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THE GOITROUS CONDITIONS

OF THE

THYROID GLAND

11 Original Drawings.

THE GOITROUS CONDITIONS of the THYROID GLAND.

In presenting this study of the Pathology of Goitre I would like to make it clear that the work arose as a corollary to a more general inquiry into the problems of 'Protein' disturbances both dietetic and inflammatory. The first observations were made, post mortem, on children that had died from unexplained causes after a tentative clinical diagnosis of dietetic disturbance varying from anaphylaxis to diarrhoea and vomiting. It became apparent that children could be placed in one of three groups :- normal, lymphoid, or a-lymphoid, if attention were directed to the thymus, spleen, pyloric mucosa, appendix and tonsils (faucial and pharyngeal). Associated with this there appeared in certain sites in the peritoneum (pyloric and caeco-appendicular) changes in the fat tissue which seemed to vary in its lymphoid character with the thymus - perhaps like the thymus the range of its meta-trophy is between lymphocytes and fat-in an endothelioid organ. From this attention was soon called to the thyroid gland, Graves' disease, and to the histopathology of appendicitis and gastric ulcer by reason of the constant lymphocytic reaction presented in these conditions.

Graves' disease provided the freshest and most prolofic material for study. In the course of a study of the lymphocytes on Graves' disease, the new conception of the precise anatomy and physiology of the thyroid gland

and thyroid apparatus was reached.

The application of this knowledge to the pathology of Goitre is embodied in this paper. I have not burdened the thesis with references to the literature on grounds of space, but also because the subject has been so very completely reviewed by Biedl (I.) in the recent edition of 'Internal Secretion'. It should be mentioned however that Wilson (2) and Plummer (3) in the Mayo clinic have arrived at some almost identical conclusions regarding Graves' disease on other grounds than those presented in this thesis. Part of this work therefore may be taken as a confirmation of some of their views. No work on the Thyroid gland can be presented without acknowledging the classical studies of Marine and Lenhart - which carry the subject as far as it may go without a precise conception of the anatomy and physiology of the gland.

It will be necessary for an appreciation of this thesis that my previous publication with Dr Innes Pearse on the Anatomy and Physiology of the Thyroid Apparatus should be fresh in the mind. Copies are therefore included as an introduction to the subject matter of the paper. Appendix 1.2.3.

PATHOLOGICAL CLASSIFICATION of GOITRE.

The classification of pathological changes in the Thyroid gland, in the absence of any known etiological factor, must be strictly referred to the physiological or anatomical basis manifest in the Normal Gland, and should not be obscured by the introduction of any clinical or theoretical consideration. The application of pure pathology to the study of the signs and symptoms of the associated diseases must follow upon a knowledge of the relation of the morbid processes to the physiology of the Thyroid organ. Pure and applied pathology must be considered independently if we are to arrive at an understanding of the causal factors of disease.

A study of 2000 goitres, mostly operative material, demonstrates the existence of the following pathological categories of goitre exclusive of the acute specific inflammatory swellings and the true neoplastic states. This classification completely covers the material examined and each goitre was quite readily placed in its class and subcless. Casual examination without the use of a specific technique does not afford so sharp a definition of the Goitres; especially between the normal and the Hypertrophic and between the Hypertrophic and the Arteriocapillary-Sclerotic groups is there a difficulty, but that is to be expected, since these categories but represent the line of progress of the underlying changes; and decision, in considering quantitative factors, must be somewhat arbitrary within the zone of transition.

I would deprecate any attempt to solve these difficulties by reference to the clinical condition of the patient: indeed that is the source of all confusion in pathological studies.

The PATHOLOGICAL CLASSIFICATION of GOITRE.

Class.	Sub-class.
I. HYPER-TROPHIC GOITRE.	PHYSIOLOGICAL PATHOLOGICAL
II. HETERO-TROPHIC GOITRE.	ADENOID GOITRE. (a) Progressive stage. (b) Retrogressive stage. VESICULAR GOITRE. (a) Progressive stage. (b) Retrogressive stage.
III. HYPER-PLASTIC GOITRE.	Simple HYPERPLASTIC GOITRE. LYMPH-ADENOID GOITRE.
IV. HETERO-PLASTIC GOITRE.	Simple INTRA-LOBULAR FIBROSIS. Simple PERI-LOBULAR FIBROSIS.

FIG. I.

THE NORMAL GLAND showing the maximum amount of opaque tissue amidst the general ground-work of vesiculated colloid.

The original should be inspected with a hand-lens.

THE NORMAL GLAND.

For purposes of comparison the following features of the normal gland should be appreciated.

Macroscopic Inspection:- A cross section of the normal gland shews the colloid in very obvious vesicles collected into lobules bounded by a meagre interstitial tissue. There is little fluidity in the colloid, so that the tissue cuts crisp, remains dry and is very refractile. On the average this appearance is maintained throughout the tissue, but it is only significant in indicating the preponderance of one phase in the functional cycle of the gland - the storage of colloid in vesicles. . Inspection of the tissue with strong indirect light or by transillumination will reveal opaque white streaks or patches amidst the vesiculated colloid. These represent areas wherein **secretory activity** is taking place. There is a minimum, a mean and a maximum in the varying amount of this phase in the tissue of the gland. The maximum (fig 1) is grossly macroscopic and occurs in 5% of all normal thyroid glands, sometimes as obvious lubules clearly circumscribed, but more usually as areas of irregular outline scattered through the substance of the tissue. (They are not to be mistaken for incorporated parathyroid bodies or lymphoid (thymic) tissue nodules.) In the average gland the mean quantity of this tissue is always apparent but in less defined areas more diffusely distributed . The minimum quantity of active secreting tissue is only discernable on microscopic inspection.

Microscopic Inspection:- Casual sampling of the gland tissue will shew uniform vesiculated follicles (fig.2) filled with colloid, and so distended as to preclude the recognition of the morphology of the gland-units of which the organ is composed. Precise sampling of the opaque areas will shew various stages of secretory activity, (figs 3.4) i.e. the granular, vacuolar, lacunar and lymphoid; such material may be very scarce or may be so lacunate as to give rise to some difficulty in distinguishing it from vesiculation unless the intra-epithelial microcapillaries and the chromatic changes are studied by the author's technique. Near the hilum of the gland the lymphoid aggregates in the interstitial tissue lymphatics may be considerable and some non-colloid fluid may occupy the lymph channels.

Emphasis must be laid on the fact that opaque white solid looking areas often present microscopically a tissue that consists very completely of lacunate follicles with little or no solid granular or vacuolar epithelium, quite contrary to what might be expected from the opacity of the tissue selected. This is a clear indication that the colloid stored in vesicles is not identical with the material which accumulates in the follicles during secretory activity. Lacunar folliculation of the solid epithelium columns is to be carefully distinguished from vesiculation; this is usually an easy matter. All three stages in the secretory phase can invariably be found in the normal gland. I. The granular phase. 2. The vacuolar phase. 3. The lacunar phase, and these are invariably associated with lymphoid aggregation in the sinusoids or interstitial lymphatics. The presence of every phase of secretion is necessary to place the tissue within the category of normal, and further (except in the foetus) colloid as a stored substance must be present in considerable amount. Variability however is characteristic of each normal feature.

It is of the utmost importance to recognise the fact that secretory activity within the gland does not entirely depend upon colloid being stored by vesiculation. In the foetal gland and often in immediate post natal life and in individuals during partial starvation, colloid is absent as a stored product, yet secretory activity occurs in these glands; every phase, granular, vacuolar, and lacunar can be encountered. There may be individuals who practically never store colloid normally Its absence, and the resultant foetal type of thyroid gland, is usually associated however with a very considerable degree of adiposity which may have a pathological significance. These foetal forms have not been included in the range of the Normal in setting out of the variation of the appearance of the gland, but are mentioned here in pointing to the fact that stored colloid is a vehicle for absorption and not essential to the production of all the appearances of a normal secretory activity in the gland tissue.

Summary of the Chief features of the Normal Gland.

I. Storage of secretion by lacunation occurs alongside storage of colloid by vesiculation: each phase in the aggregate is represented macroscopically by a characteristic texture and the lacunar follicle is readily distinguishable microscopically from the vesicular follicle.

.2. Every individual has his own quantitative standard relation between the storage of colloid and active secretion; a minimum, a mean and a maximum of secretory activity is recognisable and it always has a focal distribution in the normal.

.3. The constant association of lymphocytes with the secretory phase in the epithelium.

.4. Stored colloid is not essential to secretory activity - as exemplified in the foetal and early infantile gland, marasmus and certain individuals of an (? pathogical) adipose diposition.

With this knowledge of the normal gland it becomes possible to refer the pathological conditions to one or other of the phases of function or, from a more precise knowledge of the anatomical details, to trace the secondary effects upon the functional cycle which follow the progressive effect of an irritation of one or other of the anatomical features.

I propose considering the various goitres in strict relation to any specific change in the physiological or anatomical appearance of the tissue.

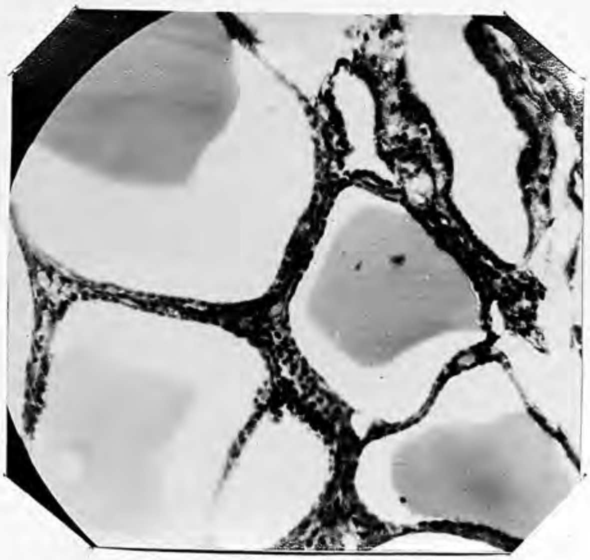

FIG. II.

Microphotograph (mag:200) to show storage of colloid in vesicles. Normal thyroid.

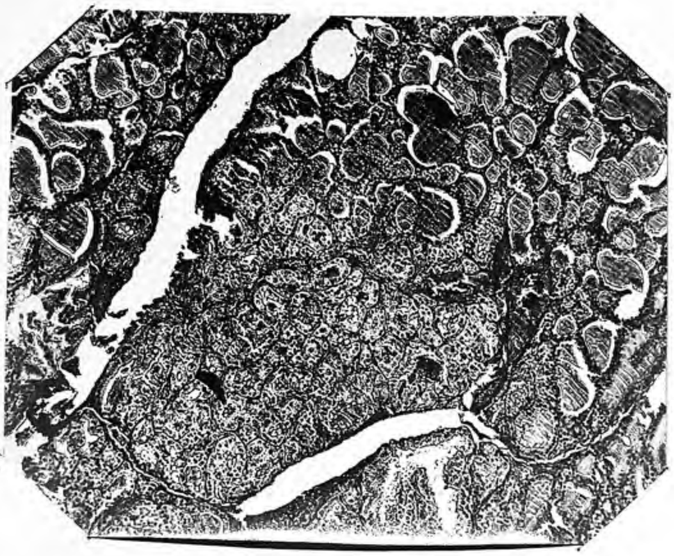

FIG. III.

Microphotograph (mag:100) of Normal thyroid to show a collection of gland-units in the active secreting phase lying in the midst of vasicular tissue.

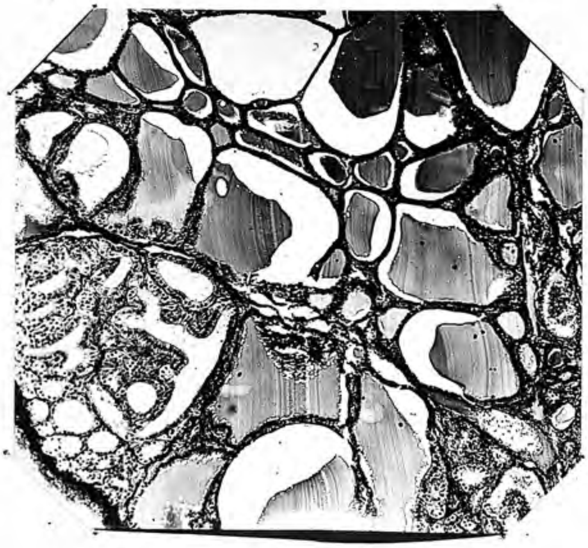

FIG. IV.

Microphotograph(mag: 70) of Normal thyroid to show contrast between gland-units in vesiculation and gland-units. The section was secured by sampling of opaque areas.

HYPERTROPHIC GOITRE.

Definition:- Hypertrophy in any organ must present nothing but an exaggeration of all the normal features of the various cycles of functional activity, and must more-over still allow for a sufficient reserve of rest-tissue to permit the proper turn over from rest to activity and vice versa. There is no need to postulate a hyperplasia of the morphological elements of the organ, though an increase in size and bulk does accompany any hypertrophy. Naturally the wear and tear will stimulate replacement kinesis and in that very limited sense there will be increased plastic activity.

The hypertrophic thyroid gland will therefore conform to the normal - but secretory activity will be the feature of the tissue instead of vesiculated stored colloid. Colloid storage however, will be evident.

As I have indicated in my paper "The Thyroid Apparatus " hypertrophy, if the average normal gland is taken as the standard of measurement, occurs in normal individuals as a decadal incident, in early puberty (9-16), and the menopause - and as a seasonal incident in pregnancy, and perhaps menstruation.

Further it would seem that the actual quantity of activity in the thyroid gland is a function of the individual. Thus even a goitrous state may be part of the normal physiology of certain individuals at certain seasonal and decadal periods.

It is difficult to believe that hypertrophy is ever anything but compensatory, or that of itself it can operate as a cause of any intoxication.

Continued hypertrophy will of course exercise a continual strain on the morphological elements in their plastic effort to live up to the functional requirements, and for that reason certain fibrotic sequelae follow hypertrophy. No doubt this will affect the efficiency of the functional effort - but that would essentially result in a non-compensating condition strictly referable to the cause of the hypertrophy. Furthermore the hypertrophy itself may be inefficient as a compensation for the underlying demand, or may become so, as the demand is permitted to continue. It is inadvisable therefore to refer the clinical state that may ensue in the course of hypertrophy to the thyroid gland and then to deal with the gland as an offender.

The prevailing obfuscation of all thyroid problems by strict endocrine considerations has made hypertrophy synonymous with hyperthyroidism and thereby placed all clinical conditions having an active goitre in the category of intrinsic thyroid states. However true that may be concerning some of the other categories of goitre, I would question the existence of any hyperthyroidism in a true hypertrophy so readily comparable to the conditions seen in the normal gland.

I will have to refer again to 'hyperthyroidism' and will then volunteer a rational explanation of such an intoxication based on the pathological histology of the active goitres.

Meanwhile it is necessary to note that hyper-

FIG. V.

HYPERTROPHIC GLAND shewing the diffuse admixture of the secret[illegible]
phase and the colloid storage phase in the gland.

The original should be inspected with a hand-lens.

trophy may be associated with two possibilities:- (1) The inefficiency of the compensating effort, leaving the primary cause to operate unchecked on the general physiology, and (2) The sequal, strain fibrosis, may lead to absorption of pervert thyroid secretion.

Macroscopic Inspection:- A cross section of the hypertrophic gland is characteristic. (Fig 5) It differs from the normal in the absence of marked vesiculation. Vesiculated colloid is present but is diffusely distributed over the gland. The interstitial tissue stroma stands out and is generally injected. The exudate on the surface is very fluid, has a thin glairy consistency and is not so refractile as in the normal gland. The colour is usually golden yellow. The secreting tissue is as diffusely distributed as the colloid tissue, and it is liable to appear as circumscribed nodules of solid ischaemic tissue. Distension cysts may be found in the tissue. The effect on the appearance ~~of the gland~~ of the gland of this diffuse admixture of secretory and colloid storage tissue is not difficult to recognise, since it gives a certain solidity and opacity to the tissue.

Often the parathyroid bodies, also in a state of activity, are impacted in the swollen bulk of the thyroid gland and stand out as circumscribed ischaemic nodes. With this, lymph nodes, normally situated at the hilum, may also be impacted and can be confused (Fig. VI) orig with parathyroid bodies. Sometimes the lymph aggregates in the sinusoids and interstitial tissue produce similar nodes deep in the substance of the gland. This description applies to well established hypertrophy but it will be understood that such a goitre may completely simulate some normal glands.

Microscopic Inspection:- The characters are those of the normal gland, except that any casual sample will serve to reveal both colloid storage and secretory activity. Secretory tissue presents the granular, vacuolar, lacunar and lymphoid phase of its cycle. Adjacent gland units may shew examples of either cycle and different degrees of both.

The distension of the interstitial lymph channels with fluid and lymphocytes may be very marked. The secretion can be followed into the parathyroid bodies. The same fluid appears in the thymic tissue in the hilum of the thyroid and can be followed to the thymus itself.

The feature of the tissue is, undoubtedly, the great increase in secretory activity and, in general, a proportionate decrease in the amount of colloid stored in vesicles. The decrease in colloid may not always be apparent. Further the secretory activity may be less diffuse and more focal in its distribution, rendering the distinction between the hypertrophic and the normal possible only on microscopic evidence of a casual sample.

Goitrous hypertrophy of the thyroid gland has been encountered as a result of pregnancy, either during the pregnancy or remaining after pregnancy. A similar association seems to occur in diseases implying the destruction of the ovaries or after ovariectomy. The menopause seems also to be a period when goitrous swellings of this order occur. The most important as-

HETEROTROPHIC GOITRES.

Definition:- Heterotrophy will indicate a want of balance in the relation of the two cycles of functional operation in the thyroid gland.

Thus the secretory cycle may operate throughout the gland to the complete exclusion of any possible storage of colloid. Or, the storage of colloid material may occupy the whole gland to the exclusion of any possible secretory activity.

But this is not all that is involved in such an unbalanced hypertrophy With the exclusive operation of one cycle of active function, there arises the possibility of this being carried to the extreme of inhibiting its own turn-over. Thus, in heterotrophy the thyroid gland may become choked with stored colloid material, or, choked with the products of secretory activity. The physiological turn-over of either cycle may thus be rendered impossible and conditions of loculate vesiculation or loculate lacunation of the epithelium ensue. These conditions of the colloid cycle on the one hand, and secretory cycle on the other, may actually render the whole effect of hyperactivity nugatory and the underlying stimulus to thyroid activity may then, an and then only, produce its effect upon the general physiology. This choking effect in the gland, so long as it is uncomplicated by secondary changes in the tissue, can presumably be relieved by rest from the maximum effort. From this it may be anticipated that the progress of heterotrophy will shew exacerbations of any symptoms referable to the choking of the gland mechanism

Following the continuous activity of the morphological elements concerned in the progress just as in hypertrophy, there will arise a condition of continued strain especially manifest in the endothelial elements, and fibrosis must follow.

This fibrosis may effectually interfere with the proper exchange of material between the blood or lymph and the follicles, so that complete encystment of colloid and secretion can arise,- a stage further than mere choking; lacunation and vesiculation thereby become irreversible. Behind this encystment of colloid matter and secretory amtter lies the possibility of the trapped secretion or colloid being reabsorbed through other than the proper channels (we have an example of this in the jaundice following the trapping of bile). Thus, theoretically two probabilities arise to explain any intoxication that may follow in the course of these heterotrophic states.

1. That the inhibiting effect of irreversible storage of colloid or of secretion may for the first time in the course of the progress of the disease allow the underlying stimulant or causal factor to operate unchecked on the general physiology - an extrinsic intoxication.
2. That irreversible storage of colloid and secretion may force the re-sorption of the colloid or the secretion through other than the proper channels; the intoxication in this case will be intrinsic, and thyroid amputation would relieve it.

(There is reason to assume that such a hetero trophy occurs in the kidney, as well as in liver and t thyroid, in which case the probability arises of an analogous renal intoxication underlying the clinical condition in terminal parenchymatous nephritis.)

If these probabilities of resorption are considered in association with colloid - it is not possible to detect any evidence of intoxication, so that colloid, as such, would not seem to have any of the vices associated with the thyroid intoxicant. Re-sorption of colloid may nevertheless be a factor in the clinical state of vesicular goitre, since it would be idle to dismiss the possible effect of the re-sorption of colloid on the grounds of clinical evidence alone; vide:- the insidious progress of hyperglycaemia of a hepatic or alimentary origin, which seldom manifests itself as a disease until either the kidney or the tissue threshold is strained to breaking point. When we know more of the purpose of the two thyroid secretions we shall be better able to judge of the effect of colloid stored outside the thyroid gland.

On the other hand the second of these possibilities, the re-sorption of secreted material, seems to operate in a precise manner in Graves'disease. The so-called 'hyperthyroidism' of that disease becomes the vicious absorption of the pent up secretory material. Whether or not this secretory matter is absorbed in toto or only selectively remains to be seen. But in any case the absorbed material is produced by a pathological gland and not by a physiological gland, so that the term "hyperthyroidism" must be used with that reservation in cases of Graves'disease in all its forms. This may explain the failure to induce Graves' disease experimentally by the injection of various extracts and could equally explain the failure of any attempt to detect in Graves' disease evidence of any excessive autocoid activity. ( ) It is not contended here that secretion is the 'autocoid' material of the thyroid gland any more than glygogen for example is an 'autocoid' product of the liver.

Apart from this intoxication by pervert secretory matter, it is as well to note that, in both the hypertrophic and heterotrophic states, the manifest compensatory activity of the thyroid gland may be insufficient to meet the needs of the physiology, so that a relative inefficiency of thyroid activity may be present; i.e. a state of so-called hypothyroidism may run concurrently with any intoxication. This is a probability well worth clinical investigation.

With two distinct functional cycles in the thyroid mechanism there will be two types of heterotrophic goitre, each manifesting two stages.

1. The Vesicular or Colloid Goitre.
   - (a) Progressive Stage.
   - (b) Retrogressive Stage.
2. The Adenoid Goitre.
   - (a) Progressive Stage.
   - (b) Retrogressive Stage.

FIG. VII.

VESICULAR GOITRE. Vesiculation of colloid is universal through the gland and secreting tissue is entirely absent.

The original should be inspected with a hand-lens.

.I. Vesicular Goitre.

(a) Progressive stage:- There is general bilateral enlargement of the thyroid organ. During this stage the vascular engorgement is extreme and is by no means confined to the viens on the surface of the organ, but is so general as to give a decided colour to the tissue.(Fig VII) The swelling of the gland is uniform and no doubt the direction taken by the increased bulk is largely controlled by the fascial tissue compartment in which the gland lies, so that it is usual to find a considerable bulk of the gland thrusting itself into the mediastinum. It i is liableto become impacted at the boney ring of the Thorax and, when fixed within this confined space, to exercise the maximum pressure on the surrounding structures. The engorgement of the vessels is not to be explained by this. The vascularity is very intimately associated with the special perilobular anastomosis ( ) and is to be taken as an expression of enhanced physiological activity.

Macroscopic Inspection:- A cross section of the gland shews only vesiculated colloid. The vesicles are obvious and enlarged. Under no circumstances have I found any evidence of opaque tissue of a secretory nature in this condition. It is rare to find a specimen entirely free from defined cysts - even in the early stage of the disease and before general retrogression has set in. The colloid is even more translucent and refractile than usual, and is also more fluid, so the surface remains wet with the viscid exudate.

Microscopic Inspection:- Every field is filled with thin walled vesicles so tensely stretched as to preclude the recognition of any other structure. The perilobular anastomotic capillaries are even more in evidence in this condition than they are in the normal gland.

The passive part played by the epithelium of the follicles in this process of vesiculation of colloid is a striking feature of the sections. In the epithelium the nuclei are diffusely but weakly stained, the intra-epithelial microcapillaries are thin empty structures; the protoplasm is clear and devoid of granules and vacuoles. The cubical celled appearance of the epithelium is maintained in the extreme distension of the follicles. Fig VIII

Very careful and comprehensive search for tissue exercising the secreting function has failed to demonstrate it. No secretory activity occurs in vesicular goitre. This negative feature may be of considerable importance.

(b) Retrogressive stage:- Two forms of this are seen to exist - but both depend upon the development of fibrous tissue consequent upon the continued strain of maximum functional effort. The forms are seldom pure, and differ only in the size of the units in which cyst formation occurs.

In one form the fibrosis is strictly perifollicular and each vesicle has become a cyst of small size. Fig IX In the other the vesicles would seem to have coalesced or more probably ruptured one into the other, within the limits of a lobule, to form a larger cyst. The second form is very liable to be a focal occurence in a generalised fibrosis, so that one lobe or part of a lobe becomes a circumscribed cyst. Different forms of actual degeneration occur in the cysts. Thus, vesicular goitre may have as a sequel the formation of unilateral tumefaction with a considerable perilobular distribution of the fibrosis. Or, if the vesicular goitre declines before general fibrotic encystment occurs, these unilateral tumours remain manifest as cysts in an apparently normal tissue.

Cysts in the thyroid gland, like cysts else where can be the seat of various degenerations - haemorrhagic, hyaline, calcification or colliquifaction.

This retrogressive stage of vesicular goitre is to be compared and contrasted with the primary process of coarse interstitial fibrosis in the thyroid gland.(p. It is to be remembered that retrogression need not be the invariable sequal of vesicular goitre. It can revert to the normal, and only at some late subsequent stage manifest the full effect of any focal stigmata of the heterotrophy - such as localised cysts, cyst-adenomata etc, and in this way it can be one of the causes of the coarse interstitial perilobular fibrosis of the thyroid gland.

Vesicular goitre and its sequel, cystic goitre, is particularly associated with the clinical condition of endemic goitre, but there is also a distinct sporadic form. Much has been written of an inflammatory cause of this form of thyroid swelling. It is difficult to believe that inflammatory conditions would give so uniform a result unless the causal toxic factor was operating on the genral physiology of the body. It certainly does not operate directly on the thyroid tissue. Such thyroid conditions as are due to obvious inflammation e.g. in typhoid fever, tuberculosis, syphilis, certainly do not cause a defined heterotrophy but, as is usual, a focal interstitial change in the organ. But that does not preclude the operation of intestinal infection or the intestinal absorption of noxious matter from affecting the turn-over of the special metabolites dealt with by the thyroid gland.

Colloid material, as I have indicated, would seem to be of the nature of a vehicle for the carraige of some metabolite, either to or from the thyroid gland; (the analogue of the bile salts in the liver mechanism) Any excessive storage of this substance , on that hypothesis, would therefore indicate either (I) an excess of the vehicle or (2) a decrease in the amount of the metabolite to be carried. On the second theory the physiological condition of the person with a vesicular goitre would be the inverse of that of Graves' disease - so that the two conditions should be investigated together. The major incidence of the progressive vesicular goitre is at puberty, II-I4 years. At that age the average thyroid gland is very actively secretory with a diminution in stored colloid. The excess of stored colloid may imply an extensive destruction of the metabolite which is never permitted to rest in the thyroid or go into a reserve, and would explain the complete absence of secreting activity and the complete a-lymphoid state of the thymus and the absence of ob-

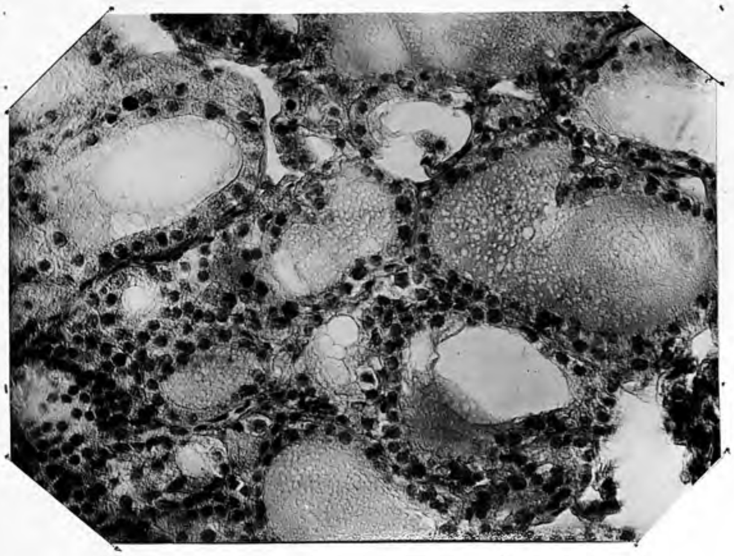

FIG.VIII.

