THE THYROID GLAND IN MENTAL DEFICIENCY: A HISTOLOGICAL STUDY.

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THE NORMAL THYROID.

THE thyroid gland has a profound influence on the mind, both in its emotional and its intellectual aspects. The emotional features of hyperthyroidism are too well recognized to need stressing. So, too, is the association between gross diminution of thyroid function and the mental incapacity of cretinism. It was suspected, therefore, that even in those types of mental deficiency in which diminution of thyroid function was not recognizable clinically, it might be possible to detect some evidence of abnormality in the thyroid gland by histological study. Further justification for presupposing the possibility of thyroid derangement may be found in the fact that in many conditions an association between the thyroid and thymus has been established, and that in mental deficiency the thymus undergoes premature atrophy.

It was in view of these considerations that the investigations, of which what follows is an account, were undertaken. These investigations represent a histological study of the thyroid glands of 90 defectives of both sexes between the ages of 1 and 19, who have died during the past 10 years at the Fountain Mental Hospital. The tissues all underwent similar treatment. They were fixed in 10% formalin in alcohol, embedded in paraffin and cut, and then stained with Ehrlich's hæmatoxylin and eosin. But certain limitations are to be noted in any study of such material as these sections. In the first place, the pieces of tissue appear to have been taken at random from any part of the gland, so that it is possible that parts which showed abnormality may have escaped observation. Secondly, the thickness of the different sections varied, thus increasing the difficulties of interpretation and comparison. Thirdly, though the reagents used were the same, they were applied by different people at different times, so that the staining reactions may not be strictly comparable. And finally, the clinical, and even the post-mortem records, as is so often the case in a retrospective investigation, are sometimes disappointingly meagre.

The material will first be dealt with in the light of the various histological

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criteria, and then, reversing the process, the histological features will be dealt with in respect of certain clinical aspects. Before attempting to consider pathological states, it is first essential to consider in some detail, by way of control, what constitutes the "normal" thyroid. It is here that serious difficulties at once arise.

Much of the gross anatomy of the thyroid gland was familiar to Galen; but his knowledge was allowed to lapse, and it was not till after many centuries that it was rediscovered by Julius Caserius or Leonado (Rienhoff (1)). Since that time it has been the subject of much study, and little has been learnt in the last two hundred years.

With regard to the microscopical anatomy, however, the situation has been entirely different. Early observers thought that the gland consisted of isolated vesicles; but many prominent histologists, among them Virchow, held that it was a tubular organ. It was not till the introduction of serial sections, combined with wax modelling, that it became possible to settle the question, and this was done in 1897 by J. J. Streiff (2), whose results corroborated the earlier theories. Unfortunately, however, the issue was complicated by the publication in 1923 of a paper by Williamson and Pearce (3), which purported to re-establish the tubular theory and combined it with certain original discoveries. On these findings they built up an elaborate theory of the working of the gland. But their observations were made on isolated sections and not on serial ones, and it remained for Wilson (4) in 1927 and Rienhoff (1) in 1930 finally to refute their views and to establish the true facts of thyroid histology.

Of these two workers, Rienhoff is the more satisfactory, in that he modelled a larger block of thyroid tissue, and combined this with the micro-dissection of the previously macerated gland. His conclusions were as follows:

1. That there is no true lobulation, the gland parenchyma consisting of continuous plates and bands which are only incompletely separated by the connective tissue.

2. These plates and bands consist of discontinuous follicles.

3. The follicles are spheroidal in shape with smooth outsides; no buds or branching exist. The number of small follicles is large in relation to the big ones. There is great variation in the size. Internally they measure from 0·02 to 0·897 mm.

4. "No epithelium except that which is completely differentiated, and also which presents the arrangement of the normal thyroid parenchyma, exists in the adult gland."

"The great preponderance of small follicles . . . in proportion to large ones, is suggestive, at least, that the thyroid tissue is completely differentiated in the adult, and after puberty the number of follicles is probably not increased by the growth of secondary vesicles from primary follicles. The small follicles would seem to form a reserve supply of parenchyma, which,

when called upon to function, does so by an increase in size due to hypertrophy and hyperplasia of the epithelium."

Nor is this surprising when we consider the many factors that influence the histology, and the rapidity with which they may do so. In 1911, Marine and Lenhart (11) wrote: "The thyroid undergoes exceedingly rapid histological changes, the causes for which are still ill understood". Since then much attention has been devoted to these causes, and some at least of them have been elucidated.

McCarrison (5) has demonstrated the influence of polluted soil in producing the chronic hypertrophic type of goitre. He has also suggested that a lack of balance between the iodine and calcium in the diet may influence the gland. In his experiments, an excess of lime led to "an abnormal accumulation of colloid, secretory activity being in abeyance. The vesicles in whole or part of the gland were greatly distended, distorted in shape and their walls much thinned".

Not only calcium and iodine, but other food substances have been held to be responsible for structural variations. McCarrison (whose work was confirmed by Marine) produced hypertrophic goitre by feeding on an excess of iodine-free fats, and showed that if iodine were given simultaneously, no such goitre resulted. But that factors other than fats are involved is suggested by Bensley (6), who showed that the thyroids of captive opossums "lose their colloid and undergo hyperplasia which can be produced or controlled by diet alone". That this is a different phenomenon from McCarrison's is shown by the fact that iodine would not prevent the change. Further evidence of the effect of diet is adduced by Chalmers Watson (7), who showed that a diet of bread and milk in wild rats produced shrinkage of the vesicles and diminution of colloid, such of the latter as was left losing its affinity for eosin and appearing faint and granular. The effect of iodine was not observed, but the fact that these changes were regressive rather than hyperplastic suggests that they were of a different nature from those produced by Bensley and McCarrison. A meat diet produced proliferation of epithelium and degeneration of colloid. Recent work by McCarrison (8) suggests that the influence of diet on the thyroid is greater than has hitherto been suspected. He has shown that goitre can be produced by a relative excess of certain substances such as iodine-free fats and lime, and conversely, by relative deficiency of iodine or phosphorus if too much calcium is present. There are, in addition, certain "positive goitre-producing" foods, such as cabbage, ground-nut, maize and bran; and certain anti-goitrogenic factors in green vegetables (other than cabbage), oatmeal and carrots. Insanitary conditions can induce goitre only with the help of a defective diet.

