1217.



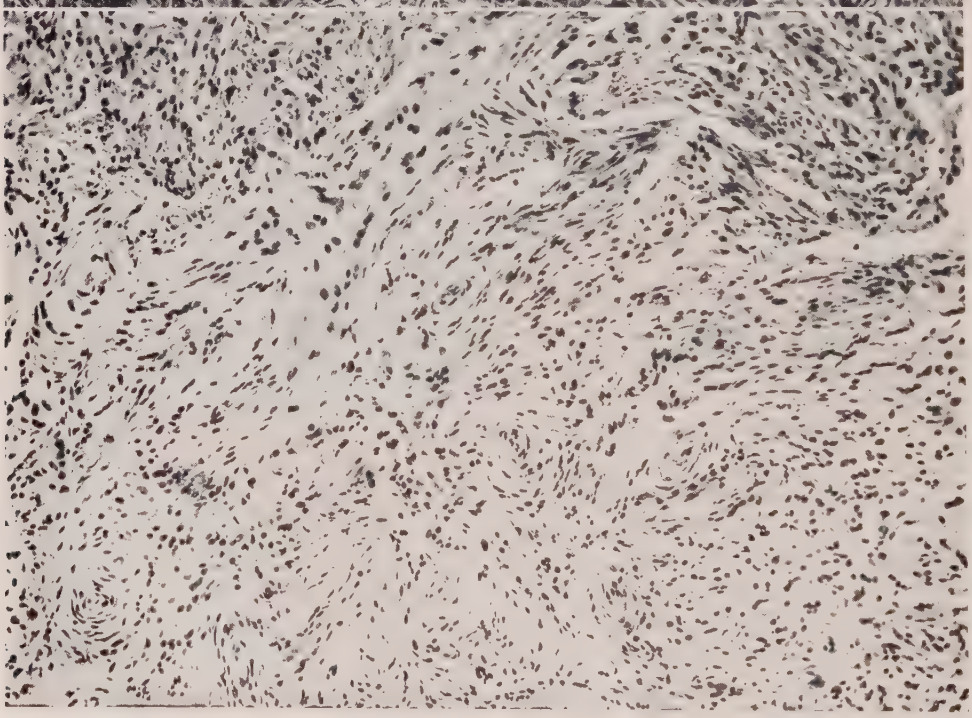


Fig. 1218.

Fig. 1217.—Meningioma (meningothelial type).
Fig. 1218.—Meningioma (fibroblastic type).

replaced the original meningothelial growth. In addition to focal fibrosarcoma of the meninges, a *diffuse sarcomatosis* is described[73] in which sarcomatous elements pervade wide reaches of the meningeal spaces. *Diffuse meningiomatosis* refers to widespread meningothelial invasion.[74, 75]

Meningeal gliomatosis is a diffuse infiltration of the meningeal spaces by medulloblastoma and retinoblastoma, actually a secondary tumor. An additional variety of malignant meningioma is the *melanomatous* type. These presumably arise from meningeal melanoblasts. While the majority of meningeal melanotic tumors are malignant, benign pigmented meningiomas have been described.[76, 77]

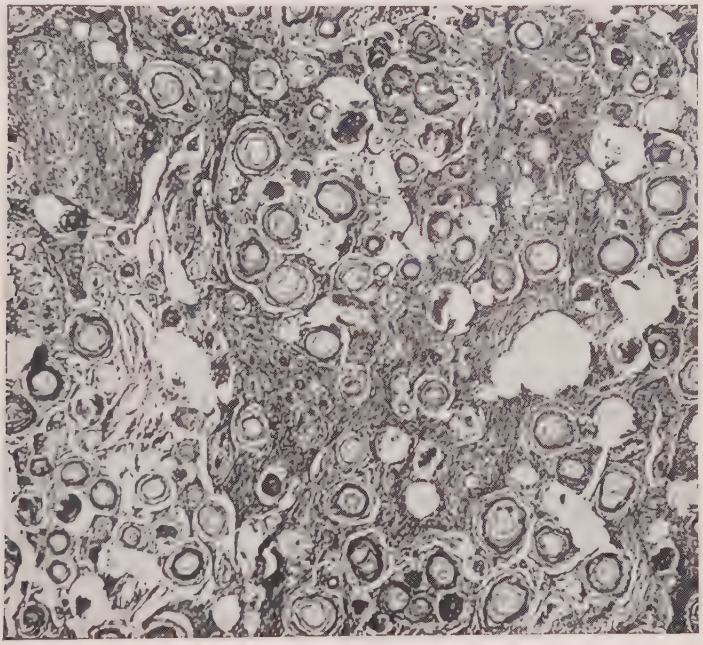


Fig. 1219.—Meningioma (psammoma). (From Anderson, Synopsis of Pathology.)

V. Tumors of Cerebral Vasculature and Perivascular Structures.

A. **Tumors of Blood Vessels.**

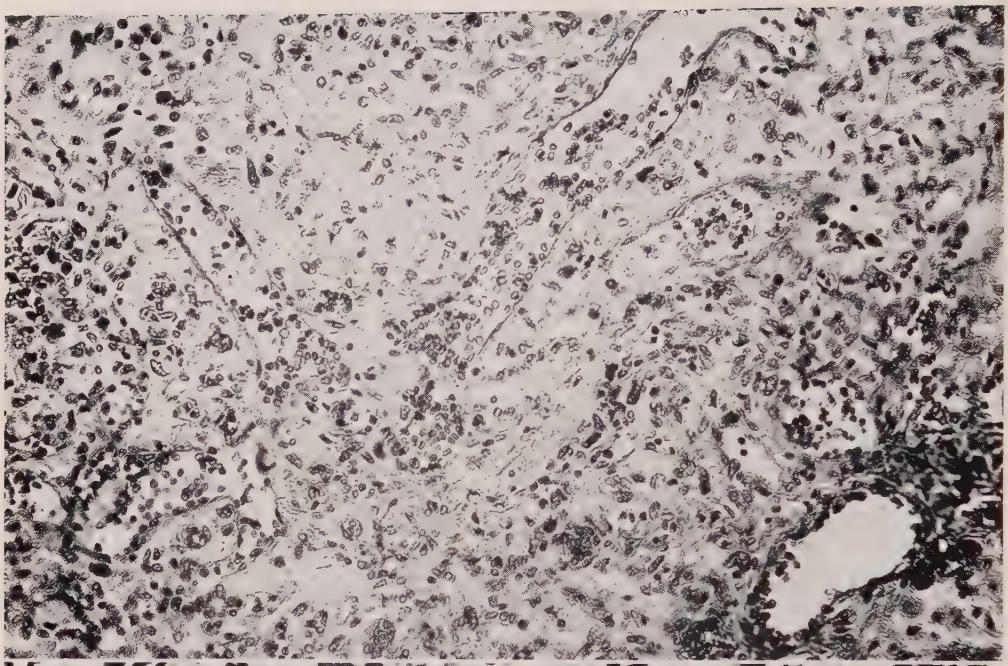
1. *Telangiectasia.* Telangiectasia of cerebral vessels is a fairly common occurrence, particularly in the midbrain, and represents a malformation rather than a neoplasm (see page 1289).

2. *Angioma.* Angiomas occupy a questionable status as to classification. They consist of masses of tortuous vessels of varying differentiation, exhibit expansive, though usually limited, growth, and behave as a space-occupying mass (see malformations, page 1289). In general they are presumed to be congenital and represent defective vascular organization and differentiation. Occasionally, they are associated with aneurysms[78] suggesting the possibility that aneurysms may represent a part of a general vascular dysgenesis (see aneurysms, page 1331). A striking feature of cerebral angioma is the frequent multiplicity and association with angiomas of retina (Lindau's disease), face, and viscera. Grossly, the lesions are sometimes massive (Fig. 1199).

3. *Hemangioma.* Hemangiomas are rare tumors of the nervous system, somewhat more common in the meninges. Meningeal hemangiomas (angiomatous meningiomas, see page 1307) are bluish-gray space-occupying masses attached to the meninges and compressing the brain. Histologically there is extensive meningeal fibrosis in a stroma supporting nests and masses of well-differentiated endothelial channels with a fine rim of supporting fibrous tissue. These may be capillary or cavernous in type and exhibit budding and irregular branching and a low degree of cellular activity (Fig. 1220). Hemangiomas of the nervous system are exceedingly rare if angiomatous malformations are excluded. The differential point lies in the identification of glial or true nervous stroma interrupting the vessel mass in the malformations. True hemangiomas contribute their own stroma as a part of the neoplastic process.

4. *Hemangioendothelioma.* Hemangioendotheliomas are regarded as true endothelial tumors and exhibit, histologically, tangles of fine capillary channels with poorly differentiated fibrous supporting tissue. The tumors are highly cellular, with evident proliferative activity of the endothelial cells which obliterates most of the lumen area, in sections imparting a compact appearance. Again these tumors are more commonly meningeal than intramedullary (Fig. 1221). In an intramedullary position they appear primarily in the

Fig. 1220.



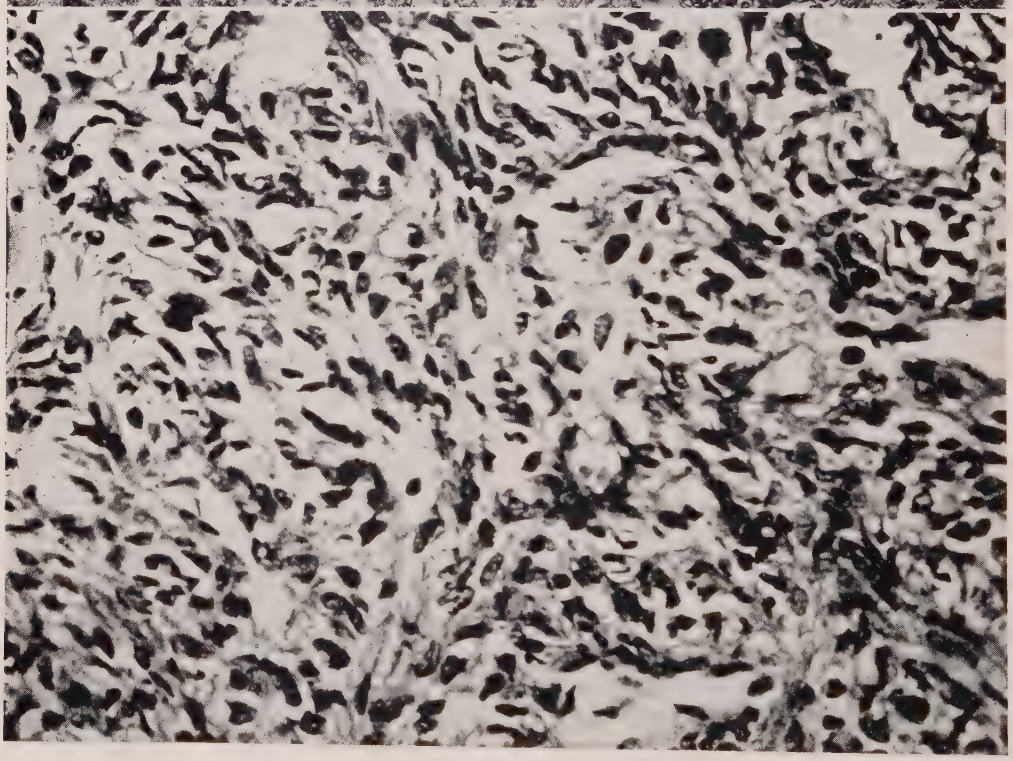


Fig. 1221.

Fig. 1220.—Hemangioma.
Fig. 1221.—Hemangioendothelioma.

cerebellum where they exhibit a histology warranting separate description (hemangioblastoma).

5. *Hemangioblastoma.* Hemangioblastomas are highly cellular neoplasms occurring primarily in the cerebellum. Grossly they produce a hemispheral cyst, in the wall of which the cellular mass exists as a mural nodule (Fig. 1222). Histologically, they represent an exaggerated cellular hemangioendothelioma with the added features of marked degenerative changes and the production of foam cells (pseudoxanthoma). The cellular areas are markedly vacuolated and exhibit hyperchromatism and mitoses. These cerebellar tumors occur frequently in conjunction with angiomatosis of the retina (Lindau's disease). Hemangioblastomas as well as hemangioendotheliomas have occurred in the spinal cord or its membranes.[53]

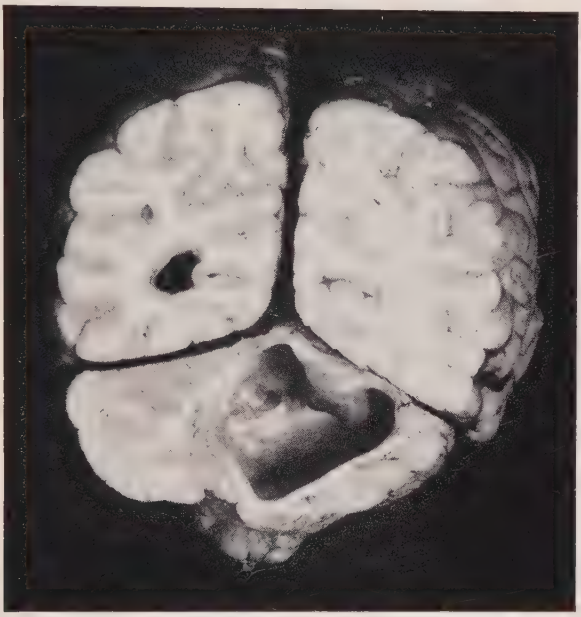


Fig. 1222.—Hemangioblastoma of cerebellum showing mural nodule. (Courtesy Dr. John Raaf.)

6. *Hemangiosarcoma.* Hemangiosarcomas are malignant tumors in which an angiomatous origin is said to be identified by the presence of endothelial structures and a general makeup paralleling that of hemangioblastoma. The usual measures of anaplasticity, with invasion of supporting tissue, great cellularity, and numerous mitoses, are present.

B. Tumors of Mesodermal Supporting Tissue.

Development of mesodermal tumors in the nervous system other than those which are vascular in origin depends upon stem cells which are perivascular in position or upon microglia. Primary tumors of such character are rare, and division into a wholly satisfactory classification is not yet possible. The following represent distinguishable histologic types, but frequently sarcomatous tumors appear which cause difficulty in assigning them to an appropriate heading.[79-82]

1. *Perithelioma* refers to a tumor presumably stemming from the perithelial cells of the vascular adventitia. They appear histologically as clusters of undifferentiated cells disposed in radiating pattern around a central vessel. Often the intervascular tissue is necrotic or absent. These tumors resemble the peritheliomas which are occasionally seen around visceral vasculature (appendix).

2. *Perivascular (perithelial) sarcoma.* Perivascular sarcoma occurs as a nodular primary growth of the brain and may shell out grossly. Histologically, there are markedly undifferentiated sarcoma cells disposed in irregular patterns about blood vessels. Special stains reveal a coarse reticulin net supporting the tumor.

3. *Fibrosarcoma* occurs as a rare primary tumor of the brain. These vary both grossly and histologically, exhibiting usually an encapsulated or distinctly demarcated appearance and containing varying amounts of collagen.

4. *Microglioblastomas* are described as primary tumors of microglia. They are closely related, or identical with, reticulum cell sarcomas.[81, 83]

5. *Reticulum cell sarcoma* and *lymphosarcoma* have been described as primary brain tumors. They resemble morphologically similar tumors elsewhere.

6. *Lymphoblastoma.* The principal lymphoblastomatous lesion of the nervous system is invasion in *leukemia.* The involvement of the nervous system appears with great regularity although not always apparent clinically. It is manifest as hemorrhage, thrombosis, infiltration, or tumorlike growth.[84] The meninges may be ex-

tensively infiltrated, and, rarely, the peripheral nerves (see page 889 and Fig. 1223).

7. *Metaplasia.* Response of mesodermal character is apparent in nervous tissue in myeloid metaplasia which rarely involves the central nervous system.

VI. Mixed Tumors.

Mixed tumors of the nervous system as elsewhere include those made up of tissue from distinctly identifiable heterotopic germ layers and are regarded as arising from embryonic rests (see page 1288). As might be expected these tumors are frequently associated with maldevelopment elsewhere.

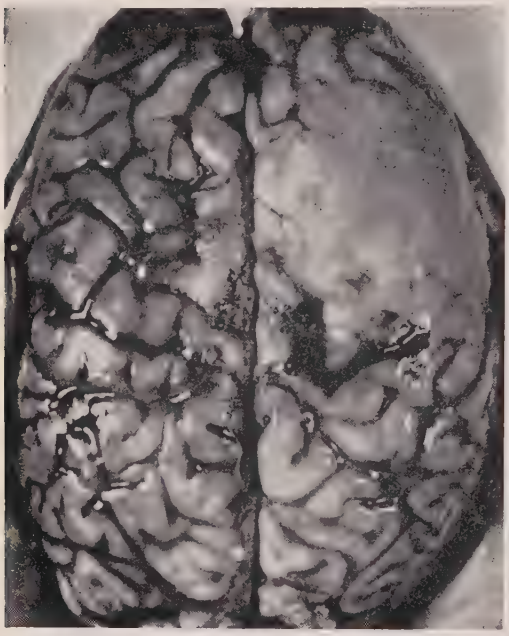


Fig. 1223.—Tumorlike leukemic infiltration of leptomeninx.

A. **Epidermoid cyst** (cholesteatoma, pearly tumor). Epidermoid cysts arise from aberrant epithelial rests as slowly growing intracranial or intraspinal masses. Histologically they are made up of a capsule of well-differentiated squamous epithelium surrounding a mass of keratohyalin which may be compact, flaky, and shiny (pearly tumors) and may contain cholesterol crystals (cholesteatoma).[85, 86, 87]

B. **Dermoid cysts** are similar to epidermoids with the addition of hair, sebaceous glands, and other skin appendages.[86]

C. **Teratomas** are distinguished from epidermoids and dermoids by the presence of cartilage, muscle, or other representative tissues of mesodermal origin. These are extremely rare tumors of the nervous system.[88]

D. **Craniopharyngiomas** include tumors developing from rests derived from the hypophyseal duct and embryonic pharynx (duct cysts and adamantinomas) (see also page 972).

1. *Rathke pouch cysts* develop from cell rests closely related to the capsule of the anterior lobe of the pituitary gland. The commonest site is the suprasellar ridge, hence *suprasellar cyst.*[89] The tumors are occasionally solid but are usually cystic. They often contain cholesterol crystals in the fluid. The tumors are often calcified and are thus demonstrable by x-ray. Histologically, the picture varies from columnar epithelium to epidermoid. Most commonly there occur irregular patches of squamous epithelium interrupted by whorls set in a reticulated fibrous background.

2. *Adamantinoma* occurs rarely as an intracranial tumor. It resembles its counterpart in the jaw (page 743) with formation of identifiable enamel organs (Fig. 1224).