Microphotograph(mag:200) of a vesiclar goitre in the progressive stage, showing the appearance of the tissue in the phase of colloid - storage.

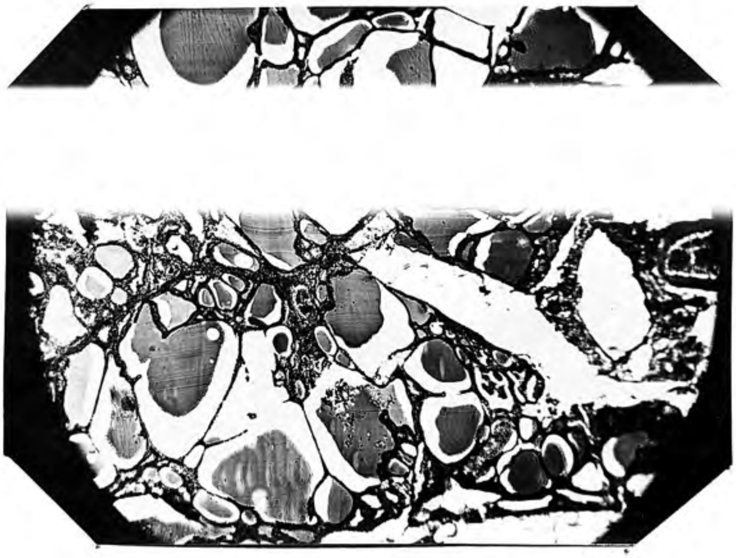

FIG.IX.

ograph(mag; 60) of the retrogressive stage of vesicular goitre, showing the perifollicular fibrotic encyst ment of colloid.

vious lymphoid tissue in the hilum and poles of the thyroid gland in these cases.

Sexual puberty in the male goes more or less with the sporadic vesicular goitre where-as statural puberty (17-23) in the female goes with the inception of Graves'disease. The Creatin-Creatinine factor (Schiff) is worth study in the same relations in male and female.

.2. Adenoid goitre.

This goitre is associated in 100% of cases with true Graves'disease - Exophthalmic goitre. It is a non-colloid secreting gland. An alternative descriptive term might be a-colloid goitre, but its use might perpetuate an error, in that it suggests that the condition is fundamentally due to the absence of colloid material. Colloid is probably only a vehicle, so that the absence of stored colloid need not imply a lack of sufficient colloid in the body, but, may merely emphasise the excessive secretory activity. The term adenoid, on the other hand, is closely associated in the clinical mind with other conditions; nevertheless, it so completely describes the essential gland-like (pancreas or salivary gland) solid tissue of this gland that it will be used in preference to the much abused term "parenchymatous" which, on the analogy of the pathology of the kidney and liver, could describe the condition of adenoid goitre.

Adenoid goitre then, represents the height of secretory activity carried to the extreme of excluding colloid storage as a possibility and is thus a heterotrophic condition.

(a) Progressive stage:- The cross section of the gland

FIG.X.

A TYPICAL ADENOID GOITRE.

The orginial should be inspected with a hand-lens.

has the adenoid appearance and a soapy consistency. The lobules are clearly marked, so that the surface could be mistaken for the cross-section of the pancreas or salivary glands. The pallor of the ischaemic lobules is usually relieved by an injection of the coarser bundles of interstitial tissue surrounding them. Most lobules will have at their centre a dilated lymph space, very often distended and filled with a clear yellow fluid. These are more obvious at the hilum of the lobe. The surface is dry and granular and does not shine, nor is it to any degree translucent, Fig X

Microscopic:- Microscopic examination will serve to classify the stages of progress of the condition. These may be divided into the (I) granular, (2) the lacunar stage. In the early stages of the disease the secretory cycle is found in all its aspects; the epithelium appears as a granular, vacuolar or lacunar column, with many purely solid columns corresponding somewhat to the indefinite phase of the functional cycle. With this, the inde finite other signs, lymphoid aggregates and intra-sinusoidal fluid, of secretory activity prevail. In other words the whole cycle of secretory turnover is apparent in the gland tissue during the early progressive stage. Fig. XI & XIII XIV.

As the disease progresses this diversity abates and lacunar follicles ultimately occupy the Fig XV. XVI whole gland, so that all the reserve of tissue in which secretion can be initiated is exhausted. It would seem safe to conclude that this condition of 'choking' can only be relieved if a period of rest from maximum secretory effort is possible. The universal distribution of widely dilated lacunar follicles filled with the

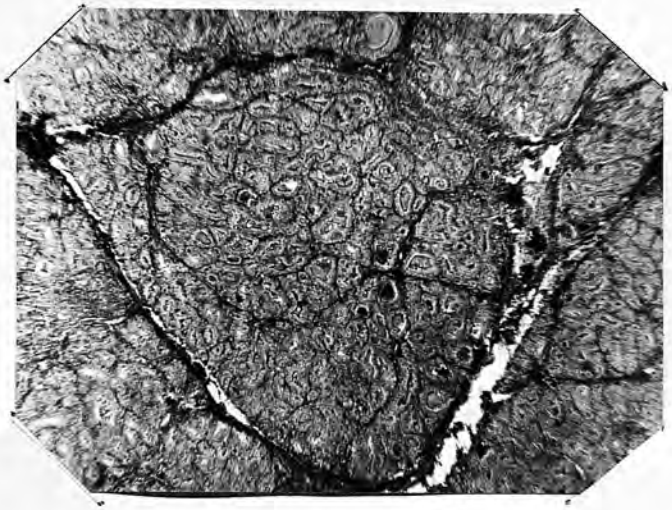

FIG.XI.

Microphotograph (mag:50) showing the solid appearance of the granular phase of progressive stage of Adenoid Goitre.

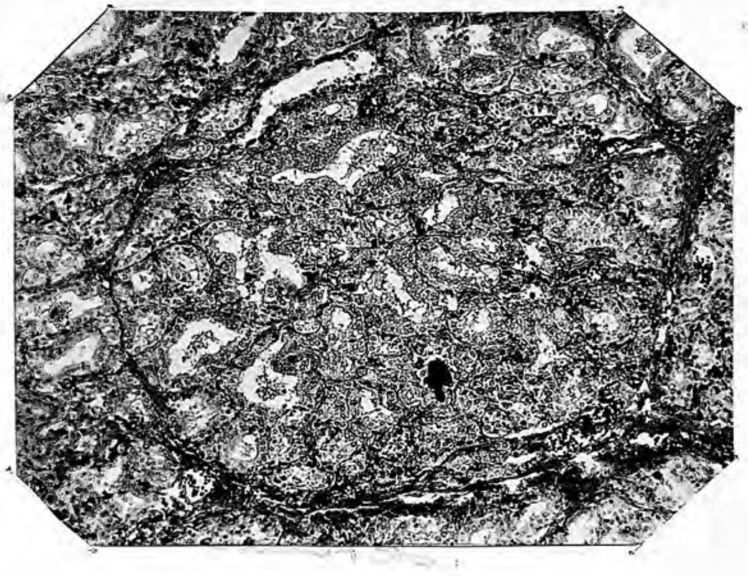

FIG.XII.

Microphotograph (mag:100) showing the progressive stage of Adenoid Goitre. A gland-unit in which the epithelium is in the granular and lacunar phase and in which lymphocytes are seen in the Sinusoids.

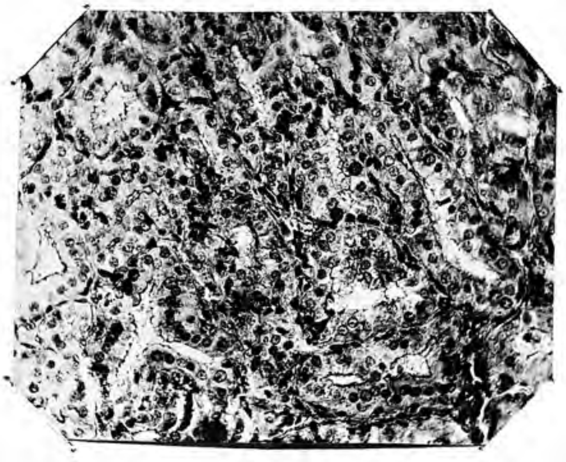

FIG.XIII.

Microphotograph(mag:300) to show the secretion beginning to form lacunae within the epithelium.

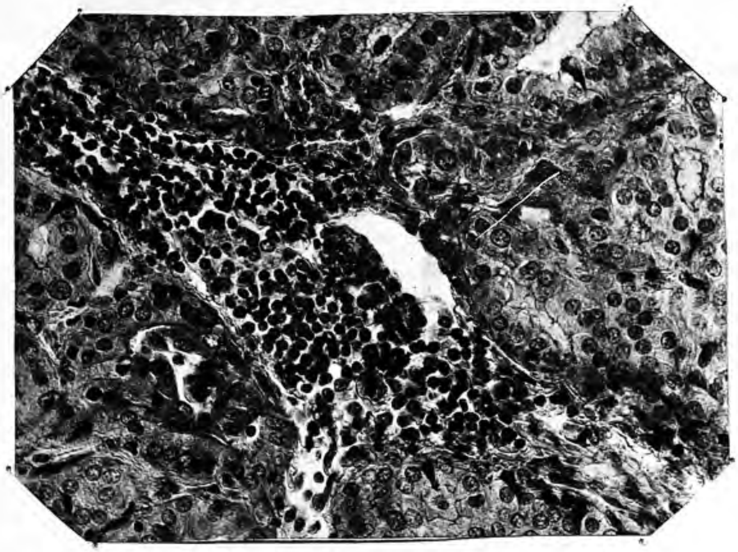

FIG.XIV.

Microphotograph(mag:400) showing a lymph-aggregate subtending gland-units in the granular stage of a progressive Adenoid Goitre.

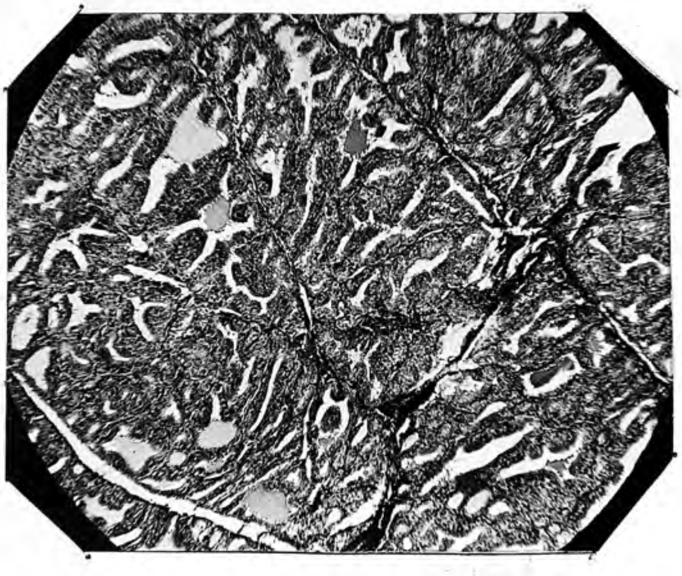

FIG.XV.

Microphotograph(mag: 60) taken from a progressive Adenoid Goitre showing the stage of universal lacunation of the epithelium. Note the lymphocytic aggregate in the centre of one gland-unit.

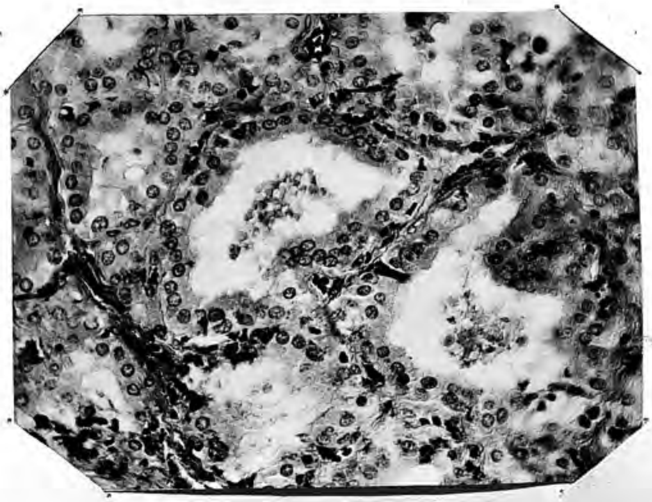

FIG.XVI.

Microphotograph(mag:300) showing the choking effect and exhaustion of the epithelium in uniform lacuna-tion of progressive Adenoid Goitre.

granular semi-fluid matter does not in any way affect the macroscopic appearance of solid soapy dry tissue - proof enough almost that this secretion is not identical with vesiculated colloid. Uniform lacunation in the thyroid gland of adenoid goitre has some relation to t the intoxication seen in the clinical state. Fig. XV, + XVI

(b) Retrogressive stage:- The persistent operation of the maximum secretory effort induces changes in the adenoid goitre; these usually begin at different foci but often become quite uniform. The end result is atrophy of the gland, whether this be a spontaenous process or induced by ligation or X Ray therapy.

Macroscopic Inspection:- The gland of the retrogressive stage on cross section shews various degrees of carnification, such as is seen in pericellular fibrosis of the liver, and in foetal syphilitic fibrosis of liv liver, lungs and kidneys. The increased interstitial tissue is very vascular; the parenchyma still remains lobulate but the ischaemia is less obvious. The consistence is firm and fleshy and the surface moist and rough having lost the soapy consistency. The surface may suggest the extreme papilliferation of the epithelium.

Microscopic:- The parenchyma is uniformly lacunar and each follicle is outlined by a firm fibrous tissue. Fig XVII & XVIII The change is confined to the gland-units and is distributed about the intra-sinusoidal capillary plexus and the endothelium of the sinusoid. The appearances suggest the sealing up of the sinusoid more or less completely. Lymph-aggregates occur but are confined to the interstitial tissue lymph channels. Papilla-like projections into the lacunae often appear. Gradual degeneration of the epithelium results, and can be traced in the gland-units and here and there a replacement fibrosis is obvious. The uniform lacunation and the perifollicular fibrosis make it probable that no period of rest from a maximum secretory effort would allow of a return to the granular phase - i.e. the lacunation is irreversible.

Thus in an adenoid goitre of Graves' disease there occurs a parenchymatous condition, pursuing an exacerbative course, which ultimately ends in an atrophy of the thyroid gland - a histological picture entirely analogous to the condition of parenchymatous nephritis which ends in an interstitial fibrosis and atrophy of the kidney. Clinical studies indicate that it is the loculation of secretion in lacunar follicles which corresponds to the intoxication in the course of the disease.

There exist other states of the thyroid gland, quite as definite from a pathological point of view as adenoid goitre though closely related to it, in which Graves' disease is an occasional incident. Discussion therefore of adenoid goitre must be reserved until these goitres have been considered.

(page 59. et seq:)

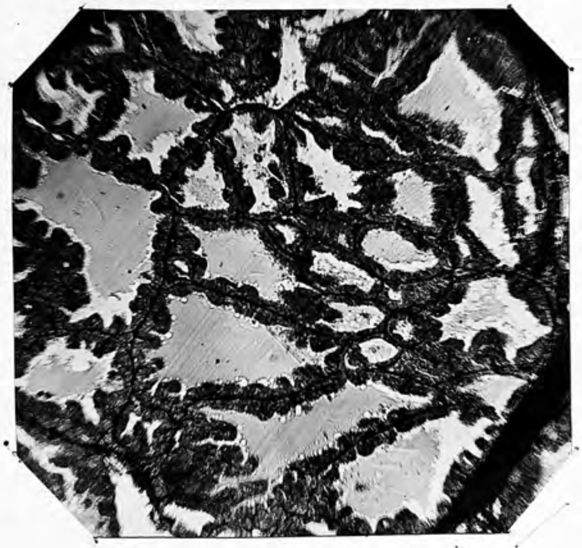

FIG.XVII.

Microphotograph (mag:100)
section of the retrogressive stage of an adenoid goitre showing the perifollicular fibrotic encystment of secretion in papillate lacunae.

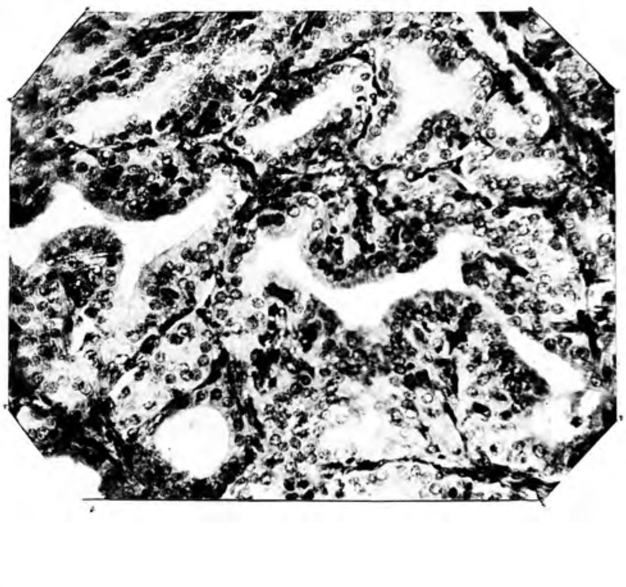

FIG.XVIII.

Microphotograph (mag:200)
A higher magnification of FIG.XVII. The lacunae should be contrasted with the wesicules shown in FIG.VIII.

HYPERPLASTIC GOITRE.

Definition:- Hyperplasia is a balanced overgrowth of an organ or functioning unit of a tissue; it affects the organ as a whole or the individual morphological units of which the tissue is composed. The basis of hyperplasia is both morphological and physiological and the manifestation of hyperplasia will imply hyper trophy. There is therefore an inevitable difficulty in distinguishing hypertrophy and hyperplasia and it may be that any distinction must be arbitrary.

Nevertheless in the pathological conditions in the thyroid gland, a group of goitres can be defined having a distinct tendency to compensate for any inefficiency by growth rather than mere hyperactivity. They will naturally tend to approach a neoplastic state as their terminal sequelae; as distinct from the atrophy and exhaustion which follows simple hypertrophy. The neoplastic tendency is an important characteristic of hyperplastic goitres. Indeed though theory may define a 'histioma' as a focal hyperplasia within the limit of a morphological unit (i.e. as an unbalanced growth;) and hyperplasia as an increased growth of the whole morphological unit of function, (i.e. as a balanced growth;) practically, the distinction is difficult, if, at all capable of definition.

It would appear that hyperplasia represents a definite response to a quite normal stimulus of demand applied to an intrinsically sub-efficient or sub-normal gland tissue - so that there is a direct stimulus to growth and an increase in the number or extent of the functioning morphological units, and with that a considerable, if not complete, encroachment on the available 'reserve tissue'. This may imply that the need to maintain a sufficient reserve tissue is the main stimulus to growth. In the absence of any reserve tissue the reversible process - "growth function" becomes irreversible, so that growth results where function should ensue. This recalls the effect of the concentration of the substrate on the direction of ferment action or the effect of seeding on supersaturated solutions, and would form the subject of a nice speculative inquiry into the effect of normal resting gland tissue on malignant disease in that particular gland. In that respect extracts of foetal tissue are known to exercise such an effect in general. It raises also the question of inducing neoplastic growth in a sub-efficient organ by keeping it at the maximum level of functional activity - which may be the actual effect of age in the individual in relation to the incidence of cancer, or the explanation of the influence of sub-lethal irritation in both natural and experimental neoplasia. The thyroid gland affords good material for experiments of this kind.

If sub-normality or sub-efficiency in an organ is an underlying factor in hyperplasia, then two types of hyperplastic response must evolve. The one form, an anatomical subnormality, and the other form a physiological subnormality. In the thyroid gland it is possible to distinguish each type and to associate them with neoplastic sequelae. The physiological sub-efficiency would be due to an intrinsic failure of the secretory elements to supply sufficient material in relation to time - a slowing up of the physiological turnover. In the physiological form the signs of activity must be at a minimum:(hypo-trophy) whereas in the anatomical variety activity would be at a maximum:(hypertrophy.) The two types of hyperplastic goitre are:-

(I) Simple Hyperplastic Goitre.

(2) Lymph-Adenoid Goitre.

(I) Simple hyperplastic goitre.

The anatomical sub-efficiency is induced by the atrophy of an encroaching fibrosis. These goitres occur in thyroid glands that are the seat of focal perilobular fibrosis, and most commonly in association with the anomolous condition of the non-compact gland, to which attention was called in my paper the "Thyroid Apparatus". In this anomaly the individual lobes of the gland may be scattered widely over the fascial plane of the neck or mediastinum, or on the other hand, may appear as a loose collection of lobules, giving the appearance of a bunch of grapes to the right and left, or on the one side only of the thyroid organ. Solitary lobes having the characters of this hyperplasia, can be found in the midst of a compact gland which is the seat of a fibrosis. In a diffuse fibrosis in such a compact gland there is little opportunity for continued hyperplasia, and hyperplastic lobules rarely seem to reach any size, so that hyperplastic goitre is not very closely associated with the retrogressive types of cyst, cyst-adenoma

FIG.XIX.

Simple Hyperplastic Goitre to show the hyperplastic lobules in a semi-compact gland, which is the seat of a coarse peri-lobular fibrosis. Tumour from second operation.

The original should be inspected with a hand-lens.

and foetal adenomata which accompany perilobular fibrosis. The anatomical circumstances under which uncomplicated hyperplasia can arise is therefore, more or less, limited to those loosely constructed glands where the normal lobes are very free and may be entirely independent. This feature may be of value in dealing with the condition from a surgical point of view, and in matters of prognosis.

Macroscopic Inspection:- The hyperplastic goitre, Fig. XIX whether in the multilobular gland or in the semi-compact gland, presents the appearance of a collection of two or more adenomata in a gland in which there is an obvious interstitial fibrosis of a perilobular distribution. The cut surface of these adenomata entirely simulate the appearance of hypertrophic goitre; they have usually a diffuse distribution of vesicular and secretory tissue, and a golden yellow colour. As in hypertrophy this may go on to accumulate an excess of secretory tissue and so tend to look like adenoid goitre.

Microscopic Inspection:- The appearances are identical with hypertrophy, colloid is never absent and secretion may manifest any or all of its various phases, up to complete lacunation. Retrogressive changes, of a perifollicular nature with fibrosis may follow. Indeed the hyperplastic adenomata entirely resemble the hypertrophic condition of the thyroid gland tissue and will therefore occasionally give rise to the various clinical manifestations of the retrogressive stage of hypertrophy - i.e. forme fruste or even typical Graves'disease. They constitite the 'toxic adenomata' of Wilson and Plummer and other writers.

The adenomata of hyperplastic goitre are readily distinguished from the so-called foetal adenomata which will be dealt with in a subsequent section. (p.46)

The pathological history of some of these hyperplastic goitres has a bearing on the discussion of this condition.

In 5 out of 20 goitres of this nature the first operation did not suffice to remove the whole of the active gland tissue and the other lobules either on the same or the opposite side took on an active hyperplasia and had to be removed later.

Two other cases were first operated on for glands in the neck. The glands proved to be a collection of isolated hyperplastic lobules of the thyroid gland. In one case a second operation did not suffice to remove all the active gland tissue and recurrence of the tumefaction on the opposite side of the neck ensued, and a third operation was needed to clear up the condition. In the other case at a fourth operation a portion of the gland in a compact form had to be removed and this tissue shewed a definite adenopapilliferous carcinoma.

In 4 out of the 20 cases adenopapilliferous cancer was known to follow the removal of part of the hyperplastic goitre. Metastases are not associated with this form of cancer but infiltration may be wide-spread making eradication difficult but not impossible. (see Marine (8))

In the 3 other cases the central lobules of the more compact form of hyperplastic goitre shewed changes quite indistinguishable from adenopapillomata - the appearance being identical, as it is in these neoplasia

plasia of the thyroid, with other forms of intracystic adenopapilloma whether malignant or not. The neoplasm arising from this hyperplastic goitre is analogous to the various intrafollicular papillomata of the breast, prostate, ovary, and other organs, and any malignant change is of the same order.

In the compact gland the hyerplastic goitre tends more to the production of scirrhus forms of neoplasia due perhaps to the delimitation induced by the fibrosis; scirrhus forms will however be rare in proportion to the adenopapilliferous neoplasia of the multilobular gland.

It is not suggested that all hyperplastic goitres go on to neoplastic changes. Degenerative changes also occur and presumably are the more common sequelae. The degeneration is usually of a colliquative nature with a cyst formation; or a diffuse fibrosis delimits the area of hyperplasia forming a typical fibro-adenoma This is usually more apparent in the compact form of the gland.

There is a practical consideration in the recognition of this type of goitre, among the so-called adenoparenchymatous goitres and toxic adenomata, as the type of change which has a decided tendency to recurrence and malignancy. Such recognition should lead to early and more radical treatment of the condition. The fact that infiltration has to advance to a very considerable degree before metastases occur may indicate the necessary scope of any operative procedure and lead to a more accurate prognosis. Simple resection-enucleation of isolated hyperplastic adenomata will not provide material for diagnosis, they must be seen in relation to the gland tissue, but any polylobular gland should rouse suspicion. Any recurrence, within a reasonable time of the primary resection leads to the anticipation of a hyperplastic goitre. It must be reiterated, however, that all adenomata, so called, are not of this nature - but essentially retrogressive conditions with little possibiility for neoplastic change.

(2) Lymph-adenoid goitre.

This hyperplastic goitre and the various typical retrogressive changes that occur in it have been described in the literature as "woody thyroid", Riedel's goitre, syphiloma, tuberculoma, endothelioma and sarcoma

It is the physiologically subnormal gland undergoing compensatory hyperplasia. Just as the maximum of trophic activity in the first form of hyperplasia gives rise occasionally to toxic symptoms of Graves' disease and forme fruste, so with this minimum trophic activity of the lymph-adenoid goitre there is an associated symptomology of myxoedema more or less advanced.

In normal individuals this type of response has been encountered as a focal change, after the age of 50 years.

These goitres are generally large - and may be more manifest on one side of the neck than the other. In one case there was complete atrophy of the other side whether infantile, congenital or secondary could not be determined.

The Progressive Stage of Lymph-adenoid Goitre :-

Lymph-adenoid goitre - as its name implies - cannot be distinguished with certainty from adenoid goitre by macroscopic inspection, though it is usual to find in lymph-adenoid goitre a distinct absence of the lobulation of the surface. It has the ischaemic dry appearance and solid soapy consistency of the adenoid goitre but careful inspection may reveal some areas of colloid storage and vesiculation.