He has drawn attention to the protective function of the vitamins. Vitamin A protects against the goitrogenic agent in "diet", and against the unknown agent in lymphadenoid goitre. Vitamin B is of doubtful potency,

but seems to protect against the goitrogenic factor in ground-nuts and, perhaps, in cabbage. And a deficiency of vitamin C causes enlargement of the thyroid, with the accumulation of iodine-rich colloid.

Besides the age of the individual and his diet, sexual activity plays its part. The gland of the adult female resembles that of the male, but during pregnancy, and perhaps during menstruation, hyperplasia is found (De Quervain (9)). In the female, but not in the male, the relative size of the thyroid is greater during sexual activity than it is when the sexes are separated (McCarrison (8)). Sexual emotion has been held by Dunhill (10), following Langdon Brown, to be a prominent causative factor of thyrotoxicosis; other forms of mental stress doubtless play their part.

As an active accelerator of metabolism (11), the thyroid "excites about 40% of the total heat production of the body" (Hadfield and Garrod (12)). It might therefore be expected that the increased call for metabolism experienced during cold weather or during fever would affect it. Roger and Garnier (13), examining thyroids from cases of many of the acute exanthems, constantly found cellular proliferation and desquamation with absorption of colloid and occasional hæmorrhages.

Whatever the factor influencing the gland, as Hadfield and Garrod (12), among others, have pointed out, the histological evidence in different parts of the same gland may vary very greatly. What they write of the sequence of events in the hyperplasia of primary thyrotoxicosis is probably equally true of other hyperplasias: "It is probable that when the maximum degree of hyperplasia is attained by one group of vesicles, it is regularly followed by some degree of involution, and that this cycle, as in simple goitre, is repeated many times, ultimately ending in exhaustion and fibrosis. The histological picture owes its complexity to these changes, to the fact that the cycle is at different stages in many groups of vesicles at one time, and the size of these groups is very variable".

Instead, therefore, of searching for a somewhat chimerical normal as the basis of investigation, I propose now to consider each different histological feature, as to its significance in general, and as to its occurrence in this series. But as far as the histological assessment of activity or rest is concerned, these conditions, if they are capable of definition at all, are best considered according to the criteria specified by De Quervain (9). "Activity" he writes, "is suggested by—

"1. Cylindrical form of epithelium.
2. Tendency to formation of papillæ.
3. Irregular vesicles deficient in colloid.
4. Colloid badly stained, vacuolated or reticulated, staining preferably, but feebly, with hæmatoxylin.
5. Considerable desquamation.
6. Great frequency of mitochondria.

" Rest is suggested by—

" 1. Squamous shape and flattening of epithelium.
2. Absence of papillæ.
3. Circular-shaped vesicles.
4. Colloid homogeneous; intensely stained by hæmatoxylin or by eosin, or by both. Complete absence of colloid in other cases.
5. No desquamation.
6. Few mitochondria.

" The value of these signs is not by any means uniform. A malignant goitre may exhibit an increase of mitochondria and other signs of activity, when actually its function may be very deficient."

The normal gland, then, in the adult, consists of closed vesicles of very varying sizes. The largest may be nearly fifty times the size of the smallest, though " these extremes are rarely seen together ". There are very few empty vesicles (Joll (14)), and the majority contain non-granular colloid (Hadfield and Garrod (12)), which takes a bright red colour with eosin (Kauffman (15)). The parenchyma lining the alveoli is low cubical, or low, but not frankly, columnar (Hadfield and Garrod (12)). But even syncytial masses of epithelium have been described by Hertzler (16), who says they resemble tissue in the placenta rather than ordinary gland epithelium. Between the alveoli, lying in a scanty fibrous stroma, are masses of cells which give a fallacious appearance of solidity, and are in reality the edges of normal alveoli (Rienhoff (1)).

Thus far only the adult gland has been considered. But it seems not unlikely that, in view of the well-known influence of the thyroid on growth and metabolism, the histological characteristics might differ somewhat in the gland of childhood and adolescence.

De Quervain (9) has recorded the fact that at birth there is no colloid; hyperplasia is the rule. Up to the age of 5 years this latter feature declines, and colloid storage makes its appearance. Thereafter, the hyperplasia again becomes conspicuous and may progress till it overshadows the colloid storage. With the onset of puberty the picture varies with the sex: in the male, storage of colloid is evident, in the female, hyperplasia. Cooper (17) has made a detailed study of the thyroid at different ages, but she gives no particulars either of the sources from which her material was derived, or of the number of specimens on which she bases her conclusions. It is perhaps for these reasons that Joll states that " it is doubtful whether all her conclusions are justifiable ". In brief, her findings are as follows: At the age of one year the vesicles vary only slightly in size, and are lined by cubical parenchyma without evidence of hypertrophy or hyperplasia. Colloid is present in most of them. Solid masses of parenchymatous cells between the vesicles are conspicuous, and the stroma is scanty. About the age of 5 years differentiation into alveoli is clear, though many are irregular or very small. The most conspicuous feature is " piling " of the epithelium, which tends to be columnar

in shape and many layers thick, occasionally being actually embedded in the colloid, which still fills the alveoli. The cell masses are conspicuous and push the vesicle walls in; young vesicles are forming among them. In "older children" the gland is "similar to exophthalmic goitre". Many vesicles, especially those in the middle of the gland, are empty; the peripheral ones are large and full. The parenchyma cells are tall and columnar, piling is marked and desquamation common. The cell masses are many, large and highly vascularized, and the connective tissue is obscured.