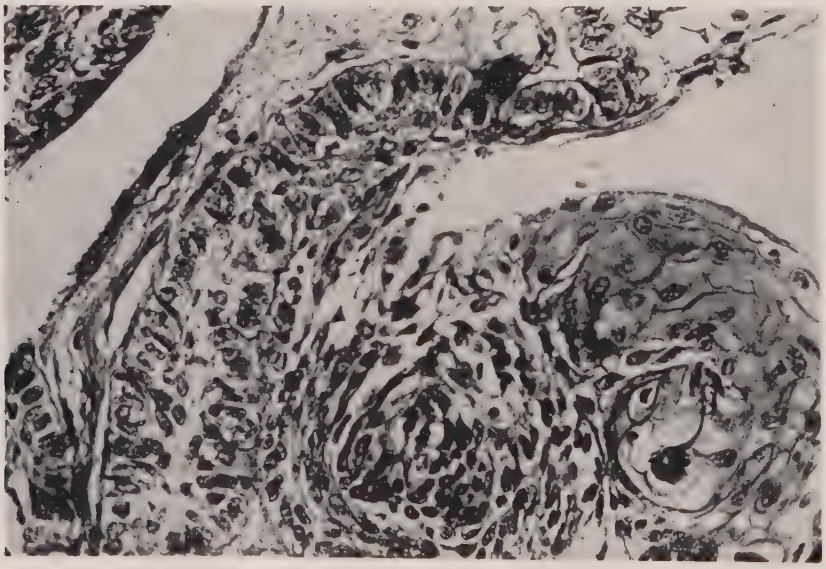


Fig. 1224.—Adamantinoma.

VII. Hypohyseal Tumors.

Tumors of the hypophysis are discussed in detail in the section on endocrine glands (page 967). Their close relationship to the nervous system arises from the topography of the parent tissue and the neurologic effects of expanding lesions in the hypophyseal area. The anterior lobe tumors include: *chromophobe adenoma, acidophile adenoma,* and *basophile adenoma.* Globus and Globus[90] described a tumor arising from infundibulum which presented histologic characteristics simulating neurohypophyseal tissue. The cells were fusiform with long tapering processes and occupied a highly vascular stroma. The tumor is designated *infundibuloma.*

VIII. Metastatic Tumors.

Metastases to the brain occur by direct extension and infiltration, by vascular emboli, and by migration through the meningeal spaces (retinoblastoma). Carcinoma of the lung is the major offender although metastases from carcinoma of thyroid, intestine, breast, stomach, kidney, adrenal, skin, and prostate also occur in approximately that order of frequency. Metastatic tumors can usually be identified by their globular shape, distinct demarcation, enucleability, and frequent multiplicity. Microscopically, they resemble the primary growth.

Degenerative Malformations of Obscure Nature

A number of diseases occur which by hereditary or familial trends and apparent faulty substance of special parts exhibit features relegating them among the malformations. Some are characterized by faulty metabolism (lipodystrophies) others by absence of groups of nerve cells, still others by peculiarities in myelination or loss of myelin. The last will be discussed under a separate heading (demyelinating diseases) and certain others (e.g., Huntington's chorea) are best discussed as topographic entities. Those nervous disabilities in this category dominated by muscular changes are described under neuromuscular disorders. Remaining is a heterogeneous group including spastic diplegia, amaurotic familial idiocy, and mongolism.

Spastic diplegia (Little's disease) is characterized clinically by spasticity of the lower extremities, choreiform movements, and, sometimes, mental deficiency due to central neuronal degeneration. Grossly, the brain is usually small and shrunken, with patches of microgyri, and there may be gross defects in the cerebellum and pons. Although the inciting cause is thought to be a defect in development, it is possible that some diffuse active process as well may be at work to induce the symptomatology. The syndrome is duplicated in infantile encephalomyelitides and in toxic reactions. There is some evidence implying dissolution of the small internuncial cells in the spinal cord gray matter,[11, 91] imposing a block between cerebral influence and the final-common-path. Microscopically, the atrophied areas show gliosis.

Amaurotic family idiocy (Tay-Sachs disease) is a familial condition which occurs in infantile and juvenile forms. The infantile form is found mainly in the Jewish race. Progressive muscular weakness develops in the early months of life, and mental development fails. There is a characteristic peculiar cherry-red spot in the retina, and, later, optic atrophy and blindness develop. The brain is atrophic and firm. The cerebellum may share in the atrophy. The characteristic histologic feature is distention of many of the nerve cells by a granular deposit of lipoid (lecithin) in the cytoplasm. The lipoid deposit also involves cell processes. The degeneration of nerve cells and processes is followed by widespread gliosis. The condition bears some relationship to Niemann-Pick's disease, in which, likewise, lecithin may be found in nerve cells. The condition probably represents a lipodystrophy and, as such, may be related to the Hand-Schüller-Christian syndrome, Gaucher's disease, and xanthomatoses (page 950).

In the juvenile form, which is more common in Gentiles, the cherry-red spot in the macula is absent, and the lipoid in nerve cells is not lecithin, but stains with the usual fat stains.

Mongolian idiocy is characterized by mongoloid features in an idiotic child of Caucasian parents. The head is usually small, the tongue prominent, and the musculature hypotonic. The brain is small and there may be gross defects in the gyri. There is apparently a diminished number of cortical neurones and the cortical architecture is distorted. Hypophyseal changes have been described (see page 962). The etiology is obscure.

Cerebral Atrophy

The atrophies are characterized by noninflammatory gross wasting of tissue apparent as microgyria. The etiology in most cases is poorly understood. There are a number of topographic subdivisions which are of descriptive value, including circumscribed cerebral atrophy, lobar atrophy, and hemiatrophy. Most impor-

tant in this category are senile and premature senile atrophies.

Circumscribed cerebral atrophy (Pick's disease) is manifest pathologically as patchy shrinkage of cerebral tissue with accentuation of sulcus volume and diminished size in the gyri (Fig. 1225). The atrophy occurs in parts of frontal, temporal, or parietal lobe, or in combination. Histologically, there is cellular bareness and gliosis. **Lobar sclerosis** (ulegyria) is a similar involvement covering an entire lobe. **Hemiatrophy** refers to a one-sided hemispheral atrophy, probably of varying pathogenesis.[92]

Senile Atrophy.—It is not surprising that loss of brain substance is attendant upon the shortcomings of senility. Nerve cells and fibers are lost[93] and sclerosis appears whether active or relative. Atrophy in senility to the extent of microgyria is a common occurrence and it varies in severity from barely visible sulcus accentuation to striking sclerosis. The frontal lobes are most often affected. There is frequently an associated thickening and opacity of the arachnoid over the area of microgyria. Extensive atrophies are common in senile dementia. The condition is usually ascribed to vascular deficiency. Histologically there is diminution in number of nerve cells, gliosis, and arteriosclerotic change. The appearance of senile plaques made up of argyophilic debris is a constant finding. Corpora amylacea and other nonspecific degenerations (page 1280) appear in the sections.

Premature senile atrophy occurs in a number of diseases, particularly syphilis (page 1327). A nonsyphilitic presenile atrophy associated with psychosis is **Alzheimer's disease.** The gross and microscopic findings are similar to those in senile atrophy but are usually more striking. Senile plaques (Alzheimer) occur in great abundance and active degenerative processes (fatty deposit in nerve cells and vessels, rod cell production) are identifiable.

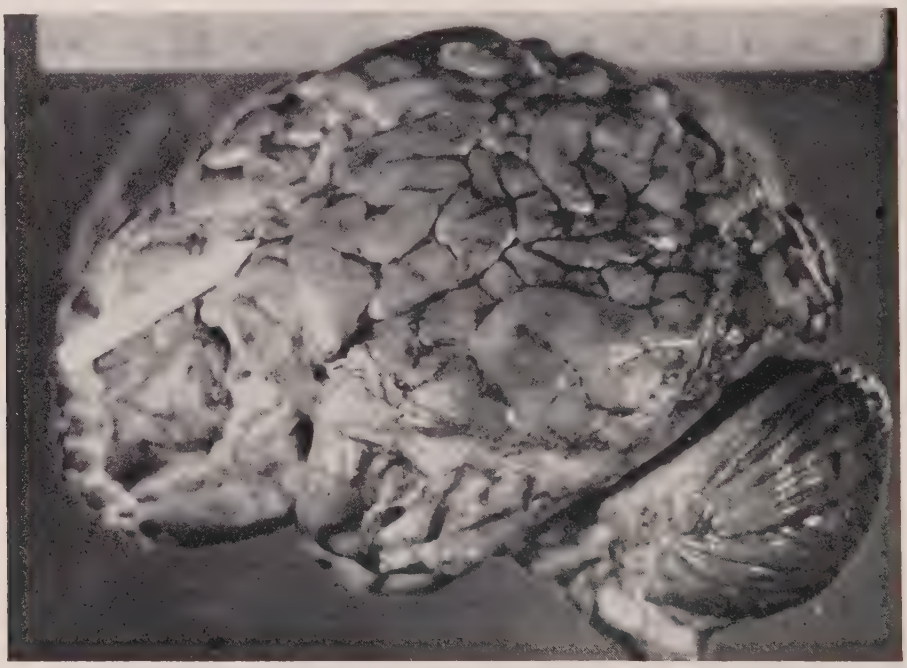


Fig. 1225.—Circumscribed cerebral cortical atrophy. Note the microgyri scattered over the hemispheral surface and the contrasting macrogyrus over the temporal lobe.

Cerebellar Atrophy

A number of cerebellar atrophies attended by ataxia and showing hereditary and familial tendencies occur. These include: Friedreich's ataxia, olivocerebellar atrophy, olivopontocerebellar atrophy, progressive cerebellar dyssynergia, and parenchymatous cortical cerebellar atrophy. **Friedreich's ataxia** is manifested in myelin degeneration in the spinocerebellar tracts and posterior columns with reduction of the size of the cord. The degeneration apparently be-

gins in the cells of Clarke's column. Late in the disease the pyramidal tracts may be involved. Gliosis follows myelin destruction. **Olivocerebellar atrophy** (Fig. 1226) appears as a degeneration of the inferior olive and opposite cerebellar hemisphere. In **olivopontocerebellar atrophy** the pons and inferior olive of one side are atrophic. **Progressive cerebellar dyssynergia**[94] exhibits degeneration of the dentate nucleus and superior peduncle without involvement of the olive and pons. **Parenchymatous cortical cerebellar atrophy** shows a striking loss of Purkinje cells in the cerebellar cortex (Fig. 1227). The possibility of this condition being a subacute encephalitis analogous to louping ill in sheep has been cited.[95]

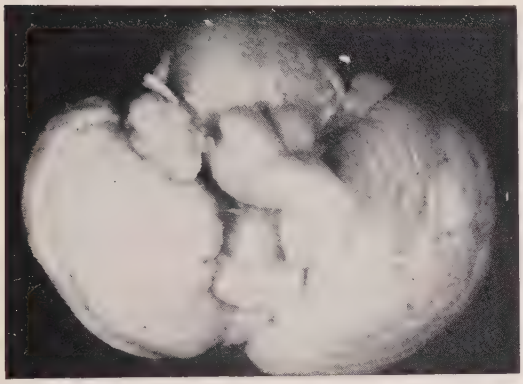


Fig. 1226.—Cerebellopontine atrophy. Note the crossed relationship of the atrophic change in pons and cerebellum. The inferior olive on the side of pontine atrophy is also small.

Diseases of the Extrapyramidal Motor System

In diseases of the extrapyramidal motor system, the lesions are localized or predominant in extrapyramidal parts known to affect motor activity. These parts include thalamus, basal nuclei (caudate, putamen, globus pallidus, claustrum, amygdaloid), and several lower stem nuclei (subthalamic body, nucleus ruber, substantia nigra). Cerebellar disabilities contribute to motor dysfunction of extrapyramidal type and often combine as a locus of pathology (see above). Clinically, in extrapyramidal disease there are disturbances in motor activity, manifested by tremor, choreiform movement, torsion spasm, or rigidity without true motor paralysis. The symptomatology varies with the topography of the lesion.

Progressive lenticular degeneration (Wilson's disease) is a familial condition appearing in an adolescent or young adult, its varying course progressing to a fatal ending in a few months to ten years. There is a bilateral symmetrical degeneration and cavitation of the putamen and, occasionally, the caudate nucleus. The involved tissue develops a spongy consistency. Microscopically, there is a cirrhosis of the liver (see page 818). In addition to the tremor and spasticity of skeletal muscles there is often striking emotional disturbance. A characteristic feature is the appearance of greenish pig-

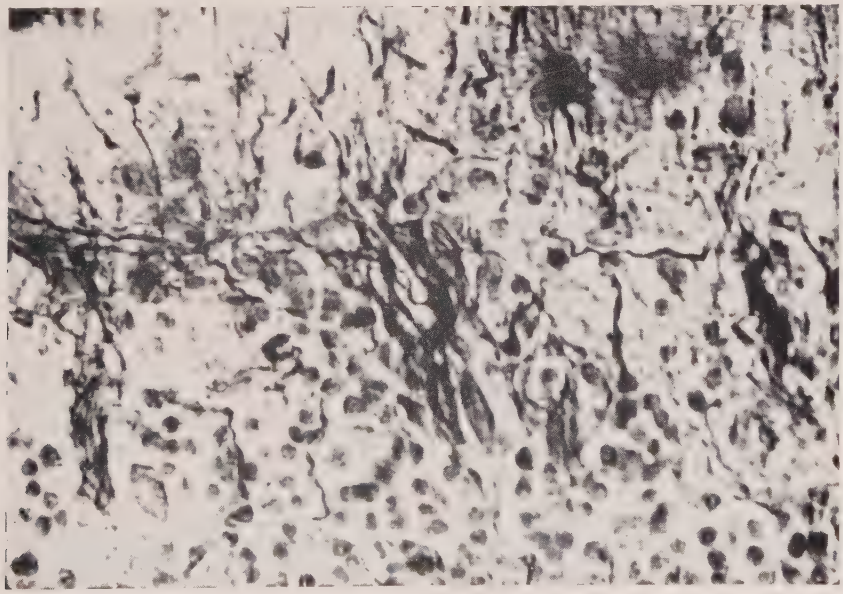


Fig. 1227.—Parenchymatous cortical cerebellar atrophy. Note loss of Purkinje cells with preservation of baskets.

mentation along the corneal margin (Kayser-Fleischer ring).

Pseudosclerosis (Westphal-Strümpel) occurs sporadically and in a younger age group (under 10 years) than Wilson's disease. The basal nuclei, with predominant thalamic involvement, are enlarged and sclerotic, but without a characteristic gross appearance. Microscopically, there is glial proliferation and gliosis. Cortical lesions may be present. The condition is often regarded as a form of Wilson's disease, which it resembles clinically.

Acute chorea (Sydenham's chorea) usually appears between the ages of 5 and 15 years. It is commonly associated with rheumatic fever, tonsillitis, exanthems, and various toxic and infectious encephalitides. There may be an associated rheumatic myocarditis. The cerebral lesions are difficult to localize, but such striatal involvement as embolic softenings, focal degenerations, toxic changes in striatal cells, and even focal structures resembling Aschoff bodies have been described. Clinically, the disease is characterized by rapid, involuntary, purposeless movements and marked incoordination, especially of the upper extremity. Mentality is not affected. Recovery occurs in a few weeks to several years.

Chronic progressive chorea (Huntington's chorea) is a familial progressive disease appearing after 30 years of age. Sporadic cases are said to occur also. Profound mental changes are associated with the grimacing, gesticulation, and incoordination of the chorea. The corpus striatum is severely shrunken, with dissolution predominant among the smaller cells, and degeneration is found in the supragranular layers of the cerebral cortex. Secondary gliosis is present in lesions of long standing. The cerebellum may also be involved in the pathologic process.

Paralysis agitans (Parkinson's disease, shaking palsy) is characterized clinically by course tremor (at rest) and muscular rigidity, most prominent in the upper extremity. Ordinarily the condition is progressive, with eventual appearance of the tremor in lower extremity, jaw, and tongue, and marked alteration in gait. Two distinct forms, "essential" and "secondary," are recognized. Essential Parkinson's disease begins during or after the involutional period and progresses slowly. The secondary form is associated with epidemic encephalitis, cerebral trauma, and degenerations due to chemical poisoning (manganese, carbon monoxide). There are degenerative changes in the basal nuclei, which rarely may be evident grossly as lacunar softenings associated with vascular disease. Senile changes may accompany the essential form. Often the changes in the basal nuclei are evident only on quantitative study. Loss of nerve cells and nonspecific cellular changes (pigmentation, degeneration, swelling, and shrinkage) predominate. The substantia nigra is the principal site of involvement in postencephalitic Parkinsonism, while the globus pallidus and putamen are damaged more prominently in the essential form.

Lesions of the basal nuclei may be associated also with **torsion spasm** (dystonia musculorum), a pattern of writhing distortions of the trunk; **spasmodic torticollis** (wryneck), a paroxysmal, jerky rotation of the head, often with eventual fixation; **athetosis,** purposeless writhing movements of the distal parts of the extremities; **hemiballismus,** unilateral, wild flinging, exhaustive movements suggesting exaggerated chorea; and **myoclonus and tic,** twitchlike, rapid muscle movements. The exact location of the lesions in these conditions is uncertain, and the symptoms are thought to arise from premotor cortical influence no longer modified by basal nuclear activity.[96, 97]

Neuromuscular Disorders and Muscular Dystrophies

Dissolution of muscle may occur from pathologic involvement of the central nervous system, peripheral nerves, or muscles themselves. Hence, the diseases are grouped as *myelopathic, neurotrophic,* and *myopathic.* Those in which the primary lesion is an inherent disability within the muscle itself are often referred to as *dystrophies.* It should be recognized that muscular atrophies are frequent consequences of distant central nervous system disease (e.g., cerebral hemorrhage). These are not properly relegated to the group of neuromuscular disorders. Since the term myelopathic is arbitrarily restricted to involvements of the final-common-path-cell within the central nervous system, these disorders may be combined with neurotrophic as *neuronogenic* disorders, implying a neuromuscular disability having its inception in disability of the final-common-path-cell or its peripheral extension.[98]

Neuronogenic Muscular Atrophy.—Acute atrophies of neural origin include poliomyelitis, Landry's paralysis, infectious and toxic neuritides, and traumatic neuropathy. These disorders are discussed elsewhere (pages 317, 1283, and 1324, respectively). Remaining are a number of chronic neurogenic myopathies which may be subgrouped as myelopathic and neurotrophic depending on central or peripheral pathologic dominance.

Chronic Myelopathic Atrophies.—Chronic myelopathic atrophies include: amyotonia congenita, progressive muscular atrophy, amyotrophic lateral sclerosis, and poliomyelopathia chronica. Clinically, these diseases present involvement of motor neuron systems, both the final-common-path and the "upper" motor neuron, in combination or in succession.

This feature is striking also, pathologically, in which degeneration of anterior horn cells and of corticospinal tracts can be demonstrated. It should be noted, however, that a striking similarity to primary muscular atrophy may appear in the course of tabes. Clinically, the differentiation is usually apparent from serologic studies and, pathologically, posterior column degeneration accompanies or precedes the motor neuron dissolution. There occur, then, two rather distinct clinical groups of chronic muscular atrophies, those obviously secondary (tabetic and possibly poliomyelopathy chronica) and those which are primary and whose etiology is obscure (amyotonia congenita, progressive muscular atrophy, and amyotrophic lateral sclerosis). Certain features of each deserve special mention.

Amyotonia congenita (Oppenheim's disease) has as its essential feature a paucity of cells in the anterior horn of the spinal cord. The disability is usually evident clinically shortly after birth. In a related condition (Werdnig-Hoffmann type) there is active degeneration of anterior horn cells with neuronophagia. Muscle groups lacking appropriate nerve supply exhibit profound weakness and atonia with consequent hyperexcursion. The etiology is unknown. Microscopically, the muscle fibers show marked variation, many being of embryonic type and others very large. The total number of fibers appears to be reduced.