Microscopically the tissue contains both secretory follicles and colloid storage follicles; secretory follicles predominate, they are lacunate, but the lacunae are small and never papilliferous. The chromatism of the nuclei and protoplasm of the epithelium is at a minimum, suggesting exhaustion. Unlike the exhaustion that occurs in adenoid goitre, it does not produce catarrh into the lacunae. The striking feature is that the lymphocytes pervade the gland-units, so that the section looks like a sea of lymphocytes in which float Fig. XX. XXI islands of solid or lacunate epithelium and endothelial capillaries. At the hilum of the gland-units these lymphocytes may form huge aggregates looking like granulomata Fig XXII; they may also lie in the interstitial tissue lymph channels and free lymphocytes may be found in the surface lymphatics. The appearance is one of secretory hypertrophy with a reserve of stored vesiculate colloid but with the lymphocytic activity exaggerated to an unusual degree. Trophism is at a minimum judging by the quantity of chromatic matter in the nuclei and protoplasm. Mitosis is a marked feature of the epithelium and especi

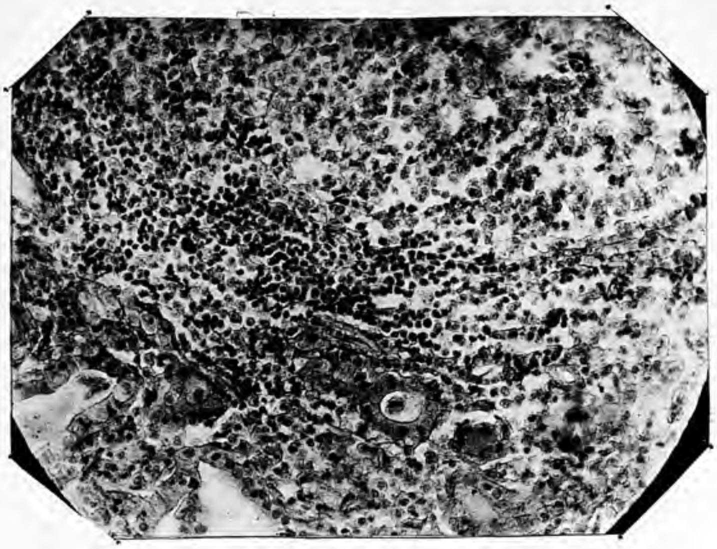

FIG. XX.

Microphotograph (mag: 200) from the progressive stage of lymph-adenoid goitre showing the pervasive infiltration of the sinusoids with lymphocytes. Some disintegration of the epithelium has already occured.

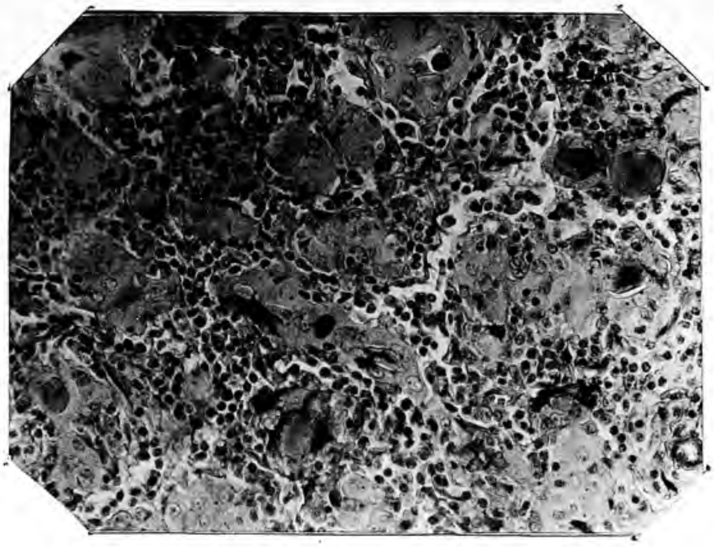

FIG. XXI.

Microphotograph (mag: 3.0.0.) A higher power of the same. Note the suggestion of "giant-cells produced by the isolated atrophic epithelial elements.

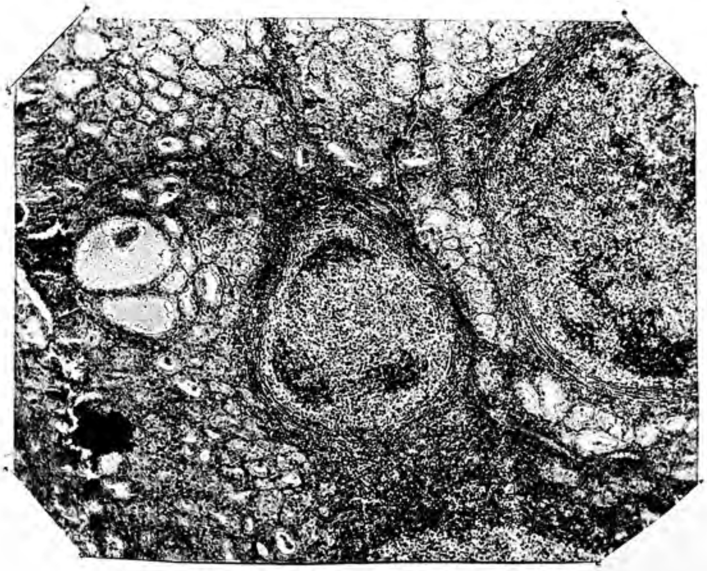

FIG. XXII.

Microphotograph (mag: 7a.) from the progressive stage of a lymph-adenoid goitre showing the atrophying gland units. Densely infiltrated with lymphocytes.

ally of the endothelium of the sinusoids and lymph channels. The whole forms a very characteristic histological picture.

Retrogressive Stage of Lymph-adenoid Goitre:-

The retrogressive stage of this goitre, can be traced in different parts of the same gland or equally in various glands. The epithelium suffers a gradual atrophy, with this the endothelial elements of the gland-units take on a more intense activity until, in the extreme degree of retrogression, the epithelium disappears and a node of lymphocytes remains as the shadow of the gland-unit, which itself becomes obliterated. Fig xxiii a.b.c.

With this progressive atrophy the sub-endothelial tissues assume an intense fibroblastic activity growing as the atrophy progresses. Ultimately, a whorl of fibrosis, Fig xxiv now devoid of fibroblasts, encloses a few lymphocytes or endothelial cells representing the atrophied gland-unit - the 'woody thyroid' and the gland of non-goitrous myxoedema.

Every degree and stage of each of these events can be connected one with another. Moreover similar events are seen as focal conditions in the non-goitrous gland of the aged. Fig XXV The end result is that seen in established non-goitrous myxoedema and in non-goitrous myxodematous cretins. It is very clearly a specific form of atrophy.

Obviously, the probability of these goitres being a granulomatous reaction to a specific ifection must be considered. For what it is worth, and that is little; careful inspection with special stains and cultural tests do not afford any confirmation of that probability. The histological features of the granulomas of a focal nature, syphilis and tuberculosis in the thyroid gland are not identical with that of lymph-adenoid goitre. The granulomas are formed by round cells of a fibroblastic origin and they all retain their continuity one with the other; whereas in the lymphocytic aggregates of the open spaces of the thyroid gland in lymph-adenoid goitre, the round cells (lymphocytes) are individual and free cells. I know of no satisfactory differential stain for lymphocytes, or for the round form of fibroblast - but the continuity of the cytoplasm of the fibroblastic round cells is diagnostic , and the term infiltration can not be applied to the round cells of the granulomata. The giant cell of tuberculous and syphilitic formation has little resemblence to a cross section of a solid column of thyroid epithelium; casual inspection will preclude this error. Lastly the granulomata of syphilis and tubercle are essentially avascular areas the central capillaries being entirely oblitered. Apart from this the various secondary degenerations, caseous and gummatous, do not occur in lymph-adenoid goitre. Nor are the lymphocytic aggregates in lymph-adenoid goitre circumscribed by a reactive tissue capsule of induration as in the granulomata; any new fibrous tissue formed in lymph-adenoid goitre lies outside the layer of endothelium bounding the sinusoid and lymph channels, and is always a very marked spindlecelled reaction - there is no transition through endothelioid and round cells to spindle cells as in the granulomata.

The most important feature, however, is that in the early stage of the lymph-adenoid goitre , the lymphocytes exactly resemble the normal in their distribution and association with obviously functioning epithelium. This and the fact that the mild degrees of atrophy can be traced back to the normal would indicate that the lymph-adenoid goitre is definitely not a mere granulomatous state.

It is more difficult to exclude the probability of the condition being a progressive lympho-sarcoma or endothelioma; as any focal sarcoma or endothelioma certainly does resemble this condition in the gland. The objection to that explanation is, that, in lymph-adenoid goitre usually the whole gland is affected and the condition is equally apparent in each gland-unit, and that functional activity though at a minimum is till discerned in the tissue. Further in lymph-adenoid goitre the lymphocytes and endothelioid cells occur within the lymphatics of the loose fibrous tissue capsule of the gland so that if the round cells have any neoplastic attributes they must set up metastatic growth with comparative frequency. Lymph-adenoid goitre however is not associated with any secondary metastatic neoplasms. If the lymph-adenoid goitre is neoplastic from the beginning it is peculiar in that it equally affects the whole organ and is peculiarly non-malignant in its course. Focal lympho sarcomata and endotheliomata have also in fact a low degree of malignancy and do not tend to recur after amputation of the lobe in which they arise. They certainly seldom occur apart from lymph-adenoid goitre. The suspicion arises therefore that so-called endothelioma and lympho-sarcoma are indeed focal conditions of lymph-adenoid goitre. Apart from this, fibro-sarcoma, of a definite spindle-celled variety, and very malignant, also seems to be associated with this lymph-adenoid goitre. There is no possibility of confusing the fibro-sarcoma with the possible lymphosarcoma or endothelioma, but the transition from true retrogressive lymph-adenoid goitre through endothelioma to fibro-sarcoma is highly probable.

I therefore consider the condition of lymph-adenoid goitre to be a hyperplasia with all the potential probabilities of that state in its relations to neoplasia. Lymph-adenoid goitre is a true hypertrophy peculiar in the quantity of lymphocytic activity. The lymphocytic reaction is proportional to the failure of the hyperplastic effort and is itself an exaggeration of the normal procedure in the gland. The strain induced in the endothelium, which seems to produce the lymphocytes, can go on to create a definite neoplastic condition whereby endothelioma and fibro-sarcoma arise as focal changes in the lymph-adenoid goitre, in much the same way as adeno-papilliferous cancer can follow the simple hyperplasia.

In conclusion it may be as well to point out that myxoedema can arise in the very earliest phase of the goitre, long before any atrophy has ensued and in this respect it differs from the thyroidea priva of secondary atrophic conditions such as follow this and all other goitres of long standing. Probably in this case myxoedema is a symptom of the underlying subnormal res-

ponse in the gland, and not of the atrophy alone - a
disease sui generis with a typical thyroid-gland-response
which bears out that contention.

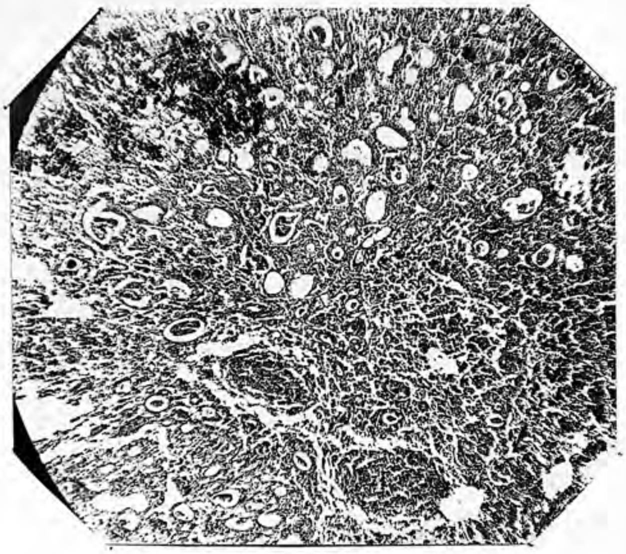

FIG.XXIII.a

Microphotograpg (mag: 70.)
Lymph-adenoid goitre. An area showing the Lymphocytic changes from a dense woody Thyroid.
See Fig. XXIV.

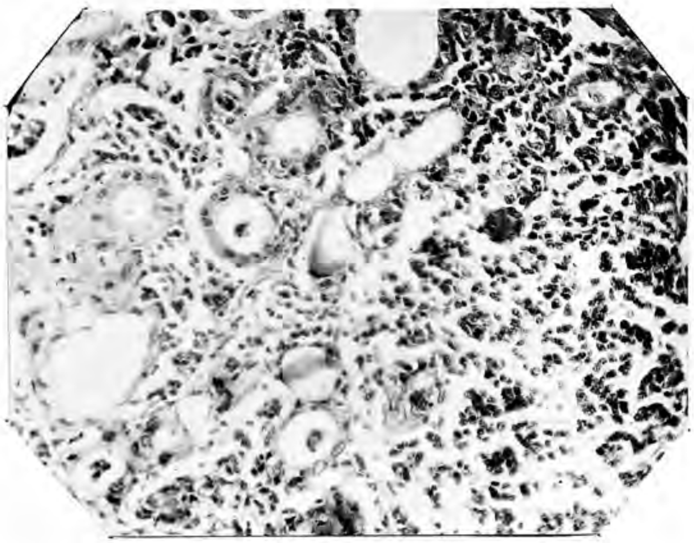

FIG.XXIIIb.

Microphotograph (mag: 250)
Higher power picture of the above.
From gland Fig. XXIV.

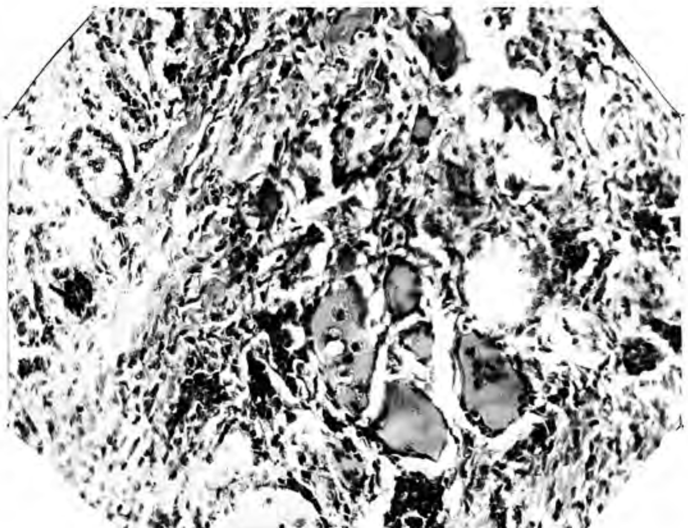

FIG.XXIIIc.

Microphotograph (mag:250)
From the same gland as Fig.XXIIIa-b - showing early fibrosis, lymphocytic changes and atrophy of epithelium.
Same as Fig. XXIV.

FIG.XXIV.

Microphotograph (mag:70.)
Retrogressive stage of Lymph-adenoid Goitre. Showing the fibrous tissue replacing the atrophic lymph-adenoid gland-units of the Thyroid, so-cal Woody Goitre.

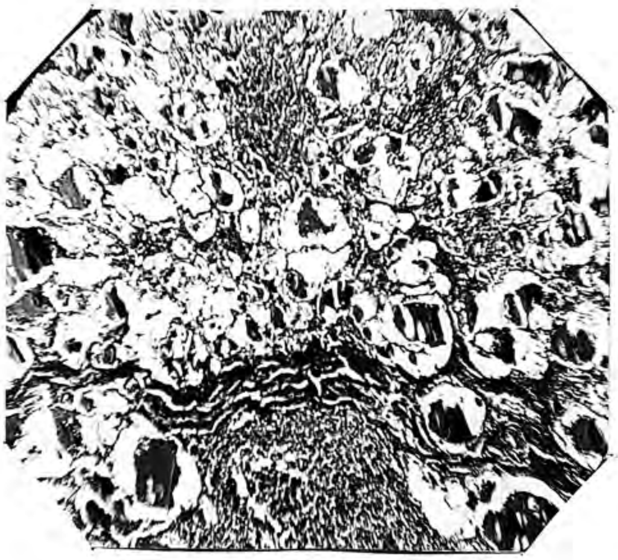

FIG. XXV.

Microphotograph (mag:60)
A Senile Thyroid undergoing Lymph-adenoid changes and atrophy. From a healthy male death from fractured skull P.M. changes are evident in the epithelium of vesicles.

HETEROPLASTIC GOITRE.

Definition:- Heteroplasia is an unblanced growth of the various tissue elements forming the organ, or the functional morphological unit of the organ - an irregular hyperplastic response not fundamentally reactionary. It thus stands midway between hyperplasia and neoplasia and it is doubtful if neoplasia can ensue in the absence of some heteroplasia which limits the direction of the response to functional stimulation. Thus heteroplasia of the parenchymatous elements of an organ will be indistinguishable from the benign forms of epithelial and endothelial growth.

It is in the interstitial tissue of an organ that heteroplasia manifests itself as a clearly defined condition of a progressive order.

Heteroplasia of the interstitial tissue of any organ, would seem to be a fibrosis due to some irritation induced by hyperactivity in the organ, or to some perversion in, either, the quantity or quality of the secretion or excretion. A continued functional hyperaemia, or a continued excess of drainage lymph, or the continued functional activity of the ducts of an organ seem to provide the necessary 'strain' to induce an increase in the fibrous element of the supporting matrix behind the endothelium or epithelium. Or again the endothelium of blood and lymph channels may pass on to the matrix of the supporting tissues an excess of metabolic and katabolic products thus carrying the stimulus deeply into the supporting fibrous tissue producing a plastic response at some remove from the endothelium.

The majority of heteroplastic fibroses in the various organs have such an origin, and the site of the heteroplastic fibrosis will no doubt have some relation to the cause of the 'strain', i.e. perivascular, or about the functioning gland-unit, lymph channels, ducts etc.

This by no means precludes the possibility of some extrinsic irritative factors, such as coal-dust coccidia, blastomyces, the treponema pallida exercising a 'stimulus' effect. Nor does it exclude the possibility of toxins operating in a progressive as opposed to a reactionary manner, either by acting directly on the sub thelial tissues, or, indirectly, through an effect on the activity of the parenchyma of an organ, and in that way acquiring an influence on the incidence of the plastic responses in the body.

Hence, though the effect may be summarised as heteroplasia, the cause may be in a variety of etiological factors.

It is easy to understand the fibrotic sequelae in any 'hyperergasis' as has been already noted in hypertrophic and heterotrophic goitres. In 'hypo-ergasis' the condition is usually explained as a replacement fibrosis, but it is probable that exactly the same factors are at work in both hypertrophy and atrophy; i.e. the increased strain thrown on the blood and lymph-vascular elements of the functional unit. If it is recalled that any gland-unit must be fundamentally an adeno-vascular mechanism- then any failure in the epithelial elements will have its first effect on the endothelial elements and through them on the sub-endothelial fibrous tissue. Thus atrophy and fibrosis must be as closely linked as hypertrophy and fibrosis - as is seen in the retrogressive phase of lymph-adenoid goitre and simple hyperplastic goitre. In these cases the fibrosis will have, primarily, a very intimate relation to the morphological unit of function. 'Anergasis' on the other hand implies an absence of the stimulus to function and, though atrophy ensues, so-called replacement fibrosis does not - as is seen in the vestigeal vascularised fibrous tissue representing the thyroid gland in some cretins.

Heteroplastic goitre can arise apart from this secondary variety of fibrosis, as a primary condition, or rather under conditions in which there is no obvious preliminary change to which attention is called before the manifestation of fibrosis.

Two varieties of primary Heteroplastic Goitre occur:-

.I. The Perilobular or Perifollicular Fibrosis.

(Arterio capillary sclerosis.)

.2. The Perilobular or Coarse Interstitial Fibrosis.

.I. Intralobular Fibrosis or Perifollicular Fibrosis has already been noted as a secondary condition or consequence of Hypertrophic, Heterotrophic and Hyperplastic goitre.

As a primary condition intralobular fibros-

FIG XXV.

The Intra-lobular Fibrotic Goitre to show the diffuse admixt
of the secreting and colloid storage tissue in the indurated
gland.

The original should be inspected with a hand-lens.

is with or without swelling of the gland occurs in the Post Mortem room as a normal senile retrogression in generalised senile changes such as arterio-capillary sclerosis at all ages (e.g. congenital syphilis) with similar changes in the kidneys and liver - as part, in fact, of an arteriocapillary sclerosis.

As a goitre it occurs with or without symptoms, and when symptoms occur most commonly with the symptoms of the forme fruste of Graves'disease (in 80% of the goitres) and less frequently with symptoms of established Graves'disease (about 10% of the goitres.)

The condition is analogous to primary interstitial nephritis and pericellular cirrhosis of the liver, and, like these conditions, it will be characterised by the very variable quantity of parenchymatous activity present in the gland. The fibrosis is closely associated with the functional gland-unit and that probably indicates that some perversion of physiological activity is the underlying cause of this goitre. The parenchymatous change may be the result of a continued hypertrophy, but it is equally possible that any evident hypertrophic activity is caused by the encroaching fibrosis reducing the efficiency of the gland tissue.

Macroscopic Inspection:- The characteristic feature of the goitre is the vascularised fibrotic tissue uniformedly distributed through the gland giving to the cut surface a fleshy appearance,(this is difficult to preserve). The fibrosis extends to the fascial compartment of the neck which encapsules the gland and the (Fig XXV) firmness of the adhesions must make removal a difficult matter.

The parenchyma of the gland manifests all the vagaries presented by the normal and the hypertrophic gland in the quantitative relation of the opaque secreting tissue to the colloid storage tissue. But, both cycles of function are always present in the gland and, however excessive in quantity the secretory tissue, it never obscures the glistening translucency imparted to the cut surface by vesiculated colloid. It can be confused only with the retrogressive stage of hypertrophic goitre on macroscopic inspection, and this difficulty may be insurmountable.

Microscopic Inspection:- The feature of the tissue is the uniform fibrosis closely applied to the endothelium of the sinusoids and capillaries within the lobule; occasionally it is confined to the gland-unit of the lobule. In operation material the secretory activity has resulted in complete lacunation of the follicles, only very rarely is the vacuolar and granular phase of secretion encountered. In the presence of some exhaustion of the epithelium, lacunae and vesicles can b be confused unless the special technique of the author is resorted to and the tissue searched for lymphocytic aggregates. That is rarely necessary. Vesicles of stored colloid are always present in the tissue, though often reduced to a minimum and may be cystic. Fig. xxvi Fig. xxvii Fig. xxviii. Definite distension of the lymph channels of the lobule is common; they contain a thin serous fluid, like normal secretoyr matter; never colloid. Here and there

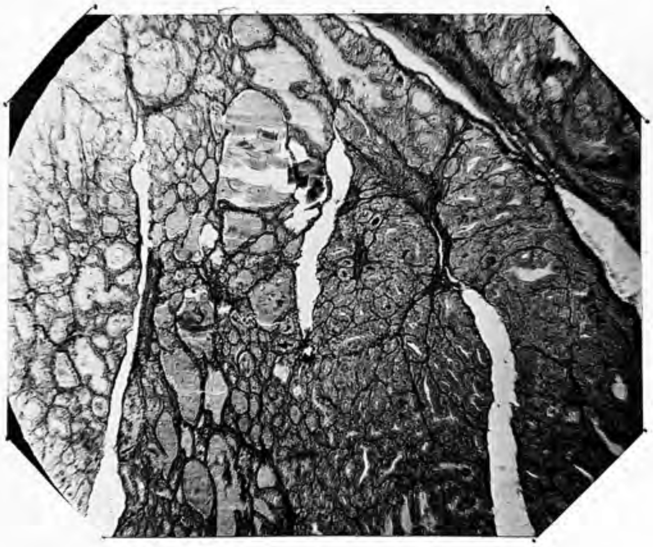

FIG. XXVI.

Microphotograph(mag:60)
An intralobular fibrotic goitre, showing the focal admixture of solid secretory tissue and the vesiculated and cystic tissue.

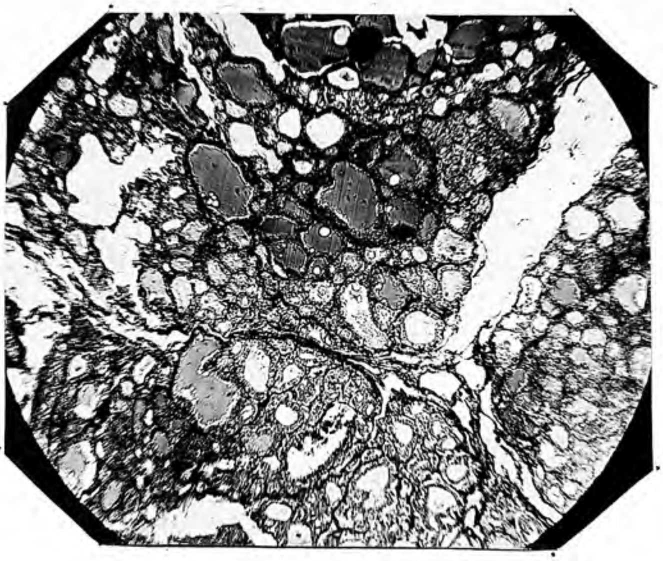

FIG. XXVII.

Microphotograph (mag: 60.)
taken from a primary intralobular fibrotic goitre showing the diffuse fibrotic enlargement of both secretion and colloid.

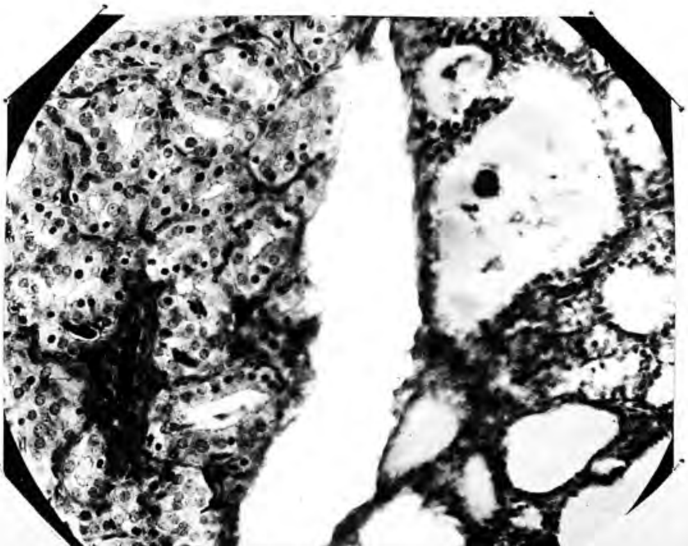

FIG. XXVIII.

Microphotograph (mag:200.)
High power magnification to show the two phases of activity in a primary capillary sclerotic goitre. There is encystment of the colloid.

foci of atrophy, more or less complete, are represented by whorled fibrous tissue.

The catarrhal stage of this atrophic process is often seen; the lacunae contain cells in advanced degeneration as well as a few red blood cells. Papilliferation is almost uniform in the active lacunae, and distension of the lacunae may be extreme. On the other hand, the tissue may be indistinguishable from a normal or hypertrophic gland.

It is hardly necessary to point out that the fine intralobular fibrosis can be associated with some degree of coarse fibrosis. This fibrotic goitre is related to Graves' disease in the same way as Interstitial Nephritis is to Bright's disease. Its significant histo-pathology will be considered under the section of applied pathology.

.2. Perilobular or Coarse Interstitial Fibrosis.

Perilobular fibrosis is by far the most common incident in the thyroid gland.

It is analogous to the coarse interstitial fibrotic changes of other organs - e.g. the liver. The thyroid gland has as diverse a functional cycle as the liver or kidney but is handicapped by the absence of a duct. Excretions and various secretions are conveyed in the lymph- and blood-vascular channels in the interstitial tissue of the organ. The thyroid organ has also extreme vicissitudes, as we have noted, in the course of its functional activities at the various decadal and seasonal periods of life. Excessive activ ity in one direction or another is a common incident in the organ. Thus the factor of 'strain' and local physiological intoxication would seem to account for the frequency of this form of fibrous heteroplasia among goitres.

It is not, however, the fibrosis that gives to these goitres their characters, but the secondary consequence of the circumscribing effect of the fibrosis on the conducting channels in the interstitia.

Retention of the secretions and excretions will follow the complete or partial closure of these channels; thus, retention cysts are common; they resemble those of the vesicular goitre in some cases, and in others the retention is not in the vesicles but within the capsule of the gland-unit or lobule:- two types of cysts are thus formed one containing nothing but colloid, and the other a mixture of pent up colloid in which lies parenchymatous tissue - cysts & cyst-adenomata.