Another author who stresses the occurrence of the cell-masses in the glands of children is Hertzler (16), who appears to regard them not as solid masses of normal parenchyma, but as a tissue of separate identity; for he writes that "the large number of interstitial cells is characteristic of the gland in childhood", and further that "in infants it is impossible to distinguish the acinal from the interstitial cells. Even in the earlier years of life the distinction is not clear".

Apart from the conflicting views concerning the identity and significance of these so-called cell masses, my two main authorities seem to agree that for the first few years the gland is in a state of colloid storage and shows little cellular activity. Towards the age of 5 colloid becomes less conspicuous, and hyperplasia predominates increasingly, and then tends to diminish after the onset of puberty.

In reading published accounts of thyroid histology, and still more in studying a series of specimens, I have been chiefly struck by the very wide variations in structure that may be encountered within the bounds of normality. This aspect of the question, which seems to have been somewhat overlooked in the earlier literature of the gland, has been receiving more attention recently. Joll (14) confesses that "great difficulty has been encountered in determining the range of normal histological variation", while Hertzler (16) writes, "it is important to note that there is no definitely established normal".

The Histological Characteristics.

The Vesicles.

As has already been described, the size of the vesicles may vary very widely, without exceeding the bounds of normality. In this series, however, no extremes were met in any one section, though very small and moderately large ones were often seen close together. None showed the typical appearances of the "fœtal" type of gland, though No. 10, from a female imbecile, who died at the age of 3 of broncho-pneumonia and rickets, approached it. Here the vesicles were small and regular, often with an only just distinguishable lumen and seldom containing any colloid; the epithelium was cubical, and the stroma abundant and pale-staining. In only two other

cases did the alveoli seem to be particularly small. One, No. 36, was from a male microcephalic, who died from what was probably a terminal meningitis at the age of 2 ; the other, No. 51, was from a female secondary imbecile, who died of broncho-pneumonia at the age of 10.

At the other end of the scale, the fact that most of the alveoli appear more or less large is not to be taken as itself a pathological feature, but probably simply indicates the fact that at one time or another colloid storage was a predominating characteristic. Nine specimens showed an extensive, if sometimes patchy, largeness of the alveoli. In two of these, Nos. 48 and 83, the epithelium was flattened, the stroma was scanty, and the vesicles were uniformly and quite considerably distended with hyaline pink colloid, so as to give the appearances of a colloid goitre. The history of the second case was quite unknown. The only suggestive feature in that of the first was a course of treatment by " polyglandin ", but this is probably without special significance, since the preparation was being used for a good many cases at the time. Moreover, the gland was not enlarged macroscopically. The origins of these specimens with large alveoli may be tabulated as follows :

TABLE I.

No.	Sex.	Type.	Age.	Cause of death.
20	Female	Diplegic imbecile	15	Asphyxia.
37	,,	Primary	3	Pneumonia.
48	,,	Mongol	2	Nephritis.
83	,,	Primary	11	Influenzal pneumonia.
22	,,	,,	13	Carditis.
17	Male	Mongol	5	Phthisis.
38	Female	Paraplegic	12	Carditis.
35	,,	Secondary (toxic)	2	Broncho-pneumonia.
87	,,	,, (epileptic)	4	*Status epilepticus.*

In the first four of these specimens the gland was full of colloid, in the last it was exhausted. It will be seen that no constant feature connects the type of case with distension of the vesicles.

As regards the outline of the alveoli, it will be remembered that Rienhoff disproved the existence of buds in the adult gland. Some workers, however, notably Isenschmid (19), have maintained that growth by budding is a normal event in the glands of childhood. In this series, pronounced irregularity was almost always due to papillary formation, and the lesser degrees, being almost certainly the product of tissue shrinkage in the course of fixation, do not merit separate consideration. One case, however, No. 62, from a female cretin, æt. 7 (Fig. 1), showed appearances strongly suggestive of the breaking down of septa and the fusion of adjacent alveoli. In three others, Nos. 54, 74 and 68, the irregularity seemed too pronounced to be simply the result of tissue shrinkage, and looked more like the product of irregular growth. The first was from a male primary imbecile, who died at the age of 6 from scarlet fever

of six weeks' duration. He was remarkable for the long, downy hairs all over his face, especially the temples, cheeks and upper lip. The second was from a male mongol, æt. 5, who died from broncho-pneumonia of three weeks' duration, but in whom there was no evidence of a hormonic dyscrasia. In both cases the testes were undescended, but this feature was seen in many in whom there was no evidence of increased growth of thyroid alveoli. The last was from a simple primary imbecile, æt. 8, who died of pneumonia. His thyroid was enlarged, but no other abnormality was noted.

If budding were a feature of the young thyroid, it would almost certainly have appeared clearly in this series; but it did not do so. Apparent irregu-

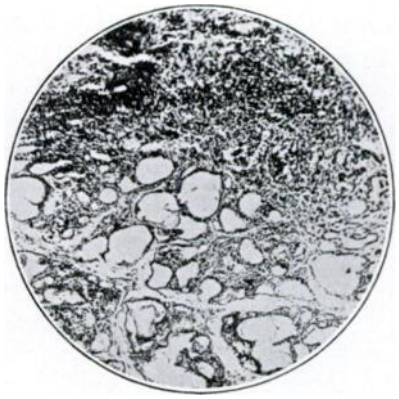

FIG. 1.

larity of the vesicles may be due, not to the epithelium itself, but to the growth of the stroma which was found in both the above specimens. Fusion of alveoli is very rare, but may occasionally occur.

The Colloid.