Progressive muscular atrophy is a sporadic disease attacking young adults. Pathologically, there is a degeneration of anterior horn cells with consequent muscular atrophy. The degenerative changes in muscle include variation in fiber size and fragmentation of myofibers.[99] The disease is slowly progressive. Its course may be interrupted by spontaneous stationary periods lasting many years. It differs from amyotonia congenita principally in its later onset and progressive course. Eventually there is usually associated degeneration of tracts in the central nervous system, particularly the pyramidal tracts. The disease may appear first in a *spinal* or *bulbar* position, the latter being rapidly fatal due to involvement of vital centers.[100]

Amyotrophic lateral sclerosis is closely allied to progressive muscular atrophy. It begins later in life and ordinarily leads to an earlier fatal termination. Beginning as a bilateral atrophy of the pyramidal tracts there is an initial period of spastic paralysis. This is followed by degeneration of anterior horn cells and muscular changes similar to progressive muscular atrophy. The muscular denervation atrophy usually begins in the hands, spreading to the shoulders and is coexistent with bilateral spasticity of the lower extremities.

Poliomyelopathica chronica (poliomyelopathy, chronic poliomyelitis)[98] is a degenerative, noninflammatory neuromuscular disorder closely allied to progressive muscular atrophy but occurring, usually, as a sequel to poliomyelitis. The volume of gray matter in the cord is reduced, anterior horn cells are lost, and there is extensive replacement gliosis often encroaching on white matter.

Chronic Neurotrophic Atrophy.—Chronic neurotrophic atrophies include: hypertrophic interstitial neuritis, peroneal atrophy, and those occurring with avitaminosis and gradual pressure. Avitaminosis is discussed on page 412, and pressure atrophy is a slow traumatism eventuating in peripheral nerve degeneration (page 64). **Hypertrophic interstitial neuritis** (Dejerine-Sottas) is characterized by the appearance of nodular expansions along a peripheral nerve. The nerve shows loss of myelin and the nodular zones are made up of proliferated sheath cells in an edematous mucinoid matrix. **Peroneal atrophy** (Charcot-Marie-Tooth) is a slowly progressive wasting of leg muscles below the knee with a resultant equinus deformity. The initial lesion is thought to appear as a peripheral nerve degeneration. Involvement of forearm muscles sometimes succeeds the peroneal atrophy.

Chronic Myopathic Atrophy—Dystrophy.—The myogenic atrophies are referred to as dystrophies and include: progressive muscular dystrophy, pseudohypertrophic muscular dystrophy, myasthenia gravis, and myotonia congenita. Several poorly understood dystrophies also deserve mention. These include *family periodic paralysis,* characterized by recurring bouts of paralysis in different members of a family; and *dystrophia myotonica* in which there is both wasting and marked atonia.

Progressive muscular dystrophy may be generalized or localized to special muscle groups, e.g., facioscapulohumeral (Landouzy-Dejerine), distal forearm (Gowers). The pathologic process is similar in all and consists of a profound degeneration of muscle tissue varying in degree in different muscles and at different times in the course of the disease. The histologic picture is one of marked variation in size of fibers, proliferation of muscle nuclei with invasion into the sarcoplasm, hypertrophy of some fibers with vacuolation, partial loss of striation, fatty infiltration, and fibrosis. Vasculature and muscle spindles are preserved.

Pseudohypertrophic muscular dystrophy (Duchenne) is a progressive muscular dystrophy in which a pseudohypertrophy of muscle is the

dominant feature. The hypertrophic changes begin in the thigh and calf muscles and spread to trunk and shoulder. The disease is most common in males under 10 years of age. Gradually, atrophy occurs and the picture described for progressive muscular dystrophy supervenes.

Myasthenia gravis is characterized by periodic occurrence of flaccid paralysis involving muscles of mastication, swallowing, and of the eyelids. The distinguishing histologic feature is the presence of lymphorrhages, clusters of round cells, in the interstices of otherwise normal-appearing muscle. Some cases are associated with thymic tumors (see page 957). The condition is relieved by administration of parasympathetic stimulators.

Myotonia congenita (Thomsen's disease) is an hereditary disease of childhood in which muscle groups exhibit sustained contraction after stimulation. The affected muscles show hypertrophy, indistinct striations, and slight perimysial fibrosis.

Degenerative Encephalopathies

Various degenerative lesions of the nervous system occur due to soluble toxins, chemical poisons, anesthesia, uremia, diabetic coma, hypoglycemia, hepatic disease, metrazol and shock therapy, deficiency diseases, anoxia, and erythroblastosis fetalis.

The group due to soluble toxins includes: tetanus, botulism, diphtheria, and a heterogeneous group of undetermined etiology referred to as "toxic" encephalopathy. *Tetanus* (see page 215) exerts its effect by its neurotropic toxin. Morphologic changes in the nervous system are not striking although there are hyperemia, swelling of nerve cells, and failure of staining of synaptic structures. *Diphtheria* toxin frequently results in diphtheritic neuritis (page 214). *Toxic encephalopathy* is the term which may be applied to many conditions having symptoms of encephalitis, and sometimes occurring in pneumonia, typhoid fever, scarlet fever, erysipelas and other streptococcic infections, and pertussis. The gross pathologic changes of hyperemia, edema, and petechial hemorrhages are nonspecific. Microscopically, the tissues are free of neutrophilic infiltration but may show satellitosis, nerve cell body changes including swelling, chromatolysis and nuclear damage, and vascular responses such as hemorrhages and endothelial proliferation. *Chemical poisons,* such as arsenic, lead, manganese, carbon monoxide, and alcohol, may give rise to degenerative changes in the nervous system. The mechanism is ascribed to actual toxic necrosis implicating vascular structures primarily, or to relative or absolute anoxia. Pathologic alterations include edema, congestion, focal softenings, and hemorrhages. Actual inflammatory changes are rare. The changes being nonspecific, demonstration of the toxic substance is essential to diagnosis. *Anesthetic agents* such as ether, chloroform, nitrous oxide, cyclopropane, and barbiturates have all been incriminated as occasional causes of death. Relative anoxia usually is described as the mechanism by which neuronal degeneration is induced. Ether and chloroform, as strong fat solvents, have been known to precipitate demyelination and are generally regarded as dangerous in any patient with a demyelinating disease. Microscopically, there may be found satellitosis, glial proliferation with the formation of glial nodes, and nonspecific changes in the nerve cell bodies, such as shrinkage and nuclear pyknosis. *Uremia* may be accompanied by marked edema of the brain, with pressure marks and coning, and anemia, believed due to the swelling of the brain. The nerve cells are swollen and sometimes there is perivascular cuffing. The pathogenesis is obscure. *Diabetic coma* is usually accompanied by little morphologic change. It is usually considered due to relative anoxia, rather than toxemia. *Hypoglycemia* due to insulin therapy or a tumor of pancreatic islet tissue may exhibit cerebral signs. Changes in the nervous system include chromatolytic, vacuolar, and pyknotic nerve cell alterations (nonspecific), formation of pseudogiant cells, gemistocytosis, degeneration of axis cylinders, and petechial hemorrhages.[101] Hepatic disease of severe degree is so commonly associated with disturbance in cerebral function as to suggest the entity, *hepatic encephalopathy.* The changes are nonspecific degenerations in nerve cells and perivascular tissue. The lesions are presumed to be toxic in origin possibly from circulating toxins arising as a consequence of the failure of the detoxifying function of the liver.[102] *Metrazol* and *shock therapy* may produce cerebral brain damage similar to that of hypoglycemia. Hemorrhage may be prominent, particularly in electric therapy. *Vitamin deficiency diseases,* particularly pellagra, beriberi, rickets, and scurvy, may have associated degenerative changes in the nervous system (see page 411). *Inanition* eventually results in degenerative changes in the nervous system. There is, however, a remarkable sparing of nervous structure in starvation.[103]

Anoxic encephalopathy resulting from oxygen deprivation from any source includes the degenerative states listed above in which the mechanism is based on oxygen lack (many chemical poisons, anesthetic agents, hypoglycemia). Also, ischemia from any cause (e.g., arteriosclerosis) and diseases resulting in partial or complete asphyxia induce an anoxic encephalopathy. Indeed, probably few diseases exercise their destruction in the nervous system without an anoxic factor in the pathogenesis. There is, however, a rather specific entity in actual oxygen deprivation (anoxic anoxia) as occurring in high altitude flying.[104, 105] Experimental equivalents to human anoxia are represented to include the following changes: selective neuronal degeneration manifest as chromatolysis, shrinkage, hydropic change, and nuclear pyknosis; glial changes including proliferation, gliosis, and swelling; vascular changes, principally hyperemia, perivascular hemorrhages and lipoid deposits in the adventitia. The changes in nerve cells exhibit a topographic dominance being most pronounced in hippocampus, Purkinje cells, basal ganglia, and the

third layer of the cerebral cortex. The effects of asphyxia in the human being (asphyxia neonatorum, slow strangulation) are essentially similar to the experimental findings in anoxic anoxia above. It is generally felt that oxygen-want is quickly reflected clinically in neurologic disorders because of the particular vulnerability of nerve cells. The histologic evidences of this effect are most indefinite, however, since the changes incident to varying agonal periods of poor oxygenation are present in practically all postmortem material.

Kernicterus.—A degenerative encephalopathy associated with erythroblastosis fetalis occurs in which the hippocampus, basal nuclei, midbrain, medulla, and floor of the fourth ventricle are bile stained. The nerve cells in the areas which are discolored are shrunken and stain with eosin, and a few contain yellow pigment. There is little effect on the glia and connective tissue in the stained regions.[106]

Irradiation Encephalopathy.—While mature nervous tissue is extremely resistant to irradiation, adverse effects appearing as an amyloid-like degeneration has followed large doses of x-ray to the head region.[107]

Demyelinating Diseases

A process of demyelination has been described as a secondary phenomenon following damage to continuity of nerve fibers (page 1283). The damage may be traumatic, ischemic, or result from pressure or inflammation. Apart from this obviously secondary demyelinating process, loss of myelin occurs as a dominant pathologic feature in the absence of recognizable cause. In the search for etiological clarification, demyelination has been successfully induced by a great variety of experimental procedures—enough, in any event, to allay incrimination of any single agent. In a review of recent observations on demyelination, Hurst[108] concludes that the phenomenon appears to be the "response of the white matter to injuries short of those immediately lethal to the tissues." In human disease demyelination appears as both a diffuse and a disseminated process.

Diffuse Leukoencephalopathy.—The term **diffuse leukoencephalopathy** includes a large, heterogeneous group of diseases varying in age of appearance from infancy to adolescence, in onset from acute to gradual, and in course from a few months to many years. Familial or hereditary trends in some types are described. All are characterized by diffuse dissolution of white matter, usually bilateral and symmetrical, and beginning in the occipital lobes with extension forward. The terminus is often by aspiration pneumonia or respiratory paralysis which interrupts the process at various stages. Grossly, the brain is soft and the white matter gelatinous. In some brains there are sclerotic plaques. Weigert stains show absence of myelin, with sparing of the short associational axones at the cortical margin (Fig. 1228.) Older areas of degeneration show glial proliferation with formation of many bizarre cell forms and various areas of gliosis. Areas of active degeneration show a fat-granule cell reaction, with perivascular cuffing by fat-laden macrophages, and the meningeal spaces may contain large numbers of these cells. There may be diffuse sclerosis or none at all. References to this condition and its variants may be found under the terms diffuse sclerosis, leukoencephalopathy without sclerosis, progressive degenerative subcortical encephalopathy, encephalitis periaxialis diffusa, Schilder's disease, Krabbe's disease, and Pelizaeus-Merzbacher's disease.

Fig. 1228.—Diffuse leukoencephalopathy (Schilder's disease). Note almost total loss of myelin except for remaining stainable short association bundles from gyrus to gyrus. There is a lacunar cystic softening between the insula and basal nuclei.

Disseminated sclerosis (multiple sclerosis) is a relatively common disease of undetermined etiology, with onset usually between the ages of 20 and 40 years. Pathologically, there are widespread scattered irregular lesions, predominantly in white matter, which appear grossly as yellow-gray areas on the cut surface of the brain or cord. These stand out prominently as pale areas in Weigert preparations (Fig. 1229). They are most prominent in the long tracts of the cord, and lesions of the stem and cord figure conspicuously in the symptomatology. Microscopically, the lesion is a plaque of demyelination, and in degenerated areas of long standing there may be gliosis. The early degeneration is said to spare the axis cylinders, accounting for transient remissions. The observations of Alexander and Putnam[109] tend to discount this classical explanation. As in diffuse sclerosis, the microscopic picture depends on the duration of the lesion.

In the active process, fat granule cells are operative, form perivascular cuffs, and spill into the subarachnoid space. The optic nerve is often involved. If the optic neuritis dominates and is associated with an acute patchy encephalomyelitis, the condition is called *ophthalmoneuromyelitis* (Devic's disease). The role of disorders of the vascular bed in disseminated sclerosis is controversial. Putnam[110] maintains that thrombotic vascular lesions play an important part in the pathogenesis. Hassin[111] views the disease as unrelated to vascular pathology. From a detailed study of sixty lesions in five cases of disseminated sclerosis, Dow and Berglund[112] concluded that the lesions are most often oriented about veins (40 out of 60), but that thrombosis might result from liberation of thromboplastic substances in the breakdown of myelin. The induction of the breakdown of myelin is variously postulated to be due to emboli, anoxia, ischemia, toxins, viruses, vitamin deficiency, abnormal enzymes, and to allergic reactions (see review by Hurst[108]).

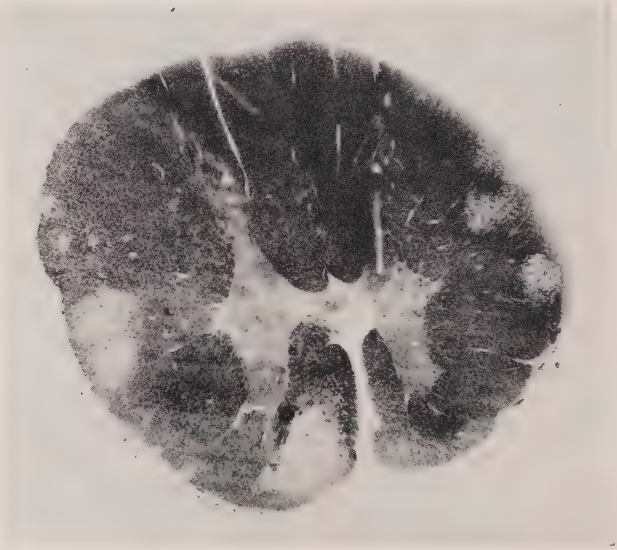


Fig. 1229.—Disseminated sclerosis.

In **subacute combined degeneration** there is patchy degeneration affecting the posterior and lateral columns of the spinal cord. It is associated with macrocytic (pernicious) anemia and achlorhydria. The early lesions are focal areas of destruction of axis cylinders and myelin sheaths, with softening and removal of degenerated material by microglial cells. Fusion of the areas and ascending and descending degeneration of cord tracts result in extensive damage of the posterior and lateral columns. Inflammatory reaction is absent, and little glial repair occurs. The damaged areas show only a delicate, spongy network of glial fibers. The exact relationship to pernicious anemia is still unknown. There is some evidence that early adequate liver treatment will prevent involvement of the nervous system. Since repair does not occur in the central nervous system, liver therapy will not undo the damage. Peripheral nerve demyelinization is also common in pernicious anemia, and improvement in nervous symptoms following liver therapy is due probably to repair of peripheral nerve degenerations.

Encephalitis

The term, encephalitis, implies an inflammatory disease of the brain. The inciting agents are many and varied and include parasites, fungi, bacteria, rickettsiae, and viruses. Encephalitides are closely related to meningitides, and coexistence is the rule. It is, however, convenient to describe the diseases in categories based on topographic dominance of the lesion. By combining terms (encephalomyelitis, encephalomeningomyelitis) more descriptive appellations may be devised. It should be recognized that inflammation of the brain is, in most instances, a part only of a general pathologic complex. Clinically, as a rule, cerebral involvement is such a striking event that the neurological features dominate the symptomatology. In the same way the lesions in the nervous system often dominate the pathologic picture. As a consequence, brief summaries of the neuropathologic characteristics of these diseases are presented here. For descrip-

tions of the complete pathologic complex refer to appropriate chapters.

Allergic Encephalitis.—As might be expected, a true inflammatory reaction in the brain from injection of antigenic substances does occur experimentally. Histologic observations as well as imprints in successive stages of reaction reveal edema, necrosis, and perivasculitis as the characteristic responses to sensitizing agents. These are observed both in meningeal and intramedullary vasculature.[113, 114]

Parasitic Encephalitis.—In *cysticercosis* a cysticercus may lodge in the brain, meninges, or ventricles. Apparently the living parasite is well tolerated in nervous tissue, but profound foreign reaction appears with the death of the organism. There is a reactive glial encapsulation with slow calcification.[115] Purulent meningoencephalitis may result from cysticercosis.[116] *Schistosoma* infection may involve the nervous system inducing epileptiform seizures.[117] In *trichinosis* trichina embryos may spread to the nervous system, resulting in meningoencephalitis. The lesion is one of cellular exudate incorporating the trichina together with degenerative parenchymatous changes.[118] *Trypanosomiasis* (African sleeping sickness) is primarily a neurologic disorder with chronic nonpurulent leptomeningitis and widespread intramedullary perivascular cuffing. Rarely *E. histolytica* invades the nervous system. *Malarial organisms* may produce thrombotic lesions of cerebral capillaries, resulting in small infarctions and petechial hemorrhages. Histologically, there are thrombi of pigment, red cells, and plasmodia, and pigmented capillary endothelium. *Toxoplasmosis* is a recently recognized important agent in encephalitis, inducing obliterative ependymitis in the infant and diffuse encephalitis in the adult (page 475).

Mycoencephalitis.—Meningoencephalitis due to pathogenic fungi is being reported with increasing frequency. Blastomyces, Actinomyces, Coccidioides, and Torula are the most common causative agents. Of these, Torula (Cryptococcus) is most important and will be discussed as a meningitis because of the predominant involvement of brain membranes.

Encephalitis Due to Bacteria.—Bacterial disease of the nervous system occurs principally as a granulomatous encephalitis (tuberculoma and gumma) or as a suppurative encephalitis or *brain abscess.* Bacteria can frequently be demonstrated diffusely throughout cerebral tissue in autopsied specimens. These organisms ordinarily represent a bacterial spread occurring in the agonal period and are usually saprophytes unrelated to the disease. Exceptions include systemic invasions by gas-forming organisms which may or may not play a role in pathogenesis. Frequently, the brain as well as other organs (particularly liver) is shattered and completely filled with gas spaces from which gas-forming organisms can be cultured, and in which enormous numbers of organisms can be identified histologically. As a rule such pathologic change is regarded as agonal except when the gas-forming process was a definite part of the clinical picture, antedating the agonal period. While histologic evidence of inflammatory reaction is slight, very striking gross lesions of the nervous system appear in *Welchii infections* (as generalized sponginess or multiple crevices).

Granulomatous Encephalitis.—Granulomas of the brain include gummas and tuberculomas. Other organisms producing granulomas elsewhere (actinomyces) tend to produce acute suppurative lesions of the nervous system. *Gummas* appear commonly as minute extensions of the lesions in the arteries. A space-occupying tumefaction of gummatous nature simulating brain tumor is a rare finding (see section on neurosyphilis). *Tuberculomas* of the brain are similar morphologically to tuberculomas elsewhere. In general the term applies to grossly apparent tumefactions. Small tuberculomas, however, occur with greater frequency and are usually identified only by careful search in patients dying of tuberculous meningitis. The gross, space-occupying lesions are confused clinically with neoplasms and appear occasionally as incidental findings. Occasionally the age of the process is suggested in elaborate calcification and other evidence of a long-standing process.[119] In the more common, smaller lesions, evidence of active growth is apparent and meningitis is the usual accompaniment.[120] (See Tuberculous meningitis, page 1327.)