Colloid is not the only material pent up behind the obstruction in the interstitial tissue, This other material, secretion or excretion widely infiltrates the spaces of the stroma and parenchyma and undergoes a characteristic inspissation producing a very striking Hyaline Infiltration Tumour or symple serous cysts. may form in which it is common to find considerable quantities of cholesterol.

Needless to say, the blood vessels are often implicated in the circumscribing fibrosis and add further complications to the condition. Haemorrhage into the cyst, cyst-adenomata and infiltration tumours are common. Necrotic changes may also follow this in-

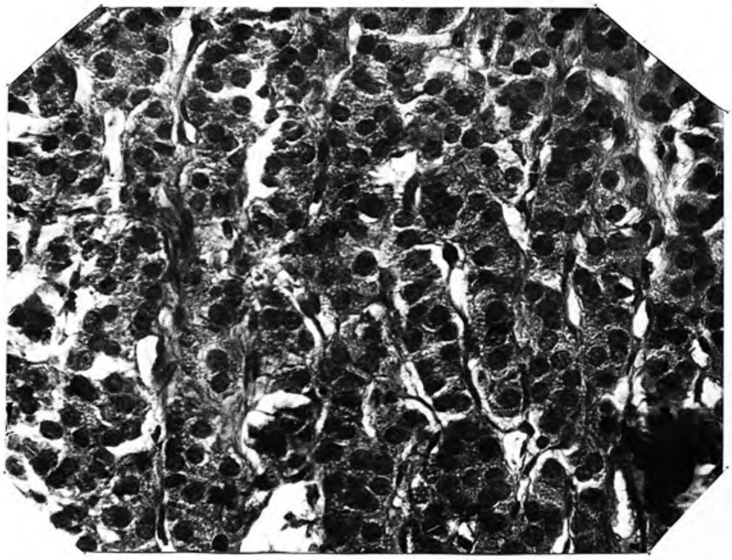

FIG: XXIX.

Micro-photograph (mag 400.)

Typical FOETAL ADENOMA . Note the closely circumscribing fibrous tissue about the capillaries and the simple columnar arrangement of the epithelium.

terference with nutrition and various retrogressive changes - hyaline scar formation, calcification or ev even ossification can follow.

There is a very interesting and charactertistic type of adenoma associated with perilobar fibrosis the so-called Foetal Adenoma. This tumour or rather retrogressive change derives its name from the solid pigmented (or darkly coloured) epithelium, arranged in more or less long parallel columns, resembling the foetal tissue and the rest phase tissue of the thyroid organ. This arrangement would seem to arise as the result of a sealing up by fibrosis of t the sinusoidal and intergland-unit spaces - so that the epithelium acquires a fibrous basement membrane directly applied to it, in which is incorporated the specific capillaries of the gland-units. The possibility of function is abrogated by the absence of the specific mechanism of physiological interchange of materials. This condition can be accompanied by a considerable vascularisation of the new basement membrane sufficient to ensue a luxurious existence for the epithelial cells. This parasitism is not of course always complete, but the very most that is ever found in the way of activity is the accumulation of tiny droplets of colloid. The epithelial cells are fat and luscious not granular, with no striking avidity for stains, but are deeply coloured. Such is the foetal adenoma which may grow to a very considerable size - but which sooner or later shews some evidence of central ischaemic necrosis, haemorrhagic necrosis calcification or ossi fication. This adenoma may of course have arisen con genitally - but that I doubt, not having encountered one apart from the incidence of perilobar fibrosis within the remainder of the gland.

It is difficult to deny these adenomata some tendency to neoplasia, but I have no complete records such as the hyperplastic adenomas provide. Theoretically I would question the ability to grow as independent organisations or cells, in the absence of the active stimulus of function. I consider them essentially retrogressive having neither progressive or reactionary tendencies, and I think they are "foetal" only in their architecture and certainly not in their potentialities.

These constitute the various secondary retrogressive changes due to the perilobar and coarse interstitial fibrosis. They are analogous to similar changes in the liver and kidney arising under the similar conditions.

I would emphasis the fact that perilobular fibrosis and secondary retrogressions arise both as diffuse conditions and focal conditions - producing the so-called adeno-parenchymatous goitres or the focal adenomata, cyst adenomata or infiltration tumours.

Perhaps it as well to state the fact that the hyperplastic goitres and adenomata arise in any portion of a thyroid gland that is free from the invasion of the interstitial fibrosis and may thus complicate perilobar fibrosis or any of its focal manifestations.

CLINICAL ASPECTS of the PATHOLOGY of GOITRE.

Using a more precise knowledge of the anatomy and physiology set out in my original papers it has been possible to classify the various goitres into categories indicating definite departures from the normal anatomy and physiology.

The relation of this pathological classification to the various clinical conditions of which Goitre is a sign has a very practical value.

Simple compensatory hypertrophy of the thyroid gland has been recognised as a definite goitrous swelling. Even "Goitre" therefore is not necessarily a sign of disease. Individuals who have goitrous hypertrophy may actually be 'normal' in virtue of their goitres. They can be afflicted by various diseases and disturbances causing the 'goitre' to receive an undue amount of attention. Pregnancy and the menopause, or even menstruation can add to the hypertrophic activity of such a physiological goitre. Of even greater moment is the peculiar influence of 'sexual puberty' (II - I6) and 'statural puberty' (I8 - 24) in formulating increased demands on the hypertrophic activity of the normal gland, likely, therefore, to aggravate any degree of 'physiological goitre'. Were we able, as easily, to gauge the enlargement of the kidney or liver in the course of the decades and seasons of growth and function, or in the course of general diseases, there is no doubt a similar physiological enlargement would manifest itself (and might even afford a justification for some surgical interference with this swelling). I think it is necessary to emphasise therefore the existence of a physiological goitre.

Apart from this normal physiological goitre - there occurs the goitrous hypertrophy associated with some underlying disease or diathesis. Of t these the most important is the hypertrophic goitre not infrequently encountered in generalised lymphatism or status lymphaticus. This association of cirstances would seem to explain completely the incidence of sudden death in cases of goitre.

This fact is of greater moment when it is found that simple hypertrophic goitre can by its chronicity induce secondary changes in the gland which give rise, in a small percentage of cases, to symptoms of Graves' disease with or without exophthalmos.

The question therefo-re of status lymphaticus in this relation to goitre and to sudeen death requires separate consideration.

SUDDEN DEATH in CASES of GOITRE.

The cause of sudden death in cases of goitre, has been the subject of much speculation. When it follows upon operation it is usually attributed to faulty operative technique, since in the hands of the more experienced the incidence of sudden death declines to nothing. There is a danger in this explanation, s since it encourages any surgeon with sufficient confidence in his technique to extend, on that ground alone, the field of operation in people suffering from goitrous conditions. The accidents which follow this applied confidence are usually said to result from some 'toxic' material which at operation escapes, is reabsorbed, and exercises a lethal effect.

The application of a more precise knowledge of the physiological action and the anatomy of the thyroid organ points to another explanation which may serve to exclude the danger and reduce the mortality in operations on goitre to the incidence of operative technical failure only, and this is surprisingly small.

It becomes possible to separate fro m some 2,000 goitres examined, agroup of glands having the characters of a true balanced hypertrophy - Hypertrophic Goitre. They form a clearly defined group distinct from the typical adenoid gland of established Graves'disease, or the equally typical sclerotic gland of the forme fruste Basedowii, though they have a certain features in common with these groups. The hypertrophic goitres are invariably associated with a particular phase of thymic activity, and in that respect also they differ from the two other groups of goitrous swellings.

An examination of material from 54 post-mortems on cases of goitre collected from various ~~sou~~ sources during fifteen years, brings out a very striking relation between hypertrophic goitres and sudden unexplained death.

Of the 54 cases 46 died suddenly.

Of the 46 suddendeaths - 8 had a definitely determinable cause as follows:-

4 cases of tracheal compression in vesicular goit goitre without thymic enlargement.

4 cases of mediastinal sepsis with an adenoid goitre (true Graves'disease, death on 2nd day.)

I case of pneumonia with an adenoid goitre.(True Graves'disease.)

I case of mitral disease with an adenoid goitre of true Graves'disease.

With these cases we are not concerned for the moment. In the remaining 38 cases - the only uniform feature was a hypertrophic goitre in a status lymphaticus. Of these 38 cases - I2 shewed a massive haemorrhage, but the cause of the haemorrhage was not determinable and I have not met a case of death from haemorrhage in goitre except in these hypertrophic goitres in a status lymphaticus.

Thus 38 out of 54 post-mortems reveal the fact that hypertrophic goitre and sudden death are peculiarly associated, and that unexplained sudden death in cases of goitre has a specific pathology and characteristic morbid anatomy.

Turning to the clinical aspect of these cases of hypertrophic goitre we find no such close association.

In the 38 sudden deaths the clinical diagnosis was, in 5, Graves'disease; in 10 forme fruste Basedowii or so-called 'toxic goitre';in 12 parenchymatous goitre; in 2 adenoma of thyroid; and in 9 goitre with dyspnoea. There is thus no clinical uniformity in these series, nor is there an overwhelming number of any of the more defined clinical conditions e.g. Graves'disease, so that we are dealing with an indefinite clinical state. The tumour had existed in the neck in all cases, from 3-7 years. The 38 cases occured in 33 women and 5 men. ages 17- 23 years. In all but two cases operative procedure had been attempted, 3 died during the induction of general anaesthesia, 4 during the operation and the remainder within 12 hours of the operation and before complete recovery from the anaesthetic. Two of the cases, both diagnosed as Graves' disease, died on admission before operative procedure was taken, and could have been considered clinically as acute cases of Graves'disease.

The cases can be divided into two groups 12 cases associated with massive haemorrhage and 26 cases without haemorrhage.

The same primary pathological changes were found in the 38 cases whether haemorrhage had occured or not.

In all cases the bodies were well nourished, even adipose for their age. All had a peculiar pallor of a definite chlorotic type. All had enlarged thymus, peritoneal, mediastinal and lymphatic glands; enlarged Peyer's patches and lymph follicles and particularly enlarged glands in the caeco-appendicular peritoneal fold and the pyloric region. The back of the tongue was covered with hyperaemic lymph nodes. The thyroid gland was enlarged, the size varied very much, but was always uniformedly swollen. Engorged veins filled the fascialspace in which the thyroid-thymic apparatus lay, but were much more striking in the thymic region than over the thyroid gland itself; venous congestion made the vessels look like caverns at the root of the neck.

The macroscopic section of the thyroid g gland had the characteristic appearance of hypertrophy. Fig XXX. XXXI. It contained both colloid storage and secretory tissue either diffusely admixed, or focally distributed throughout the gland. It shewed a mere quantitative departure from the normal gland. This gland can be distinguished even by macroscopic inspection from the typical gland of Graves'disease, or from the forme fruste of Graves'disease, or from vesicular goitre.

The microscopic section of the gland confirms the macroscopic findings. There is nothing pathological about the tissue; it is a mere exaggeration of the normal active gland, so occupied in functional a-activity as to preclude any great degree of colloid storage. Every microscopic field contains folliculated epithelial columns, shewing each stage of secretory activity, and along side these, gland-units in which some colloid is being stored. While every gland shews a decided hypertrophy in every phase of activity the interrelation of the secretory phase and the colloid storage varies quantitatively, but never at any time is vesiculated colloid absent from these glands. Microscopically it is difficult to distinguish itfrom the normal gland on the one hand and from the capillary sclerotic gland of the forme fruste Basedowii on the other.

As I have indicated in my paper - The Thyroid Apparatus ( ) the thymus is to be considered as sharing in any secretory activityof this nature. In these cases the thymus was in the lymphoid phase Fig xxx. xxxi. of its meta-trophy so advanced as to obscure the endothelial gland structure and even the Hassell elements. The thymic tissue in the hilum and at the upper end of the lower poles of the thyroid, share in this lymphoid action and may lose all fat in the course of this activity. The parathyroids are infiltrated with fluid and lymphocytes and their structure may be obscured Fig VI orig. and demand careful study. Lymphoid aggregates may abound in the interstitia of the thyroid gland in the sinusoids of the gland-units.

In the I2 cases of haemorrhage associated with this morbid anatomy it seems probable that the bleeding is not referable to any failure in surgical technique, Careful search for a bleeding point fails to disclose any one area from which the flow was apparent. It does reveal, however, an almost cavernous distension of all the venous plexus of the thyroid-thymic apparatus. In two cases the haemorrhage was almost confined to the mediastinum and thymic region, the area of operation being in the neck. There remains a strong suspicion that these haemorrhagic accidents are secondary to the removal of the active thyroid gland and occur from the effort of compensating for this loss - are not in fact due to any technical failure but to a secondary physiological engorgement, (vide strangury after kidney amputation.)

It will be clear then that the cause of sudden death must be attributable to whatever condition underlies this constant morbid picture of hypertrophic goitre in a status lymphaticus.

An identical morbid picture with or without an evident or excessive swelling of the thyroid gland occurs in other cases of sudden death. I have encountered 9 such cases of sudden death following exertion in well nourished individuals, 8 females and I male between the ages I9 - 22. All were chlorotic in colour and post mortem shewed an extreme status lymphaticus. The point of interest is that the thyroid gland in the 9 cases showed a condition identical with that seen in the cases of goitre. The whole pathological picture is the same. This is equally true of all cases of status lymphaticus but in the children and young adults it is normal to find a hypertrophic thyroid gland in at least 75% of post mortems whatever the cause of death. For that reason the comparison is made at the same age level as the goitre cases.

It is generally taught that the thymus is enlarged in cases of Graves' disease. The more acute the disease the more would that seem to be true. In 8 cases of Graves' disease dying from secondary causes, the thymus was by no means so lymphoid as in the status Fig: XXXII XXXIII lymphaticus. It shewed an endothelioid reaction and the more characteristic the thyroid is of Graves' disease the less is the thymus tissue likely to be excessively lymphoid.

Further, it is not possible to confuse the hypertrophic thyroid in this condition with the thyroid gland in established Graves' disease as seen after operation. Fig XXXII XXXIII In Graves' disease the thyroid gland on section looks like the pancreas or salivary gland. It contains no colloid. The thyroid gland of Graves' disease is an unbalanced condition - not a hypertrophic but a heterotrophic state, in which the gland shews a diffuse storage of non-colloid secretion and the thymus an endothelioid or fatty meta-trophy and no status lymphaticus exists. Many observers believe that the status lymphaticus is the precurser of Graves' disease and that may well be so - but at the moment it is not possible to go further than to state that exophthalmic symptoms or the symptoms of the forme fruste Basedowii can arise in the course of status lymphaticus, Of still greater significance is the fact that the status lymphaticus can give rise to a goitre without manifesting any of these symptoms, except the swelling of the neck.

The thyroid gland of vesicular goitre cannot be confused with the hypertrophic gland. Colloid goitre never shews even a vestige of active secretory tissue, it is wholly given over to the storage of colloid.

Dyspnoea from tracheal compression causes sudden death, and in the same indefinite clinical conditions , except that the tumefaction must be at least partially substernal or mediastinal to affect the trachea in such a way as to cause sudden death. There was no such condition of the trachea in these 38 cases, nor was the swelling always substernal.

It would therefore appear that generalised lymphatism with a hypertrophic thyroid is a clinical entity not primarily referable to the thyroid gland; and that much more consideration must be given to the intercurrent hypertrophies of the thyroid of a purely functional and compensating order. My recent records of examination of thyroid glands removed at operations shew a very manifest tendency to include many simple hypertrophic glands in the scope of surgical therapeutics.

Can these cases of goitre be diagnosed for what they are ? , a compensating hypertrophic thyroid swelling with underlying generalised lymphatism.

It would seem so - since the older and the more experienced surgeons largely exclude these cases from operation. On what grounds I do not know, but perhaps this note will raise the question.

The recognition of an adipose chlorotic diathesis underlying this condition and differing from the diathesis in Graves'disease, as would seem to be the procedure of Mr James Berry, F.R.C.S., may reduce the incidence of sudden death in goitre operations; or, a critical study of the basal metabolism in all goitres, as Sir Harold Stiles F.R.C.S. has suggested may serve to exclude this condition from operation; or, the examination of the base of the tongue for acute lymphoid enlargements (generally hyperaemic) and the inspection of the glands of the body and mediastinum may, as Sir David Drummond M.D. has suggested, induce caution or even provide a means of diagnosis.

In any case the extension of the scope of surgery of the thyroid gland demands great judgement and extreme caution sine it is herein shewn to be a clinical question rather than a question of surgical technique.

It would seem that the physician has almost abandoned the study of the Diseases of the Thyroid Gland. I find it a constant complaint among general practitioners and some surgeons that none but the surgeon will take any interest in cases of goitre. The most serious effect of this is that the student of medicine knows of goitrous conditions only from the surgical point of view.

Conclusions:- The first practical application of this study of goitre would appear to be that:-

A peculiar morbid picture can be ascribed to the majority of cases of goitre which died suddenly with or without operative interference.

The morbid picture is identified with the picture of status lymphaticus in adults.

Some diagnostic criterion of this condition should be sought in a more detailed clinical study of all cases of goitre.

GRAVES' DISEASE.

The most typical condition associated with goitre is Graves'disease, though in fact the goitre as regards its size may be a negligible factor. The term Graves'disease has been made to include a certain atypical symptom-complex in which there is no exophthalmos. This has been described as a 'forme fruste', of Graves' disease or as 'toxic goitre'. The older clinicians object to this confusion between the two symptom-complexes, principally I gather, because they are able to recognise in the age and diathesis of the patients a distinct type of individual that suffers from the true or, as I would call it, primary Graves'disease, so that with them Graves'disease maintains its identity despite the similar symptom-complex. Toxic goitre and toxic adenoma are objectionable terms on other grounds- they get over the confusion with Graves'disease, but add new difficulty in implying some infectious cause. The term exophthalmic goitre is equally inapplicable since very various pathological conditions can be associated with Graves'disease proper. I hope to shew that the conditions are really related just as the groups of conditions that are included in the term Bright's disease.

The typical Graves'disease has been found associated with the following pathological conditions of the thyroid gland:-

.I. Adenoid Goitre, in 100% of 213 cases

.2. Intralobular Fibrotic Goitre, in 57 - 163 cases.

.3. Hypertrophic Goitre, in 8 - 49 cases

.4. Simple Hyperplastic Goitre, in 5 - 29 cases.

Adenoid goitre never occurs in my experience without causing typical Graves'disease. Adenoid goitre alone among all the other forms of goitre contains no vestige of stored colloid material.

These two 100% incidents must be connected.

Histologically adenoid goitre is a heterotrophic state in which the secretory activity in the gland is so extreme as to exclude the passive process of storing colloid in vesicles.

It will be necessary therefore to explain the occurence of the symptoms of Graves'disease in other goitres in which there is obvious colloid.

The other goitres never shew any symptoms until there is definite fibrosis about the gland-unit, until in fact it becomes probable that the colloid material is trapped in the vesicles or encysted. This is borne out by the frequency of obvious cysts and degeneration of the material in the cysts. The fibrosis, then, would act so as to render the hypertrophy in these glands a one sided effect, or heterotrophy identical with the primary condition seen in the adenoid goitre, but focal instead of general in its distribution. The obvious colloid in these goitres is thus ineffective and incapable of circulating, and the difference in the pathology is more apparent than real.

Graves'disease is in fact clearly associated with heterotrophy however it may arise.

Graves'disease proper is therefore associated with two well-defined pathological factors:-

.I. The absence of effective stored colloid.

.2. The presence of extreme secretory activity of the epithelium.

These factors merit separate consideration. The absence of effective stored colloid need not imply the absence of colloid from the body. Colloid material as a vehicle may in fact be so occupied in carrying some metabolite from or to the thyroid gland as to preclude any possibility of storage. However that may be, so very fine an adjustment of the balance bewteen secretory effort and colloid can hardly be maintained for long, and sooner or later some deficiency of circulating colloid must ensue. This will create a break in the chain of compensatory events which may contribute its own effect to the symptom-complex in virtue of the perversion of the secretion that would follow. (In this connection the probable relation of the parathyroid body to the lymphatic channels of the thyroid gland should be recalled. (See Thyroid Apparatus.)

The condition of affairs in the thyroid gland in some cases of Graves'disease goes no further. The secretory effort manifest in the epithelium completely simulates a simple hypertrophy in which all the natural phases of the secretory cycle are present. Such normal secretory activity of itself need give rise to no symptom, as in hypertrophy and hyperplasia, and normally in early infancy and in marasmus and in starvation.

In Graves'disease it is the rule however to note that the secretory effort passes beyond thisand goes on to stage which precludes the possibility of the formation of any more secretion. The adenoid goitre is then converted into a store house for secretion - the follicles having an extreme degree of lacunation, with papilla formation and great irregularity of outline. This is associated with very definite changes in the staining affinity of both the nuclei and the cytoplasm of the the epithelium and the gradual disappearance of all lymphocytic activity in the sinusoids and the lymph channels. Concurrently the lymphocytes disappear from the thymus to a marked extent and the parathyroid is also a-lymphoid . Physiological turn-over, as it normally manifests itself in the thyroid apparatus, is completely stopped and a condition of check-mate is established in the cycle of thyroid secretion.

In fact there is a complete cessation of function - it might be said a state of hypothyroidism ensues in an individual whose dependence on thyroid activity is great.

Thus hypothyroidism may constitite a further cause of symptoms in Garves'disease. It is known however that hypothyroidism as seen in lymph-adenoid goitre, and aplasia and atrophy does not give rise to symptoms at all like those of Graves'disease. It is therefore more probable that this hypothyroidism is a constant

, of Graves'disease either as an exacerbative or a cumulative phenomenon not necessarily contributing to the symptom-complex of Graves'disease.

While allowing for the existence of some hypothyroidism it is obvious that the intoxication in Graves'disease must be sought elsewhere; it must in fact be looked for as an intrinsic effect of the thyroid gland, since there is no doubt of the curative value of radical amputation of the adenoid gland.

Histopathology suggests another explanation of the intoxication. The feature of the tissue as we have seen is the excessive storage of secretion , and inhibition of physiological turnover, either from the mechanical effect of the swelling or more probably from the exhaustion of the epithelium. From these swollen lacunae the secretion could be forced back into the circulation, it may be into the blood instead of the lymph,the sinusoidal space having lost its dynamic effect by closure - as happens in the liver in jaundice. In this connection the cessation of activity in the lymph channels, sinusoids and thymus is significant.

This vicious re-sorption of secretion, like the a-colloidism, would be an exacerbative condition, capable of relief by rest from maximum stimulation, and the intoxication in Graves'disease would be intrinsic to the thyroid and would progress by exacerbation.

The vicious resorption of stored secretion would, I suggest, be the essence of the so-called hyperthyroidism acclaimed as the cause of Graves'disease. It is, however, an intoxication by means of a vicious absorption occuring in a pathological gland and under pathological conditions in that the secretion itself is probably vicious owing to the a-colloidism. The intoxication is thus far from being an expression of the 'autocoid' or endocrine activity of the thyroid gland. Such an intoxication is not likely to simulate the effect of the injection of any 'autocoid' compound existing in the normal gland, nor is the blood likely to exercise a 'thyroid' effect in Graves' disease (see Schafer)

The two factors, resorption of pervert secretion and want of effective colloid could each of them contribute to the symptom-complex and there is reason to suspect that each has its own train of symptoms, as will become apparent after a consideration of the other goitrous conditions.

It has been noted already that intralobular fibrotic (capillary-sclerotic) hypertrophic and hyperplastic goitres can manifest symptoms identical with that of adenoid goitre, in a small percentage of cases. In a much larger percentage of cases these goitres produce symptoms variously described as forme fruste of Graves' disease, toxic goitre, etc.

When these glands, producing only an intoxication, are critically examined they present certain features in common with the retrogressive adenoid goitre. In them also the characteristic of the greater number of the follicles is the extreme lacunation, exhaustion of the epithelium, absence of lymphocytic reaction and not infrequently actual fibrosis of the endothelial tissue about the lacunar gland-units. That is to say they have the same fundamental features which have been associated with the 'intoxication' stage of adenoid goitre though still containing stored colloid. It is difficult to avoid the conclusion that these common features are the cause of common symptoms if each complex is compared. Wherever in fact intoxication symptoms arise they are referable to the peculiar character of the histopathological changes, in whatever goitre they appear.

It is justifiable to conclude that the symptoms-complex of Graves'disease proper arises from:-

.I. The want of effective colloid which would seem to be peculiarly associated with the development of exophthalmos and a change in the distribution of fat in the body. It occasionally occurs in the earliest stage of Graves'disease as an uncomplicated condition.

.2. The development of a vicious re-sorption of stored secretion when physiological turnover is inhibited. This we have seen does occur as a pure condition in the forme fruste and the so-called toxic goitre, and it also occurs, either concurrently with, or secondarily to the a-colloidism of the typical adenoid goitre.

.3. The order of inception of these symptoms may be reversed and the a-colloidism follow the development of the vicious absorption. This we have seen arises under the same histopathological conditions as in the forme fruste of toxic goitres, i.e. apart from the typical adenoid goitre of Graves'diseaseproper. So that secondary Graves'disease exists.

.4. A most important fact to bear in mind, in dealing with Graves'disease from an experimental point of view, and may be from a clinical point of view, is that each group of symptoms must be associated with some degree of hypothyroidism. (It is interesting to recall the fact that some cases of Graves'disease do well for a time under thyroid administration.)

.5. Furhter, there is a very obvious distinction to be made between the primary Graves'disease of Adenoid Goitre, and the secondary Graves'disease (in either form) of hypertrophic, intralobular, fibrotic or hyperplastic goitres.

Adenoid goitre is obviously due to an effort on the part of the thyroid gland to meet a quantitatively or qualititively excessive demand, which of itself, is by no means relieved by the atrophy or amputation of the thyroid gland. The older clinicians recognise this underlying condition in Graves' disease proper, and have for that reason always objected to the use of the term forme fruste of Graves' disease for the secondary form of Graves' disease.

The other goitres which occasionally manifest Graves' disease proper are glands in which there is a gradual amputation of effective gland tissue by the encroaching fibrosis - so the inefficiency is established in the presence of a normal demand and may be of a normal physiology; thus no peculiar diathesis need underlie these secondary forms of Graves' disease.

If the foregoing considerations are summarised a striking analogy arises between Graves' disease and the thyroid gland, and Bright's disease and the kidney.

Primary Graves' disease of adenoid goitre is associated with typical parenchymatous thyroiditis, in every way comparable to the parenchymatous nephritis of one form of Bright's disease.

Secondary Graves' disease and the other forms of goitre are as strictly comparable to that form of Bright's disease which is associated with interstitial nephritis, and in which there is as distinct a secondary parenchymatous change in the kidneys as we have had to note in the fibrotic form of goitre. A comparative study of the liver in Diabetes would seem to establish a similar analogy.

We have long ceased to look for the underlying etiological factor of these analogous conditions in the organ which shews some pathological change, even though the tissue may contribute something of its own to the symptom-complex or rather the terminal symptom-complex. (e.g. Ketosamia and perhaps Uraemia.)

I venture to suggest that the same is true of the etiological factor in Primary Garves'disease. It lies outside the thyroid gland.