It may not be out of place to consider here briefly the function of the colloid, as a guide to its significance as a histological criterion. At first sight it might appear that colloid and secretion are identical, but this view has long been in doubt. Marine writes, "The colloid within the vesicles of the thyroid is believed to be the only vehicle for storing the active secretion in an inert manner". This view has received wide support, and Bensley (6), using a special fixation and staining technique, claims actually to have shown a true secretion differing from the colloid and lying in vacuoles at the peripheral end of the cell. Further confirmation comes from a biochemical source, for thyroxin can be isolated from the gland by proteolytic digestion—a fact which suggests that thyroxin exists in the gland in combination with a protein.

The colloid, then, probably represents the thyroid secretion in an inert

form. Its presence would indicate excess of supply over demand, its absence, exhaustion. But such assumptions are weakened by two well-known pathological observations, namely, that in both secondary thyrotoxicosis and in cretinism, conditions in which the individual is in the first case using, and in the second demanding, much thyroid secretion, there may be an abundance of colloid present. Consequently, although Joll (14) is probably right in asserting that very few empty follicles are found in the normal gland, too much importance should not be attached to the mere presence or absence of colloid in assessing the activity or otherwise of the thyroid tissue.

In this series, taking a tissue approximately half full of colloid as a mean, 14 specimens are found in this group. Besides these, about equal numbers seem to occur in either side, that is to say, that 34 seem to be more than half-full and 42 less. In these are included 14 in which the colloid uniformly distended the alveoli, and 11 in which it was entirely absent. If these two extreme groups be again tabulated, it will be seen that no constant factor emerges in either, since in both may be found children of both sexes and a variety of ages, both fat and thin, who died from acute and chronic illnesses with and without fever. The same types of deficiency appear in both series. It may be noted that in only one of the colloid-free specimens, No. 87, were the vesicles so enlarged as to suggest that at another time it might have fallen into the group of specimens with much colloid. Even so there is nothing except the presence or absence of colloid to make the two groups real.

Not only did the colloid show variations in quantity, but its staining reactions were by no means constant. In one specimen it would be represented by a dense hyaline eosinophil substance; in another its consistency would be the same, but its staining affinities different, since it would be coloured mauve by the hæmatoxylin. In yet a third group its consistency would be the prominent feature, since instead of being hyaline it would appear granular, and this type was nearly always mauve and rarely eosinophil. As far as the staining reactions are concerned, the differences might appear to be simply the product of variations in the technique of staining. Such an explanation is put out of court by the fact that in a number of cases both types appear simultaneously, either in the form of a central eosinophil mass, or as a zone of pink to one side of, or (less commonly) surrounding, the mauve substance. If these specimens are put through a variety of stains, it is found that two types of colloid can be distinguished. The first type retains Gram's stain long after it has been washed out of the rest of the tissue, stains orange with Mallory's stain, and blue when treated with eosin and methylene-blue. The second kind has a very weak affinity for Gram's stain, stains blue with Mallory's aniline-blue-orange-G stain, and pink with eosin and methylene-blue.

These two types of colloid correspond to Types I and II already described by Hewer (18), who examined the fresh material of 16 glands removed at operation, 13 being cases of Graves' disease and the remaining 3 from other

TABLE II.—*Specimens with much Colloid.*

No.	Sex.	Age.	Type.	Cause of death.	Nutrition.	
11	M.	12	Juvenile general paralytic	Pneumonia	Wasted	—
15	F.	5	Primary	Gangrene of lung	,,	—
20	F.	15	Secondary (diplegic)	Asphyxia	,,	—
37	F.	3	Primary	Pneumonia	,,	Four months' fever.
40	F.	7	,,	,,	Fat	One day's illness.
47	M.	10	Secondary (hemiplegic)	,,	Thin	,, ,,
48	F.	2	Mongol	Nephritis	—	Treated with polyglandin.
52	M.	2	Hydrocephalic	Broncho-pneumonia	Wasted	—
56	F.	10	Congenital diplegic with hydrocephalus	Inanition	,,	—
59	M.	4	Microcephalic	Pneumonia and fibroid lung	,,	—
60	M.	6	Secondary hemiplegic	*Status epilepticus*	Plump	Undescended testes.
70	M.	6	,, ,,	Diphtheria	,,	—
83	F.	11	Primary	Influenzal pneumonia	—	Two days' illness.
86	M.	9	,,	Phthisis	Wasted	Undescended testes.

TABLE III.—*Specimens with no Colloid.*

No.	Sex.	Age.	Type.	Cause of death.	Nutrition.	
3	F.	4	Mongol	Broncho-pneumonia (six days)	Thin	—
14	M.	7	,,	Pneumonia and measles	,,	Undescended testes.
19	M.	1	Microcephaly	Bronchitis and ? syphilis	Wasted	—
34	M.	4	Mongol	Generalized tuberculosis	,,	—
50	F.	13	Primary	*Status epilepticus*	Thin	—
54	M.	6	,,	Scarlatina	Wasted	—
61	M.	5	,,	Acute phthisis	,,	—
75	F.	8	Cretin	Pneumonia	—	Treated with thyroid.
80	M.	5	Primary	Phthisis	—	Testes undescended.
85	F.	10	,,	Pericarditis	Thin	—
81	F.	4	Secondary epileptic	*Status epilepticus*	Fat	—

forms of goitre. Her conclusions were that the " type of staining is directly correlated to activity as determined by microscopy and clinical history, but not by the basal metabolic rate; the alkaline colloid (staining blue with Mallory's stain) indicated 'marked activity'; the acid (which takes the orange-G) indicates 'secretory inactivity'. Fresh secretion stained faintly, old deeply; and the reaction was found to be independent of the iodine content ".

