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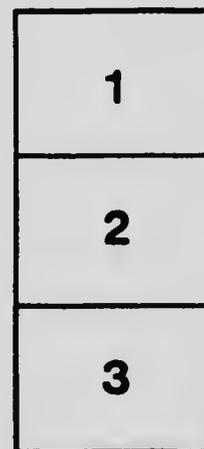
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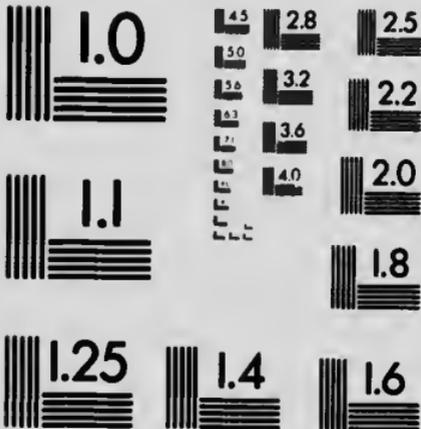
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THE HISTOPATHOLOGY OF GOITRE.

BASED UPON THE MICROSCOPICAL STUDY OF OVER FIFTY CASES OF THYROIDECTOMY, WITH HISTORIES OF THE MOST IMPORTANT.*

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MACCALLUM, of Baltimore, in a recent article on the pathology of exophthalmic goitre, describes certain histological changes in the thyroid gland which he regards as diagnostic of the disease. These microscopic changes he depicts as a budding or infolding of the acinal epithelium, together with certain alterations in the morphological character of the lining cells. His observations were made upon a number of cases of exophthalmic goitre, every one of them presenting the characteristic picture to a greater or less degree. Even in the very early stages of the disease the histopathological change could be made out in some part of the gland.

In view of this work we were led to make a careful comparative study of fifty or more consecutive cases of thyroid conditions, including all varieties of gland disturbances and without special reference to Graves's disease. In this way we considered it possible to ascertain whether any pathological picture characterizes the thyroid gland in exophthalmic goitre distinctively from other conditions.

Fifty-nine cases in all were carefully studied histologically. Eighteen cases were unquestionably Graves's disease, two of which proved fatal. The infolding and budding of the acinal epithelium was present in some parts of the gland in 20 cases. The gland presented tumor formation in three cases of the series, viz.: carcinoma in one, intercystic papilloma in another, and angioma in still another. Chronic inflammation in the

* Read before the American Surgical Association, June 4, 1909.



form of lymphoid- and plasma-cell infiltration, together with an increase in fibrous-tissue stroma, occurred 29 times. Eleven cases were of a simple cystic condition. In each case many sections were obtained for microscopic study and from various parts of the gland. The tissue was fixed in Zenker's fluid, formalin, and alcohol, and embedded in paraffin. Sections were stained in eosinomethylene blue, hæmatoxylin-eosin, and Mallory's connective-tissue stain.

For convenience of description the histopathological changes that occurred in this series of thyroid glands may be divided into six groups:

The *first* type is characterized by a subacute inflammation in which the supporting framework of connective tissue is infiltrated with lymphoid and plasma cells. The cellular exudate is usually focal, though sometimes it is diffusely distributed throughout the interacinal tissue.

The *second* type of lesion is distinctly proliferative in character; the connective-tissue trabeculae and acinal framework are markedly increased. This fibrous new growth presents the essential change. Often dense foci of leucocytes, including plasma and lymphoid cells and polynuclear neutrophiles, infiltrate the areas of connective tissue. One of the striking features in this type of chronic thyroiditis is the occurrence of sharply defined collections of cells. The architecture resembles the so-called "tracoma bodies," seen in the lymph nodes. Encircling these bodies are dense collections of mononuclear lymphocytes. The cells comprising these bodies are 10-12 microns in diameter and possess a single ovoid vesicular nucleus and pale-staining granular protoplasm. Whether the cells are of endothelial origin cannot be definitely stated, though in our opinion it would seem to be the explanation.