The complete preoccupation of the literature with the autocoid and endocrine function of the thyroid gland has obscured the issue and led to the neglect of the other factors - such as the persistent high nitrogen excretion. Still more recently the studies of the raised basal metabolic rate - which is more usefully and significantly termed 'A-pyrexial Fever', have served to fix that attitude, yet this a-pyrexial fever is as significant in diabetes, and indeed in every condition in which there is some need for the synthesis of endog-enous meta bolites. It is a little alarming for example to see the association of a-pyrexial fever and menstrual disturbance being taken as a justification for radical destruction of the thyroid gland by way of treatment. From what has been demonstrated in the foregoing chapters it seems clear that this a-pyrexial fever should be considered apart from the thyroid since there is little analogy between the injection of, say thyrexin, and the intoxication of adenoid goitre. It should in fact be considered for what it surely represents - a metabolic adjustment designed to deal with some pervert form of metabolism. It would be as well to consider also the facts which Van Slyke demonstrated concerning the relation of the blood and kidney efficiency (acid balance) to the lung respiratory quotient, since the R.Q. is too glibly taken as a standard in making these B.M. measurements - these elaborate calculations may do nothing more than indicate a loss of weight or a peculiar acidosis in the blood. In any c case it is sufficient to emphasis the unscientific attitude of considering an a-pyrexial fever or raised Basal Metabolicm Rate as the **exclusive** product of a hypothyroidism, which does not in fact exist.

There are other factors of importance in primary Graves' disease. Its relation to the female and to the age of 'statural puberty', 18 - 24, in that sex. Contrast the two forms of heterotrophy - adenoid goitre and vesicular goitre. In adenoid goitre there is excessive secretory function, the female and the age of statural puberty; in vesicular goitre (only the sporadic form) there is an entire absence of secretory activity, a preponderance in the male , and the age of 'sexual puberty' (11 - 14). Compare this with the movements of the Creatin - Creatinine factor of Schiff at these ages in the sexes, and the suggestion of some disturbance in nitrogen metabolism is emphatic.

Or again take the fixed association of lymphocytes with active thyroid secretion to say nothing of the different current activities in the thymus in hypertrophy and heterotrophy. The relative purin nitrogen value of the lymphocytes gives another significant indication of some involvement of the nitrogen-metabolic cycle. Link these suggestions with the question of the sexual and statural ages, and the different protein necessities associated with these, and the subject of Graves' disease and the physiology of the thyroid apparatus becomes a question of a study of nitrogen metabolism pure and simple. Paton's (10.), Jackson's (11.), and Bensley's (12.) work is very significant in this respect. So also may be the classical observations of Marine and Lenhart (13.) if there is any possibility of there being, as in diabetes, at least three thresholds, the alimentary, the tissue, and the thyroid apparatus (and probably a fourth protein threshold in the gonads) whereat disturbances of nitrogen metabolism may arise. I would point out that this study arose as a corollary to a study of dietetic disturbances and sudden death in infants and children, and from a comparison of the Pyrexial Fever of Inflammation (vicarious digestion, or cata-thesis of endogenous proteins) and the A-pyrexial Fever of endogenous synthesis of proteins (experimental thyroidism.)

The subject seems fraught with attractive hypotheses that demand critical study. As for example the dietetic treatment of Graves' disease along the lines of Allen's treatment of diabetes giving to nitrogen (or rather to each form of nitrogen i.e. the amino-acid nitrogen, and the purin nitrogen) the significance of the carbohydrate in diabetes.

CONCLUSIONS FOLLOWING from a CONSIDERATION of the PATHOLOGY of GRAVES'DISEASE.

.I. Graves'disease represents a failure of the compensatory effort made by the thyroid apparatus.

.2. It occurs as a primary condition with a typical pathological gland - adenoid goitre.

.3. It occurs as a secondary condition by loss of gland substance following intrinsic pathological conditions, such as fibrosis, in Heteroplastic goitre and Hyperplastic goitre, and Hypertrophic goitre.

.4. Graves'disease involves a degree of hypothyroidism.

.5. The so-called'hyperthyroidism' of Graves'disease is shown to have a clearly defined pathological basis.

.6. Attention is called to probabilities, other than autocoid intoxication, as the fundamental factors in Graves'disease involving a consideration of the Nitrogen cycle of Metabolism.

.7. An experimental diatetic treatment is suggested.

THE GOITROUS CONDITIONS of the THYROID Gland.

CONCLUSIONS SUMMARISED.

The research work in this report point to the following conclusions grouped under three headings-

.I. Pathological

.2. Clinical

.3. Experimental.

Pathological.

.I. The new conception of the anatomy and physiology of the thyroid organ gained from my earlier studies, provides a sure basis for a comprehensive and scientific classification of Goitre.

.2. The classification shews the relation of one type of goitre to another and points clearly to the particular break in the functional cycle of events underlying the condition.

.3. It brings out the certain specific relations of Goitre to more general diseases.

.4. It affords its own substantiation of the new conception of the Anatomy and Physiology of the gland.

.5. It demonstrates the value of treating Pathology in a pure as well as an applied manner, in seeking clues to the solution of the problem of diseases.

.6. It illustrates the general principles of pathology as applied to the Thyroid gland - bringing that apparatus into line with the pathology of Hepatic and Renal apparatus. Incidentally it demonstrates that any organ may be made the basis for the study of certain General Principles of Pathology, e.g. with reference to the relation of trophic to plastic disturbances; i.e. the anatomical causes of physiological changes or vice versa; so also neoplastic changes can be suggestively referred to some form of physiological disturbance.

CLASSIFICATION & DESCRIPTIVE PATHOLOGY of GOITRE.

SUB-CLASS.	CLINICAL ASSOCIATION.	DESCRIPTIVE SUMMARY.
I. HYPERTROPHIC GLAND.		
PHYSIOLOGICAL.	Goitre associated with:- Puberty, Pregnancy, Menopause, Ovarian disease. Ovariotomy.	Vesiculation is less obvious than in the average normal gland, and secreting tissue is not focal in distribution; both are diffuse throughout the gland.
PATHOLOGICAL.	Goitre associated with:- Status Lymphaticus. Forme fruste Basdowii Toxic goitre.	Secondary fibrotic conditions, coarse & fine arise in these goitres.
II. HETEROTROPHIC GLAND.		
ADENOID GOITRE.	Primary Exophthalmic Goitre.	(a) Progressive Stage:- Solid gland-like, such as pancreas; an ischaemic parenchymatous condition. (b) Retrogressive Stage:- Carnification of gland which is vascular and fleshy: analogous to small white kidney. A secondary capillary sclerosis.
VESICULAR GOITRE.	Colloid Goitre { Endemic. Sporadic. Parenchymatous Goitre. Cystic Goitre. Adenoparenchymatous Goitre.	(a) Progressive Stage:- Uniform & universal vesiculation: absence of all secretory activity. (b) Retrogressive Stage:- Cystic loculation of the colloid and atrophic secondary interstitial fibrosis. Degeneration of encysted matter, haemorrhage etc:
III. HYPERPLASTIC GLAND.		
SIMPLE HYPERPLASTIC GOITRE.	Recurrent Adenomatous Goitre. Toxic Adenoma. Secondary Graves' Disease.	Anatomical Insufficiency. The adenomata are true hypertrophic lobes occurring in a fibrotic gland, not at all like the foetal adenomata of the perilobular fibrosis. If malignent they are organomata. Cancerous tendency is considerable. The condion can be focal and non-goitrous.
LYMPH-ADENOID GOITRE.	Myxoedematous Goitre. Woody Thyroid. Riedel's Disease. Lymphosarcoma ? Endothelioma ?	Physiological Insufficiency A hypertrophic reaction with preponderance of lymphocytic aggregates, fibrosis & atrophy of the parenchyma. Often diagnosed as sarcoma. The glands are like adenoid goitres which have lost their lobulation. Condition can be focal & non-goitrous. Sarcomatous translation is probable.
IV. HETEROPLASTIC GLAND.		
PRIMARY INTRALOBULAR FIBROSIS.	Secondary Graves' Disease. Forme fruste of Graves' Disease. Toxic Goitre.	Carnification in a normal gland tissue with both vesiculate & lacunate follicles. Fibrosis is perifollicular - a gland-unit affection. Can be non-goitrous.
PRIMARY PERILOBULAR FIBROSIS.	Solitary & multiple Colloid Cysts. Serous Cysts. Cyst-adenomata. Adenomata. Infiltration Tumours. Adenoparenchymatous Goitre Fibro-adenomata.	Fundamentally a coarse fibrosis of the interstitia with every form of degeneration of the parenchyma. May be intoxicative.

Clinical.

.I. An explanation is offered for the peculiar frequence od suddendeath in cases of goitre. This lies in the constant relation of status lymphaticus to hypertrophy of the thyroid gland, which can be goitrous.

.2. Graves disease has a primary form, with an underlying diathesis - which demands clinical definition.

.3. Graves'disease has a secondary form without a specific diathesis.

.4. Graves'disease primary and secondary includes a dual symptom-complex. Each group of symptoms can happen as a more or less separate entity.

.5. The forme fruste of Graves'disease exihibits one of these groups in a pure form.

.6. The forme fruste may go on to acquire the other group of symptoms as the secondary Graves'diseasesupervenes.

.7. Graves'disease is related to the Thyroid gland as Bright's disease is to the kidney or as Diabetes is to the liver.

.8. The misnamed condition Hyperthyroidism us shown to have a distinct pathological basis.

.9. The general disease of which Graves'disease is a critical and terminal phase is probably related to a disturbance of Nitrogen Metabolism - analogous to diabetes of which ketosaemia is the critical and terminal phase.

.IO. The relation of the Raised Basal Metabolism (herein designated A-pyrexial Fever) to Graves'disease is questioned as to its specific origin in 'Autocoid intoxication'. It may represent the terminal synthesis of protein under a specific protein starvation - ?Purin. Some forms of Acidosis or Alkalosis should be excluded, on the basis of Van Slykes experiments before the R.Q. is used as a standard measurement.

.II. Thyroid insufficeincy must accompany all forms of Graves'disease.

.I2. A tentative hypothesis is put forward concerning the relation of 'Gonadal' upsets and Thyroid disturbances - both having their basis in Nitrogen disturbances.

.I3. A Dietetic therapy is suggested as an experimental clinical problem in Graves'disease.

Experimental.

Certain tentative hypothesis arise out of this study of value in formulating a programme of experimental studies.

.I. The very inconclusive results of all previous experimental studies of the Thyroid apparatus - thyroid parathyroid and thymus - arises from a lack of knowledge concerning the anatomy and histophysiology of thr apparatus on the one hand; and

.2. On the other hnad from a too conclusive concentration on the probable 'Autocoid' activity of the functioning apparatus.

.3. A wider view of the function of the Thyroid apparatus arises froma consideration of the clinical and pathological features of specific disturbances of the Thyroid Gland and incidently from an analogy with the pathology of other organs.

.4. Without question a 'specific' Autocoid action for the Thyroid apparatus, there exists evidence of a definite participation in the metabolic cycle by the Thyroid apparatus, strictly analogous to the participation of the Liver in carbhydrate metabolism which just as endocrine in its mechanics .(the duct of the liver does not make the liver 'exocrine' qua its glycogenic action.) Any close consideration of the Thyroid apparatus as to its Autocoid activity is only dealing with ½ the problem. All previous work except Patons, Jacksons, and Bensley's has suffered from this circumscribed method of approach.to the Thyroid problem.

.5. Perhaps even the Autocoid action of the Thyroid arises from the fact that it is engaged in the most vital of processes - the Nitrogen Metabolism; There may be an Autocoid function in the liver apart from its Glycogenic function but a carbohydrate effect is hardly vital and easily substituted. The same of course may be true of all other organs. But in the Thyroid, it would be as well, for the moment to get away from Autocoid activity as a fundamental and exclusive function of the gland if only for experimental considerations.

.6. It seems possible to separate the Thyroid, parathyroid and thymus and assign to each its specific action. Experimental interference with the thyroid the parathyroid or thymus under the circumstances in which an individual is not using the thyroid apparatus may lead to no results. It is necessary in all enqüireis to place the individual in the critical position of dependence on the activity of the apparatus before ablation of any part of the apparatus, just as starvation or overfeeding is used to render the Glycogenic action of the liver 'critical'. Some means to this end may be to hand- Mellanbys, Jackson's and Bensley's experimental work.

.7. Lymphocytic activities - focal and general - are peculiarily associated with Active Secretion in the Thyroid gland. The question of the function of the Lymphocytes is therefore a critical one in this enquiry. There is enough known concerning the chemical constitution of the Lymphocytes to give decided direction to the enquiry. Some tentative work of my own on the Lymphocytes in inflammation indicate that the Purin values for Lymphocytes is only one side of the picture and suggests that the lymphocyte is a carrier of 'Active Nitrogen' of varying composition, purin or amino-acid. The possibility of Creatin-Creatinin being the 'Keystone' of this Nitrogen bridge will arise from a consideration of the Schiff factor at the ages at which secreting activity of the Thyroid apparatus is peculiarily manifest.

.8. From this it is perhaps permissible to enquire into the specific action of Iodine and Calcium in the endogenous synthesis of Proteins from the purin base or from the amino-acid base. In other words to look on these minerals as subsidery factors instead of the present persistent tendency to give them major sognificance inthe function of Thyroid apparatus.

.9. Not the least significant though purely tentative hypothesis is that arising from the association of the Thyroids with the 'Gonads'. Are these to be looked on as 'Nitrogen' excreting organs? The type of of Nitrogen varying in the sexes. In how far does their ablation affect the cycle of events in the Thyroid gland at the critical ages of Infancy, Sexual Puberty, Statural Puberty and the Menopause?

.10. Vicious resorption of pervert secretion is probably the underlying factor in the misnamed 'hyperthyroidism. of Graves'disease. Does this alsoapply to the Kidney in Bright's Disease? What is the difference, if any, between the extracts of hterotrophic gland, normal glands and hypertrophic glands administered experimentally?

There are many other questions that arise, particularly out of a comparison of Diabetes and Graves'disease - qua Carbohydrate and Nitrogen and to say nothing of the problems associated with the Fat and Lymphocytes in Metabolic disturbances and diseases of the Digestive Tract - e.g. appendicitis, and gastric ulcer (9.) The relation of the a-lymphoid conditions (e.g. of the Adenoid Child) of lymphatic tissues to the Thyroid function is receiving consideration, and in the hands of two of my pupils has already advanced a step. (10)

Though I have presented the subject matter in a categorical form I would emphasise the fact that the conclusions are not arrived at by inductive methods but strictly bt deduction from a comparison of the individual goitres with the normal gland in each of its phases of functional activity. The theoretical considerations and classifications presented arise directly from observed facts. I have been conscious in fact that it is too easy to make facts fit theory especially when dealing with the thyroid gland I have not of course, expected to establish precise, let alone absolute, lines of division between one fact form of goitre and another, I ahve chosen, therefore, for discussion and description the typical form of each goitre. It is worthy of note, nevertheless, that it is rare to encounter insurmountable difficulty inplacing a pathological gland in its proper category, or to fail to recognise clearly the existence of two or more processes going on in one gland.

Further confirmation of the practical value of the classification is found in the fact that it serves equally well to cover the various changes of a pathological nature associated with other organs - e.g. the kidney, the liver, lung. It has a general as well as a special application and it may be that deductions having an experimental and clinical value for goitre may equally arise in kidney and liver disease, affordinga new experimental basis for investigating on these organs. In any case it emphasises the value of dealing with morbid conditions from the point of view of 'pure pathology' so as to establish a basis for the use of 'applied apthology'.

It ahs in fact cleared the ground of much confusion and will permit of a new approach to the problems underlting the Physiology and Pathology of the Thyroid Apparatus.

Geo Scott Williamson
April 3. 1924

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MD. THESIS

THE GOITROUS CONDITIONS OF THE THYROID GLAND

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APPENDIX 1

The Structure of the Thyroid Organ in Man

BY

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THE STRUCTURE OF THE THYROID ORGAN IN MAN.

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(PLATES XXXIV.-XLII.)

IT is proposed to demonstrate a new conception of the anatomical and physiological morphology of the thyroid organ. The facts to be set out were first noted as consistent features of the histology of the thyroid gland in Graves' disease. Each feature looked at as an isolated fact is familiarly noted in the literature and usually dismissed as representing the effect of the ætiological factor of Graves' disease. Taken together, however, these facts present so complete an anatomical picture as to throw doubt on any such pathological explanation. This made it necessary to examine the normal thyroid gland to look for confirmation of this morphology.

Literature.—The publication of the recent works of Swale Vincent (1) and of Biedl (2)—the latter including a complete bibliography—precludes the necessity of reviewing the literature to date. In these publications little has been added to our knowledge of the morphology of the organ, and the understanding of the mechanism of the gland has not advanced from the position summed up by Launoy (3) in 1914: "Ainsi l'histologie et la physiologie ne paraissent pas être en accord parfait : la question de voies d'excrétion de la sécrétion thyroïdienne, comme d'ailleurs la majeur partie des questions concernant la physiologie ou l'histophysiologie de l'appareil thyroparathyroidien reste donc ouverte : nous aurons trop souvent l'occasion de nous en aperçevoir." The description of the thyroid organ in *Quain's Anatomy*, 1914 (4) represents a concise picture of the current opinion on the histology of the gland.

Material.—Material from 800 normal thyroid glands has been studied, mostly taken post-mortem. They were selected by reason of the absence of any recognisable pathological or reactionary changes. That all these were normal seems certain since eighty-three of them taken from cases of uncomplicated accidental death exhibited identical features. It was impossible of course to exclude all post-mortem changes; these, however, affect the epithelium alone and are readily recognisable as such after any experience with surgical material. In the surgical removal of adenomata, for example, the excised area often includes functioning gland tissue or pieces are removed from the other side for diagnostic purposes; such pieces are a useful guide to the post-mortem or autolytic changes that take place in the epithelium of the gland. Occasionally material is removed under local anæsthesia; this likewise can be relied upon to show the state of the epithelium in a condition of ordinary function.

The selection of samples of the tissue is the key to a satisfactory demonstration of the facts. Normal glands are first cut serially into lamellæ about 20 mm.

thick. These are examined by transmitted light. In the general translucent tissue opaque areas are encountered, which vary very much in quantity and distribution. They are found in all normal glands, in 64 per cent. as gross macroscopic areas, in the remainder on examination with a hand lens. This tissue is the predominant feature of fœtal glands, and incidentally of the experimental glands examined by Jackson (5), Bensley (6), and Mellanby (7). The tissue of these opaque areas is pale and solid and looks like pancreatic or salivary gland tissue, *i.e.* it is essentially a non-colloid gland-like tissue. The choice of this tissue for examination overcomes the obscurity of the anatomical details that has resulted from the exclusive use of colloid-containing tissue, and makes it apparent that the thyroid gland is an adenovascular organ structurally analogous to the liver in that the epithelium lies in a sinusoid and has peculiar and specific relations to the circulating blood and lymph.

Methods.—The description in the text, except where specifically stated otherwise, depends upon the use of the authors' fluorchrome-bichromate-sublimate (F.B.C.) fixative and mordant and Mallory's phosphotungstic acid hæmatoxylin (for details see Williamson and Pearse) (12). The material has also been examined as a routine or for the confirmation of specific details after alcohol, formalin, and Bouins' fixation and stained with Scott's standard hæmatoxylin (13), hæmatoxylin regressively, Mallory's eosin-methylene blue, Unna's collagen method, and Weigert's resorcin fuchsin method. Some normal thyroid tissue has come to us from the surgical theatre. This was examined fresh by teasing in Ringer's solution to which osmic acid was added; or cut by the freezing method and examined unstained or stained by adding methyl green to the mount. Osmic acid of all fixatives has least effect upon the colloid material or secretion. Sections after freezing are to be floated on cold Ringer's solution. A slide clean enough to remain wet after dipping in 90 per cent. alcohol is held wet over some osmic acid in a shallow vessel for a moment, then plunged into the Ringer's solution and the section rapidly picked up. The section stretches out well and adheres firmly after slight pressure. The polychromatic effects secured by the "F.B.C." technique are consistent and remarkable, showing up differentially much cytological detail usually demanding special and precarious processes such as the silver methods.

THE GLAND-UNIT OF THE THYROID ORGAN.

The thyroid organ consists of two lateral lobes joined by an isthmus. The lobes are composed of an aggregation of *lobules* lying in the meshes of the interstitial tissue of the organ. The parenchyma of the lobule is divided up by loose strands of fibro-elastic tissue into a series of well-defined functional areas or *gland-units* (fig. 3).

The fibro-elastic tissue forms a capsule which completely circumscribes each gland-unit (figs. 1 and 2) and carries the intralobular blood and lymph vessels. The blood vessels are peculiar in that they possess no muscle coat. They are formed of endothelium supported by fibrous tissue only, so that artery and vein are indistinguishable.

There are abundant perivascular lymphatic channels accompanying these vessels. The loose fibro-elastic tissue capsule of each gland-unit is lined by a pavement endothelium. The serous cavity so formed is directly continuous with the intralobular lymphatic channels. The intralobular lymphatic channels penetrate the fibrous capsule to become continuous with the serous cavity at several points in the circumference of the gland-unit. Each serous cavity is fed or drained by several intralobular lymphatics, and is in fact a sinusoidal expansion of the lymphatic system. This lymphatic sinusoid is as characteristic of the thyroid organ, as is the portal blood sinusoid of the liver. At those points in the capsule of the gland-unit where the conjunction of the sinusoid and the lymphatics occurs, the afferent and efferent branches of the intralobular blood vessels enter and emerge from the gland-unit and in so doing penetrate both the endothelium and the fibro-elastic tissue of the capsule.

Structures within the lymphatic sinusoid.—The epithelium of the gland-unit appears in the sinusoidal space as long cylindrical columns. Generally these twist and turn in various planes to accommodate themselves to the circumscribed area of the sinusoid. Occasionally in adult tissue and commonly in fœtal tissue they are disposed in long straight cylindrical columns within the sinusoidal space. Seen in section the column may appear cut transversely as circular areas, cut longitudinally as short oblong areas, or as short branching areas depending upon the plane of section and the plications in the length of the column (see also Streife[8]). Graphic reconstruction has not proved a satisfactory means of determining the number of convoluted cylindrical columns of epithelium per gland-unit. We are inclined to think, however, as plastic work progresses, that there is but one long convoluted column within each lymphatic sinusoid. The average diameter of the column when it is regularly cylindrical is 25 μ; the length has not been determined. No point of attachment of the epithelial column to the wall of the sinusoid has been noted. The column of epithelium would seem to float in the sinusoidal space.

The only other permanent structures within the lymphatic sinusoid are the blood capillaries of the gland-unit. These are arranged in a very definite pattern (fig. 2). Concomitant capillaries accompany the cylindrical column in their length. Communicating capillaries at regular intervals unite the concomitant capillaries and appear to encircle the columns of epithelium. An anastomotic basketwork of finer capillaries fills in the space between the rungs of this ladder-like arrangement. This apron of capillaries closely enwraps the epithelial column. A striking feature of this plexus of capillaries in the gland-unit is the entire absence of any supporting connective tissue, either fibrillar or collagenous. Endothelium alone intervenes between the blood content of the capillaries and the sinusoidal space. At the points where these capillaries emerge and join the intralobular vessels their endothelial wall becomes continuous with that of the lymphatic sinusoid.

Concisely stated, therefore, the *functional gland-unit of the thyroid organ is essentially a lymphatic sinusoid in which float columns of epithelium enmeshed by a highly specialised plexus of blood capillaries.*

Natural injection of the lymphatics by fluid material or lymphocytes or both, occurs quite commonly in the normal gland, being indeed a feature of one phase of activity. This natural injection mass can be found in the interlobular lymph spaces, in the intralobular lymph spaces and within the serous cavity of the gland-unit, and in a considerable number of cases can be traced in continuity from the intralobular perivascular lymph spaces directly into the substance of the gland-unit. In this connection the injection experiments of Matsunaga (9) are to be recalled. His results do not represent so complete a picture of the continuity of the lymph channels and the sinusoids as is obtained from the examination of naturally injected material, nor have we succeeded in obtaining the same even and complete penetration by experimental injection. There is probably some mechanical interruption, *e.g.* valves, to the flow of the artificially injected mass. For this reason we would not reject Matsunaga's conclusions as emphatically as does Sobotta (Biedl).[10] The same curious anomaly is noticeable in injection experiments on the blood vessels. In natural hyperæmia and congestion, the injection usually gives a very complete picture of the vascular distribution and peculiarities. But in nine out of ten experiments with normal glands the masses do not penetrate beyond the intralobular vessels and only in about one in twenty experiments are the capillaries of the gland-unit effectually distended.

THE EPITHELIUM OF THE THYROID ORGAN.

The literature recognises two types of epithelium in the thyroid organ: the follicular epithelium enclosing masses of colloid forming the bulk of the normal gland and the non-follicular epithelium forming the so-called interfollicular tissue. There is some doubt about the identity and relation of each type of epithelium.

The gland-units of the thyroid organ contain epithelium columns which are entirely non-follicular, entirely follicular, or both non-follicular and follicular. Further, each of these different appearances of the epithelium may be encountered within the limits of one gland-unit suggesting the probability of folliculation being a physiological and not an anatomical characteristic of the thyroid organ. This probability becomes a certainty when columns of epithelium cut in their length are found to contain follicular areas alternating with non-follicular areas with every degree between the two extremes also manifest (figs. 4 and 6).

In tracing the development of the follicles two distinct processes become apparent: each has different characters and different end-results. (*a*) *Vesiculation* is a passive process in which the epithelial column alone participates and which ends in a blister-like distension of the column by colloid. (*b*) In the *active secretory process* the whole gland-unit takes part, and it may end in the accumulation of the products of secretion in a flaccid swelling (*lacunation*) of the column of epithelium.

The *indifferent phase* in the epithelium from which these two processes can be traced has certain characteristics. In microscopic sections the columns of epithelium of the gland-unit are encountered in both cross and longitudinal section, described in the literature as buds or nests and cords of epithelium respectively, the chief features of which are:—

1. No basement membrane subtends the epithelium of the columns. The endothelium of the capillaries or of the lymph sinusoid is applied directly to the surface of the columns. Where endothelium does not thus intervene, the epithelium of contiguous columns appears continuous, appears in fact to have a common protoplasm.

2. The protoplasm of the epithelial column is syncytial in character.

This syncytial arrangement of the epithelium is a matter of small moment so far as this thesis is concerned. Nevertheless in the human thyroid none of the stains that have been used to build up the hitherto accepted description of the gland structure demonstrate the existence of internuclear membranes or lines of condensation or similar stainable effects at the peripheral margin of the epithelium; nor do the application of Golgi and other silver methods, the gold chloride method or regressive staining with hæmatoxylin reveal a tangible limitation of the domain of each nucleus in the epithelium. This, however, is a matter of moment only to the cytologist.

3. The column of nucleated syncytial epithelium is solid. There is no preformed lumen.

4. A system of tubules (Williamson and Pearse [12]) lies embedded in the protoplasm internal to the nuclei. They occur in the form of a network, through the mesh of which the protoplasm is continuous; a central core of protoplasm is thus demarcated. The tubes of the mesh are thin, compact, and appear in this phase solid. They stain uniformly with about the same intensity as the nuclei.

5. In this phase the nuclei are huddled together towards the centre of the column nearer the tubular system than the periphery.

6. The nuclei stain lightly but uniformly and exhibit no clear internal structure.

7. The protoplasm of the syncytium stains feebly and cannot be differentiated into spongioplasm and hyaloplasm. It contains no granules, is relatively small in amount, and is mostly placed peripheral to the nuclei in the mass.

The process of vesiculation.

Within the limits of a gland-unit, epithelial columns exhibiting this indifferent phase lie side by side with epithelial columns in which colloid appears. This colloid may amount to no more than a minute droplet, microscopic in size, but even this amount has influenced the appearance of the epithelium enclosing the droplet. The colloid is immediately subtended by a zone of clear hyaline protoplasm, invariably present but attenuated proportionately to the quantity of colloid. This zone of protoplasm is marked off by the tubular system, the mesh of which is beginning to open. Peripheral to the tubular system the nuclei have assumed a very ordered arrangement, midway between the periphery of the syncytial mass and the tubules, giving the cubicle-cell appearance of other writers. This precise position of the nuclei is most characteristic of vesiculation. The protoplasm throughout the epithelium is hyaline and looks spongy; it stains uniformly pink and is entirely devoid of granules. The nuclei take a sharp clear stain, and their linin structure shows up well; within the linin mesh no granules are ever found. Except that the mesh of the intra-epithelial tubular system is more open, the appearances presented are those of the indifferent phase. Whatever the degree of accumulated colloid these appearances are maintained (fig. 5).