Brain Abscess.—Focal suppurative lesions of the brain are common sequelae of infections, usually of chronic type, elsewhere in the body. The primary sites of infections, in order of importance, include: middle ear (otitis media), lungs (bronchiectasis, empyema, abscess, gangrene), bones (osteomyelitis, mastoiditis), paranasal sinuses (suppurative sinusitis), systemic infections (septicemia, endocarditis), focal infections of skin and mucous membranes, particularly head region (furunculosis, carbuncle, pharyngitis).[21] In addition to the secondary abscesses, suppurative lesions occur primarily in the brain from direct implantation of septic material in trauma. In a rather large number of cases the primary site of infection is totally obscure. There will be no history of disease that is related, and careful search fails to reveal suppurative disease anywhere. The general feeling is, however, that, except for direct implantation, brain abscess is always secondary to some other focus of infection.[121] In these cases, then, it must be assumed either that the source of the infection was not found or that it disappeared as a focal lesion during the development of the abscess.

An understanding of the pathogenesis of cerebral abscess, then, depends largely upon

recognition of the mode of transmission. Carmichael, Kernohan, and Adson[21] have classified the lesions on this basis as follows:

1. Direct implantation
   a. Trauma
      (1) Penetrating wounds
      (2) Fracture of the skull
   b. Surgery
2. Contiguous extension
   a. Direct suppurative extension
   b. Extension via blood vessels
      (1) Phlebitis
      (2) Thrombosis
      (3) Embolism
   c. Extension via Virchow-Robin spaces
      (1) Perivasculitis
      (2) Perivascular stasis
      (3) Alterations in pressure of cerebrospinal fluid
   d. Extension by preformed paths
      (1) Nerve sheaths
      (2) Foramina
3. Metastatic extension
   a. Without antecedent trauma
   b. With antecedent trauma
4. Origin and mode of extension undetermined

Direct implantation of septic material occurs in penetrating wounds and skull fractures, particularly if a paranasal sinus has been traversed or opened. The traumatized cerebral substance provides a favorable medium for bacterial growth and the injury is often aggravated by the presence of foreign material. It is not essential that cerebral tissue be directly entered. An osteomyelitis from a compound fracture of the skull or a superficial dural infection may traverse the meningeal spaces to result in cerebral abscess. Septic material may be conveyed to an intramedullary position by backflow along superficial cerebral veins which occurs from focal thrombophlebitis in the meningeal spaces. There is invariably an attendant meningitis which may be distinctly limited to the traumatized area. Surgical procedures involving probing not uncommonly result in abscess formation. Brain tissue traumatized by surgical manipulation shows tremendous polymorphonuclear mobilization even in the absence of culturable infecting organisms. As a consequence, diagnosis of a septic condition in cerebral tissue on histologic grounds alone is probably not justified. A rather common experience is the development of a cerebral abscess near the site of trauma or surgical procedure some weeks or months after superficial healing. It is assumed that the lesion develops slowly from an organism of low virulence left as an inoculant or that the area of traumatization, as a locus resistentiae minoris, has acquired the infective agent in the course of healing.

In contiguous extension a suppurative process may pass directly from bone through dura and meninges and into brain. This phenomenon is observed constantly in temporal lobe abscess following otitis media. The bone is eroded and a fused mass of meninges and brain occurs, with suppuration pocketed in the soft nervous tissue. Not infrequently the course of the extension is not so apparent and the abscess, though adjacent to the infected primary site, may lie deeply and exhibit no track along which the process extended from primary to secondary locus. With extension of the infection to meninges a phlebitis occurs which may be transmitted along the vein wall to set up an infected focus at some distance. If thrombosis occurs, extension of the septic thrombus may inoculate a distant focus. With occlusion of the vessel and reversal of blood flow, fragmented septic emboli may lodge intramedullarly at some distance from the primary infection.[122, 123] With meningitis adjacent to the infected site the causative agents have access to the perivascular spaces and set up a perivasculitis. With increased intracranial tension there may be a reversal of flow of the interstitial fluid in the Virchow-Robin space, with movement of the agent from a subarachnoid to an intramedullary position.[124] Extension of infectious agents along perineuronal sheaths is described in relation to olfactory and acoustic nerves. The foramina of the skull would undoubtedly facilitate transmission of suppurative material from the outside to the interior of the skull. Once inside, however, inoculation of cerebral tissue would undoubtedly follow one of the several mechanisms outlined above.

Metastatic extension of infection occurs by arterial emboli or bacterial showers or by traversing the vertebral and epidural venous plexuses. The mechanism of the transfer is no different from that of tumor metastasis.[1] Metastatic lesions are often multiple. They occur most commonly from suppurative pulmonary disease and from endocarditis.

The most common sites for brain abscess are the temporal lobe of the forebrain and the cerebellar hemisphere. Grossly, the abscess is made up of a fluid, purulent center surrounded by a capsule of varying thickness. Usually the purulent material is yellow or greenish, depending apparently on the nature of the causative agent. Frequently there are satellite abscesses of small size which appear to be entirely separate from the main lesion. Occasionally the capsule is poorly formed, with purulent material appearing in indistinct gelatinoid pockets which are irregular in shape (diffuse suppurative encephalitis). This situation obtains in infection by organisms of peculiar type or virulence and when a previously encapsulated abscess has ruptured.

Bacteriologic studies reveal a large number of organisms which are presumed to be capable of causing brain abscess. *Staphylococcus aureus* is a common agent, often mixed with streptococcus and pneumococcus. *Ps. aeruginosa,* Friedländer's bacillus, fusiform bacilli, *H. influenzae, Proteus vulgaris, E. coli,* and actinomyces have all been incriminated. *E. coli* and actinomyces tend to less capsulation, produce more disseminated, less well-defined abscesses.

Following inoculation there is an intense leukocytic infiltration with the production of a miliary mass of polymorphonuclears and a resultant focal necrosis. With destruction of nerve tissue a fat granule cell reaction occurs and the abscess appears as a mass of leukocytes with necrotized debris, red blood cells, fibrin, and fat granule cells. If the lesion occurs as a septic thrombus, the histologic appearance is that of a small infarct with a surrounding zone of hyperemia and small hemorrhages related to a central cellular core. The lesion gradually becomes demarcated by production of a fibroblastic wall in the zone of hyperemia. The origin of the fibroblasts is in dispute and is attributed to conversion from lymphocytes,[125] to development from endothelial cells,[21] or to stimulation of neighboring adventitial or meningeal fibroblasts.[126] Peripheral to the encapsulating fibrosis there is a mild glial reaction with both proliferation of astrocytes and gliosis.

The striking feature of abscess formation in the brain is the fibroblastic capsule. In destructive lesions without suppuration or meningeal involvement (infarction, hemorrhage, nonsuppurative inflammations) fibroblastic activity is exceedingly limited in the central nervous system.

A brain abscess probably never heals spontaneously. The eventual result is rupture, with disseminated suppurative encephalitis, purulent meningitis, or intraventricular spread. One or the other of these conditions is the usual finding at autopsy. Surgical relief by tapping or drainage has been accomplished repeatedly. The repair phases leading to "healing" are those resulting from surgery. Prolonged drainage is sometimes accompanied by gradual enlargement of the abscess until enormous cavities are formed. In more favorable cases a gradual closing occurs, with formation of a dense contracted cicatrix which, in itself, may be a serious lesion associated with the appearance of convulsive seizures.

Rickettsial Encephalitis.—Cerebral lesions in rickettsial diseases represent a part of an elaborate histologic complex (see Chapter 14). The characterizing neurological lesion is the glial (typhus) nodule (Fig. 1183), a pericapillary cluster of mononuclear cells variously described as one, or including several of the following: oligodendroglia, lymphocytes, perithelial cells, plasma cells, macrophages, microglia, and occasionally polymorphonuclears. In a comparative study of cerebrospinal lesions in rickettsial diseases, Allen and Spitz[127] point out certain histologic differences among scrub typhus, epidemic typhus, and Rocky Mountain spotted fever. In topographic disposition the nodules occur predominantly in cortical gray matter in scrub typhus and epidemic typhus with sparing of the white matter. In Rocky Mountain spotted fever the nodules occur predominantly in white matter with sparing of the gray matter. The lesions are diffuse throughout the central nervous system with great regularity in epidemic typhus, less so in the others. An intense mononuclear meningitis is common to both epidemic and scrub typhus, with exudate including acidophilic macrophages, lymphocytes, and plasma cells. The nodules in scrub typhus present 18 to 40 cells in a single section plane, while those in epidemic typhus vary from 55 to 75. The cells in the nodules of scrub typhus include oligodendroglia, with occasional other mononuclears. There is greater pleomorphism in the epidemic typhus nodule with marked karyorrhexis. Capillary and arteriolar damage with endothelial hypertrophy, karyorrhexis of endothelial cells, and thrombosis is more intense in epidemic than in scrub typhus. The nodular lesion of Rocky Mountain spotted fever is essentially a microinfarct with periarteriolar nerve tissue destruction into which migrant elements are attracted. Scheinker[128] believes

these "miliary granulomas" to be derived from mesodermal elements (pericapillary tissue or capillary adventitia).

Primary Encephalitis.—The primary encephalitides of man are those not associated with chemical, parasitic, or bacterial agents and thought to be induced by neurotropic viruses. In general, identity of the disease is established by means other than morphology (see page 323). Although several specific lesions do occur, many encephalitis cases appear in any autopsy service which are never satisfactorily classified. The lesions may be disseminated or focal, and occur both as reactive and degenerative processes. Often a virus is postulated on histologic grounds, but fails to appear in laboratory procedures designed to identify specific agents. As a consequence, many encephalitides are assigned to an unknown virus etiology. There are, however, several known virus agents causing encephalitis in man. These include: (1) rabies, (2) poliomyelitis, (3) St. Louis type encephalitis, (4) Japanese B encephalitis, (5) equine encephalomyelitis[136-150] (Western and Eastern), (6) herpes,[142, 143] and (7) x-disease. In addition, laboratory transmission to man of "B" virus of monkeys and of louping ill virus of sheep has been reported.[129, 130] (See page 315.) While a virus agent has not been identified in postvaccinal encephalitis,[144-146] epidemic encephalitis, and hemorrhagic encephalitis, these diseases possess a number of pathologic features linking them with the primary encephalitides. The viral encephalitides are discussed in Chapter 14.

Poliomyelitis (Acute Anterior Poliomyelitis, Infantile Paralysis).—The lesions of poliomyelitis vary strikingly with the stage of the disease at which the tissue comes under observation. The gross appearance of early fatal poliomyelitis is that of hyperemia with injection of both meningeal and intramedullary vasculature and a pinkish color of the cut surface of brain and cord. In patients dying several days or weeks after the onset, areas of intense hyperemia in the cord may be replaced by grayish softened areas. There may be widespread opacity of the meninges, and universal edema of the nervous system is apparent. In ancient poliomyelitis the residual lesion can often be identified as a striking loss of gray area in cut sections of the cord, particularly in the enlargements.

Numerous topographic studies point to the anterior gray columns of the spinal cord enlargements as the site of most intense histologic change in poliomyelitis (polio—gray). While this predilection is unquestioned, few inspections fail to reveal evidences of microscopic disarray throughout the nervous system. In early fatal poliomyelitis there is a rather intense meningeal infiltration with inclusion of many polymorphonuclear leukocytes in the exudate. The intramedullary vasculature is frequently universally distended and perivascular cuffing may be diffuse. There is patchy interstitial exudation with occasional polymorphonuclears. The lesion most often cited is neuronophagia. The phagocytosing elements may be seen invading a nerve cell or may be seen as a cluster occupying the site and contour of a completely phagocyted nerve cell. Neuronophagia is most striking when identified in the large anterior horn cells but the process may be widespread and often conspicuous in the smaller cells of the intermediate gray area. Rarely the posterior rootlets exhibit inflammatory changes and the dorsal root ganglia may be involved. In ancient poliomyelitis the histologic changes are essentially loss of nerve cells and gliosis with general shrinkage of the anterior gray columns.

It would be most helpful to understand the pathologic physiology of residual poliomyelitis. Loss of anterior horn cells fails to explain adequately the clinical behavior in the convalescent and old cases. There appears to be general agreement that the usual case presents maximum involvement early, with the supposition that the virus has spent itself for any single patient in a matter of days. With denervation or disuse atrophy the pathologic process should end. Physiologically, however, there are continued spasms and contractures of such longevity as to be incompatible with the idea of continued irritation from inflammatory changes. The possibility must be considered that these residua are related to damage to internuncial pools in the course of the acute attack.[11, 91] The result is faulty transfer of impulses arising in higher centers to the remaining final-common-path-cells. The spasticity results from uninhibited activity in the neuromuscular complex of these viable cells. Of particular importance in understanding the pathogenesis of poliomyelitis are the studies of the virus, its transfer, and its spread (see page 317 and recent reviews: Tooney,[131] Howe and Bodian,[132] Siegel[133]).

Landry's Paralysis.—Landry's paralysis is a progressive ascending poliomyelitis beginning with lower extremity palsy and eventuating in bulbar paralysis. The certain identity of the causative agent is not established.

St. Louis Type Encephalitis.—St. Louis encephalitis exhibits a diffuse inflammatory picture with general hyperemia, widespread perivascular mononuclear infiltration, and mild nonsuppurative meningitis. It differs from epidemic encephalitis in showing a more widespread disposition of inflammatory changes which are somewhat less intense. The residua are known to be less severe. (See also page 319.)

Japanese B Encephalitis.—Japanese B encephalitis is epidemiologically and clinically closely allied to St. Louis encephalitis. The histopathology is summarized by Zimmerman[135] as: (1) widespread focal destruction of nerve cells with varying degrees of infiltration by lymphocytes and polymorphonuclears; (2) satellitosis; (3) perivascular lymphocytic infiltration; (4) mononuclear infiltration of leptomeninges; (5) occasional ring hemorrhages; (6) glial proliferations in the molecular layer of the cerebellar cortex; (7) acellular plaques; (8) astrocytic gliosis as a reparative effect in smaller lesions; (9) large zones of encephalomalacia; (10) focal and diffuse calcium deposits at sites of injury sometimes with surrounding foreign body reaction. (See also page 320.)

Hemorrhagic Encephalitis.—Hemorrhagic encephalitis is characterized by diffuse petechial hemorrhages throughout the brain.[147] A virus etiology has been postulated although the patho-

logic picture may be imitated very closely in a number of toxic encephalitides. Petechial hemorrhages in the absence of pronounced vasculitis are the diagnostic criteria.

GUILLAIN-BARRÉ SYNDROME (INFECTIVE MENINGOMYELONEURITIS).—A syndrome of involvement of nerve, nerve roots, cord, brain, and meninges, occurring separately, combined, or in sequence, presents the protean clinical features of Guillain-Barré disease. Commonly the condition is transient, although deaths have occurred from bulbar paralysis. The etiology is obscure. The disease appears to be related at times to infectious mononucleosis, and may represent the neurological complication of this widespread disorder. A characteristic is the albumino-cytologic dissociation apparent in lumbar puncture spinal fluid, wherein the cell count remains low in the presence of an elevated protein. The reversibility and transient character of the frequently profound disabilities associated with the disease may be explained by swelling of nerve fibers both in the spinal cord and in the peripheral nerves. Thus the disturbance may be partly on mechanical grounds, and subsides with the disappearance of the swelling.[148] The pathologic changes include degenerations in the peripheral nerves and spinal cord, and gross alterations in consistency of the central nervous system have been described. Lymphocytic infiltrations of the posterior roots and ganglia are the most consistent findings.[149, 150]

Meningitis

Meningitis signifies inflammatory disease of the covering membranes of the brain and spinal cord. As might be expected, meningeal irritation is frequently apparent in encephalitis owing to the fact that interstitial drainage empties into the meningeal spaces by way of the perineuronal and perivascular spaces. Conversely, septic lesions which are primary in the meninges may be conveyed to the brain by back pressure along the same channels. In general, however, intramedullary tissue is strikingly free of inflammatory change in purulent meningitides, the pia-glial membrane providing a protective barrier to spread. It is convenient to classify meningitides topographically as *pachymeningitis* and *leptomeningitis*.

Pachymeningitis is inflammation of the dura due in most instances to extension from osteomyelitis of the skull, compound fracture, or penetrating wounds. Usually the dura will limit the spread to an *epidural abscess* which occurs as plastic exudate between bone and dura. The overlying scalp is swollen, congested, and edematous (Pott's puffy tumor). *Peripachymeningitis* occurs as an annular inflammatory change around spinal dura incident to Pott's disease. *Pachymeningitis cervicalis hypertrophica* is a pronounced thickening of dura in the cervical region which may be associated with syphilis. *Acute pachymeningitis* of the spinal dura with marked thickening and fusion with the leptomeninx occurs in the rapid development of a septic or syphilitic transverse myelitis. *Subdural abscess* may occur secondary to neighboring infections. This consists of a broad, limited sheet of purulent material or organized exudate in a subdural position.

Leptomeningitis is an inflammation of the pia-arachnoid usually characterized by exudate in the subarachnoid space. The inflammation may be purulent due to bacteria or actinomyces; or nonpurulent due to viruses, tubercle bacilli, treponema, parasites, and some fungi.

Fig. 1230.—Purulent meningitis with fixed suppurative membrane and scattered exudate in the subarachnoid space surrounding the nerve roots.

Purulent meningitis (Fig. 1230) may be caused by meningococcus, pneumococcus, streptococcus, staphylococcus, gonococcus, influenzal bacillus, actinomyces, colon bacillus in infants, and occasionally by mixed infections. All purulent meningitides present similar gross and microscopic appearances, diagnosis depending upon demonstration of the specific agent. They are characterized by plastic, colored exudate in the subarachnoid space. Infection by *Hemophilus influenzae* produces

the most striking exudate, with purulent material of great depth appearing over all surfaces. The exudate in meningococcic meningitis tends to aggregate at the base and in streptococcic and pneumococcic meningitis the exudate is commonly most abundant over the vertex. In leptomeningitis from direct extension the exudate clusters at the site of entry.

Purulent meningitis arises through direct extension from neighboring foci of infection, particularly middle ears and mastoid cells, from blood-borne infections, and possibly, in the case of epidemic meningitis, through migration of the agent along the olfactory filaments from the nose to the subarachnoid space. Frequently the infection will spread to the ependymal lining and choroid plexus of the ventricles, causing a pyohydrocephalus. In addition to the necrosing, toxemic, and irritative effects of the infection, the exudate in purulent meningitis operates to obstruct the flow of cerebrospinal fluid. The obstruction may occur in the constrictions of the ventricular spaces, at the vertex where absorption into the venous sinuses occurs, or at the tentorial aperture, through obliteration of the basal, interpeduncular, and superior cisterns. The result is the development of hydrocephalus and a rise in intracranial tension.

Epidemic meningitis is the most important of the meningitides, occurring as an infection by the meningococcus. Fulminating cases are septicemic and systemic with involvement of many organs including petechiae of skin (spotted fever). Meningococcemia is a common cause of rapid death in infants and young adults. In these acute cases, the meninges may be only slightly involved and the major lesion appears in the adrenal with a striking necrotizing hemorrhage and adrenal failure (see page 207). A more common course is extension to the cerebral meninges with rapid spread to the spinal spaces. Once established, the lesions are those of purulent meningitis as described above.

Fig. 1231.—Tuberculous meningitis.