The *third* type of lesion is characterized by vascular changes. These usually take the form of an obliterating endarteritis, though in some vessels the lesion appears as a degeneration especially of the media. Thrombosis is occasionally seen. There is often associated with the vascular changes a well-marked perivascular increase in fibrous tissue. With this

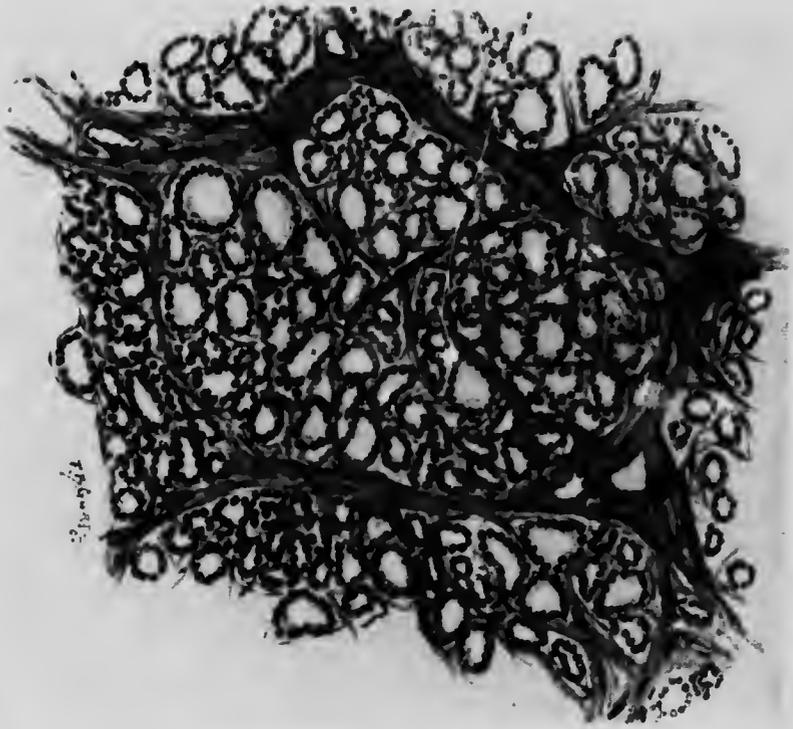


FIG. 1.

Normal thyroid gland.

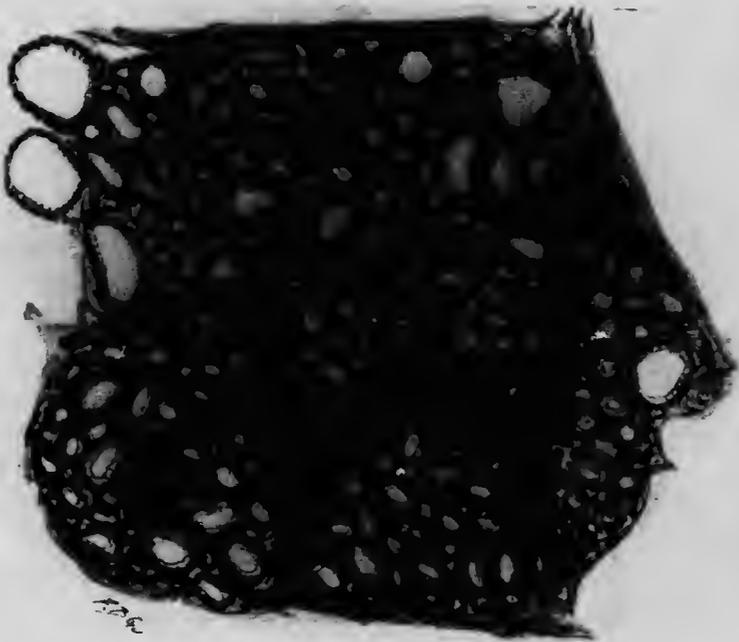


FIG. 2.

Chronic inflammatory globule infiltrated with lymphoid cells.

FIG. 3.