The very sharp contrast between these two types may be seen in Fig. 2 from No. 12, which shows a section stained with eosin and methylene-blue, though unfortunately the photograph does not bring out well the chromatic distinctions. Unfortunately, only 9 other specimens could be put through

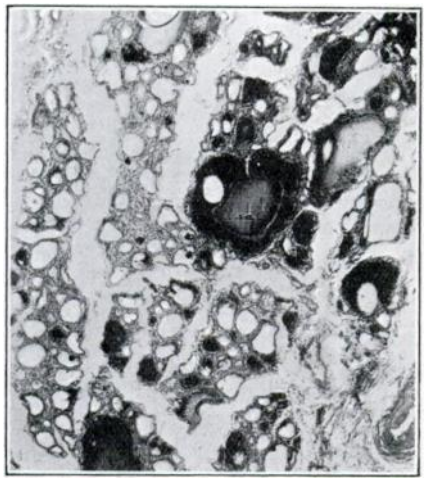

FIG. 2.

the full range of staining, but these were enough to show a wide variety in the distribution of the two types of colloid. As may be seen in Fig. 2, the alkaline type may occur alone, the acid alone, or the alkaline in the middle of the acid. In others, but less commonly, the acid might be found in the middle of the alkaline. The association usually seemed haphazard. The only specimen in which this was not the case was from No. 62, a cretin, in which a small area of the alveoli at the centre of the gland was full of acid colloid, while the more peripheral ones contained the alkaline form. As far as consistency was concerned, the acid in these cases was always hyaline, but the alkaline might be homogeneous or granular, and often both of these were found in the same section.

What, then, is the meaning of these two staining reactions? Is their significance only apparent, the product of a chemical change in the course of the preparation of the tissue? Or does it represent two different types of

thyroid secretion, or is one a stage in the development of the other? If the acid and alkaline colloid depended on the fixatives, the appearances should be the same in each specimen, since all were treated alike. Instead of this, one is alkaline throughout, one is acid in the middle, and in the others the two are mixed, apparently at random. Moreover, the transition from one kind to another is abrupt and not gradual, as it would be were it the product of chemical action during preparations. Since the appearance of different secretions is not purely artefact, it might be that one is the precursor of the other. Is one the protein basis with which thyroxin is combined, possibly for purposes of storage? This possibility is disproved by Hewer's demonstration that the iodine content is the same in both types, for a protein menstruum would scarcely contain iodine to the same extent as the thyroid secretion. There remains the third possibility that two thyroid secretions can be thus demonstrated, and in view of the improbability of other explanations, this seems to me the most likely, though there is as yet no evidence to show whether this duality is normal or pathological. Hewer's specimens were from glands that were known to be diseased. In this series there was no record of clinical abnormality, nor are the associated microscopical features consistently pathological. That two secretions should be produced by the normal thyroid is an old and not a very surprising postulate. One can imagine that in response to one kind of stimulus the thyroid might produce a quantity of alkaline secretion. Then, before this is entirely absorbed, a different stimulus might result in the production of an acid secretion that would surround the alkaline. But such an explanation will not account for other forms of distribution, *e.g.*, where the two occur alongside one another, nor for the fact that though associated the two are never intimately mixed.

In the following table particulars of the 10 specimens in which the appearances were worked out are given. In it the colloid quantity is roughly indicated by the number of plus or minus signs, three of either being the extreme of storage or emptiness respectively. The percentage figure after these signs represents a rough estimate of the proportion of this colloid which is alkaline. The degree of activity is assessed according to the degree of epithelial hypertrophy or hyperplasia.

TABLE IV.

No.	Colloid.	Percentage alkaline.	Activity.
12	±	40	Slight.
16	++	80	Moderate.
20	+++	100	Pronounced.
22	++	80	None.
23	++	75	Moderate.
28	++	20	,,
56	−−	10	Slight; much fibrosis.
62	−	80	None; ,, ,,
68	−−	60	,,
76	−	20	,, moderate fibrosis.

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This table does not bear out Hewer's contention that an alkaline colloid is evidence of activity. For in No. 62, in which there was comparatively little acid colloid (from a cretin), the epithelium was cubical or slightly flattened and unreduplicated, while the stroma was a good deal increased, suggesting that the gland had been overworked and was now exhausted ; while No. 28, in which the greater part of the colloid was acid, showed low columnar parenchyma with a fair amount of reduplication and a good deal of acid colloid in the lymphatics, suggesting that the gland was actively producing and absorbing its secretion. It may, however, be significant that the only gland in which the reaction was uniform was that of No. 20, which was remarkably hyperplastic and quite full of alkaline secretion.

The result of tabulating these cases of dual colloid in order of the approximate relative quantity of the alkaline secretion is shown in Table V.

The only evidence that emerges from this table is the suggestion that alkaline colloid may be found in the glands of girls about the time of puberty. On the other hand, Case 20 had never menstruated, and showed no secondary sexual characteristics.

Though additional presumptive evidence might be obtained from specimens stained with hæmatoxylin and eosin, I have refrained from doing so, since such specimens, not having been stained by the methods indicated, are open to misinterpretation. The evidence here available throws some doubt on the truth of Hewer's presumption of activity, but is not enough to furnish any definite conclusion. It can only be claimed that the very distinct staining reactions observed, and the constancy of their appearance in appropriate specimens, but their absence from others, do, indeed, strongly suggest that two secretions are present.

Besides these differences in staining reactions must be mentioned the differences in consistency. In 15 the colloid was mauve and granular, a fact which recalls Chalmers Watson's (7) bread-and-milk-fed rats, in which the colloid presented similar appearances. There is nothing in common among these cases, but it is possible that there may indeed be a dietetic origin for abnormal colloid. For though the dietary of the children was the same, the very young and those who are spoon-fed must of necessity have depended on " slops ", and of the above 15, no less than 8 were blind or paralysed, 3 were under the age of 3 years, and 2 were seriously ill; of the other two there is no definite evidence. It may be objected that other spoon-fed children did not show this change, and that for a dietetic deficiency to be postulated where all are taking the same food, all must be affected. That this latter assumption is unjustifiable is shown by the fact that of 500 of these children on a standard diet, 7 developed scurvy and the rest did not. Proof, however, of a dietetic origin of variation in colloid is lacking.