Nonpurulent meningitides include syphilitic meningitis, tuberculous meningitis, lymphocytic choriomeningitis, torula meningitis, and coccidioidal meningitis. Rarely, other agents are identified (see list under Encephalitis, page 1324). Syphilitic meningitis is described in the section on Neurosyphilis, page 1327).

Tuberculous meningitis is secondary to a tuberculous lesion elsewhere and often is but part of a generalized miliary tuberculosis. In other cases it is the most prominent focus of tuberculosis in the body. It is almost invariably fatal. The brain is swollen, and a gelatinous translucent, slightly greenish exudate may be evident in the subarachnoid space, particularly along the base (Fig. 1231). Almost invariably tiny grayish flecks (tubercles) can be identified in the arachnoid over the basal and Sylvian cisterns. Microscopically, the inflammatory reaction and exudate are in general similar to tuberculous lesions elsewhere, but tend to show more neutrophilic leukocytes, and fewer classical tubercles (Fig. 1232). The predominant cells are large mononuclears, lymphocytes, plasma cells, and epithelioid cells; small areas of caseation and definite tubercles may occasionally be found. Giant cells are not numerous. The inflammatory process often involves the superficial portions of the cortex, so that the condition is really a meningoencephalitis. Blood vessels passing through the exudate show adventitial inflammation and intimal thickening (tuberculous arteritis). Fibroblastic proliferation causes a meningeal thickening. Tubercles may be found involving choroid plexus and ependyma. (See also page 261.)

The pathogenesis of tuberculous meningitis is a matter of dispute. The three main theories are: (1) hematogenous infection of the cerebrospinal fluid, (2) hematogenous spread to choroid plexus with development there of a tubercle which later infects the meninges, and (3) hematogenous spread to superficial cerebral cortex with development of a localized tubercle which later ruptures or spreads infection to meninges.[120] The sensitization of the meninges to the products of the tubercle bacillus emanating from a tuberculoma lodged adjacent to the meningeal spaces probably accounts for the dramatic suddenness of the meningeal inflammatory reaction.

Lymphocytic choriomeningitis is believed to be caused by a virus, has a transitory, nonfatal course. There is marked lymphocytic infiltration of the subarachnoid space with appearance of large numbers of lymphocytes in the cerebrospinal fluid. (See also page 321.)

Torula meningitis is a chronic meningeal irritation by a fungus, *Cryptococcus hominis.* Invasion by the organism is poorly understood but is presumed to occur as a spread from pulmonary or gastrointestinal infection. Grossly, the subarachnoid space is thick with tenacious exudate, and there is opacity of the membranes. Microscopically, enormous numbers of refractile yeastlike bodies appear in the meningeal spaces. Cryptlike pockets appear in the brain tissue which communicate with the subarachnoid space through flask-shaped openings.

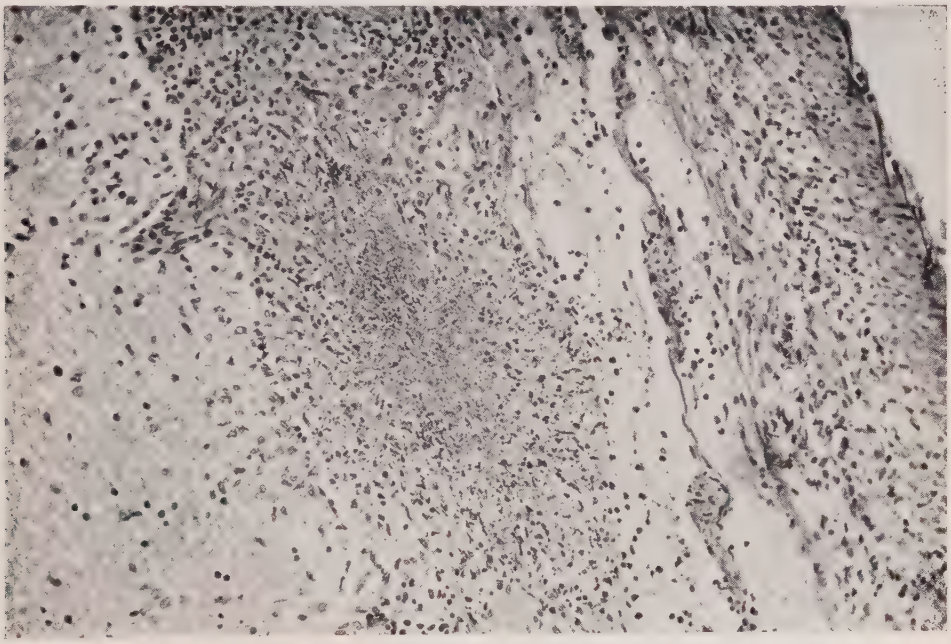


Fig. 1232.—Tuberculous meningitis.

Coccidioidomeningitis occurs in coccidioidal infection. The organisms appear in large number in meningeal spaces where they generate a marked fibrosis and exudative reaction predominated by mononuclears.

Neurosyphilis

Evidence of invasion of the nervous system in syphilitic infection even in the primary phase may be apparent by pleo-

cytosis and increased globulin in the cerebrospinal fluid. A greater percentage of cases will show evidence of neuromeningeal involvement in the secondary stage, manifested principally as headache and presumed to be due to meningeal irritation. The initial process is undoubtedly self-limited and evidence of neurosyphilis disappears. In a relatively small proportion of cases (variously estimated from 5 to 10 per cent), neurosyphilis reappears after a latent period varying from a few to many years. Rarely an acute syphilitic meningoencephalitis may occur in secondary syphilis. However, neurosyphilis appears in two rather distinct clinical entities, each with subtypes depending on dominance of the lesions: (1) *meningovascular syphilis* which may be predominantly arteritis, leptomeningitis (chronic or, rarely, acute), or pachymeningitis; and (2) *parenchymatous syphilis* which may occur as paresis, tabes, taboparesis, or myelitis. Rarely, the cerebral manifestations of the disease will be that of a tumefaction, gumma. Occasionally, nerves are involved (primarily syphilitic neuritis). (See also page 275.)

Syphilitic Arteritis.—Inflammatory involvement of cerebral arteries in syphilis is extremely common and accounts in large measure for the variegated manifestations simulating widely separate clinical pictures, including senile dementia, Parkinsonism, aneurysm, arteriosclerosis, cerebral hemorrhage, and cerebral infarction. Histologically, the arteritis may be acute, with periarterial lymphocytic infiltration and proliferative endarteritis (Fig. 1233). Later the media thickens and undergoes fatty degeneration which may lead to aneurysmal dilatation. The elastic membrane may be thickened and reduplicated. Fibrosis occurs in the productive intimal lesion with partial or complete thrombosis. In the smaller vessels the endothelium is hyperplastic and swollen often to occlusion, and microscopic fields exhibit increased vascularity. Small infarctions result from the occlusions and account for the progressive loss of cerebral substance leading to psychosis. Arteritis is almost invariably accompanied by meningitis of greater or lesser severity.

Syphilitic Leptomeningitis.—Leptomeningeal invasion in syphilis is presumed to occur both in primary and secondary stages. As a rule the involvement is transient and becomes inapparent throughout a latent period. Rarely, the disease occurs as an *acute leptomeningitis* in which there is a striking amount of exudate predominantly mononuclear but including also varying numbers of polymorphonuclears (Fig. 1234). Intracranial tension rises remarkably, sometimes with choked disc and hydrocephalus simulating brain tumor. Merritt and Moore[151] describe, as well, acute or subacute cases in which the involvement is primarily of the vertex or primarily basal. Usually, the condition is confused clinically with tuberculous meningitis. The differentiation pathologically depends upon the serologic reaction and demonstration of organisms. The microscopic appearance is not absolutely distinctive although an accompanying arteritis and encephalitis in syphilis aid in the diagnosis. *Chronic syphilitic meningitis* is exceedingly common in neurosyphilis of all types. Occasionally it is the dominant pathologic change. Ordinarily, it is manifest grossly as a nonspecific arachnoidal thickening and opacity occurring along the vertex, over the lateral and anterior surfaces of the hemispheres, particularly over the Sylvian cisterns, and over the basal cistern. The arachnoid is gray in color, opaque, and is often flecked with grayish-white patches of increased density. These flecks differ from meningeal tubercles in being stellate and of irregular shape and size. Occasionally the meningitis will be predominantly basal and exhibits a thick tenacious basal exudate on gross inspection. Rarely, true gummas appear in the subarachnoid material in a basal meningitis. Microscopically, there is great variation in the intensity of the inflammatory reaction. Epithelioid and giant cells are rare, as is caseous necrosis. Exudate varies in amount and is mononuclear in character except in the rare acute type in which polymorphonuclears appear. One important histologic feature is the intense arteritis with extension of the arterial inflammatory change into the intramedullary substance. Chronic arachnitis with thickening and opacity over the frontal lobes is conspicuous in paresis. It should be noted that arachnoidal thickening occurs in senility and other conditions and is not peculiar to syphilis.

Paresis (General Paresis, Paralytic Dementia).—Paresis develops in some 2 per cent of syphilitics, most frequently in early middle age and appears in males more often than females. Clinically, psychotic features predominate and the disease is the most important of the presenile dementias. Grossly, there is sclerosis and atrophy of the frontal lobes. The overlying arachnoid is thickened and opaque and the dura is frequently adherent to the calvaria. Histologically, the arachnoid is thickened and fibrous and infiltrating lymphocytes and large mononuclears appear in the meningeal spaces. There is an associated meningeal and intramedullary arteritis. The cortical vessels show perivascular infiltration and intimal thickening often with thrombosis and reduplication. There is subsequent gliosis in response to vascular deprivation and infarction resulting in sclerosis and convolutional atrophy. The cortical areas show large numbers of rod cells derived from mesoglia. Striking changes occur in the cortical neurons. There is loss of polarity and lamination. The nerve cell bodies show degenerative changes with shrinkage and loss of processes resulting in patchy subcortical demyelination. There may be small cortical hemorrhages and softenings. Treponema can usually be demonstrated in cortical tissue. Paresis is invariably associated with chronic leptomeningitis and often occurs in combination with tabes.

Tabes Dorsalis.—The pathology of full-blown tabes is easily demonstrated and often illustrated as a demyelination of the posterior columns of the spinal cord. The degeneration is most intense in the lumbosacral ascending column (gracilis) and may extend partially to the lateral parts of the dorsal columns and in a patchy disposition to the lateral columns. The juxtagriseal fibers are usually preserved. Cellular degeneration in the gelatinous substance occurs. Posterior rootlet degeneration and fibrosis have been described but are not constant.[152, 153] The pathogenesis of the condition is evasive. In general it falls in the category of obscure demyelinating diseases (see page 1319). Most logically one would presume involvement of the dorsal root ganglia or dorsal roots with secondary demyelination of the dorsal column. Ordinarily, however, histologic alterations in the rootlets and ganglia are inapparent. A primary demyelination selectively involving the posterior columns is the pathologic picture and remains unsatisfactorily explained.[108, 154]

Taboparesis.—Not infrequently tabes occurs in combination with paresis in which the pathologic changes are those of both diseases.

Gumma.—Gummas of the brain as space-occupying lesions are rare. They represent expansions of gummatous vascular degenerations. Grossly and histologically they are similar to gummas elsewhere (page 273).

Fig. 1233.

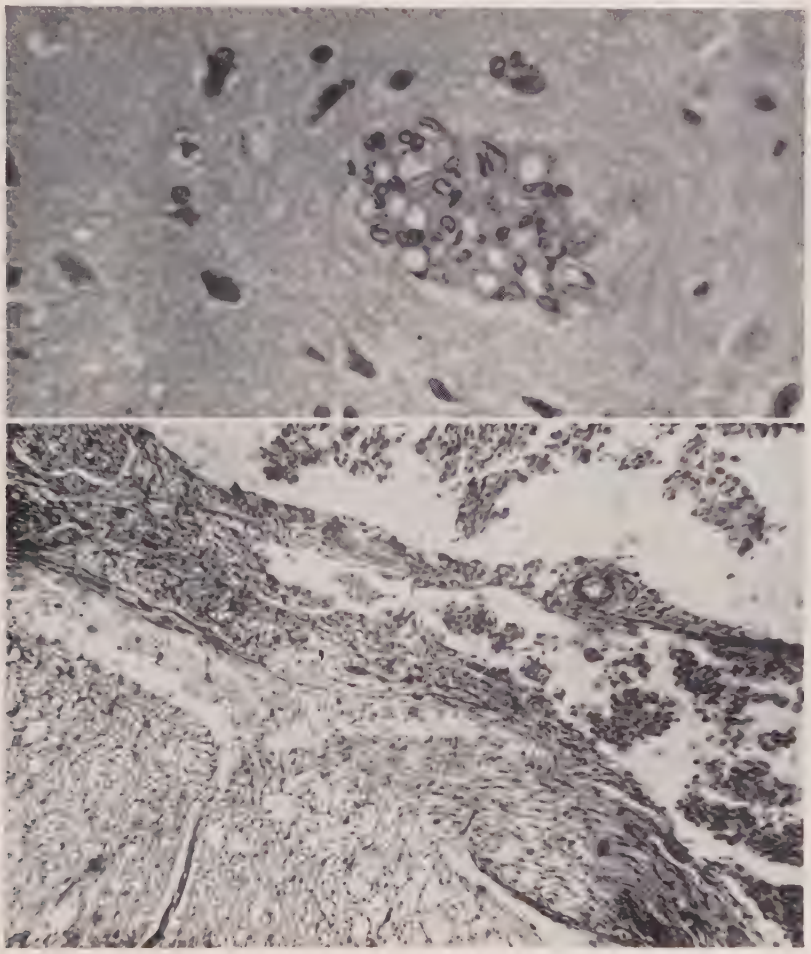


Fig. 1234.

Fig. 1233.—Endothelial hyperplasia in cerebral syphilis.
Fig. 1234.—Chronic meningitis (syphilis).

Diseases of Peripheral Nerves

The diseases of peripheral nerves fall into the three ill-defined categories of neuralgia, neuritis, and traumatic injury.

The changes resulting from peripheral nerve trauma are those of Wallerian degeneration and neuroma formation (see pages 1282 and 1283).

Neuralgia refers to pain in the distribution of a nerve supply. The character of the pain is distinctive, being intermittent or remittent and very severe. Morphologic changes in the involved peripheral nerve are absent or negligible. Changes in ganglia are sometimes described, such as chromatolysis and shrinkage, but it is difficult to ascribe the symptoms to these nonspecific alterations. The pain has been attributed to peripheral nerve or ending involvement, reflex vasospasm, possibly related to histamine hypersensitivity, and to heightened central synaptic activity which accentuates above the pain threshold the normal afferent impulses from a region. The principal neuralgias include: trigeminal, glossopharyngeal, sphenopalatine, occipital, phrenic, brachial, intercostal, sciatic, and sacrococcygeal. The distribution pattern of the pain in each type presents a distinctive clinical differential.

Neuritis is a term used loosely in referring to any condition associated with inflammatory or degenerative (neuropathic) changes in peripheral nerves. When many nerves are involved, the condition is described as *polyneuritis,* if one nerve, as *mononeuritis.* Various changes which may be found include hyperemia of the nerve sheath, transudation and swelling, cellular exudate, myelin degeneration, and swelling and fragmentation of axis cylinders. Once continuity of fibers is broken, secondary Wallerian degeneration occurs. From an etiological standpoint, Cobb and Coggeshall[155] have grouped the neuritides under the following headings: (1) virus (herpes), (2) bacteriotoxic (scarlet fever), (3) deficiency or metabolic (beriberi), (4) chemical (lead), (5) focal mechanical (tumor pressure), (6) focal infectious (diphtheria). A large number of etiological agents operate in each category. An infiltrating tumor surrounding a peripheral nerve is associated clinically with the symptoms of neuritis of intractable type. In addition to the alterations within the peripheral nerve itself, defects in the structures which the nerve supplies, both sensory and motor, are apparent. These are manifest as loss of motor function with muscular wasting, alterations in autonomic control (vasodilation, vasoconstriction), and as "trophic" skin changes.

Diseases of Intracranial Vessels

Meningeal Vasculature.—The vascular system of the meninges include three distinctive sets of vessels; the dural sinuses and their tributaries (emissary veins and superficial cerebral veins), the meningeal arteries, and the subarachnoid arteries (see page 1272). Their involvements are manifest principally as infections or hemorrhage. The traumatic diseases are discussed on page 1335.

Sinus thrombosis occurs usually as a thrombophlebitis of a dural sinus. Cavernous sinus thrombosis is related to infections of the nose, upper lip, cheek, orbit, and sphenoid and posterior ethmoid paranasal sinuses. Superior sagittal sinus thrombosis occurs as a sequel to frontal sinusitis. Transverse sinus thrombosis is most often related to middle ear and mastoid infections. Superficial infections of scalp and neck and retropharyngeal abscesses can also give rise to sinus thrombosis by conduction along appropriate emissary veins (page 200, Plate I). There is usually an associated leptomeningitis, and sinus thrombophlebitis is thought to be important in the pathogenesis of some brain abscesses (see page 1321). Phlebothrombosis, either septic or bland, engenders phlebostasis in the drainage field which may result in infarction of venous type. Such a picture is a striking event in sagittal sinus thrombosis where bilateral longitudinal vertex necrosis occurs. Nonseptic phlebothrombosis of the sagittal sinus may occur as a result of prolonged debility with venous stasis, especially in children (marantic thrombosis).

Subarachnoid hemorrhage (Fig. 1235) is from subarachnoid arteries which lie superficially in the subarachnoid spaces of the base of the brain and deep in the sulci over the other surfaces. Occasionally bleeding may occur from subarachnoid veins which occupy a superficial position over the vertex. Bleeding from the latter vessels occurs as a result of trauma, blood dyscrasias, or rupture of a surface angioma. Not infrequently the cause of bleeding is extremely evasive, a situation covered usually by the term "spontaneous subarachnoid hemorrhage." Blood may also appear in the subarachnoid space by rupture from a hemorrhage in brain tissue or by conduction with cerebrospinal fluid from an intraventricular source. However, subarachnoid bleeding most commonly is from a ruptured aneurysm. The aneurysms are usually basal in position at points of branching. The most important aneurysms are congenital and mycotic, but some have been ascribed to arteriosclerosis and syphilis.

"Congenital" aneurysms[156] are of fairly frequent occurrence. The angles of bi-

furcation of the arteries about the base of the brain are common sites (Fig. 1236). The "congenital" aneurysm is the "berry" type and represents the lesion related to subarachnoid hemorrhage in the vast majority of cases. Fusiform basal aneurysms are fairly common on an arteriosclerotic basis and while they form formidable masses they seldom give rise to basal hemorrhage. "Berry" aneurysms are attributed to many diverse etiological formulas. Most tenable of these are: (1) persistence of embryonic vessels from the primitive vascular plexus, and (2) defective muscular wrapping, particularly at points of branching.[156a] The aneurysm itself is not always congenital, though the defect in the vascular wall is a congenital or developmental abnormality which is apparent on histologic inspection (Fig. 1237). Small leakages may occur through the wall of the sac, giving rise to pigmentation and thickening of meninges in the neighborhood of the aneurysm. Rupture of the aneurysm results in a subarachnoid hemorrhage, often rapidly fatal (Fig. 1236). The subarachnoid space about the region of the aneurysm (hence usually at the base of the brain) is found filled by recent blood clot. The clot may easily hide the aneurysm unless it is carefully removed. Occasionally hemorrhage extends into the ventricle, usually by dissecting through the medial surface of the frontal lobe into the anterior horn.[157]

Fig. 1235.—Basal subarachnoid hemorrhage.