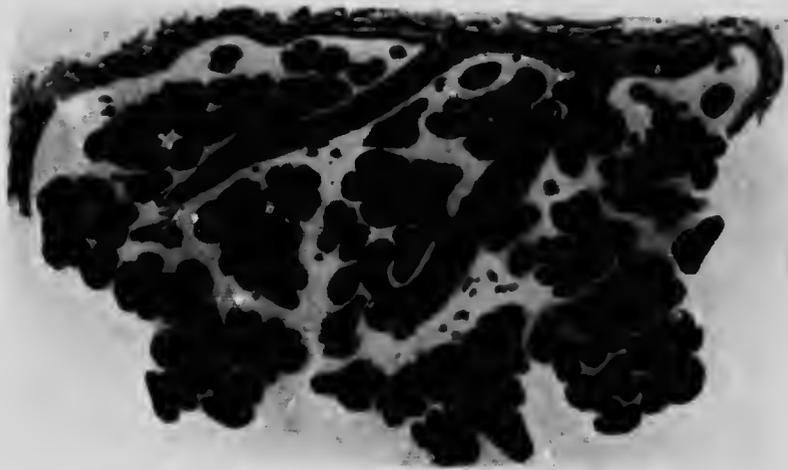
Cystic thyroiditis.

FIG. 4.



Adenocarcinoma.

FIG. 5



Intracystic papilloma.

FIG. 6.



Interacinal hyperplasia.

FIG. 7.



Marked glandular hyperplasia, showing infolding and budding of the acini. *Not* a case of exophthalmic goitre.

FIG. 8.



Slight hyperplasia (infolding and budding). Fatal case of exophthalmic goitre; not operated upon.

type of lesion hemorrhage into the acini is frequently encountered. The most interesting change, however, occurs in the gland epithelium. Here large areas of the parenchyma undergo necrosis, but the individual cells lining the alveoli remain intact; the picture is analogous to an extensive focal necrosis of the liver. The destruction undoubtedly results from occlusion of the vessel supplying a particular area, in which the occlusion is either endarteritic, thrombotic, or both.

A fourth group of changes includes the neoplasms, such as carcinoma, interstitial papilloma, and angioma.

The fifth type consists of an interstitial cellular (inter-acinal) hyperplasia which in many ways resembles a sarcomatous growth. Though the acini are apparently unchanged in size and structure they are uniformly separated by the enormous cellular increase in the tissues interposed.

The sixth type is represented by distinct hyperplasia of the gland parenchyma, which results in more or less tortuosity of the alveoli and infolding of the epithelium, the degree largely dependent upon the amount of colloid substance within the lumen.

The microscopic study of a large number of sections from each specimen of gland showed neither cellular arrangement nor cytological changes ordinarily detected by routine staining methods which could be regarded as specific for any special type of disease of the thyroid gland. Though infolding and budding of the acinal epithelium occurred in the gland of exophthalmic disease, the histological picture, however, was not at all constant. Occasionally infolding of the alveoli is entirely absent in unquestionable cases of Graves's disease; while, on the other hand, infolding and budding of the alveolar wall frequently occurs in simple goitre and other benign conditions of the thyroid gland in which there is hyperplasia.

In our series of examinations five pronounced cases of Graves's disease failed to show the slightest suggestion of infolding of the gland epithelium, though many sections and from all parts of the specimen, were examined. Again, in our cases we encountered a number of cystic goitres and glands,

the seat of extensive neoplastic growth, that presented the perfectly typical picture of infolding and budding of the parenchymal cells.

Alterations in the morphological character of the epithelium—for example, several layers of cells lining the alveolar walls, the flattened type of cell becoming columnar, the change in chromatin-content of the nuclei, etc.—we have not found constant for any one pathological condition of the thyroid gland. Whether the lining epithelium of the gland is columnar or flattened depends upon the amount of colloid material within the lumen. It is noteworthy, in parts of the glands that show distinct histological changes of a hyperplastic nature, to find a marked diminution of the amount of colloid; very often there is an apparent absence of this material. Though the epithelium shows no appreciable microscopical alteration in cell morphology, there is undoubtedly a decided change in cell function as evidenced by the lack of colloid production. The absence of acinal contents naturally permits of a columnar type of cell lining.

Only rarely in thyroid hyperplasia were we able to detect more than two layers of epithelial cells lining the acini. Not even in the extreme grade of exophthalmic goitre were the cells heaped up. Often what appeared as several layers of "focal budding" could be explained by the fact that the knife had sectioned the gland alveoli at various places.

Infolding of the epithelium may occur in any thyroid gland when active hypertrophy is going on, especially in the absence of colloid production, no matter what the cause. The same fundamental principle governing the phenomena is also met with in other glandular organs which are the seat of hypertrophy: for example, the prostate, where the infolding is sometimes beautifully illustrated.