Finally must be mentioned a series of 15 specimens, in which the secretion was not in the form of a homogeneous hyaline or slightly granular material,

TABLE V.

No.	Sex.	Age.	Type of amentia.	Illnesses.	Cause of death.	Nutrition.	Season.
20	F.	15	Secondary	Measles, whooping-cough, otitis media	Asphyxia	Wasted	May.
16	F.	14	Primary	Rickets, measles, enteritis (? tuberculous)	Phthisis	Normal	August.
22	F.	13	,,	Whooping-cough, pneumonia, otitis media, measles, scarlet fever	Carditis	,,	April.
62	F.	14	Secondary	?	?	Fat	March.
23	M.	3	,,	Tonsillitis	Myocardial degen.	Normal	,,
68	M.	8	Primary	?	Pneumonia	,,	February.
12	M.	3	Secondary	Whooping-cough, measles, pneumonia	? Phthisis	Wasted	April.
28	F.	7	Primary	Whooping-cough, measles, erysipelas	Broncho-pneumonia	Normal	January.
76	M.	6	,,	Rickets, chickenpox, measles	Pneumonia	,,	February.
56	F.	10	Secondary	Measles	Inanition	Wasted	?

but occurred in a mass of radiating strings in a way reminiscent of mucin. Possibly this appearance was actually caused by the presence of larger and more numerous vacuoles than those usually seen. And if the presence of vacuoles is evidence of absorption, as it probably is, these 15 cases might be expected to yield evidence of rapid utilization of thyroid secretion, such as might perhaps be found at a period of rapid development or of increased metabolism, *e.g.*, in fever. But in point of fact these specimens came from all ages from 2 to 8, and all types, including mongols, in whom the clinical evidence of thyroid activity is not conspicuous. And though most of them had had more than a week's fever before death, in one case there was none, death being due to spontaneous subarachnoid hæmorrhage. It can only be said, then, that the secretion looks like mucin, but that no evidence of its true nature or causation can be offered.

Hypertrophy.

In the adult gland the vesicles are lined by a single layer of low cubical or low, but not frankly, columnar epithelium. Hypertrophy, or elongation of the individual parenchyma cells, is generally accepted as evidence of activity. This would be in keeping with the observations of Cooper (17), according to whom hypertrophy is one of the most characteristic features of the thyroid in childhood; for she states that the histological picture becomes increasingly like that usually considered typical of exophthalmic goitre from the age of 3 into adolescence.

But in this series, the epithelium was of the tall columnar type in only 9 instances. In another 30 there was either slight elongation, or else there were patches where the epithelium was more fully developed than in the rest of the gland, so as to suggest that some degree of hyperactivity was indeed present. Of the remainder, 22 were cubical, 21 were slightly flattened, and the rest, 8 in number, were decidedly flattened, one very much so.

At the columnar end of the scale, 4 showed features reminiscent of the changes usually associated with primary thyrotoxicosis. These cases were as follows:

No. 5, the most close resemblance—partial exhaustion of colloid; columnar cells sometimes two or three deep or infolded, sometimes desquamated; stroma scanty, with full capillaries and absence of cell masses.

No. 61: Colloid completely absent; alveoli rendered very irregular by intense proliferation of columnar cells, which are often several layers deep, thrown up into several layers, and desquamating freely. The stroma is scanty, the capillaries are empty, and there are very few cell masses.

No. 85 is almost identical, save for an increase in the interlobar connective tissue, while in No. 2 fibrosis between the individual alveoli is found in addition.

The clinical histories of these and of the other hypertrophic cases are

as follows, and again, any classification can be only histological, for though 6 of them showed prolonged invalidism, death followed short illnesses in 2, and in 2 was quite sudden.

TABLE VI.

No.	Sex.	Age.	Type.	History.
5	F.	3	Microcephalic	Died of bronchitis.
61	M.	5	Primary	Pertussis, colitis, measles, acute phthisis.
85	F.	8	,,	Pneumonia, empyema, pericarditis.
2	F.	6	Microcephalic	Pertussis, measles, otitis media, pneumonia.
58	M.	6	Secondary (inflammatory)	,, ,, meningitis.
60	M.	6	Secondary (vascular)	*Status epilepticus*.
74	M.	5	Mongol	Scarlet fever, chicken-pox, broncho-pneumonia.
87	F.	4	Secondary (epileptic)	Pneumonia, *status epilepticus*.
88	M.	6	,, ,,	Pertussis, measles, chickenpox, broncho-pneumonia.

In the remaining 30, which showed hypertrophy, there was again nothing else in common except in one group, and as the characteristic of this was not so much hypertrophy as hyperplasia, they will be considered under that heading.

At the other end of the scale come the 8 cases in which the epithelium was flattened. In all of them there was a total absence of hyperplasia, the stroma was scanty and cell masses inconspicuous. The only difference is in the amount of colloid present. But here again a tabulation of sex, age, type and past history, cause of death and post-mortem appearances reveals no common factor.

Hyperplasia.

1. Like hypertrophy, hyperplasia, or numerical increase in the epithelial cells, is evidence of activity. When the functional demands on the tissue are very heavy, as has been investigated after experimental ablation of a large part of the gland, hyperplasia is the result. Similarly, during the active development of later childhood there is hyperplasia, as evidenced by "piling" (Cooper (17)). Even syncytial masses have been described in the normal gland, but so considerable a change seems to me suggestive of an almost pathological demand on the gland. But "piling" is not the only evidence of hyperplasia, and the process is best considered under the headings of "piling" and "papillary formation", "desquamation" and the "cell masses." Owing to the way in which these features overlap and are masked by other features, a classification on the basis of hyperplasia presents more difficulties than one dependent simply on the condition of the alveoli or the existence of hypertrophy.