Mycotic aneurysms are produced by infected emboli lodging in cerebral vessels. Subacute bacterial endocarditis is the commonest source of the embolus, and the middle cerebral artery is the commonest site. Emboli bearing organisms of high

virulence produce abscess or meningitis rather than mycotic aneurysm.

Intramedullary Vascular Disease

Arteritis and vascular degeneration, with resulting thrombosis or hemorrhage, occur as a result of vascular damage from many poisons (carbon monoxide, arsenic), in septic conditions (scarlet fever, pneumonia), blood dyscrasias (purpura, leukemia), periarteritis nodosa, Buerger's disease, and syphilis. The brain tissue shows multiple small hemorrhages or softenings. Syphilitic arteritis is probably the most important (see page 1328).

Fig. 1236.

Fig. 1237.

Fig. 1236.—Ruptured aneurysm of anterior communicating artery. This hemorrhage penetrated to the anterior horn.

Fig. 1237.—Defective vessel wall of basal aneurysm.

Arteriosclerosis.—Cerebral vessels are similar in structure to vessels elsewhere, though the small arteries contain a disproportionately large amount of connective tissue in their walls. With advance in age, muscle decreases, the internal elastic lamina undergoes reduplication, and there is a medial fibrosis. Arteriosclerosis of the larger vessels at the base of the brain is of the atheromatous type. Through weakening of the wall distortions and even aneurysms may occur. Cerebral arteriosclerosis may have no direct correlation with sclerotic changes elsewhere in the vascular system. Cerebral arteriosclerosis has no constant relationship to hypertension. (See, however, Malignant Hypertension, page 1334.) Narrowing of the vascular lumina diminishes the blood supply and exerts a serious effect on brain tissue. Multiple perivascular zones of atrophy may be found in the brain as a result of arteriosclerosis in addition to larger softenings from thrombosis. Particularly susceptible to diminished blood supply are the striatum, the hippocampus, dentate nucleus, and cerebral cortex. Degeneration of these areas plays a role in pathogenesis of arteriosclerotic or senile cerebral atrophy. Arteriolar sclerosis also occurs in cerebral vessels and is characterized by the same hyaline changes seen in other organs.

Thrombosis develops in cerebral vessels from the same causes as elsewhere. A sclerotic vessel is usually involved and arteriosclerosis is the most frequent underlying cause of cerebral infarction (Fig. 1195). *Embolism* of cerebral arteries originates from thrombi in the

lung or, more commonly, from the left side of the heart. Paradoxical embolism occurs from emboli breaking off in the right circulatory field and gaining access to the left side of the heart through an open foramen ovale. *Air* and *fat* also act as emboli (see page 117). Massive infarction results most commonly from occlusion of branches of the middle cerebral artery, probably because this vessel is a direct continuation of the internal carotid artery. Consequently, the middle cerebral artery is in direct line for receiving emboli, as well as being subject to the wear and tear of direct pressure effects from the heart.

soft, semifluid area, with a slightly yellowish color and an edematous sometimes hemorrhagic, edge. Later, when the necrotic and liquefied material has been removed, the region is shrunken and depressed. If the infarcted area is large, it may have a cystlike center containing yellowish fluid *(apoplectic cyst)* encapsulated by glial tissue.

Microscopically, a very recent infarct transiently contains neutrophilic leukocytes, but they soon disappear. Nerve cells, axis cylinders, and neuroglial cells degenerate, and lipoid of the myelin sheath is broken down and liquefied. The fatty and necrotic material undergoes phagocytosis and is removed by the ameboid microglial cells. These scavengers appear abundantly as rounded cells with a foamy or vacuolated cytoplasm (fat granule cells, compound granular corpuscles) (Fig. 1195). Healing occurs by proliferation of a granulation tissue composed of astrocytes, capillaries, and a few fibroblasts of the adventitia of adjacent vessels. Eventually a dense neuroglial scar is formed. The damage is permanent, as there is no regeneration of the injured nerve cells and fibers.

Fig. 1238.—Multiple cerebral hemorrhages showing intraventricular and surface rupture.

Cerebral Infarction.—Occlusion of a cerebral artery results in infarction of the region supplied by the vessel. Even though abundant anastomoses are present, they are insufficient to maintain nutrition if an artery is blocked: i.e., functionally they are end-arteries. Cerebral infarcts are characterized by softening. The clinical effects depend upon the area of nervous tissue involved. The appearance of a cerebral infarct depends upon its age. A recent infarct may be indistinguishable in a fresh brain, but after fixation it remains soft in comparison with surrounding tissue. If its age is greater than two or three days, it appears as a

Cerebral Hemorrhage.—Hemorrhages into the brain tissue itself may be either small petechial or perivascular hemor-

rhages, or a massive hematoma (Fig. 1238). Small petechial hemorrhages result from many types of relatively minor trauma (page 1337). Petechial hemorrhages also may result from poisons, such as carbon monoxide and arsphenamine, or from

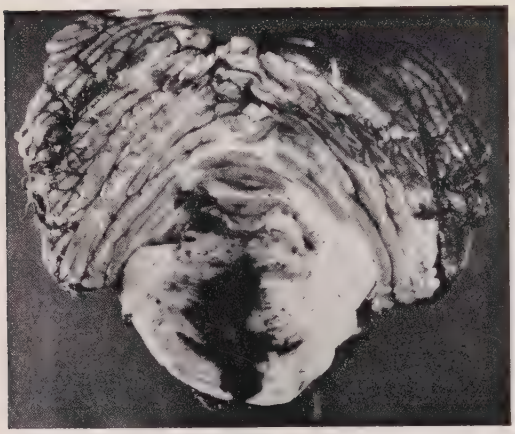


Fig. 1239.—Central pontine hemorrhage. This lesion can be spontaneous but is more often a secondary feature related to displacement of pons from intracranial hypertension.

purpuric or leukemic conditions. Massive intracerebral hemorrhage is due to vascular disease, with or without high blood pressure. It is a frequent end result of hypertensive cardiovascular renal disease. The vessels most commonly affected are the lenticulostriate branches of the middle cerebral artery, involving the basal ganglia and internal capsule. Less frequently hemorrhage is into white matter of the cerebrum, or into the pons or cerebellum. The actual mechanism of the hemorrhage is debatable, and it is usually impossible to find the point of vascular rupture. The brain bulges slightly on the side of the hemorrhage, where there is some flattening of the convolutions. Cutting through the brain tissue reveals the area of hemorrhage lacerating the brain substance. Rupture into a ventricle often occurs, and in such cases blood appears in the spinal fluid. Hemorrhage into cerebral tumor tissue may be grossly indistinguishable from the ordinary type of cerebral hemorrhage. Microscopic examination is necessary to confirm or rule out this possibility. Central pontine hemorrhage deserves a special note inasmuch as it occurs both spontaneously and secondary to intracranial hypertension with pontine displacement (Fig. 1239).

The Brain in Malignant Hypertension.—In malignant hypertension the brain may be edematous or sclerotic. Arteriolar changes, hyaline or vacuolar, constantly occur, with narrowing of the lumina. The ratio of thickness of vessel wall to diameter of the lumen may be altered from the normal of 1:3.5 to 1:1.7.[158] Hemorrhages varying from petechial to massive size may be found, and areas of infarction, usually multiple and small but sometimes massive. Sometimes there is edema, slight perivascular lymphocytic infiltration, and gliosis (see page 566). *Hypertensive encephalopathy* occurs in benign as well as malignant hypertension and represents the changes incident to vascular sclerosis.[159]

Trauma of the Nervous System

Birth Injury.—The term, birth injury, has come to infer intracranial hemorrhage in the newborn accompanied by asphyxia and intracranial hypertension, and often leading to death. The origin is ascribed to molding of the head in the birth canal or from instrumentation. These manipulations of the movable bony parts put a strain on the dura, particularly the falx and tentorium, with resultant tears. The tears themselves are probably unimportant unless a sinus or cerebral vein is opened. While the bleeding point is extremely difficult to identify, the blood usually centers in the neighborhood of the tentorial aperture and is both subdural and subarachnoidal in position. Because of obstruction to the internal cerebral vein or because of subarachnoidal obstruction at the tentorial aperture there is an attendant intracranial hypertension which produces hydrocephalus of varying degrees. The condition may be related to the production of spastic diplegia (see page 1313).

Peripheral Nerve Injury.—Peripheral nerves may be injured by wounds, amputations, compressions, and infections. Their topographic involvement results in clinical rather than pathologic entities. Peripheral nerve degeneration and repair have been discussed (page 1283) and these phenomena are common to all injuries. Among the many injury patterns some of those involving the brachial plexus deserve special mention. *Brachial palsy* is not an uncommon sequel to difficult birth. By extreme lateral retraction of the head the upper constituents of the plexus may be torn. The lower roots of the plexus may be similarly damaged by traction on the upper extremity. The injury is manifest by withering of the extremity in appropriate distribution. Occasionally the nerve trunks themselves are torn, but more commonly the roots are avulsed from the cord which

markedly reduces the chance for recovery. An interesting lesion is Adson's *scalenus anticus syndrome*[160] which is presumably engendered by pressure on the brachial plexus from elevation of the first rib due to contraction of the scalenus muscles. A similar syndrome may arise from pressure against a *cervical rib*.

Skull Fracture.—Fracture of the bony coverings of the brain are of concern here only to the extent of involvement of the nervous system or its vasculature. A number of cranial anatomical features are important in resisting fracture. These include: (1) membranous tissue in cranial sutures providing a degree of mobility which decreases with age; (2) soft spongy diploë between tables of cranial bones; (3) ridgelike reinforcing thickenings in regular patterns throughout the skull; (4) shape of the skull favoring glancing blows and in direct impingement lateralizing the force; (5) overlapping of many of the flat bones of the skull. Certain other features lead to concentration of cranial fractures in the base of the cranial vault: (1) transmission of force along sphenoidal and petrous ridges to the base; (2) thinness of bones in orbital plates and middle cranial fossa with relatively small amount of diploë; (3) abundance of foramina and grooves near the base. The direct consequences of skull fracture are those resulting from (1) displacement of bone and (2) rupture of vessels. The two conditions may, of course, exist together.

1. Bony Displacement.—Not infrequently, fractures of the skull appear as *linear fissures* apparent on x-ray. These, in themselves, are of no consequence neurologically although they serve as an index to the severity of a blow and imply the possibility of brain damage by concussion (see below). *Inner table* fractures may occur rarely in the absence of fracture of the outer table from focal blows by blunt objects. The inner table is more brittle and, executing a shorter curvature, is more liable to break from a depressive force applied exteriorly. The displaced inner table fragments may or may not lacerate the dura and depress the underlying brain, resulting in minor contusion with focal superficial hemorrhage. *Depressed fracture* occurs when a blunted force on the bony tables results in a saucer-shaped depression in the skull. The underlying brain is compressed and contused. If the bone shatters, the depressed fracture is called *comminuted*, and fragments of bone may be displaced widely. In comminuted fracture there is danger of laceration of both meninges and brain with lodgment of bone fragments as foreign material. Fracture from penetrating wounds (gunshot, stab) usually results in fragmentation of bone. In *compound fracture* the scalp is also lacerated, and hair and skin as well as bone fragments and, frequently, the assaulting missile, are carried into the brain. Compound fracture which occurs in all penetrating wounds is particularly liable to septic transformation.

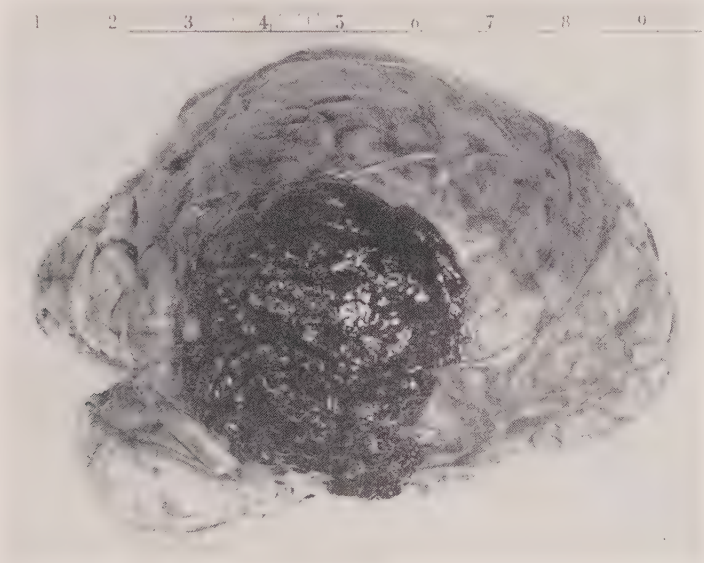


Fig. 1240.—Epidural hemorrhage showing typical limitation.

2. Rupture of Vessels.—As a result of skull fracture almost any meningeal vessel may rupture. Most common among these is hemorrhage from the *middle meningeal artery* (see below) (Fig. 1240). Rupture of dural sinuses from fracture are occasionally seen. These are, however, more common in tentorial tear in birth trauma (see above). Rarely, emissary veins may be torn at the point where they enter the dural sinus. In fractures varying through the orbital and cribriform plates there may be bleeding through the nose, possibly meningeal in origin, and also leakage of cerebrospinal fluid into the nasal cavity (rhinorrhea). Basal fractures may rupture the carotid artery in its canal with profuse hemorrhage into the neck. Fractures of the petrous

ridge may produce bleeding into the middle ear cavity and through the Eustachian tube into the throat or into the external auditory meatus if the membrana tympani is ruptured. If the meningeal spaces are opened, cerebrospinal fluid will drain through the external auditory meatus (otorrhea). Fracture through the wall of the cerebellar fossa releases hemorrhage into the neck and mastoid regions.

Fracture of Vertebral Column.—The seriousness of fracture of the spinal column depends upon the extent of involvement of the spinal cord. The cord is injured by compression, contusion, and perhaps by concussion, with subsequent hemorrhage and edema. The commonest fracture results from falls on the shoulders or buttocks or from objects falling on the shoulders inducing acute flexion angulation. There is usually a compression fracture of the vertebral body with posterior angular displacement into the vertebral canal. The defect is most serious in the cervical region because of danger of damage to respiratory control and because the canal is relatively small in proportion to the size of the cord. The direct damage to the cord is extended by edema and hemorrhage so that the lesion viewed pathologically may be surprisingly large. Secondary tract degenerations occur both ascending and descending.

Ruptured Intervertebral Disc.—One-fourth to one-third of the entire length of the vertebral column is comprised of intervertebral discs. These structures possess a nodular semifluid central matrix (nucleus pulposus) surrounded by circumferentially laminated fibrous tissue and fibrocartilage (annulus fibrosus). The fibrous ring is thinner posteriorly as many of the fibers of the lamellae carry over the edges of the vertebral bodies. The discs impart much of the normal curvature to the vertebral column and are subject to the stresses and tensions of the column. With atrophy of the disc or subject to unusual stresses, the fibrous ring may rupture posteriorly with herniation of the nucleus. The condition is more common in older individuals and occurs with the greatest frequency (over 90 per cent) in the lower lumbar discs. Damage arises from compression of the cord or spinal roots, giving rise to a characteristic clinical syndrome.[161, 162]

Penetrating Wounds.—Penetrating wounds of the nervous system are principally bullet wounds, rarely from other foreign objects (bayonets, flying steel). (For detailed classification, see Cushing.[163]) Two features characterize these lesions: (1) lacerating and explosive effect of the missile and (2) presence of foreign material. In penetrating cerebral substance the brain is lacerated to a degree depending upon the size, configuration, and speed of the bullet. In addition to the laceration the expanding gases attendant upon the flight of the missile induce an explosive effect. Courville[164] summarizes the immediate effects of gunshot wound as follows: (1) initial shocking (explosive effect) which may cause immediate death from damage to vital centers; (2) laceration accompanied by varying amounts of hemorrhage, rarely excessive; (3) induction of cerebral edema from vasomotor paralysis, an extremely important feature in patients dying a number of hours after the initial shock. The remaining effects are those related to the foreign material and their sequelae and repair of the injury. In entering the cranial cavity a missile may carry fragments of clothing, hair, bits of skin, and bone into the brain. In addition, air may enter the cranium, particularly if a sinus has been traversed, forming an *aerocele*. The foreign pieces may be inert or may set up inflammatory changes manifest as abscess or meningitis. The repair process in direct injury includes liquefaction necrosis of damaged tissue with fat granule cell infiltration followed by appearance of scar of both glial and fibrous nature, the latter being more prominent in healing of septic lesions. Contraction of extensive scar tissue may lead to convulsive seizures.[165]

Concussion.—Concussion refers to jarring of the nervous structure with loss of function characterized clinically by loss of consciousness. The mechanisms of concussion are not, in general, agreed upon.[166] Alterations in intracranial tension and vibrations set up by the shocking blow are thought responsible for the transient loss of function. Severe concussion is usually attended by contusion and even by laceration of the brain. The contusion is often apparent over the brain immediately underlying the point of impact (coup). In addition there is very often contusion of the brain at some more distant point, usually over the inferior frontal and anterior and inferior temporal regions (contrecoup).[164] It is generally felt that the contrecoup effect is opposite the point of impact although Courville has shown the lesions to be clustered principally about the basal ridges of the cranial cavity. In general the amount of hemorrhage resulting from contusion and laceration dictates the severity of the concussion.

Traumatic Intracerebral Hemorrhage.—Intracranial hemorrhages from trauma exhibit a somewhat characteristic pattern and are described as (1) epidural, (2) dural (subdural), (3) subarachnoid, (4) massive intramedullary, and (5) petechial. While fractures and penetrating wounds are attended by hemorrhage, bleeding intracranially is extremely common, with no evidence of fracture. Indeed, seemingly insignificant traumatisms may induce hemorrhage. The bleeding may appear as frank blood in a meningeal space or as a massive clot involving cortex and white matter. Often the bleeding (contusion) will appear as a focal soft hemorrhagic area surrounded by petechial extensions. Similarly, lacerations will exhibit a focal or linear channel of hemorrhage often surrounded by miliary hemorrhage spots.

1. *Epidural hemorrhage* ordinarily refers to blood in the temporal region from traumatic rupture of the middle meningeal artery or its branches but, rarely, is due to a tear of an emissary vein as it enters a dural sinus. This may be found in the posterior fossa from rupture of the mastoid emissary as it enters the transverse sinus. The hemorrhage is limited in extravasation to individual bone areas due to the dural attachments at the suture lines. The clot forming between dura and bone compresses the underlying brain tissue (Fig. 1240). Epidural hemor-

rhage occurs with skull fracture of the middle fossa but is also common in the absence of fracture.

2. *Dural or subdural hemorrhage* (subdural hematoma, pachymeningitis hemorrhagica interna) occurs when bleeding from dural vessels extravasates in a subdural or intradural position forming a hematoma. Whether the hematoma is limited internally by a thin strip of dura or by false dural membrane is debatable. The bleeding point may be difficult to localize, but in recent traumatic cases can often be traced to the junction of superficial cerebral veins with dural sinuses. Usually there is a small amount of subarachnoid extravasation due to arachnoidal tears. The hematoma is most frequent over the frontal and parietal areas and is often bilateral. Although generally regarded as traumatic, spontaneous cases do occur in blood dyscrasias, infections, and toxemias. The hematoma organizes at its periphery, usually retaining a fluid center. Its clinical effects are due to the fact that it is a space-occupying mass. (Fig. 1241.) (See Fig. 90, page 127.)