In some instances three or more of the above described types of lesions occur in the same gland, while in others the histological change is confined to one type. It is especially noteworthy in the gland of exophthalmic disease to find multiple lesions, widely separated and distinctive in character, though

the lesion may be single and confined to one area and without histological variation.

The following cases are detailed in illustration of our findings:

CASES OF TRUE GRAVES'S DISEASE WITHOUT ANY INFOLDING AND BUDDING OF THE EPITHELIUM, WITH OR WITHOUT MUCH INCREASE IN CONNECTIVE TISSUE.

CASE I.—Miss G., aged 29. Has had a slightly enlarged neck for some years; on examination only a small nodule can be felt above the sternum. Is excessively nervous, has tachycardia (pulse 100-120), tremors, marked exophthalmos. Operation: removed two large lobes situated beneath the sternum. Microscopic examination shows no infolding or budding of the epithelium, but there was a cystic condition and acini filled with colloid, some increase of connective tissue which contains collections of lymphoid and plasma cells; and some interstitial hemorrhage.

CASE II.—Miss B., aged 38. Had been treated in the medical wards of the Montreal General Hospital for six months for a very severe form of Graves's disease. Tachycardia (130-140), tremors, exophthalmos, dilated right heart, extreme emaciation, etc. Removed most of a not very large thyroid and ligated all the vessels; and yet the microscopic examination showed no infolding and budding of epithelium, but much colloid and slight increase of connective tissue.

CASE III.—Miss C., aged 24. Some years ago noticed a small lump in the thyroid. At the same time got excessively nervous, pulse ranged from 130-140, with marked palpitation. When I saw her she had an enlarged thyroid, tremors, slight exophthalmos, Stellwag's sign, pulse 130, breathlessness, unable to go upstairs. Removed the right lobe and isthmus and tied all the thyroids. After operation marked thyroidism for twenty-four hours. On microscopic examination no infolding or budding of epithelium found, but much colloid and some increase of connective tissue.

CASE IV.—Henry H., aged 53. Great nervousness, tachycardia, tremors, emaciation, Stellwag's sign, commencing enlargement of right heart. On microscopical examination found no infolding of epithelium but very small acini, intra-acinal hemorrhage, and the gland markedly cystic in many places.

CASE V.—Miss P. B., aged 25. For two years had been excessively nervous, but no enlargement of the thyroid gland. Then enlargement was noticed and at the same time her eyes became prominent. Became unfit for her work of teaching and consulted Dr. Shepherd. At this time it was noted that she had considerable enlargement of both lobes of the thyroid, which were soft and vascular. Eyes very prominent and both Stellwag's and Graefe's signs present. Excessive nervousness, tremors, loss of flesh, with tachycardia (130-140), breathlessness. She also had temperature and some swelling of legs. The right heart was moderately distended. The case was one of well-marked Graves's disease, and she was admitted to the Hospital and treated medically for some weeks. At her earnest request an operation was performed and the right lobe of the thyroid and the isthmus removed; the left superior thyroid was tied. She did well for twelve hours, when her pulse became uncountable; she was excessively nervous, tossing about the bed, and soon became delirious and died twenty-four hours after operation. Her temperature never rose above 99.5°. The microscopic examination showed no infolding or budding of epithelium, but the acini were much increased and distended with colloid and the epithelium lining them was flattened.

CASES WITH MARKED INFOLDING AND BUDDING OF EPITHELIUM
OF THE GLAND AND YET NO GRAVES'S DISEASE.

CASE I.—Mrs. B., aged 33. For many years had an enlargement of the neck on right side; at times larger than at others. Some two months before seeing her it had grown very rapidly. On examination was found a round, smooth tumor of the right lobe of the thyroid the size of a Tangerine orange; did not extend below the bony thorax, and appeared to be a large tense cyst. No tachycardia, no tremors, no exophthalmos, and no difficulty in breathing or swallowing; evidently a very nervous woman. Removed right lobe of thyroid which contained one large cyst and several small ones.