The most important feature of the process of vesiculation is the effect on the continuity of the columns of epithelium (fig. 6). The columns are sometimes encountered cut in very considerable length. When the amount of contained colloid is small, there will be seen a series of drops lying in the central core of the protoplasm of the continuous column. Vesiculation begins at discrete points in the length of the column. It can be no accident that these points are clearly governed by the distribution of the communicating capillaries. The droplets appear first in the middle of the area of syncytial epithelium enclosed by the basketwork anastomosis stretched between the communicating capillaries. Within this limit the colloid accumulates. As the quantity increases it becomes impossible to trace the continuity of the column from one vesicular area to another, and it is in fact fragmented into a number of discrete vesicles. The communicating capillaries assume an intervesicular position.

Other characteristics of the process of vesiculation are seen on examination of unfixed material, teased or cut after freezing. One is the bladder-like distension of the epithelium suggesting that the colloid is accumulated under considerable tension just as fat is stored in fat cells. This tension is sufficient to resist the compression of the interstitia, so that the vesicles maintain their form even in the extreme degrees of accumulation in the massive glands of cystic goitre. The colloid responds as a whole to the action of various acids and alkalis, crenating or swelling. A bright or dark line of refraction can always be detected between the colloid and the containing epithelium.

The other structures in the gland-unit remain passive during the process that ends in vesiculation. As the distension of the epithelium moves towards discrete vesiculation the detailed anatomy, indeed the identity almost, of the gland-unit is lost in the effect produced (fig. 7).

Vesiculation is, of course, the predominant, though not the exclusive, condition encountered in the average normal gland, and this explains the obscurity that arises from the exclusive selection of colloid tissue for examination.

To sum up the features of the process:—

1. Vesiculation occurs in definite areas of the epithelial columns of the gland-unit.
2. Vesiculation leads to the fragmentation of the columns into discrete spheroidal vesicles.
3. Vesiculation is not accompanied by any demonstrable biochemical disturbance of the nuclei or protoplasm of the epithelium.
4. The gland-unit passively suffers distension and distortion to the extent of losing its identity under the process.

The process of secretion.

The passive accumulation of colloid is in striking contrast to the active process of secretion and the end-result is very different. The appearances to be described are those seen after fixing with the F.B.C. fluid and staining with phosphotungstic-acid hæmatoxylin. No attempt will be made in this paper to identify the nature of the intracytoplasmic granules and material, nor to compare them with similar granules described by Hurthle (11) and more recently by Bensley (6).

It is necessary to recall the appearances of the indifferent phase in the epithelial syncytium; the huddled more or less centrally placed nuclei, the comparative achromatic effect of the stain on the nuclei, the non-granular nature of the protoplasm and its comparatively meagre bulk. The process of secretion in such an epithelial column begins with the gradual accumulation in the protoplasm of very fine granules, usually rod-shaped, taking a pale lilac hue with the stain. With the first sign of this accumulation of chromatic granules, the nuclei move to the periphery of the column and arrange themselves in a regular concentric fashion. Their staining affinities alter, and the linin structure is lost in a uniform staining of the whole nucleus, the nucleolus or nucleoli standing out by their very dense granular chromatic appearance (figs. 8 and 10). Following upon this, a second type of granule appears, much larger, staining dense black and seemingly of very coarse structure. These are found in the zone of protoplasm between the nuclei and the system of tubules. With their advent the nuclei assume a similar appearance, the nucleoli being lost in the general depth of the stain (fig. 9).

Vacuoles now appear, at first in the neighbourhood of the tubules. They usually contain a clear fluid material in which are many fine granules. As vacuolation increases the coarse granules disappear from the protoplasm (figs. 10 and 11). The vacuoles migrate to the zone of the swollen central core of the syncytial mass. They may congregate without fusion, giving a honeycomb appearance to the congeries. More usually they run together to form a lake. This lake has very irregular boundaries, often biting into the protoplasm beyond the margin of tubules. The tubules seem to bridge these little bays. The head of the bays may extend to the nuclei and not infrequently the nucleus seems to lie free in the fluid of the lake. So characteristic of the secretory process is the laking of the columns as to merit a descriptive term *lacunation* to point the distinction from vesiculation (fig. 17). With the establishment of lacunation the rod-like granules disappear from the fluid; they remain in the protoplasm bounding it. The nuclei lose their coarseness and stains less intensely (fig. 12).

Collectively these changes recall those that take place in the individual cells of a mucus-secreting membrane during activity. A very striking feature of this sequence of events is the irregularity with which it is distributed in the epithelium, at one point advanced vacuolation, at another advanced chromatism, at another only the fine granules. The lake of fluid may be placed eccentrically but ultimately it is more or less confined to the zone bounded by the tubules. However much material may have accumulated or whatever the degree of chromatism in the epithelium, the main mass of protoplasm lies between the peripherally placed nuclei and the tubules, giving the columnar-celled appearance of other writers.

Another feature of the process whereby it can be readily identified is the change that occurs in the intra-epithelial tubules. They increase in diameter up to 2 μ and now have walls which stain differentially. They contain a clear fluid in which float rather coarse granules, which may have accumulated in some bulk in their radial branches (fig. 10).

In longitudinal sections of the columns of epithelium this process is found to occupy the column throughout its length. There is never any attempt at discrete folliculation or any fragmentation. The whole column appears asymmetric and baggy. This flaccidity permits the surrounding tissues to impress their form on the column of epithelium causing kinking and bending of the lacunate column, so that projections of epithelium appear in cross sections of the lake—the papilliferation of the literature. Mitosis is not particularly associated with these changes, there being no hyperplasia in the midst of all this trophic activity (fig. 4).

This lacunate follicular tissue examined in teased or fresh frozen sections does not suggest the state of tension noted in the vesicular follicle; nor is there a line of demarcation, actual or optical, between the contents of the lacunæ and the containing epithelium. Acids and alkalis dissolve, vacuolate or granulate the contents, but do not swell or contract it as a whole.

Turning now to the gland-unit during this secretory phase of its epithelium, very striking changes are to be found. The lymphatic sinusoid, at the inception of the secretory phase, contains a fluid material not unlike that ultimately contained in the lacunæ of the column. This fluid separates the surfaces of the convolutions of the columns and also isolates the blood capillaries (fig. 13). The endothelia of both the lymphatic sinusoid and the blood capillaries change their reaction to the stain. Their nuclei become densely chromatic and the protoplasm coarsely granular, taking the stain with almost as much avidity as the nuclei themselves. In the earliest stage it is rare to encounter blood in the capillaries which look like strings of spindle cells (fig. 14). Lymphocytes also appear, sometimes between the convolutions of the columns, commonly as aggregations surrounding the capillaries at each hilus, and always in the intralobular lymphatics. When these aggregates are considerable, as they often are, there is evidence of proliferative activity of the endothelium lining the sinusoid and lymphatics; free endothelial cells, epithelioid or endothelioid forms are found mixed with the lymphocytes (fig. 15).

In this way the gland-unit as a whole acquires new features, which depend upon the diverse appearances presented by the columns—semi-solid masses lying free in the distended sinusoid, regularly circular lacunæ simulating vesicles, polygonal or irregular lacunæ, or a mixture of these forms. Not at all infrequently the whole cross section of a gland-unit may be occupied by a single lacunæ with the capillary plexus bunched together at two or three points pressed against the wall of the sinusoid (fig. 16).

It is curious to note that, though there is no histological means of identifying or distinguishing the nature of the material contained in the lacunate follicles, it has a distinct effect on the macroscopic appearance of the cut section of the tissue. No matter what the amount of the contained secretion or the degree of lacunation, the macroscopic appearance is always that of salivary or pancreas gland tissue and never that of colloid.

Set forth categorically the sequence of events (fig. 17) in the process of secretion is:—

1. The opening up of the potential space of the lymphatic sinusoid by fluid matter.
2. A change in the endothelial cells lining the sinusoid associated with which lymphocytes appear in the intralobular lymph channels, and frequently also in the sinusoidal space.
3. Swelling of the epithelium, migration of the nuclei to the extreme periphery and the appearance of two orders of granules.
4. Vacuolation of the protoplasm and partial solution of the granular matter in the fluid of the vacuoles.
5. Lacunation of the epithelium by the accumulation of the contents of the vacuoles in the central core of the column of epithelium.
6. The tubules in the protoplasm of the epithelium appear to swell and conduct granular fluid, the radial branches become quite turgid.

Secretory activity is present in the average normal thyroid in very small amount. It gives character however to the tissue in which it occurs, so that macroscopically the state of activity may be estimated by the appearance of the cut surface of the organ. The amount of activity varies widely in different individuals. Certain experimental work in progress and the general results of Jackson's and Mellanby's work in the light of this new point of view indicate that this process of activity varies considerably in individual animals. Individuals are in fact very differently dependent on the activity of the organ.

Discussion.

This description of the histological and cytological details of the thyroid organ is by no means new, and the literature abounds in references to each detail. The definite sequence of events, however, is here sorted out and presented for the first time as a whole. This is largely due to the recognition of the functional morphological unit and to the use of a special technique.

By way of illustration we may point out the analogy of the thyroid with the liver. The peculiarity of these organs is the presence of a sinusoid—in the thyroid organ a lymph sinusoid, in the liver a blood sinusoid. In the sinusoid in each organ a specific epithelium lies bathed in the sinusoidal fluid. The epithelium of the thyroid organ has its intra-epithelial tubular system analogous with the bile-canaliculi; it has however no continuity with an external duct such as the bile-ducts (there may be an exception in the youngest embryo and perhaps in the lower vertebrates). In the thyroid organ the sinusoidal space is traversed by the blood capillaries, and these not infrequently present the precise appearances that have been associated with the Kupffer cells of the liver sinusoid, the position of which in relation to the epithelium is identical. The colloid is analogous with certain constituents of the bile, functioning as a vehicle: in the thyroid this is stored in an intra-epithelial position, in the liver in an extra-epithelial position. The secretory products of the thyroid organ are first agglomerated, then dissolved in a fluid, giving a vacuolated appearance, and often stored as a lake of fluid in the core of the epithelial syncytium. The method of accumulating material in the liver epithelium is not essentially different.

This of course is mere analogy and will furnish proof of nothing. It may however permit the speculative construction of hypotheses giving direction to study. With regard to the relation of secreting phase to colloid phase, it is not possible to go further than the statement that they are distinct, and that each can be traced from the smallest beginning to the largest result. It is possible that the colloid in the vesicle, once accumulated, is digested by the activity of the epithelium surrounding it and converted into the secretion of the lacunæ. This seems precluded by the fact that large accumulations of secretion do not appear as colloid to the naked eye; nor has any flow of colloid from one discrete vesicle into another so as to produce the long irregular baggy follicle of lacunation been noted in this study. Such may possibly occur, but the probability is that the processes are distinct throughout their history, and that reversion to the indifferent phase is necessary before a colloid-phase epithelium changes over to a secretory-phase epithelium. The material of the lacunæ might contain admixed colloid.

SUMMARY.

1. The thyroid organ has been shown to contain a definite functional unit, of which the vesicle of the literature forms no fundamental part.

2. The functional unit is a lymphatic sinusoid, in which the epithelium floats enmeshed in a specific plexus of capillaries.

3. The secretion of the thyroid organ is produced and stored in a specific fashion: it is not the same as colloid.

4. Colloid matter is stored after another manner; it is possibly a vehicle for the carriage of some metabolite.

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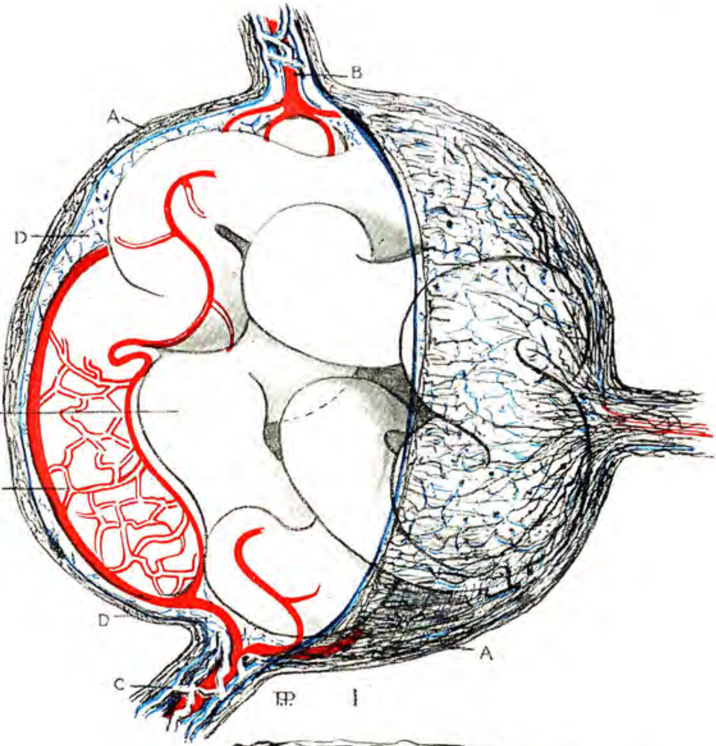
FIG. 1.—Diagrammatic representation of an isolated gland-unit of the thyroid organ.

(A) the fibro-elastic tissue capsule of the gland-unit penetrated by (B) the intralobular blood vessels and (C) the intralobular perivascular lymphatic plexus which expands to become the (D) serous cavity of the lymph-sinusoid, in which lies (E) the coiled and convoluted epithelium enmeshed in (F) the specific capillary plexus—an extension of the intralobular blood vessels (B).

FIG. 2.—Schematic presentation of a section of a gland-unit to illustrate particularly the blood vascular arrangements.

I. The anastamotic basketwork capillaries stretched between
H. the communicating capillaries arising from
G. the concomitant capillaries which run in the length of
E. the epithelial columns, seen in section lying in
D. the serous cavity of the lymphatic sinusoid which is an expansion of
C. the intralobular lymphatics emerging with
B. the intralobular blood vessels through
A. the fibro-elastic tissue capsule of the gland-unit.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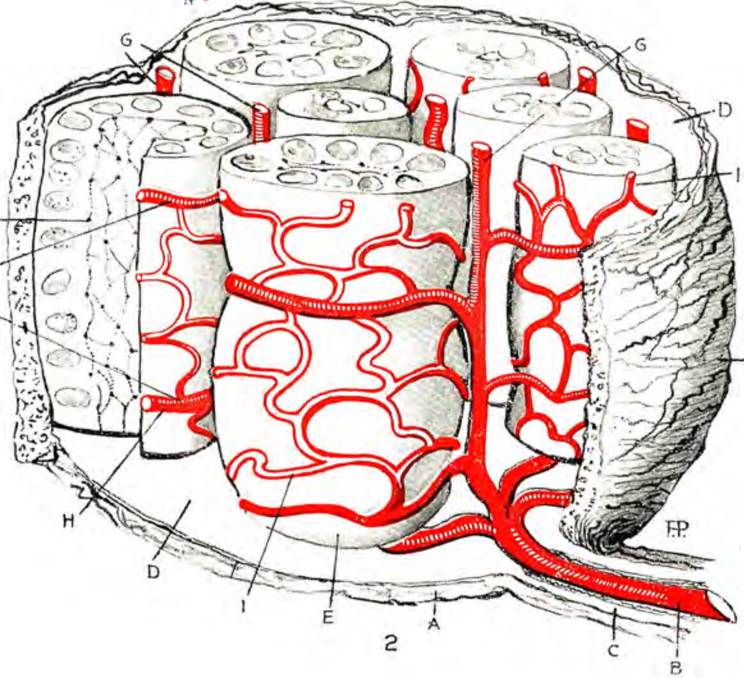
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FIG. 3.—Portion (mag. 100) of a lobule of the thyroid showing the fibro-elastic tissue septa forming the capsules of the gland-units.

a. The fibro-elastic tissue of the capsules.
b. The open sinusoidal space in which lie
c. the columns of epithelium.
d. The interlobular interstitial tissue.

The parenchyma is in the active secretory stage.

FIG. 4.—Showing a gland-unit containing both follicular and non-follicular tissue (mag. 250).

a. The capsule of the gland-unit.
b. The perivascular lymphatic channels.
c. Solid columns of epithelium in cross section.
d. Folliculate columns of epithelium in cross section.
e. Folliculate columns in partial longitudinal section.

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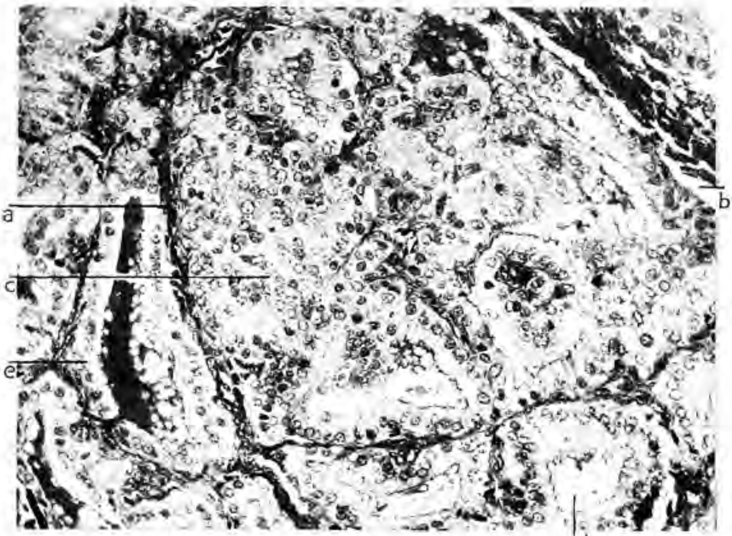

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FIG. 5.—Section (mag. 600) showing vesiculation; note the position of the nuclei; the clear placid cytoplasm; the sharp internal margin of the epithelium; the faint chromatism of the nuclei and tubular system. The endothelial cells are discrete and stain palely. Vesiculation in earlier stages can be seen in the surrounding epithelium.

a. Endothelial cells of capillaries.
b. Droplet of colloid in solid epithelium.

FIG. 6.—Microphotograph (mag. 200) showing stages in the process of vesiculation.

a. A long epithelial column between its concomitant vessels.
b. Droplet of colloid in a solid zone.
c. Vesicles of small size.
d. Vesicles of larger size already effecting the fragmentation of the column of epithelium.

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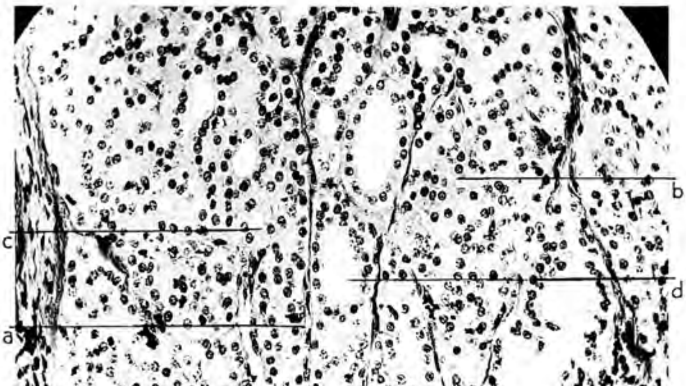

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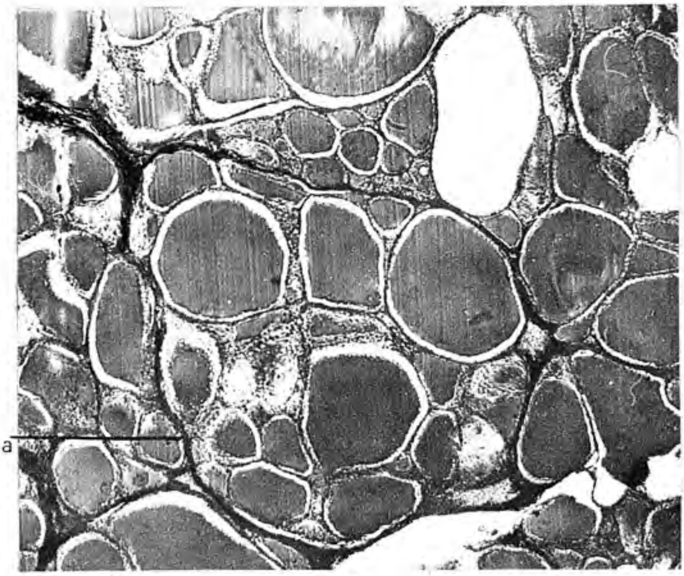
FIG. 7.—Section (mag. 70) shows the fibro-elastic tissue capsule (a) enclosing a gland-unit. The process of vesiculation obscures the internal structure of the gland-unit.

FIG. 8.—Microphotograph (mag. 750) showing the first departure from the indifferent phase in the long columns of epithelium.

a. A solid column with its tubules: the orientation of the nuclei is not yet completed.
b. Nuclei that have acquired an additional chromatism.
c. Coarse granules appearing in a column in which the mesh of the tubules is opening.
d. A column in cross section; identified by the centrally placed tubular system.
e. Endothelial cells of the concomitant capillaries.



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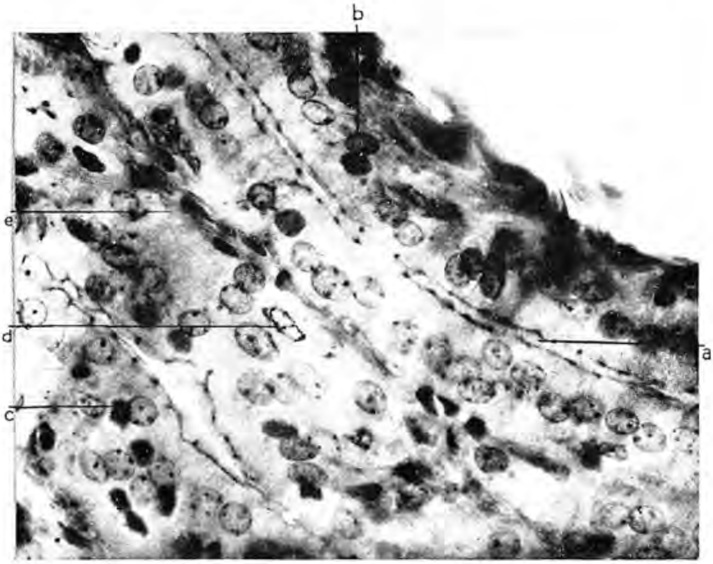

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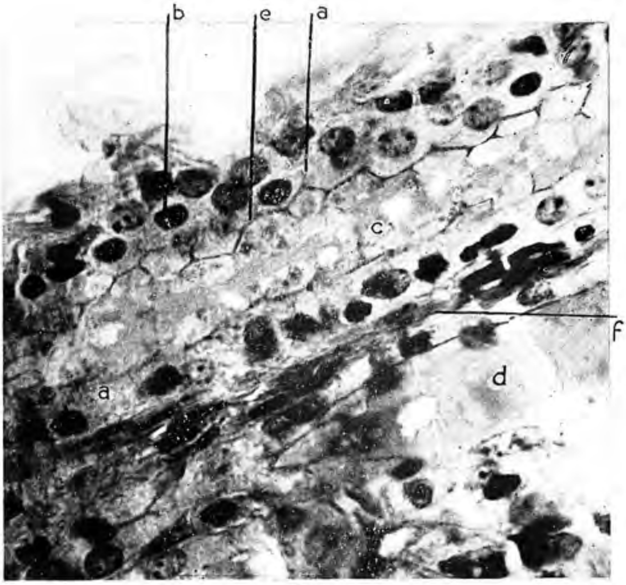
FIG. 9.—Section (mag. 750) shows a longitudinal section of an epithelial column in which lacunation has occurred throughout the length of the column. This is in strong contrast with the appearance brought about by vesiculation in a column (see fig. 6).

a. Granular condition of the protoplasm of the epithelial column.
b. Dense granular chromatic nuclei.
c. Early stage of lacunar accumulation of secretion.
d. A later stage of the same in an adjacent column.
e. Tubular system.
f. Endothelium of capillaries.

FIG. 10.—Microphotograph (mag. 1200) of a cross section of an epithelial column showing the very granular chromatic nature of the protoplasm and nuclei at the inception of the secretory process.

a. The tubular system containing granular fluid, particularly in
b. a radial branch of the same.
c. The central lake of secretion containing a vacuole.
d. Endothelium of the capillaries.



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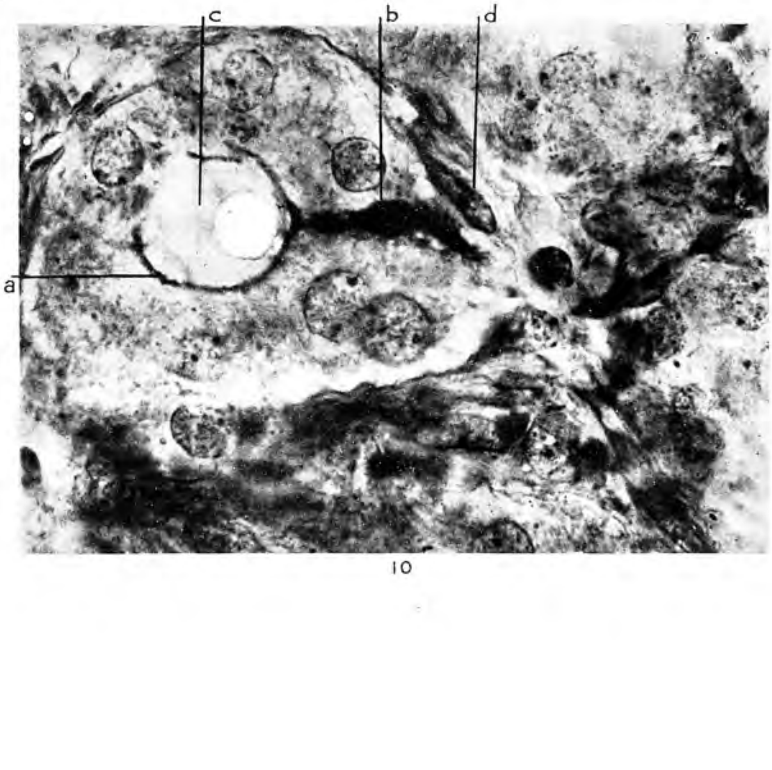

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FIG. 11.—Microphotograph (mag. 1000) of cross section of an epithelial column in secretory activity.

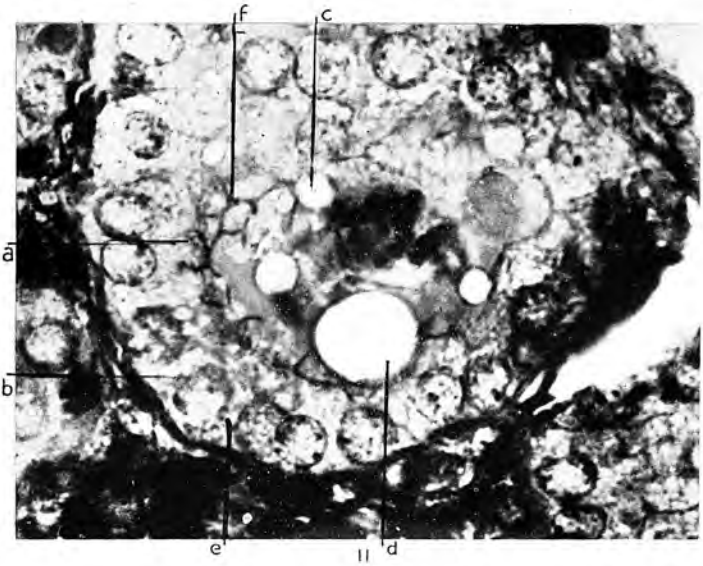
a. Protoplasm containing fine granules and many small
b. vacuoles extending between the nuclei to the periphery.
c. Vacuoles of fluid migrating to the central zone.
d. A large vacuole the result of fusion of many.
e. Coarse granules which ultimately disappear as vacuolation increases.
f. The tubular system. The broken appearance is due to the contained granules.