Piling and papillary formation may be closely counterfeited by desquamation, for if the desquamated cells lie in clumps in contact with the parenchyma lining the alveolus, they will give the appearance of having grown from it; the more so if the lining of the alveolus happens to be intact in the

plane of the section, and the desquamated cells have come from some other part of it. Allowance must be made for this possibility. But on the other hand, it is certain that true reduplication of the cell layers does occur, as does also papillary formation. A good instance of these processes may be seen in Case 82. Here a large papilla can be seen, consisting of a delicate stroma at the base from which project masses of cells, which seem to spread syncitially. These syncytial masses may burrow into the colloid and, by increase of the colloid, become detached from the parent stem, as may be seen in the microphotograph of Case 20, Fig. 3. If, now, the colloid

FIG. 3.

undergoes absorption, these isolated cells left adrift in the lumen of the alveolus will be indistinguishable from cells shed by degeneration of non-hyperplastic parenchyma. There are other ways of accounting for apparent desquamation :

2. It may be that, in response to a physiological stimulus, regeneration takes place in a previously quiescent parenchyma. A new lining forms in the alveolus, and the old cells are shed into the lumen without the new lining undergoing multiplication. This multiplication is recognizable as hyperplasia in that the new cells form solid masses or papillæ. It is possible that this is, indeed, the explanation of some of the cases, and these may then be regarded as a genuine, but mild, hyperplasia. The difference between this and the previous explanation lies in the fact that the previous type represents hyperplasia in a gland actively secreting colloid and then re-absorbing it,

while in the second type the cells of a previously exhausted gland are regenerating.

3. That desquamation is a manifestation of autolysis is suggested by the fact that it is not a common finding in material removed at operation. In 12 specimens of secondary toxic goitre, in which hyperplasia was more or less prominent, desquamation was never as conspicuous a feature as in many of these glands. On the other hand, Cooper (17), in her survey of normal thyroids based on fresh material, mentions desquamation as a characteristic which appears at the end of the second year, and increases as age advances. Moreover, in an attempt to correlate the presence of desquamation with the degree of autolysis (as presumed with respect to the season of the year and the length of time that had elapsed between death and autopsy), no connection could be established in this series.

4. A fourth possibility is that the cells were squeezed from their attachment in the course of the handling necessary for removal of the gland. This is rendered doubtful by the fact that most of the material was obtained in the same way. And further, desquamation was a feature of one of the specimens where the material for microscopic examination was removed before enucleation of the whole gland.

Desquamation may then be considered in conjunction with papillary formation and " piling " as evidence of hyperplasia. In the light of this, a short but very definite sequence of 17 specimens may readily be grouped together, and will now be considered in greater detail.

As may be seen from the microphotograph of Case 20 (Fig. 3), the characteristic feature of these glands is their highly cellular nature. In this case, colloid and cells lie mixed in inextricable confusion, so that although the alveolar structure of the tissue is recognizable here and there, it is, in the main, lost. The stroma is so delicate that it can be recognized only in places. A similar, indeed almost indistinguishable, state of affairs is to be found in specimen No. 37 and, to a large extent, in No. 82.

No. 60 shows a stage nearer to the familiar alveolar type of structure. In Fig. 4 on one side the parenchyma blends with, and infiltrates the colloid in the manner of the preceding specimens. In the middle is an alveolus composed of a solid mass of parenchyma cells, while on the other side, again, the cells have arranged themselves round the edge of a small alveolus and have secreted a well-defined colloid into the lumen. With this specimen may be classed Nos. 52, 47, 70, all showing hyperplasia of this type with colloid storage; and the same may be seen, though to a less pronounced degree, in Nos. 79 and 16, though in these the alveolar structure is as definite as in the normal adult gland.

In Nos. 35, 61, 67, 28, 18 and 19 the same type of hyperplasia is found, though not in such degree, and the colloid is largely or completely exhausted. In No. 87 hyperplasia is a fairly conspicuous feature, but a more prominent

characteristic is fibrosis, and in No. 89 both these are less conspicuous, so that, if it were not for the fact that the parenchyma may be seen here and there infiltrating the colloid, this specimen might almost be considered simply as an example of hyperplasia, rather than one showing the characteristics with which this sequence began.

There is, then, here a series of specimens which, starting with a colloid-infiltrating hyperplasia and loss of alveolar structure, passes gradually down towards a simple increase in the cellular content of a gland of the more usual alveolar structure, the sequence being interrupted only by such variations as the quantity of colloid present (which has already been shown to be without significance), and by the degree of fibrosis—a question which will be dealt with in greater detail later.

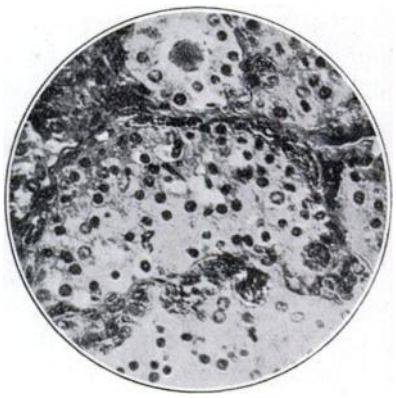

FIG. 4.

A consideration of the more typical cases from a clinical standpoint reveals the following facts: No. 20 was from a female diplegic, æt. 15, who had never menstruated and who died in May from asphyxia. The body was wasted and deeply pigmented in a way almost suggestive of Addison's disease, but the adrenals were normal macroscopically, while the thyroid looked normal and there was no thymus present. No. 37 was also from a female, a simple primary case, æt. 3, who died in May of pneumonia after a week's illness. Her body was wasted, and the thymus was vestigial. No. 82 was from a female, æt. 3, a microcephalic, who died in June of "inanition". The autopsy revealed no organic disease, but the thyroid was said to be enlarged and the thymus was absent. No. 60 was from a male, æt. 6, a secondary (vascular) ament, who died of *status epilepticus* in August. He was of a fat, eunuchoid type, with undescended testes and a large thymus. No. 52 was from a hydrocephalic male, æt. 2, who died in July of broncho-pneumonia. He was wasted, the thyroid was normal macroscopically, the thymus could not be found and the testes were undescended. No. 47 was also a male, but in this case

the testes were descended; he was a microcephalic, æt. 10, and he died of pneumonia in May. No. 70 was also from a male secondary (vascular) ament, who died of diphtheria in April at the age of 6; his testes were descended and his thymus was large.