CASE II.—Miss H., aged 25. Has had a swelling of neck since she was 16 years old; tumor in mid-line. Has never grown rapidly. Has some breathlessness on exertion and attacks of dyspnoea, no tremors, no exophthalmos; pulse 90; considerable dysphagia at times when solids are taken. Operation: removed

an adenoma by enucleation. All symptoms relieved. In addition to infolding there was chronic inflammation and increase in connective tissue.

CASE III.—Mrs. D., aged 54. Two years ago noticed a small lump on the left lobe of the thyroid; has grown rapidly. On examination found one large and one small tumor in left lobe, largest, size of a large orange and other of a walnut, evidently cystic. No tachycardia, no tremors, no exophthalmos, no evidence of Graves's disease; pulse 80. Operation: removed left lobe and isthmus. In this case there was, in addition to the infolding and budding of epithelium, chronic inflammation with a lot of lymphoid and plasma cells and considerable colloid; no increase in connective tissue.

CASE IV.—Mrs. E., aged 39. For ten years had general enlargement of the thyroid, commenced when carrying first child. No tremors, no nervousness or ocular symptoms. Difficulty in swallowing; pulse 84. Hypertrophy and dilatation of epithelium; infolding and budding and much hyperplasia.

CASE V.—Miss F., aged 28. Has had "swelling of throat" for eight or nine years, which of late has caused some difficulty in breathing. Has taken thyroid extract with benefit. Of late the goitre has been increasing rapidly. On examination found an evenly enlarged thyroid, soft and vascular; pulse 98. No exophthalmos, no tremors, but only complains of breathlessness on exertion. Examination by larynx revealed pressure on the right side of the trachea opposite the fourth to the seventh rings of the trachea. Right lobe and isthmus removed. Much relieved by operation and was practically well six months later. Microscopic examination showed infolding of acinal epithelium in places and much hyperplasia; in others acini dilated with colloid and flattened epithelium.

CASE VI.—Miss A. H., aged 26. Six years ago noticed a small lump on the right side of the neck; grew very little until a few months before admission to Hospital under Dr. Bazin. Lately has been troubled with difficulty in swallowing and shortness of breath on exertion. Growth on right side and size of a goose egg. Pulse 78. No tremors, no exophthalmos or nervousness, absolutely no signs of Graves's disease. The growth was removed and on microscopical examination showed well-marked infolding and budding of acinal epithelium, with large areas of

increased connective tissue and diminution of colloid. In some parts there was acinal dilatation.

CASE VII.—Mrs. O., aged 40. Has had for some years a cyst of the thyroid which has been constantly increasing in size and from the discomfort and difficulty of breathing caused she desired operation. There were no nervous symptoms, no tachycardia, no tremors, in fact no symptoms indicative of Graves's disease. Dr. Elder removed the cyst by enucleation and she recovered rapidly. The microscopic appearance showed well-marked infolding and budding of the epithelium of the acini.

CASE VIII.—*Graves's disease with typical infolding, etc., in the right half of gland, which was first removed. Later great increase of left lobe with return of symptoms. This on removal showed no infolding of epithelium but merely acini distended with colloid and lined with flattened epithelium.*

Miss R. R., aged 23. For four years had suffered from symptoms of Graves's disease which came on with enlargement of the thyroid. Had tachycardia, tremors, nervousness, vomiting, high temperature, great exophthalmos, and enlargement of the right heart. Was in New York at the time and had the thyroids tied in one of the large hospitals, but secured no benefit from this treatment. In October, 1908, the right half of the thyroid was removed at the Montreal General Hospital with great benefit. The pulse was reduced to below 100, nervousness was less, and she was in every way better and able to return to her work. In the beginning of 1909, the left side of the gland began to enlarge rapidly and all the old symptoms returned. On admission to the Hospital in April, 1909, she seemed to be as bad as before the operation in 1908; in addition she had dilatation of the right pupil. The left half of the gland was removed, only a small piece being left on the trachea. She rapidly recovered from the operation and a month later all the symptoms had been much alleviated. The exophthalmos had disappeared from the right eye and the pupil was normal in size. The exophthalmos of the left eye, however, was as marked as ever. The microscopic appearance of the portion of gland first removed showed well-marked infolding and budding of the epithelium in the acini. The gland removed at the second operation showed no infolding of budding of the epithelium but merely acini lined with flattened epithelium and full of colloid.