FIG. 12.—Section (mag. 250) to illustrate the great diversity in the ultimate shape of the lacunæ in the secretory process.

a. A lacunate follicle simulating a vesicle.
b. Irregular-shaped lacuna.
c. Vacuolated solid columns.
d. A solid form not yet differentiated by the process.

Note the broken margins of the lacunæ and the dense staining of the tubules and at

e. the endothelial cells of the capillaries.



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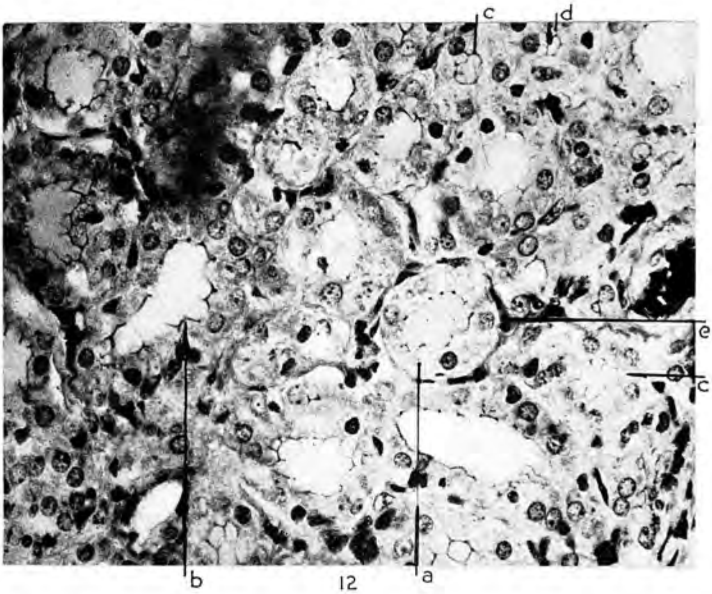

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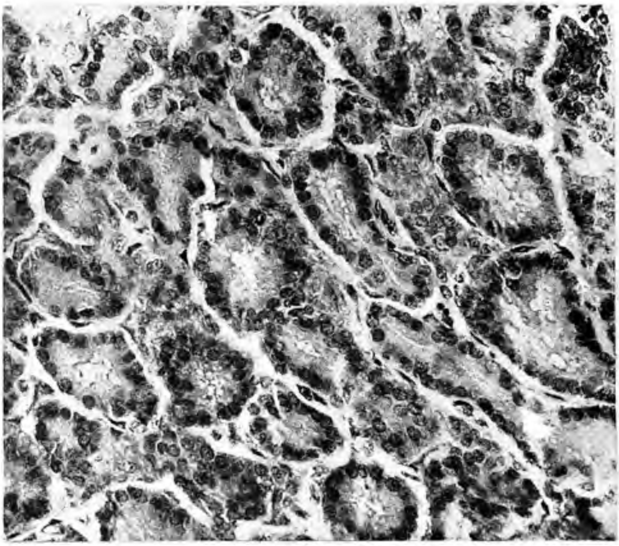
FIG. 13.—Section of the thyroid gland at the inception of secretory activity. Note the open sinusoid in which the isolated capillaries are seen; the extreme peripheral position and varied chromatism of the nuclei; the granular chromatic cytoplasm; the absence of any definite boundary between the central material and the cytoplasmic mass; the diffuse vacuolation of the mass; and the irregular shapes of the cross sections of the epithelium. Contrast this with fig. 6.

FIG. 14.—Section (mag. 750) showing the epithelial units (a), lying in the sinusoidal space (b). A fluid bathes the epithelial units, and isolates the capillaries, the endothelial cells of which (c) closely resemble the Kupffer cells of the liver.



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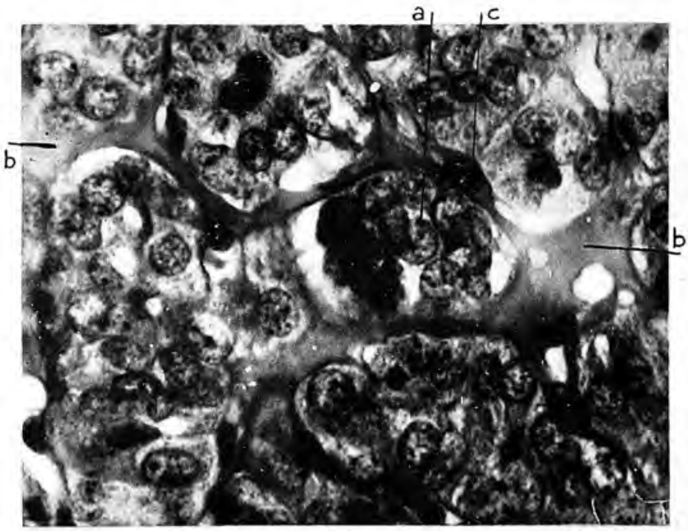

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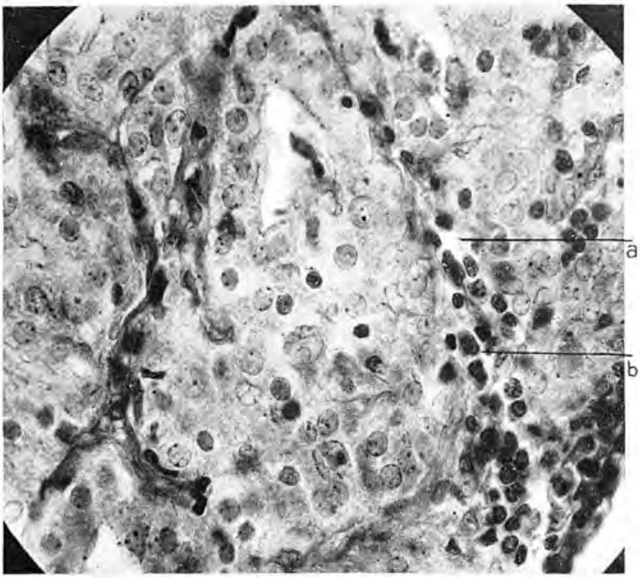
Fig. 15.—Section of a portion of a gland-unit (mag. 500) at the inception of the secretory phase, showing the lymphocytic and endothelial activity.

a. An open sinusoidal space containing
b. lymphocytes and endothelial cells.

Fig. 16.—Cross section (mag. 500) of a gland-unit in which the epithelium encloses one large lacuna.

a. Capsule of the gland-unit.
b. Capillaries of the gland-unit bunched together producing
c. papillate projections of epithelium in to the lake of secretion.



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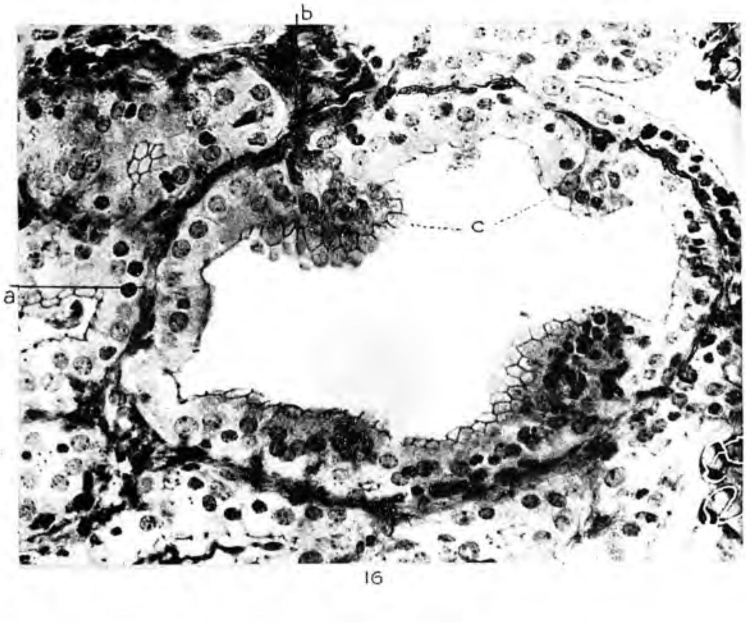

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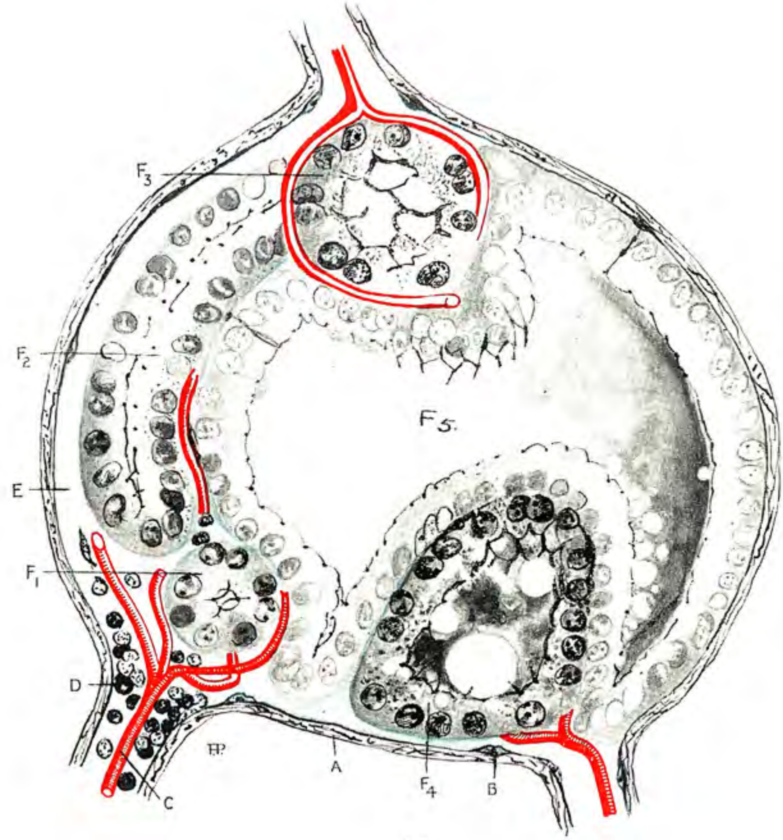
FIG. 17.—Composite diagram to illustrate the progress of secretory activity in the gland-unit.

A. The fibrous capsule of the gland-unit lined by
B. endothelium in a state of activity.
C. The intralobular vessel at the hilus of the gland-unit surrounded by
D. lymphocytes lying in
E. fluid which bathes
F. the epithelial columns seen in cross and longitudinal section.
F1. The solid stage with fine granules in the protoplasm and nuclei at the periphery.
F2. The same in longitudinal section.
F3. The coarsely granular stage with early vacuolation and a distended tubular system.
F4. A further stage with advanced vacuolation, already fusing to form the lake.
F5. Complete lacunation with loss of the coarser granules.



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APPENDIX 2

7h. Sect.

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THE THYROID APPARATUS IN MAN.*

BY G. SCOTT WILLIAMSON, *M.C.*, M.B., CH.B. EDIN.

(*From the Department of Pathology, Royal Free Hospital, London.*)

THE first application of the recently published work on the structure and physiology of the thyroid gland is to review the integration of the various organs associated with the thyroid gland function. Launoy [1] has very completely reviewed the facts in favour of considering the thymus, thyroid, and parathyroid, not merely as associated structures, but as one functional apparatus. Critical examination of material from 2000 post-mortems affords considerable substantiation of the point and perhaps affords a guide to the specific function of the apparatus.

Anatomical Features of the Thyroid Apparatus.

The Thyroid Organ.—The thyroid organ consists of two compact lateral lobes. The upper pole of each lobe is marked off by a constriction below which lies the bulk of the lobe. Immediately below this constriction a band of thyroid tissue projects across the middle line from each lobe to form an isthmus, or from each side it extends up the neck along the line of the thyro-glossal duct to form a pyramidal lobe or lobes. The lobes of the gland have no capsule proper; they lie in a special compartment of the fascia of the neck. This fascial compartment is usually shut off from the mediastinum on each side by a fibrous tissue diaphragm. Each lobe has a hilus, where the loose fascia dips into the gland substance to become the interstitial tissue of the organ. The hilus lies posteriorly on the mesial surface of each lobe under cover of the base of the isthmus or pyramidal lobe. The large inferior thyroid artery enters the lobe at the lower end of the hilus, and the smaller superior thyroid artery at the upper end, these arteries are usually united by a communicating vessel that occupies the length of the hilus. Only small venæ comites emerge from the lobe at the hilus. The veins and lymphatics emerge at the surface of the lobes and unite in the loose fascia to form a plexus

* Assisted by a grant from the Medical Research Council.

of veins and lymphatics which is continuous in the fascial compartment with a similar plexus from the thymus. The vascular supply within the lobes is characterised by a considerable capillary anastomosis between arteries and veins in the interstitial tissue of the lobe, providing, as it were, a short circuit, before the very specialised capillaries of the functional unit are given off. (Kidney and liver present a similar arrangement.) Certain anomalies in the gross anatomy must be noted. Accessory lobes are a frequent occurrence, most commonly at the lower pole of the lobe. An accessory lobe may lie in the mediastinum beyond the fibrous diaphragm. The upper pole may constitute one of these accessory lobes. The compact gland may give place to a multilobar gland, the small independent lobes being scattered in the fascial plane from the hyoid bone to the root of the great vessels in the mediastinum, there being no fibrous tissue diaphragm separating the thyroid and thymus tissue. The isthmic tissue may be absent on one or both sides. The arteries are the subject of great variation. The superior artery may be the larger or the only vessel, or may be absent. Very frequently both arteries break up on entering the fascial compartment into numerous branches, which enter the hilus independently, so that neither superior nor inferior thyroid can be recognised in the hilus. (Fig. 1.)

Microscopic Anatomy of Thyroid.[2]—The lobes of the thyroid organ are divided up by interstitial tissue septæ into lobules. The lobules consist of a collection of gland units having a specific structure. Each gland unit is enclosed in a fibro-elastic tissue capsule, giving support to the endothelium of a lymphatic sinusoid, which is an expansion of the intralobular lymphatics. Within the sinusoid lie coiled columns of epithelium. The columns of epithelium are surrounded by a peculiar ladder-like plexus of capillaries, their walls of endothelium are unsupported by any fibrous tissue. These capillaries emerge at two or three points, penetrate the endothelium of the sinusoid, and become the intralobular vessels—artery and vein being indistinguishable within the limit of the lobule.

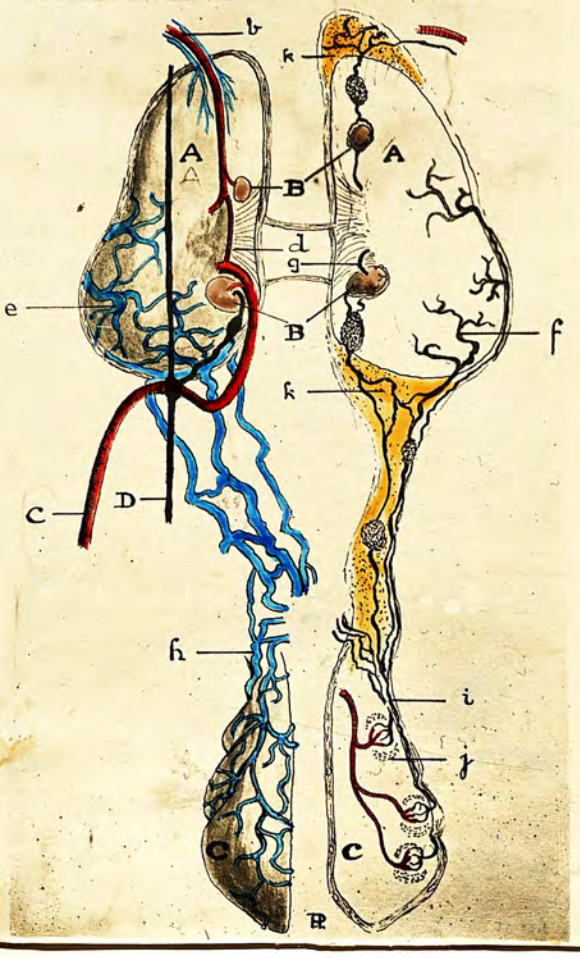
Thyroid Epithelium.—The appearances presented by this epithelium will vary with the phase of physiological activity. The architecture of the epithelium is seen only in the indifferent phase. In this phase the epithelium, seen in section, corresponds to the "interfollicular tissue" of the literature, about which controversy has raged. The existence of a system of micro-capillaries in the substance of the epithelial column [3] serves to distinguish it from parathyroid tissue and to identify it with the general body of the gland in the other phases of activity. In this phase the column of epithelium seems solid. The central zone of the column is demarcated by the system of micro-capillaries. The central core of the zone contains a homogeneous protoplasm continuous through the mesh of the micro-capillary system with the protoplasm of the periphery. The nuclei lie in a central position near the closed mesh of the micro-capillary system. The epithelium has all the appearance of a syncytium, and contains no colloid, no secretion, and there is no granular matter in its protoplasm. The opaque areas to which particular attention has been called[3] may be made up of epithelium in this phase.

Parathyroid Bodies.—The parathyroid bodies, two in number, lie at the upper and lower ends of the hilus in each lobe, in close association with the superior and inferior thyroid arteries. They are bean-shaped bodies, having a soft, almost diffluent consistency. In the cadaver they are pigmented bodies often indistinguishable from the pigmented fat in which they lie. In life, neither the pigment nor the fat with which they are associated is obvious. They are not to be confused with the special lymphatic glands that also constantly occupy the region of the hilus. Each parathyroid body draws its arterial supply from the associated thyroid artery. The venous return drains into a specially large vein, which joins the plexus on the surface of the thyroid gland. A considerable branch from the sympathetic is lost in the substance of each parathyróid body. Anomalies in the structure and distribution of the parathyroid bodies are common; there is, however, a definite relation between them and certain anomalies already noted in the thyroid. They each vary in size with similar variations in the size of their associated superior and inferior arteries. When there is only one artery entering the hilus of the lobe, there is only one parathyroid body, proportionately larger in size. When the arteries break up and enter the thyroid gland as independent twigs, there is no macroscopic evidence of a formed parathyroid body; microscopically, the tissue is spread out over the extent of the hilus. In the multilobar state of the thyroid no parathyroid tissue is to be found. When there is a single large parathyroid, the branch from the sympathetic trunk is a very obvious macroscopic structure, and is seen to end in the substance of the large body.

Microscopic Anatomy of Parathyroid Bodies.—The parathyroid bodies are composed of a series of systems of tubes. The tubes usually appear as columns of cells

FIG. 1.—Schematic drawing of the thyroid apparatus.

thyroid gland: (a) hilus, (b) superior thyroid artery with parathyroid branch, (c) inferior thyroid with branch to parathyroid body, (d) intercommunicating artery, (e) capsular veins, (f) capsular lymphatic plexus.
B, parathyroid bodies: (g) ancillary lymphatic.
C, thymus: (h) venous plexus, (i) afferent lymph channels, (j) thymic lymph nodes, (k) superior and inferior (thymic) lymph-fat-gland bodies.
D, sympathetic trunk with parathyroid branch.



generally cubical in shape. The first part of their course is more or less radial. Centrally, they are coiled and convoluted, and when empty their appearance

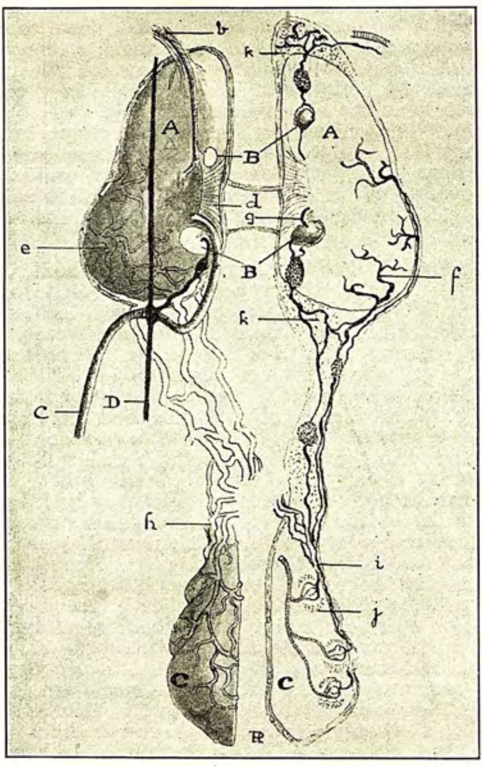


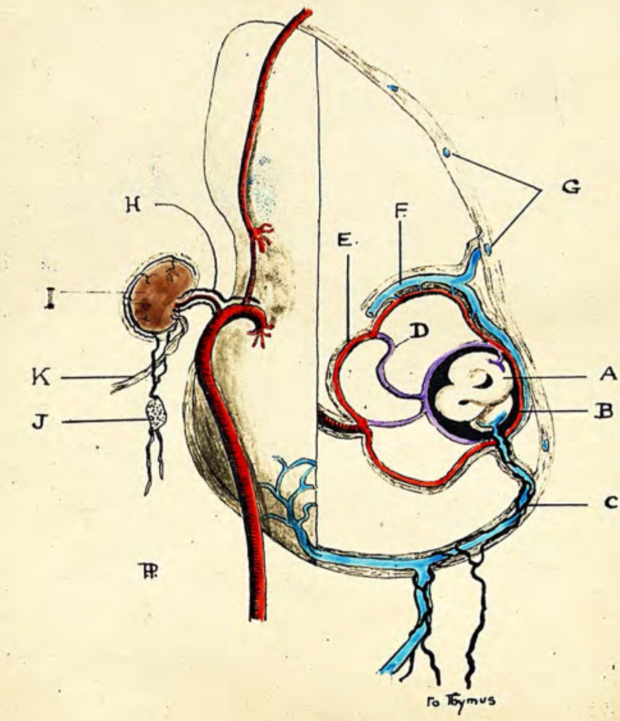
FIG. 1.—Schematic drawing of the thyroid apparatus.

A, thyroid gland: (a) hilus, (b) superior thyroid artery with parathyroid branch, (c) inferior thyroid with branch to parathyroid body, (d) intercommunicating artery, (e) capsular veins, (f) capsular lymphatic plexus.
B, parathyroid bodies: (g) ancillary lymphatic.
C, thymus: (h) venous plexus, (i) afferent lymph channels, (j) thymic lymph nodes, (k) superior and inferior (thymic) lymph-fat-gland bodies.
D, sympathetic trunk with parathyroid branch.

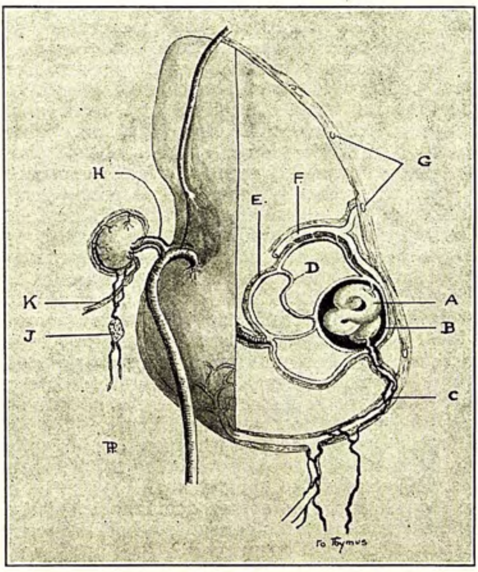
suggests a sponge work. Fibrous tissue accompanies the radial portion of the tubes, but only the capillaries penetrate to the central spongy zone. The lining cells

FIG. 2.—Schematic drawing of thyroid mechanism showing its connexions.

A, epithelial unit lying in B, the lymph sinusoid, draining into C, capsular lymphatics; D, arterio-venous vascular supply arising from E, interlobular artery which communicates with F, the interlobular vein, which empties into G, the capsular plexus; H, ancillary lymph channels emerging from the hilus to enter I, the parathyroid body from which they emerge and enter J, lymph-fat-gland tissue (? thymus); K, branch from sympathetic.



of the tubes are subtended by a reticulum of large granular polygonal cells. Nerve fibres run in this reticulum. Granules of refractile, yellow-brown pigment occupy the clear cytoplasm of the cells lining the tube; this is more abundant, as a rule, in the radial portion of the tube. Certain anomalies are of interest. The body may be divided up by fibrous



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tissue septæ, so that there is no discernible spongy centre, each member of the series of systems of tubes being more or less a separate entity. Frequently the systems that compose the body occur scattered independently through the fatty tissue in the hilus of the gland, the compact nature of the body being lost; this occurs when the thyroid arteries enter the hilus as a congerie of branches. The degree of scattering that occurs in the multilobar thyroid may explain the inability to find parathyroid tissue.

The Thymus.—The thymus lies in a special fascial compartment in the mediastinum, separated from the thyroid compartment by a fibrous diaphragm. It is composed of two leaves of tissue, each with a central branched stalk of fibrous tissue. In the fibrous tissue stalk and its branches run numerous arteries which end as glomerular tufts. About the glomerular tufts lie the reticulum cells of the thymus tissue. The blood leaves the gland at its surface by numerous veins which join the venous plexus of the thyroid gland. Large lymphatics run with the veins and form a plexus continuous with that of the thyroid gland. There are numerous lymphatic glands at the root of the neck within the thyroid-thymus fascial compartment associated with this plexus. In a generalised pigmentation of the deep and superficial cervical, the mediastinal and bronchial lymph glands, this system of lymphatic vessels and glands escapes pigmentation; it is, in fact, peculiar to the thyroid and thymus. The characteristic Hassall corpuscles lie in the fibrous tissue stalk or in its branches; they seem unconnected with the thymic reticulum, and are the only vestigial tissue in the thymus. Thymic tissue proper does not atrophy, but undergoes a very characteristic metatrophy. The lymph glands and fat in the hilus of the thyroid lobe present certain peculiarities. The lymph gland has no capsule, so that its reticulum is apparently continuous with that of the reticular mesh containing the fat. The colour of the fat varies with the colour of the thymic fat. As a rare occurrence this lymph-fat-gland tissue contains concentric bodies having the characters of Hassall corpuscles. This applies also to other lymph-fat-gland tissue encountered at the upper and lower pole of the thyroid lobe, each of them being constant structures. These appear to be part of the special lymphatic system more or less peculiar to the thyroid apparatus. This is often very strikingly brought out, in cases where the whole of the lymph glands of the neck, deep and superficial, are deeply stained with carbon-pigment. The glands of the thyroid apparatus remain as definite flesh-coloured structures devoid of pigment. This also applies to the thymic lymph-fat-gland tissue. The writer is of the opinion that these lymph-fat-gland bodies are essentially thymus tissue.

Anomalies.—The fibrous tissue diaphragm is commonly drawn up as a funicular extension attached to the lower pole of the thyroid lobe; in this lie the lymphatic plexus and lymph glands. The fascial compartment of the thymus is very frequently common to thymus and thyroid. Thymus tissue may be encountered anywhere within the compass of distribution of thyroid tissue in its anomalies. That applies not only to the endothelioid element but to the Hassall corpuscle element. In the multilobar form of thyroid the thymus and thyroid are inextricably mixed up. We have encountered an entire absence of medastinal thymus with hypertrophy of the neck nodes. The branches of the fibrous stalk may penetrate to the surface of the gland and isolate each glomerulo-reticular zone, resulting in the thymus appearing as a collection of discrete units not unlike a bunch of grapes. (Fig. 2.)