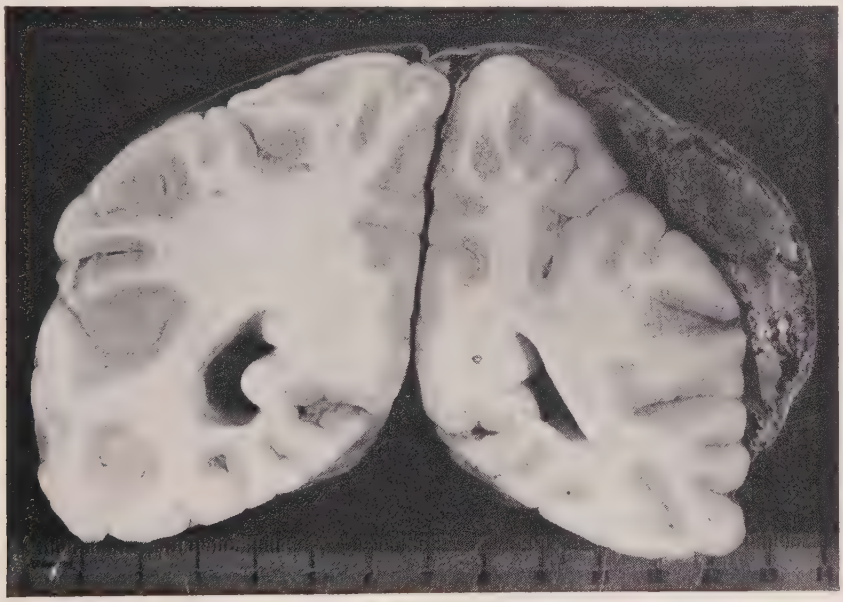


Fig. 1241.—Dural (subdural) hemorrhage.

3. *Subarachnoid hemorrhage* of traumatic origin is fairly common as extravasation from bleeding points of torn veins. Usually, however, the primary bleeding is dural or intramedullary (see Subarachnoid hemorrhage, page 1330).

4. *Massive Traumatic Intramedullary Hemorrhage.* In areas underlying depressed fractures or from concussion or contrecoup effect, large hemorrhages in brain substance may occur as a result of trauma. Multiplicity of lesions, a disposition involving cortex and white matter, and the relationship to a point of injury usually serve to differentiate traumatic from spontaneous hemorrhages. Very often blood will extravasate into meningeal spaces. Early lesions show remarkable mobilization of polymorphonuclear cells admixed with the hemorrhage and infiltrating the neighboring brain tissue. In repair the hemorrhagic mass undergoes a liquefaction, forming a brownish-colored cyst. Occasionally the hemorrhage communicates with a ventricular space (traumatic porencephaly, Fig. 1238).

5. *Traumatic Petechial Hemorrhages.* Repeated shocking blows to the head induce diffuse petechial hemorrhages throughout the white matter. This type of lesion is associated with the psychosis (punch-drunk) in pugilists who have suffered repeated severe punishment in the ring.

Arteriovenous fistula (aneurysm) of the carotid artery and cavernous sinus may be traumatic in origin.[167] Arteriovenous aneurysm elsewhere in the brain simulates closely arteriovenous telangiectases (see page 1289).

Intracranial Tension

The relative rigidity of the cranial vault leads to increased intracranial tension from changes in volume of its contents. For this reason, space-occupying lesions, conditions limiting the flow of cerebrospinal fluid, and edema of the brain give rise to an elevated intracranial pressure. This brings about certain pathologic changes of great clinical importance.

Changes in Extramedullary Fluid Volume.—In the adult, internal hydrocephalus occurs in a number of chronic diseases as a moderate dilatation of the ventricular system, often along with a slight external hydrocephalus (distended sub-

arachnoid space). This may be seen in syphilis, chronic alcoholism, and chronic subarachnoid obstructions such as after meningitis. Very often the mechanism is obscure. In syphilis, involvement of the arachnoid villi may inhibit absorption of fluid. In chronic alcoholism, successive bouts of edema of the brain may be postulated with subsequent distention of the ventricles and contraction of brain tissue by atrophy. In addition, an ependymitis with nodular subependymal gliosis and profuse vascular endothelial proliferation may be noted in alcoholism, which may cause transitory obstruction to cerebrospinal fluid flow during bouts of edema. The mechanism of obstruction due to arachnoidal thickening is less obscure. In addition to thickening following meningitis, chronic arachnitis has been observed after repeated subarachnoid hemorrhage (seeping aneurysm). At autopsy, such brains usually exhibit a moderate internal hydrocephalus. In cerebral atrophy, associated with senility, there is often a marked external hydrocephalus. The absence of ventricular dilatation in such cases indicates that pressure phenomena had little to do with the accumulation of fluid over the atrophied brain. A more acute ventricular distention in the adult occurs in purulent meningitis and with intraventricular block.

Changes in Intracranial Tissue Volume.—Changes in tissue volume within the cranium may be brought about by (1) accumulation of intramedullary (interstitial) fluid *(edema)*, (2) increase in vascular volume *(congestion)*, and (3) new tissue growth *(tumor)*. In these conditions hydrocephalus is absent. The subarachnoid space often is obliterated and the surface of the brain is dry. Underlying gyri are compressed and markedly flattened and the sulci are obscured. The opposing walls of the ventricles may be in apposition. A distinctive characteristic is the appearance of *pressure marks* along the base of the brain. The cerebellar tonsils may be shoved over the brim of the foramen magnum, grooving the cerebellum deeply *(coning)*. In addition, the swollen temporal lobes may spread over the free margins of the tentorial aperture with a consequent linear grooving on their medial surfaces (Fig. 1213). Edema may be related to cardiac decompensation, generalized septic and toxic states, transitory vasomotor depression, and cachexia. Microscopically the brain tissue is vacuolated, the cells appearing widely separated. Congestion occurs in many inflammatory conditions as well as in cardiac failure and polycythemia. With congestion alone, increase in total tissue volume is usually not excessive, as shown by absence of pressure marks.

Papilledema.—Papilledema or choked disc, while occurring from orbital and intraocular causes as well, is an important clinical index of increased intracranial pressure, as it may be visualized directly by an ophthalmoscope (see also page 723). Grossly, there is venous distention with surrounding edema, congestion, and elevation of the disc. There may be small hemorrhages in and around the papilla. If unrelieved, secondary optic atrophy follows. Microscopically, there are distention of the central vein, lateral shift of the retina, forward bulge of the anterior component of the lamina cribrosa, and distortion of the fibers entering the nerve head. The development of papilledema, incident to increased intracranial tension, depends upon two factors: (1) The vaginal spaces of the optic nerve convey the interstitial fluid of the bulb into the subarachnoid space at the base of the brain. (2) The venous drainage of the posterior retina is through the central vein which drains into the ophthalmic and thence to the cavernous sinus. The central vein bridges the vaginal spaces of the optic nerve in passing from a central position within the nerve to the ophthalmic vein. Pressure obstruction of this vein produces congestion at the papilla, and edema follows obstruction of drainage through the vaginal sheath. Diapedesis from the obstructed vein produces the small hemorrhages at the nerve head, and transudate contributes to the edema. The relative importance of the two mechanisms is not known, and, usually, both appear to be in operation. Experimentally, obstruction of the subarachnoid space alone does not induce severe choked disc. The most severe papilledema is induced by hemorrhage invading the optic sheath and, by distention of the space, obstructing the venous return through distortion of the central vein, an event which may be brought about by a ruptured basal aneurysm. In this condition, massive intraretinal hemorrhages sometimes occur.[157]

Epilepsy and Major Psychoses

Epilepsy.—In the idiopathic or "essential" forms of epilepsy, morphologic changes include only nonspecific alterations in brain tissue, the significance of which may be seriously questioned. Biochemical and electrophysiologic studies have contributed greatly to an understanding of the operative mechanisms. In the secondary form, the convulsive states are associated with pathologic changes in the nervous system. The pathogenesis is often clearly indicated and the symptoms may be related to an inflammatory, circulatory, space-occupying, degenerative, or reparative lesion.

Major Psychoses.—The "functional" psychoses are so described because of the absence of demonstrable structural changes in the nervous system, and because the functional changes occurring are presumed to be psychogenic in origin. A number of nonspecific nerve cell and glial alterations have been described as occurring regularly in these conditions. There is no general agreement as to whether these changes precede or follow the abnormal psychic state.

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Chapter 45

HEREDITY AND CONSTITUTION IN DISEASE

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As one infectious disease after another falls before scientific research, those diseases which have their primary, if not their only, basis in the constitutional and hereditary makeup of the person will become increasingly prominent in the fields of diagnosis, therapy, and mortality statistics. Typhoid is fast disappearing before the sanitation engineer; smallpox has been largely wiped out by the simple technique of vaccination; diphtheria no longer devastates where inoculation procedures are practiced; tuberculosis is steadily falling as a cause of death as sanatoria are provided for those who are in the active stage of the disease and as whole communities undergo routine x-ray examination; typhus, from which millions died after World War I, was nipped in the bud by the use of a new insecticide as a major epidemic threatened in Italy after this war; pneumonia, which Osler called the "old man's friend," has been robbed of many of its terrors to the young and so-called benefits to the old with the advent of the sulfonamides and penicillin. The causes of death are being contracted in scope; and the more efficiently the workers till the field of preventive medicine, the more important will become the seed from which the human plant springs. We all must die, and as fewer die of infections and external causes, more will die of causes having a basis in the hereditary foundation of the individual.

The inheritance of a disease is usually thought of as being dependent upon specific genes in the chromosomes of the parents' germ cells which are passed on to the offspring. They, in turn, either exhibit the disease or carry it in latent form to be passed on to future generations, in whom, under appropriate circumstances, it may become obvious. However, the determiners are not always in the chromosomes, but may be carried in the cytoplasm of the egg, and give rise to inherited tendencies which show no adherence to mendelian laws, but which nevertheless show predilection toward appearing in individuals from the same stock.

Constitution, on the other hand, is something less well defined. It is a summation of all inherited characters plus their response to and modification by the environment. Certain bodily characteristics have been associated with specific diseases, or the tendency to develop them, and numerous authors have classified these body builds under different names. The tall, flat-chested person has been looked upon as one likely to develop tuberculosis; the short, stocky, thick-necked one as having an apoplectic habitus. The reader is referred to Draper's[20] work on constitutional medicine.

One frequently finds statements to the effect that certain diseases, for example, those of lipoid metabolism, or amaurotic idiocy, are much more common in Jews; that cancer of the liver is much more common among the Chinese; that cancer is rare among the Eskimos and North American Indians, etc. Are these racially inherited traits? Are they dependent upon climate, diet, opportunities for certain forms of irritation? Or are they misstatements of fact, based upon inadequate diagnosis or data? Lipoid diseases are usually inherited as recessive traits; recessive traits are brought to light by marriages between relatives; consanguineous matings are very common among Jews because of geographical and religious isolation, especially in European countries; therefore, racially, the Jew may not be more susceptible to lipoid diseases, he may merely manifest them more frequently.

Hepatic cancer might be common among the Chinese because of some peculiarity in diet, some climatic condition, or because of high infestation with the liver fluke, or it might be dependent upon specific heredity. In the latter case, Chinese removed to different climates, to areas where liver flukes were not known, and where their diet might be more in accord with those of the surrounding persons, should still show the same high incidence of hepatic cancer. If they do not, the environmental factors would probably be the more important in causing the high incidence of hepatic cancer among Chinese. Is the low cancer rate among Eskimos dependent upon a racial resistance to cancer, or to a combination of factors, chief among which might be the less advanced age at which they might die as compared with white persons in civilized countries with adequate health programs, and the lack of diagnosis of cancer among these people where medical facilities are very few? Obvious examples of the influence of extraneous factors upon cancer death rates can be cited. The California cancer death rate is high compared with some other states. The explanation may be that many old persons go to the balmy climate of California to spend their last days, thus decreasing the cancer rate in their native state and increasing that of their newly adopted home. The pulmonary cancer rate is high in Arizona; but many persons, supposedly with tuberculosis, go to Arizona for a cure, die of their cancer of the lung, and help to swell the death rate from that disease. Cancer death rates are high in large cities where there are good diagnostic facilities as compared with rural areas far removed from such advantages. Not only is diagnosis better in the former locations, but actually persons with cancer are drawn there for diagnosis. If

they die, they are added to the figures for cancer mortality in that city.

Much of the data so far collected on incidence of various types of diseases in different communities or races which indicate racial or constitutional differences must be scanned closely for all sorts of fallacies which lurk hidden in them. As we are able to evaluate the data properly, we may ultimately find what role is played by the environmental, the constitutional, and the specific hereditary forces acting upon the organism.

Modes of Inheritance

There are five fairly simple ways in which traits may be inherited. These can be identified with ease by inspection of the pedigree in some cases. The accuracy of one's conclusions may be tested by means of statistical analysis. It will be assumed in the following discussion that the hereditary trait is in each instance a defect or a diseased condition. The mode of inheritance most easily identified is the dominant.

Dominant Inheritance.—A trait dependent upon a dominant gene shows the following characteristics: (1) It does not appear in offspring both of whose parents were free from the defect, except when it arises by mutation. The line of descent is obvious, and can be traced from parent to child through generation after generation. (2) It may be transmitted by parents of either sex to offspring of either sex, if it is not a trait involving organs present only in one sex. (3) If it is uncommon, the affected person is likely to be heterozygous, that is, he carries differing forms of the same gene. (4) It is evident in the heterozygous individual, who is indistinguishable from the homozygote in most instances. The homozygote carries the same form of the gene in both members of a chromosomal pair. (5) Approximately half of the offspring of an affected heterozygote and a normal mate are normal, and half are affected. If a child of an affected parent fails to inherit the defective gene, the child is normal, and his descendants will be normal in that respect, unless he marries a mate who has the defect which is present in his family. Hence the dictum, "Once lost, lost forever."

Recessive Traits.—The next simplest mode of inheritance is the recessive, in which the defect is obvious as such only when both allelic genes determine the same defect, i.e., it is evident only in the homozygous individual. Allelic genes are situated at the same locus in the two members of a chromosomal pair. An individual exhibits a recessive trait only when he has inherited the factors for it from both parents, either or both of whom may be normal. Recessive traits which are rare appear in children whose parents are, as a rule, both normal. Amaurotic family idiocy is dependent upon a recessive gene. This disease is fatal in early life, hence no affected person ever grows up to be a parent. Parents of children affected with this condition are always normal.

Characteristics of recessive traits are: (1) The defect may appear in one or more children of normal parents. In such cases, one expects approximately one-fourth of the offspring to be affected. (2) The defect may appear in both sexes and, of course, is transmitted by both parents. (3) If the disease is one which is not uncommon, one parent, at least, of the affected child may also have the disease. The other parent, though normal, must also carry a similar gene. In the event of one parent being affected, and the other being a normal carrier, approximately half of the children will be affected, and a study of these two generations only might lead one to conclude that the disease was caused by a dominant gene. Study of a large number of families through several generations would be necessary to determine that the disease was dependent upon a recessive gene. (4) All the children of two affected parents will be affected. (5) The incidence of cousin marriages between parents of affected children is higher than in the general population. The rarer the disease, the greater will be the incidence of consanguineous matings in the parents of the affected children.

Conditions which outwardly appear to be identical may have a different genetic basis. If they are dependent upon recessive genes which differ in their location in the chromosomes, the supposedly anomalous situation may arise in which two parents, both affected with a recessive trait, produce all normal offspring instead of all affected with the trait as would be expected. Thus, two parents, both of whom were hereditarily deaf, as shown by the fact that each had deaf brothers and sisters, produced six children all of whom could hear. When one of these six married a first cousin who was also hearing, deaf offspring resulted. If one imagines two types of deafness, one caused by imperfect development of the spiral ganglion, the second by imperfect development of the temporal lobe of the brain, it is easy to see how such a circumstance as that just described could arise.

Sex-Linked Recessive Traits.—In a third mode of inheritance the recessive gene is located in the nonhomologous part of the X chromosome, which is also concerned with determining sex. The Y chromosome of the male carries no genes that counterbalance those in the nonhomologous part of the X chromosome; hence the male shows a recessive defect when only one gene for it is present. The female, with two X chromosomes, must have two genes before the defect is obvious. Color blindness, hemophilia, many cases of pseudohypertrophic muscular dystrophy, etc., are examples of conditions dependent upon genes located in this region of the X chromosome.

The characteristics of this mode of inheritance are: (1) The defect is more prevalent in males than in females, and the rarer the defect, the more concentrated is the condition in the male sex. (2) It may affect females, but does so only when the father exhibits the defect and the mother is a carrier or herself exhibits it. (3) The incidence of cousin marriages is not higher than normal among the parents of affected males, but is higher than normal among the parents of affected females. This is because the defect comes to the male through his mother only, but to the female through both her parents. (4) Normal males

mated with carrier women will be likely to have half their sons affected. (5) Affected males mated with normal women will have all normal sons, and all their daughters will be carriers.

Incompletely Sex-Linked Recessive Traits.—The fourth type of inheritance involving only a single gene is the incompletely sex-linked recessive. The gene is carried in the homologous parts of the sex chromosomes, so that most of the rules governing its transmission are those regulating the heredity of autosomal (not connected with the sex chromosome) recessive traits. This method of inheritance shows the two following distinctive features: First, it tends to be concentrated in offspring of the same sex in any one family, that is, in one family it will be limited to the girls, in another to the boys, although not all the girls in the first case, nor all the boys in the second will be affected. Occasionally, this rule is broken and children of both sexes will be affected. Second, the sex most likely to be affected is the same as that of the parent from whom the father presumably received his defective gene.

The defect is carried in the sex chromosomes. The father passes on the Y chromosome received from his father to all his sons, and the X chromosome received from his mother to all his daughters. Therefore, if he receives a defective Y chromosome from his father, he passes it on to his sons, and if he receives a defective X chromosome from his mother, he passes it on to his daughters. The other defective gene comes from the mother.

It is possible to tell from which parent the father has received his defective gene under two circumstances: when a relative of the father is affected, and when he is related to his wife. In the latter case he probably received the gene for the defect from the parent who is related to his wife, because if the defect is at all uncommon, it is not likely that his wife and he received their defective genes through ancestors not common to both, although that is possible. Hence it is important to report not only that parents were related but how they were related, in order to determine whether a defect is inherited as a recessive autosomal or as a partially sex-linked trait.

When an incompletely sex-linked defect occurs in children of both sexes in a family, it is because of "crossing over." When two chromosomes lie side by side in the process of meiosis, they may become twisted about one another, break, and the two adjoining regions change places. If a piece of the Y chromosome destined to go into a future son and bearing a defective gene should change places with the homologous part of the X chromosome destined to make a future daughter, the result might be an affected daughter, with two defective X chromosomes.

Y Chromosomal Inheritance.—A fifth mode of transmission is conditioned by a gene in the nonhomologous part of the Y chromosome. Such a defect will pass from father to all his sons, but will appear in none of the daughters. In several families, conditions have been inherited acting as if dependent upon the Y chromosome type of transmission, although in other families conditions which are similar clinically have not followed this rule. Thus, instances of ichthyosis hystrix, hypermobility of the joints, and fused second and third toes (zygodactyly) have been reported as descending from the father to all his sons, and to none of his daughters.

More complex types of inheritance have been demonstrated in forms in which breeding experiments can be carried out to test the theory, but in man, the above mentioned are the modes of transmission most readily recognized, and verified by statistical analysis.