Physiological Features of the Thyroid Apparatus.

The architecture of the thyroid apparatus, as set out above, is modified in quite definite directions by the furniture of physiological occupation. In the thyroid gland two cycles of operation present themselves: (1) a secretory phase; (2) a vesicular colloid phase. Neither can change over to the other without passing through the indifferent phase already noted.

The Secretory Phase in the Thyroid Gland.—This is an active process in which the epithelium, the sinusoid, and all the endothelium of the gland units participate. In all its stages it gives the opaque appearance on macroscopic inspection that is also a feature of the indifferent phase. The details of this process of secretion are set forth in the original communication, from which the following summary is taken. The sequence of events is: (1) the opening up of the potential space of the lymphatic sinusoid by fluid matter; (2) a change in the endothelial cells lining the sinusoid associated with which lymphocytes appear in the intralobular lymph channels, and frequently also in the sinusoidal space; (3) swelling of the epithelium, migration of the nuclei to the extreme periphery, and the appearance of two orders of granules; (4) vacuolation of the protoplasm and partial solution of the granular matter in the fluid of the vacuoles; (5) lacunation of the epithelium by the accumulation of the contents of the vacuoles in the central core of the column of epithelium; (6) the tubules in the protoplasm of the epithelium appear to swell and conduct granular fluid; the radial branches become quite turgid.

Changes in the parathyroid bodies are definitely related to the nature and quantity of the secretory phase in the thyroid gland. The commonest condition is associated with the presence of fluid matter in the sinusoids of the thyroid gland during the course of secretory activity. The fluid matter (not colloid) can be traced directly to the tubes of the parathyroid bodies, giving to these structures a pseudo-vesicular appearance which has led to the confusing of thyroid and parathyroid tissue. One other feature of active secretion, more particularly associated with its lacunar phase, is the aggregation of lymphocytes in the sinusoids and lymphatic channels. These also overflow into the parathyroid bodies—so much so that they can completely obscure the architecture of the bodies. The lymphocytes are found, not only in the lumen of the tubes, but also in the inter-tubal tissue among the polygonal cells. These changes are proportionate to the amount of activity in the thyroid gland. The secretory activity of the thyroid gland is as intimately associated with changes in the thymus. Any increase in the secretory activity is invariably associated with an increase in the quantity of the lymphocytic element in the thymus; any decrease is associated with fat accumulation at the expense of lymphocytes. In favourable cases the fluid which we have seen in the sinusoid during activity in the thyroid gland can be traced, almost in continuity, to the lymph channels in the surface of the organ, and from thence through the plexus to the thymus. Little pools of this fluid are often found in the thymus tissue. Active changes in the endothelial element of the thymus are associated with the accumulation of lymphocytes in the tissue. It is possible to gauge the stage of secretory activity in the thyroid by studying the relation of lymphocytic accumulation in the thymus and in normal individuals the reverse is also true (this last does not hold in certain pathological states). As the lymphocytic change appears, the stored fat disappears, and there is evidence that the fat is actually used in the making of the lymphocytes—the change in the thymus from a fat to a lymphoid organ is, in fact, a metatrophy and not an atrophy, and it is the prevalence of secretory activity in the thyroid gland which determines this in health. The secretory phase in the thyroid gland is a most variable quantity. In fœtal life it is present to some degree in the midst of the indifferent tissue. In infancy it definitely increases in amount and continues to do so to about 9 years of age, and from that age remains stationary in quantity up to puberty; after puberty it increases, but not in any degree of disproportion, since the whole gland hypertrophies in a balanced manner—secretory, vesicular, and indifferent tissue in mutual relationship; after 18 to 20 years it diminishes in amount and colloid increases in amount. It cannot be sufficiently emphasised, however, that this age variation in the quantity of secretory activity is large, and difficult to estimate because each individual seems to be a law unto himself as regards the degree to which he depends on secretory activity of the gland. Further, it is very probable that each individual has seasonal as well as decadal variations. Nevertheless, the above facts stand out in an analysis of 2000 cases with considerable emphasis.

Response of Thyroid Apparatus to Age Variations.

The whole apparatus responds to these variations: thus the thymus would begin as a mixture of fat and lymphoid in the fœtus, and gradually acquire more lymphoid element at the expense of the fat up to 9 to 10 years, thereafter remaining stationary to puberty. With the hypertrophy of the thyroid and the consequent increase of secretory activity the lymphoid element would increase and the fat disappear, but without any actual increase in the bulk of the organ. When, on the other hand, the individual shows little increase in secretory activity and much colloid storage, the fat tends to d sappear as well as the lymphoid tissue. At 18 to 20, when the thyroid is set as a nearly pure colloid storage, again fat perceptibly increases in the thymus, and this increase again is more related to the extent of the decrease in secretory activity than to the actual colloid storage.

In general disease, I am of opinion that the variations seen are no greater than those encountered in health. Rupert Farrant's [4] study of the thyroid gland in acute specific fevers becomes therefore a description of the very protean nature of the gland encountered in children of the fever age. Certain specific diseases still further emphasise this relationship of thyroid and thymus. Secretory activity is linked up to the lymphoid states, such as acute lymphatic leukæmia (in children), myasthenia gravis, certain intestinal lymphoid hypertrophies extraordinarily common in infants and children, either generalised in lymph-nodes or focal, as at the appendix and pyloric antrum, and in persistent thymus and status lymphaticus. In all these states a pathological degree of secretory activity is evident in the thyroid gland.

In other conditions in which the thyroid gland shows secretory activity—as in eclampsia, status epilepticus, rickets, and the adenoid state in children—the lymphatic tissue, including the tonsils and lymphatic glands, shows a loss, often complete, of any lymphocytic activity. The thymus in these states is a simple endothelioid organ without fat and without lymphocytes—exhaustion best describes the condition. In a few cases of diabetes this condition of affairs also prevails. It is only necessary to recall the fact that a considerable school of observers look upon exophthalmic goitre as a thymic disease to emphasise the inter-relation of these two organs in that heterotrophic state in the thyroid gland.

Vesicular Colloid Phase in the Thyroid Gland.—The summary of this phase is taken from the original paper, and is as follows: (1) Vesiculation occurs in definite areas of the epithelial columns of the gland-unit; (2) vesiculation leads to the fragmentation of the columns into discrete spheroidal vesicles; (3) vesiculation is not accompanied by any demonstrable biochemical disturbance of the nuclei or protoplasm of the epithelium; (4) the gland-unit passively suffers distension and distortion to the extent of losing its identity under the process.

In the normal individual stored colloid varies inversely with the secretory activity in the gland up to a point. This is not invariably so, for in marasmus colloid disappears without any increase in secretory activity—i.e., there is a reversal towards the fœtal state in the gland. Thymic fat does not necessarily disappear in these conditions, but there is no increase in the lymphoid element. Even in children and young adults, vesicular goitre is associated with a fat-laden thymus, and this may have some specific significance. For the rest, stored colloid is almost a measure of thyroid inactivity, but so long as metabolism has a maintenance value secretory activity does not follow colloid depletion.

Conclusions.

The thyroid gland, the parathyroid bodies, and the thymus are intimately related anatomically, physiologically, and pathologically. They constitute an apparatus probably engaged in the conduct of some specific function. The thyroid gland is the main organ. The parathyroid is a sentinel gland of neuro-lymphatic nature, set in the course of the effluent, probably engaged in measuring the efficiency of the thyroid gland, and through the sympathetic nervous system adjusting its operation to the needs of the body. In the experience of the writer, certain pathological conditions of the kidney—or renal apparatus—indicate a similar relationship between the kidney and suprarenal body—the term neurotrodal gland would indicate the significance of such structures on the analogy of the electrode.

The thymus is a reservoir for the effluent—which, according to its nature is stored either as fat or in the lymphocytes. This must not be taken to imply a movement of lymphocytes into the blood or lymph; the probability is that they are manufactured in situ, and absorbed in situ. (See also Cramer's work on the possible significance of the blood platelets.[5])

The fact that colloid usually disappears to give place to any secretory activity, and the fact that it need not be so associated as in marasmus and in early fœtal active glands, make it probable that the colloid is exercising some vehicular function analogous to some of the constituents of bile. It is only passively concerned in the operation of the thyroid apparatus.

The most important feature of these conclusions is the implication of the lymphocytes in the operation of the thyroid apparatus. It presents the most promising line of investigating the function of this apparatus. Indeed, I approached the whole problem from a study of the inter-relation of purin-creatin and amino-acid nitrogen in intestinal disease of children, and was led from that to the heterotrophic lymphoid conditions, local and general, and through them to the thyroid gland.

Certain preliminary chemical studies—more particularly directed to the problem of the ætiology of gastric ulcer [6] and appendicitis—fix upon nitrogen carriage as the significant function of the lymphocyte, and this from the point of view not so much of total nitrogen as of the nature of the nitrogen (nucleo-protein, purin, amino-acid, peptide), so that the writer is working on the hypothesis that the thyroid apparatus is primarily concerned in controlling the direction of protein synthesis within the body—making it either a synthesis of plastic nitrogen, or trophic nitrogen, as the case may demand, the thymus being the reserve store of such nitrogen. Even the fat phase in the thymus yields nitrogen values for the tissue that are significant. Jackson[7] has already published observations which implicate secretory activity in the thyroid with protein metabolism, and Noel Paton's work,[8] looked at from a point of view not so exclusively endocrine, would have the same significance if lymphocytes, being the nitrogen carriers, varied their nitrogen partition from purin to non-purin according to need. Cramer's[9] work, and that of Cramer, Drew, and Mottram[10] on the lymphocyte, may have a similar significance.

Experimental work in this direction will further demand that some note be taken of the excretion of nitrogen other than the end-products of completed katabolism. This probably takes place through the gonads, making them, as it were, the kidneys of the plastic phase of metabolism, through which are excreted the end-products of completed anabolism. Protein metabolism (perhaps all metabolism) being a completely reversible chemical reaction, katabolism at the one end and anabolism at the other end, each implying complete catathesis of the substrate, the excreted end-products differing with the *direction* of the reaction.

A consideration of the significance of the conclusions in experimental ablation of the various parts of the thyroid apparatus is necessary. Clearly the effect of ablation may depend largely upon the relation of the individual to the secretory activity of the thyroid. This is the most variable feature of the gland. Thus it becomes necessary to postulate that in any experiments of that nature it will be necessary to reduce the individual to a definite dependency on secretory activity in the thyroid gland. Jackson and Mellanby's [11] work points to a means of achieving this, so that it may become possible to reconcile the contradictions which are the only striking results to date from experiments of this nature. The same criticism applies to the various thyroid extracts. Any extract of an average normal gland will largely consist of colloid extractives plus any constant peculiar to thyroid tissue, and the most variable quantity of traces of an active secretion. Here, also, it will be necessary to consider the thyroid gland as a resting organ in the indifferent phase, as a colloid storage organ, and as a secretory gland, and each of these in the lymphoid, fat, and exhausted stage of the thymic store, before we can hope to solve the problem of any autocoid activity the apparatus may possess.

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M.D. Thesis. The goitrous conditions of the thyroid gland.

APPENDIX 3

A SYSTEM OF TUBULES IN SECRETING EPITHELIA

BY

GEO. SCOTT WILLIAMSON, M.C.

AND

INNES H. PEARSE

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A SYSTEM OF TUBULES IN SECRETING EPITHELIA[1]

PRELIMINARY NOTE

BY GEO. SCOTT WILLIAMSON, M.C.
AND
INNES H. PEARSE.

From the Pathological Department of the London (Royal Free Hospital) School of Medicine for Women

THE purpose of this note is to call attention to the existence of a new structure distributed through the parenchyma of certain secreting epithelia. The structure consists of an extensive system of minute tubules linked together in the form of a network, which is stretched beneath the free surface of the epithelia.

It is here described in the secreting epithelium of the thyroid gland, because it occurs as a peculiarly isolated structure in the parenchyma of this gland. It must, however, be understood that the general description given is equally applicable to the structure as it occurs in other secreting epithelia—certain portions of the kidney tubules, bile ducts, etc.—though in these cases and in others its relationships are complicated by the existence of factors not present in the thyroid gland.

The local distribution of the system in the human body, and its comparative anatomy, have not yet been worked out.

The successful demonstration of the structure depends largely on the employment of a special technique detailed in this paper. It is essential to use for examination fresh tissue soon after removal from the body: post-mortem changes are peculiarly apt to disintegrate the structures.

HISTOLOGICAL TECHNIQUE

This is essentially an elaboration of the Zenker and phosphotungstic-acid-haematoxylin method devised by Mallory for neuroglia and fibroglia fibrils. The modification introduced is the use of a special fixing agent, which at the same time as fixing, appears to have a mordanting action on the impregnated tissues. This fixing and hardening mordant—for convenience termed F.B.C. fluid—is made as follows:—

Potassium bichromate, 40 grms.; chromium fluoride (fluorchrom), 40 grms.; distilled water, 2000 c.c. To dissolve, boil for half an hour; cool thoroughly and filter. To the filtrate add: corrosive sublimate, 100 grms. To dissolve, boil for half an hour; cool thoroughly and filter.

Pieces of tissue, not exceeding 3 mm. thick are thoroughly fixed, hardened and mordanted in 12 hours. It is necessary to wash in running water for not less than 12 hours before the tissue is taken on to paraffin, celloidin or gum.

[1] The expenses of this research were in part defrayed by a Grant from the Medical Research Council.

If the fluid is used as a simple mordant after formalin, alcohol or osmic acid, etc., washing is essential before immersion. It should be noted, however, that acetic acid, formic acid and other agents generally credited with augmenting penetration are inimical to the effect of this mordant.

The staining process used in this laboratory differs only in slight details from that used by Mallory[1] and is as follows:—

1. Xylol: absolute alcohol.

2. ½ per cent. alcoholic iodine: 10 minutes to remove the mercurial precipitate. (It seems to possess some other virtue than this and is essential to the process.)

3. 95 per cent. alcohol: ½ hour.

4. Clean alcohol: water.

5. ¼ per cent. aqueous solution of potassium permanganate, 10 minutes: water.

6. 5 per cent. aqueous solution of oxalic acid until just decolorised.

7. Running water, 10 minutes.

8. Phosphotungstic-acid-haematoxylin, 15–24 hours.

After this staining process the section should very rapidly be washed in alcohol, cleared in xylol, and mounted in xylol-balsam or other medium.

The polychromatic differentiation so obtained of the various structures in the tissue is remarkable in daylight, but ordinary artificial light cannot be used. The differentiation in tone, however, is clearly visible with light of wave length 5100–6200 A.U. (Wratten "M" screens B and C).

The staining technique is worthy of very general adoption, since it gives a high degree of differentiation of tissue, but in this note attention is confined to the intraparenchymatous tubular system which it has revealed. The stain has no keeping qualities.

We have to acknowledge our indebtedness to Miss H. M. Cunnington, B.Sc. for her valuable assistance in elaborating this technique.

THE SYSTEM OF TUBULES IN THE THYROID GLAND

The secreting epithelium of the thyroid gland appears as the lining epithelium of its characteristic follicles. The epithelium is described as both cubical and columnar, or, in other words, there is a variable depth of coarse cytoplasm, between the peripherally disposed nuclei and the contents of the follicle.

In a segmental section of the follicles this zone of cytoplasm contains short rods and dots of darkly stained material, having the appearance of a fence between the nuclei and the colloid substance within the vesicle (fig. 2). These rods and dots may alternate regularly, but more often the line of the fence is broken. This fence of rods and dots is separated from the contents of the follicle by a layer of cytoplasm which is always present no matter what the degree of distension of the follicle.

[1] Mallory and Wright, *Pathological Technique*, 7th edition, 1918, p. 149.

Follicles may be cut in such a way as to leave a roof of cytoplasm only over the colloid, or, on the other hand so as to permit a floor of epithelium to come into view through a thin layer of colloid. Under these circumstances the rods are seen to be the boundaries of the open mesh of a network, and the dots to be nodes formed by the junction of these rods. The mesh so formed is roughly polygonal.

It is apparent, particularly in thick sections, that the network occupies a plane of its own distinct from the plane of the nuclei. Occasionally the plane of section passes between the nuclei and the tubules, leaving the network exposed, and showing the mesh filled with granular cytoplasm.

The parenchyma of the thyroid gland is not infrequently devoid of vesicles, as is the case in the foetal gland, and in many areas of normal thyroid glands. In this absence of vesiculated colloid, the central zone of cytoplasm of the follicle is occupied by the system of tubules (fig. 3). When such a follicle is

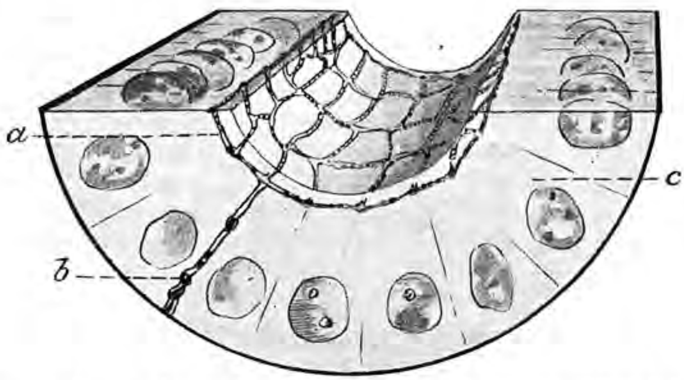

Fig. 1. Schematic drawing of a secreting epithelium showing the position of the tubular network: (*a*) tubular network; (*b*) very occasional radial branch; (*c*) cytomitome.

cut in length the system has the appearance of a loosely hanging seine, the mesh of which is partially collapsed. In cross-section of such a follicle the system appears in the central zone of the cytoplasm as a ring or rings of chromatic material. Occasionally a nodal point suggests a signet ring. Where two or more rings appear, as may be the case, they are obviously linked together and occupy different planes in the depths of the section.

From this condition of extreme collapse to the fully extended condition of the mesh in the vesicular follicle, every degree of stretching can be seen. Whatever the degree of stretching or collapse, however, the system of tubules occupies that precise position in the cytoplasm that has already been made out in the vesicular gland; that is to say wherever there is contained material in the gland parenchyma, this system of tubes subtends it, but is always separated from it by a layer of cytoplasm (fig. 1).

The system extends over a wide area of epithelium; it is not a structure pertaining to a single cell, but has a continuity in the parenchyma limited rather by the area of a functional unit than a cellular one.

Emphasis has been laid on the fact that this system of tubules occupies in the cytoplasm, a specific plane orientated about the centre of the follicle. On rare occasions, a section will reveal a branch running radially from the network towards the base of the epithelium (figs. 1, 3). Such branches are always solitary, very infrequent and usually larger in calibre than the tubes enclosing the mesh of the network.

The features already outlined represent the variations in appearance of the system of tubules as a system. Other appearances depend upon alterations occurring in the component tubules. These latter concur with the rest-phase and the active phase of the epithelium in which the system is set.

In the rest-phase of the epithelium the tubes appear as thin, solid, homogeneous structures, having a diameter of $\cdot 2\,\mu$ to $\cdot 5\,\mu$. They stain opaque purple or black. In the active phase this no longer pertains; they increase markedly in their diameter to as much as $2\,\mu$; they lose their solidity and appear as hollow structures. Their walls now stain a pale lilac colour and are transparent. The content of the tubule is either a clear homogeneous material, or a granular material (figs. 4, 5). The granules are discrete and densely chromatic, and frequently give the tube a beaded appearance (fig. 5). The staining affinities of the granules are identical with those of the granules of the cytoplasm. Occasionally a tube cut in cross-section shows a dark granule, enclosed in a pale lilac-stained wall.

DISCUSSION

The structural appearances outlined in the foregoing description cannot be artefacts since they are demonstrable in every thyroid gland, normal and pathological. They have a precise distribution and position, a very uniform size and shape, and they vary directly with the state of physiological activity of the epithelium in which they lie.

The intraparenchymatous system described has a definite disposition in relation to the cells of the epithelium. It is not to be confused therefore with the intracytoplasmic filaments of the cytomitome: nor with the intracytoplasmic canaliculi of Holmgren, D'Agata, the reticular material of Cowdry[1] and others; nor with so-called paranuclear structures, mitochondria, etc. On the other hand its position in the parenchyma is much the same as the marginal chromatic centriole of columnar epithelium, the basal particles of ciliated epithelium and the isotropic material of Englemann.

These structures, however, are described as confined to individual cells; it may be that the description of them depends upon the failure of technique to demonstrate them in their continuity[2]. This last probability is under investigation.

[1] E. V. Cowdry, *Amer. Journ. Anat.* Vol. xxx. No. I, Jan. 1922.

[2] Pensa. Quoted by Da Fano, *Journ. of Physiol.* Vol. LVI, No. 6, Oct. 1922, p. 461.

For a long time before perfection of the staining technique, a doubt remained as to whether the appearances could be due to the cut edge of cell-membranes. This possibility is not to be entertained for the following reasons:

The structures have never been seen to run in the protoplasm from the centre to the periphery of the parenchyma, enclosing the cell at its margin, as must be expected were a cell-membrane in question. The components of the network are never internuclear in position, and appear only in certain planes in the cytoplasm. It is frequently necessary to focus through the depth of the protoplasm before the network becomes visible; or the network will have long passed out of focus before an adjoining nucleus is seen. Lastly, fragments of the network are often found lying free in vacuoles within the protoplasm.

It is clear, then, the structures are not cell-membranes.

It is impossible to doubt the tubular nature of these structures if a comparison is made between their appearance in resting and active epithelium. Further, a comparison with other tubular structures—the bile canaliculi of the liver—places the matter beyond doubt. This new structure and the bile canaliculi occur as a network; they are both at times seen as dots and bars; both alter with the particular phase of activity of the associated parenchyma. When empty they are thin, homogeneous, darkly staining lines; when full they are pale membranous structures enclosing differentially stained matter or highly granular material. Indeed these two structures seem to differ only in calibre and in size.

On the whole there is every justification for considering the structures described in this paper as a specific system of tubules peculiarly arranged in the parenchyma of certain secreting epithelia.

It should be stated that these tubules can be seen but faintly, with stains other than the special stain used in this research.

No definite knowledge is claimed of the significance and function of this intraparenchymatous tubular system; the matter is under investigation in this laboratory.

One significance that could be attached to these structures is that they function as an auxiliary circulation carrying lymph, blood-plasma, peculiar contents of parenchyma, or the contents of gland-ducts.

To find so delicate a structure brought into such close approximation to the superficial surface of secreting membranes could point to some special function to do with secretion or absorption.

The lumen of the tubules is so fine—not exceeding 2μ at its maximum—as to preclude the possibility of any association with a circulation maintained by mere mechanical pressure. Flow in such tubules would depend upon some biodynamic factor—and this opens up a field of many new and significant possibilities which might provide a key to some of the more pressing problems of the moment connected with excretion and absorption.

SUMMARY

1. A system of intraparenchymatous structures is described in the secreting epithelium of the thyroid gland.

2. This system consists of a network of tubules stretched beneath the free surface of the epithelium.

3. Very occasional radial branches from the system pass towards the base of the epithelium.

4. When secretory activity is obvious in the parenchyma these tubules are distended and contain granular material.

5. The structure is described in the thyroid gland, but occurs in other secreting epithelia.

DESCRIPTION OF PLATE

Fig. 2. Section of thyroid gland showing the position of the tubular network: (*a*) dots and bars concentrically arranged within the epithelium; (*b*) network of tubules.

Fig. 3. Section of thyroid gland showing various appearances of the tubular system in follicular and interfollicular tissue. Note (*a*) radial branch running the depth of the parenchyma.

Fig. 4. Section of the thyroid gland showing the "hanging seine" effect of the partially open mesh. Note the broken granular content of the tubes.

Fig. 5. Section of the thyroid gland showing tubular network during period of activity of the gland. Note (1) the tubular nature of the structure; (2) the granules within the tubules.

NOTE. The microphotographs are untouched photographs.

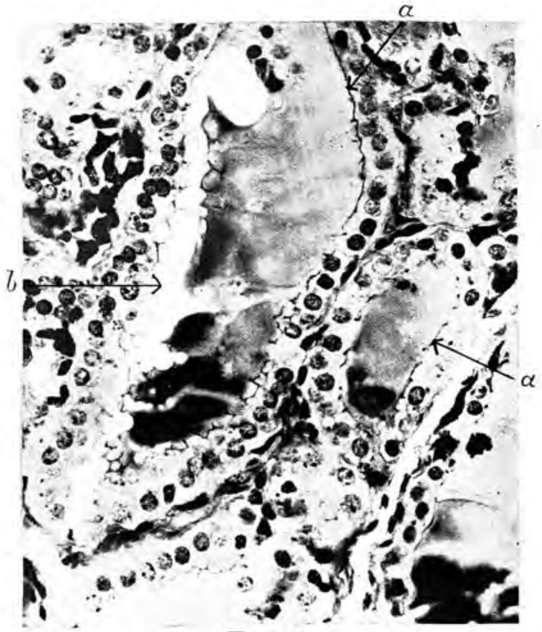

Fig. 2

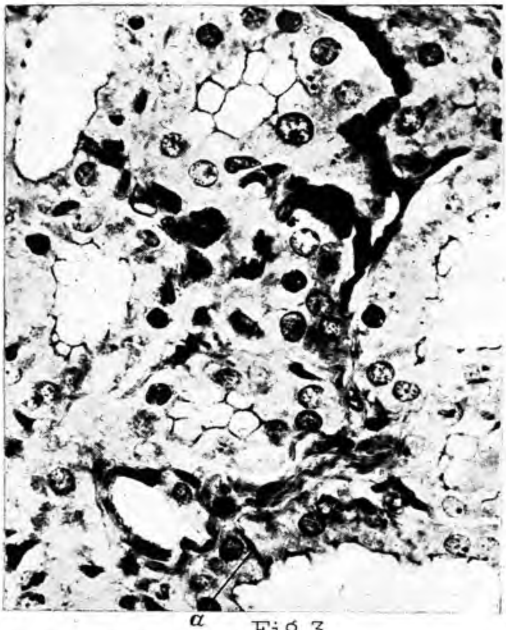

Fig. 3

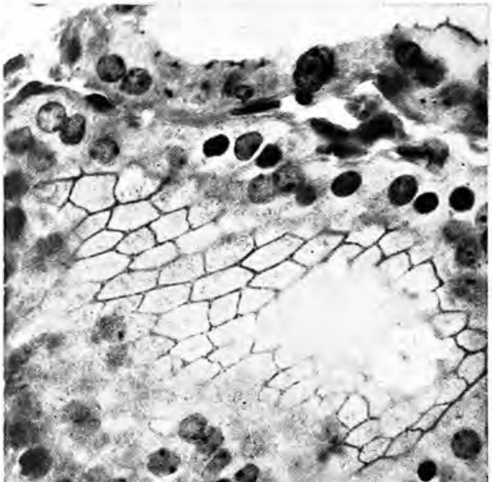

Fig. 4

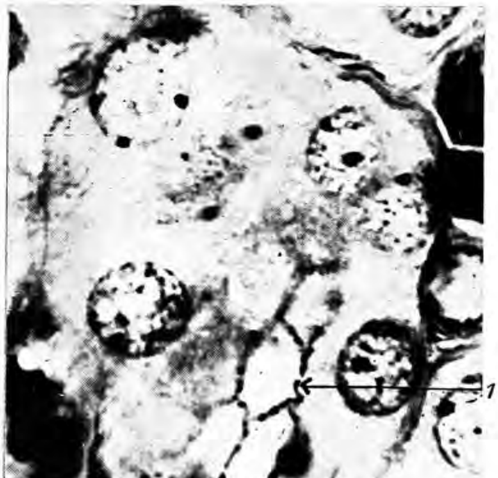

Fig. 5