Mendelian Ratio in Families With Recessive Traits.—At this point a warning should be issued against expecting that the ideal ratio of affected to normal will be made in any one family. Two unaffected parents who are heterozygous with respect to a recessive gene will have approximately one-fourth of their offspring affected, and three-fourths normal. This ratio is seldom attained in a series of families, however, for two obvious reasons. The first is that many normal parents who might produce a child with a recessive defect have only normal children, who naturally are omitted from a series of families collected because of the defect being present. This makes the proportion of affected much higher than 25 per cent. The second reason is that when families with defective offspring have less than four children, the percentage of affected must of necessity be higher than 25.

For a full discussion of this, one must turn to a book like Hogben's.[22] A brief illustration will suffice to make it clear, however. In families of two children there are three possibilities: (1) both affected, (2) both normal, (3) one affected and one normal. The chances of being normal are three-fourths, and the percentage of two-child families falling into each of the above possible classes is determined by the binomial theorem. If we let *a* stand for the chance of being affected, and *3n* the chance of being normal, we would have the three classes distributed as follows: both affected would occur in 1 family in every 16, or in 6.25 per cent. Both children would be normal in 9 families in every 16, or 56.25 per cent. One affected and one normal child would be found in 37.5 per cent. These figures are derived from the expansion of the expression $(a + 3n)^2 = a^2 + 6an + 9n^2$. a^2 is the one family with both affected; 6an, the 6 with one affected and one normal, and $9n^2$, the 9 families with only normal children. The latter class, having only normal offspring, does not enter into the series; clinically we find only the 7 families with affected children. Of these 7 families, having a total of 14 offspring, we find 8 or 57.14 per cent affected. Had we been able to include 18 normal children from the last 9 families, there would have been a total of 32 with 8 affected, giving the expected 25 per cent. Stating the number of affected per family in numbers, rather than in percentages, we find that there were 8 affected children in 7 families, an average of 1.1428 per family.

Let us carry this one step further, as it brings out several important points. What would be the expectation in three-child families?

All three might be affected, all three might be normal, two might be affected, or only one might be. What are the percentages of these four groups in a population? Again the expression (a + 3n) must be expanded, this time to the third power, giving $a^3 + 9a^2n + 27an^2 + 27n^3$. Here we have a total of 64 families, with 1 of them having all 3 affected (a^3); 9 with 2 affected and 1 normal ($9a^2n$), and 27 with 1 affected and 2 normal ($27an^2$). There are 27 with all 3 normal. These will not enter into the series. Of the remaining 37 families with a total of 111 children there will be 48, or 43.2 per cent affected. This is still higher than the ideal 25 per cent, but it is much nearer to that figure than was the percentage of affected found in two-child families. Were we to carry this illustration through 4, 5, 6, etc., child families, we would see that, as the number of children in the family rises, the nearer does the percentage of affected approach the theoretical 25. In these 37 families with a total of 48 affected children, the average number of affected per family was 1.2973. Hogben gives a table with the number of affected expected per family for each size sibship up to 20. This discussion reveals the fallacy of dividing the total number of children in a series of families by 4 and using that figure as the expected number of affected in this group, if the defect is dependent upon a recessive gene. The expectation is always greater than 25 per cent, because the families with normal children are always eliminated; and the smaller the family, the wider the departure from the theoretical 25 per cent.

Several misconceptions found not infrequently in the medical literature are as follows: Diseases not caused by infectious agents are said to be inherited when the line of transmission is obvious; to be "familial" but not hereditary when they appear in several siblings but not in either parent; and to be "sporadic" when they appear in only one child. The recognized "inherited" disease is probably a dominantly transmitted one; the "familial" disease one that is recessively inherited; and the "sporadic" case an example either of a mutation or of a recessive disease which has as yet had time to appear in only one child. The first child to show a defect must remain a "sporadic" example until a subsequent child develops the same thing. Simple as this point is, it is often overlooked.

A second erroneous idea arises through a lack of understanding of the laws of probability. The appearance of a defect in one child in no way alters the probabilities of the same defect appearing in subsequent children. If one child develops amaurotic idiocy, there is no ground for assuming that the next three will be normal; the chances are still one-fourth that each child yet to be born will show the disease. A third mistake is this: because certain defects can be experimentally induced in the fetus, the same defect spontaneously arising in fetuses is said not to be inherited. Congenital nerve deafness may be caused by rubella in the mother, but that does not exclude most cases of such deafness from being genetically determined.

Mutations

It was stated that a dominant trait was not present in children unless a parent was affected. This rule is broken when a mutation appears. This is a sudden change or variation in the genes which produces a trait not present before. The change may be a dominant one, so that once it occurs, it will reappear in those who are heterozygous for the gene. It may be such that the gene has to be duplicated before producing an obvious change, hence a recessive one. Such mutations occur spontaneously in plants and animals, as well as in man, and can be induced by such physical agents as x-rays or radium acting on the germ cells.

We know that prevention of procreation by those affected with a dominant trait eliminates that trait in that family. Prevention of procreation by those affected with a recessive trait does not eliminate the trait in one generation as is the case with a dominant trait, but it does lower the incidence of affected individuals in a population, despite the presence of carriers which permit of affected persons being born of normal parents. In the case of hemophilia, Haldane[5] points out that the incidence of the disease in the population remains fairly stationary, despite the fact that most hemophilic males die in childhood without reproducing their defect. Therefore, he postulates a rather constant mutation rate for hemophilia, which starts new lines of hemophilia as old ones die out. Such a mutation he thinks must have occurred in the germ cells of one of the parents of Queen Victoria of England, probably in the father, and points out that had the gene for hemophilia been present in the ancestors of the Queen for any length of time before that, it would probably have shown itself as the obvious trait of hemophilia in some of the collateral lines. Royal families tend to be large, permitting such traits, when present, to find expression; and royal pedigrees are kept with care, so that such traits are recorded. None of her collateral or ancestral lines showed the presence of hemophilia, and all those affected with the disease in the royal houses of Europe are related to her as affected sons, or as affected males descended from her through the female line. Thus this tragic gene which weaves itself across the tapestry of modern Europe like a scarlet thread probably originated in one of her parents as a mutation. Haldane points out what an important, although indirect, role the hereditary hemophilia of the late Czarovitch had upon the course of world history. Because of the ability of the Greek monk, Rasputin, to convince the Czarina that he could stop the bleeding spells of the young heir to the throne, he and his associates gained such an ascendancy at court that the Russian Revolution took place in 1917, at a time when it proved most disastrous to the Allied Nations in World War I, and perhaps prolonged that war because of the collapse of the Eastern Front.

Mutations have been regarded as of such rare occurrence that they can be disregarded as of practical significance in causing disease or abnormalities. In a masterful analysis of muta-

tion rates in man, Muller[27] states that mutations must "in human populations that live in a state of approximate genetic equilibrium be the differential cause of death or failure to reproduce of between one-fifth and two-thirds of the persons who escape being killed before reproduction, or being prevented from reproducing by other purely extrinsic causes. . . . On the basis of existing data in man, and supported by evidence from *Drosophila,* the total human mutation rate is judged to be probably not less than one newly arisen mutant in 10 germ cells, on the average, and not more than one in 2 germ cells."

Modifying Factors

The expression of an inherited trait may vary widely in the sibs of a given family. Although several members may inherit the factor for brown eye color, the amount of pigment may differ widely in the various members; although several may inherit the factors for excess height, not all will be tall to the same degree. In the case of disease, the various sibs are usually affected to different degrees. This variation may be dependent in part upon the other genes which the individuals inherit and which exert an influence upon the gene in question.

Because of these modifying factors, or variations in the expression of the trait, it may happen that persons who have inherited the necessary genes for the production of a trait do not show it. In the case of diabetes, it has been said that not until 90 per cent of the islet tissue is nonfunctioning, does the patient show symptoms of diabetes. If the gene or genes for diabetes were modified so that only 50 per cent of the islet tissue were nonfunctional, the patient would appear as normal, although possessing the genetic constitution of the diabetic. The same might be true of deafness. There may be superacute hearing, normal or diminished hearing, and the diminution may be of all grades through diminished sound reception to complete absence of response to all tones. Hereditarily deaf children are seldom completely deaf; they are deaf merely to the range of sounds ordinarily encountered in everyday living. If the depression is not sufficient to cause the child to be deaf to spoken tones, it will be listed as a hearing child, although genetically it is deaf.

Age of Onset.—This too may be dependent upon hereditary factors. A disease will be evident in childhood in some families, not until adult life or old age in others. If the age of onset is early, before procreation is possible, and if the disease is fatal, or decreases the opportunity for securing a mate, it gradually is eliminated if a recessive, and eradicated completely in that family if a dominant. If the disease comes on after the age of procreation is advanced, it is not likely to decline in incidence. An example is Huntington's chorea, which, though dominant, usually does not attack until the patient's children are all born.

Modes of Departure From Normal.—It is evident that the normal developmental pattern of an individual may be disturbed in several ways: (1) developmental arrest, so that structural or functional patterns are prolonged past their normal span of existence, such as harelip or undescended testis; (2) complete absence of a part, a more extreme arrest than in (1), such as absence of a limb or lower jaw; (3) excessive development of normal tissues or parts, such as hypertrophy of a limb; (4) regression or degeneration of parts formed normally at an earlier period, as in many of the atrophies in the nervous system which functioned normally for years before degenerating; (5) abnormal structure or function, not usually present at any stage of development, such as anencephaly or cystinuria; (6) combinations of any of these, such as cyclopia, polycystic kidneys, etc.

It is obvious that the complex pattern of structure and function as exemplified in the adult human body must be under the guiding principles of racial and individual inheritance reacting to a given environment, and it is equally obvious that a disturbance in these factors may alter the unfolding of the pattern at any point. At every step of development, the organism may take a right or a wrong turn, and there will be many wrong turnings but only a few right ones that will leave it still capable of vital processes. Hence many of the departures from normal development that might be hereditary in nature may be so extreme that the embryo is lost when very young. Only those departures from normal which are consistent with life until near term, or after birth will be recognized with any degree of frequency.

The hereditary defect may be dependent upon a complex of factors so that it does not appear according to any known law of hereditary transmission. It may be dependent upon a single gene, or upon the alteration of a single gene, although based upon a complex group of genes. An illustration could be drawn from many English words. The word "stationary" differs from the word "stationery" by one letter, but it takes ten letters to express the full word in each case.

One writer, in discarding the idea that some types of feeblemindedness were dependent upon a single gene, remarked that it took more than one gene to make a mind, even a feeble one. This is doubtless true, but it can be pointed out that it takes more than a gas tank to make a complex mechanism like a motor car, but that the absence of one will keep that complex mechanism at a standstill. And so will the absence of a wheel, or the spark plugs, or a great many other single parts of the mechanism! One type of feeblemindedness, that accompanying phenylketonuria, has been shown to be dependent in its expression upon a single gene.

Twins

A study of twins plays an important role in determining the genetic basis of any disease or abnormal condition. If a rare and bizarre defect occurs in but one child in a family in whose history it is unknown, it is difficult to believe that the defect was determined by

heredity. When a defect occurs in one-egg twins and does so with far greater frequency than it does in siblings or in two-egg twins, the hereditary determiners are obviously of more importance than the extraneous causative factors, or even of supreme importance. The more common the trait in the population, the less evidence will such a study furnish, since two-egg twins will be alike with respect to the trait almost as often as one-egg twins: the less common the trait, the more convincing will be the evidence in favor of heredity if one-egg twins resemble each other in a significantly greater number of cases than is true of two-egg twins.

Susceptibility to Infectious Diseases

It is clear that if a disease is caused by an organism, the presence of this organism is the first essential to the disease. Studies on inherited resistance to disease in various animals leaves little doubt that, in many infections, a second and sometimes even greater factor is the inherited resistance or susceptibility to the disease in question. Studies on *tuberculosis* in rabbits show that heredity plays an important role in limiting the infection to the portal of entry without dissemination in the resistant strains, but permitting of widespread dissemination in the susceptible strains. Studies on monozygotic and dizygotic twins have led to the conclusions that there is a heredoconstitutional mechanism determining the resistance to tuberculosis, and that it is multifactorial, that is, based upon a group of genes.

Poliomyelitis susceptibility has been regarded as dependent upon a recessive gene, nonsex-linked. This conclusion was based upon 29 individuals, all of whom were related, in a section of West Virginia. In another survey in California, about 10 per cent of the affected persons came from families with others affected. The fact that the disease appears to leave unscathed many persons who have been in contact with the ill person, while attacking several members of a family in epidemics removed in time by twenty or more years, suggests an inherited susceptibility to the virus.

Rheumatic fever has for some decades been regarded as showing familial susceptibility, the incidence in several members of a family not being dependent alone upon opportunity for infection of other members, but also upon inherited ability to develop the disease. A very careful study in the last few years has led to the conclusion that the susceptibility to rheumatic fever is dependent upon a single nonsex-linked recessive gene.

Infections in General.—Webster[15] found that by breeding mice for susceptibility and resistance to certain infections, and then creating artificial populations made up of varying proportions of susceptible and resistant animals, he could cause epidemics of varying severity. The epidemic lasted as long as there were susceptible animals left to contract the disease, and died out when the supply of susceptible animals had expired.

Neoplasms

There has been a great deal of literature written on the subject of inheritance in neoplastic diseases in man, much of it characterized more by its emotional fervor than by its critical attitude or scientific accuracy. Because of the general feeling that the prognosis is hopeless in cancer, profession and laity alike have tried to fight shy of the idea that there is a genetic basis for cancer. No attempt will be made to produce all the arguments for or against this conception, the main ones being on the one side, that since so many persons die of cancer, it is to be expected on the basis of random sampling that several members in a family will have cancer without there being any hereditary basis for it, and (2) that cancer is caused by chronic irritation of some type. On the other side, the main arguments are based upon: (1) finding the same type of tumor in the same organ at about the same age in identical twins in significantly higher percentages than is the case in like-sexed fraternal twins; (2) the finding of relatively rare tumors in several members of a family; (3) the biological principle that since many tumors have been proved to have a genetic basis in animals where controlled matings and environments can be obtained, it must follow that in man who is subject to the same general biologic laws, tumors will also have a genetic basis. The same type of tumor does not need to be inherited in man as in mice, tumors do not need to follow the same mode of transmission, and the relative roles of intrinsic and extrinsic factors do not need to show the same balance in the two species, but the fact remains that man cannot escape from what is shown to be a biologic law in much of the rest of the animal kingdom.

There are many forms of tumor, and although one in ten are dying of some form of malignancy, they are not all dying of the same type of malignancy, so that the findings of a specific type of tumor, at ages not representative of the highest incidence of that form of tumor, in several brothers and sisters may be proof of the genetic basis of the tumor. Such a concept does not invalidate the idea that extrinsic factors may play a role. We may make the following equation: H plus E = C, where H is heredity, E is environment, and C is cancer. As H is large, E need only be small to produce C, and vice versa. Should both H and E be large, then C would be obtained perhaps at a very early age. The skin cancer caused on the hands of early workers with x-rays is probably an example where H was very little, E was very large, and hence was the determining factor in the appearance of cancer.

Retinal glioma is an example of the opposite type, where H is large and E apparently very small or absent. In the majority of tumors, we cannot assign relative roles to H and E so easily, since we are not sure of the environmental factors which may assist in the precipitation of the tumor on the one hand, and cannot be sure that heredity was lacking, even when the parents did not show the tumor, on the other. The many tumors that are missed before autopsy, and the relatively few autopsies

that are performed, convince us that many persons who die, supposedly cancer-free, may in reality have tumors. Nor can we say that any one age is a cancer age, beyond which the patient can be assumed to be cancer-free, should he live to that time of life without obvious tumor. The identical twins who did not develop their breast cancer until 90, although the peak incidence age for this is usually between 50 and 55, are examples of this. Age of onset in cancer as in other diseases appears to be conditioned largely by inheritance, but can be modified apparently by external influences.

The tumors in man which seem to show the greatest evidence of genetic basis are eye, brain, and neural tumors, gastric, rectal, breast, and uterine cancers. Lung cancer, although forming 10 to 20 per cent of cancers affecting the male, is unlike lung cancer in mice in not giving evidence that it has a genetic basis. Whether this is due to a predominance of extrinsic factors in its causation, or to a multiplicity of genetic factors, or to the lack of diagnosis in many cases in which it is present, we cannot say.

Often one finds in the literature reference to "cancer families," and it is said that cancer in them is hereditary, but not in the majority of instances. There is also the tendency to look upon the genetic basis of cancer as multifactorial. If this is true, it may well be that in some families most of the factors are present and are passed on from parent to child in a group, so that cancer appears relatively frequently, while in other families the same genetic complex is not passed on in its entirety, and hence the cancer incidence is more sporadic. The same factors may be at the basis of cancer formation in each.

Finally, one frequently sees the statement that "cancer as such is not inherited, merely a cancer susceptibility," because of the long time which elapses between the time of birth and the appearance of the cancer, and during which extrinsic factors may operate. It may be pointed out that nothing as such is inherited; what is inherited is merely the potentiality to develop the structure or the trait, given a proper environment in which it may unfold. The term "susceptibility" connotes a hereditary or predisposing and an environmental or precipitating cause, as in tuberculosis. Both must be present. In cancer, however, such congenital tumors as retinal glioma, or adrenal tumors in early childhood appear to have no such precipitating cause; the "susceptibility" is sufficient. For more detailed discussion of tumors in families and in twins, reference must be made to the literature.

Much of the data dealing with freedom from or undue liability toward cancer needs critical analysis before acceptance. Eskimos and North American Indians are said to have little cancer, but how often does an Eskimo have adequate medical diagnosis? Primary cancer of the liver, said to be high among African Negroes in comparison to Negroes in the United States, would appear to be dependent upon factors other than racial. Gliomas are said to be about twice as common in white persons as in Negroes, and more common in white females than in white males. Cancer of the uterus is said to be low in Jewish women and its peak incidence occurs between 50 and 54 years of age, in contrast to that in Gentile women, which occurs between 45 and 49 years. Penile cancer is rare in Jews and in Mohammedans who practice circumcision, and common among the Hindus who do not.

Primary liver cancer is high among the Chinese, and this has been thought to be dependent upon infestation with the liver fluke, but the Chinese born in Java, where the liver fluke is absent, also show a high incidence of liver cancer. The Javanese also have a very high incidence of liver cancer. They are said to have a high general cancer rate even in early years, 4 per cent of all deaths between 20 and 30 years of age being attributable to carcinoma. Their sarcoma rate appears to have the same incidence at all ages instead of decreasing with age as is the case with the Chinese and Europeans. Gastric cancer is common in Japan, rare in China. Lung cancer is very common in the miners of the famous Schneeberg mines, but workers have had great difficulty in finding the specific irritant which is responsible. Much inbreeding in these isolated valleys may play a part in heightening an inherited tendency.

Such factors as age of death of the population, facilities for adequate medical diagnosis, x-rays, opportunities for hospitalization, adequate death records, methods of recording causes of death, etc., all play a large part in determining the published cancer death rates in various parts of the world, although not influencing the actual cancer morbidity. Some years ago, a popular writer showed that milk drinking was the cause of cancer because by a series of parallel data cancer incidence could be shown to be high where milk consumption was high, and vice versa. Equally well could it be demonstrated that cancer was caused by telephones, automobiles, electric equipment in the home, etc. The following may be stated as a truism: (1) With advances in civilization, corresponding advances are made in public health. (2) With the latter advance goes postponement in the average age of death. (3) With the latter goes an increase in the number of persons who are potential cancer victims. Therefore, practically any trait found most often in the most highly civilized communities, be it drinking milk, using telephones, or attending a Beethoven symphony, will be paralled by a high cancer death rate.

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