Judged by these factors, there was no common feature among them. It may be noticed that there seems to be no particular relationship between the age and this type of hyperplasia.

In addition to the 17 cases showing this colloid-infiltrating hyperplasia, or some recognizable stage of it, 19 showed a lesser degree of hyperplasia in the form of small papillæ or reduplication of the alveolar lining. In these, as in the others, no common factor could be found in the study of the clinical histories or of the post-mortem appearances.

The Cell Masses.

Solid masses of cells (or what appear to be such) lying between the alveoli are often a conspicuous feature of thyroid tissue. Hertzler (16) states that they are a prominent feature of the thyroid in childhood, but writes of them as if they were not the ordinary gland parenchyma at all. The existence of interstitial tissue in the adult gland is emphatically denied by Rienhoff, and it is unlikely, to say the least of it, that a tissue so prominent in childhood should vanish so completely in adult life. For even the thymus, which seems to have entirely atrophied by the time maturity is reached, may be discovered to be still present by microscopical examination.

If these masses are actually identical with the alveolar epithelium, there are two possible ways of accounting for them. They may, as Rienhoff says they are in the adult, be places where the microtome has touched the edge of an alveolus. If the alveolus is spherical only a few cells will appear, but if it be flattened quite a large patch will be seen. This explanation would well fit all cases, and is supported by the fact that in general the thicker the section the more conspicuous the masses, but that in most of these cases careful resolution would show that the lack of alveolar arrangement was only apparent and not real.

There is, however, an opposite view to which apparently Cooper subscribes, namely, that these masses are indeed solid, and represent a reserve of parenchyma which, under the stimulus of increased demands for secretion, will develop into fully formed alveoli. Though such a reserve is not met with in other glands, there is really nothing inherently improbable about its occurrence in the thyroid, on which the demands are not really exactly analogous to those on other tissues. But evidence in refutation of such a theory may be derived from these specimens, which in 9 cases showed a complete absence of any evidence of such cell masses. Now if these cells represented a reserve, one would expect these 9 specimens to be derived either

from definitely inadequate glands (as of cretins), or from glands which showed histological evidence of colloid exhaustion, combined with compensation in the form of hypertrophy or hyperplasia or both. But one would not expect a cellular reserve to be absent from quiescent or only partially exhausted glands. Yet of these 9 specimens, 2, already described as resembling goitre, seem to be quite quiescent; 3 are partially, and 1 (a cretin) quite exhausted without attempt at compensation, and only 2 show the appearances of colloid exhaustion with that compensatory overgrowth of epithelium which one might expect to be associated with exhaustion of an epithelial reserve. (The ninth specimen, being completely fibrotic, is not included in these considerations.) Further, one of the cretinous specimens shows an amount of "reserve" which is incompatible with a gland already incapable of meeting the normal demands of the body.

Consequently the balance of probability seems to be in favour of Rienhoff's view, even in the child, and the presence or absence of these apparent cell-masses is not taken as a histological characteristic of any significance.

Stroma.

Fibrosis, or increase in the supporting tissue at the expense of the parenchyma, is evidence of a period of involution or diminished function. Such changes may commonly be seen in the prostate or mammary glands as old age approaches, but it might have been expected that in such a tissue as the thyroid of childhood, on which the demands of increasing growth and heightened metabolism are being made, though periods of relative inactivity might occur, they would not be profound enough to be accompanied by actual regressive changes.

But such changes are found; indeed, in 10 of the specimens it was quite pronounced, and in another 24 it was less advanced, but quite definite. The most remarkable was No. 75, from a cretin, in which the thyroid is represented simply by a mass of fibrous tissue, in which no parenchyma can be traced. Unfortunately, further details of this specimen are lacking, so that it cannot be said that the thyroid did not exist, but rather that that part of it selected for examination had become obliterated. The 2 other cretins in the series both showed fibrosis; little is to be seen in No. 81 (Fig. 5), but in No. 62 (Fig. 1) a mass of young fibroblasts can be seen at the periphery of the gland.

One of the most striking examples of overgrowth of fibrous tissue is seen in a specimen, No. 14, from a boy, æt. 7, in whom no clinical evidence of hypothyroidism was recorded. He was a mongol with undescended testes, who though short, as all mongols are, was not conspicuously so, and whose only previous illnesses were gastritis and stomatitis. He died of measles and pneumonia, and at autopsy the most remarkable feature was complete absence of the thymus. As may be seen in the microphotograph (Fig. 6),

the parenchyma is compressed into bands by a strangulating overgrowth of the stroma; the alveoli are flattened out and infiltrated with lymphocytes.

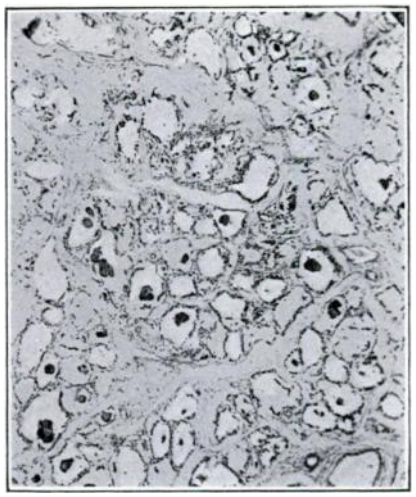

FIG. 5.

A similar, though less pronounced appearance was seen in No. 73, also from a mongol, in whom no thymus was found. She died at the age of 5 of pneumonia and empyema, and had had no previous illness. Another

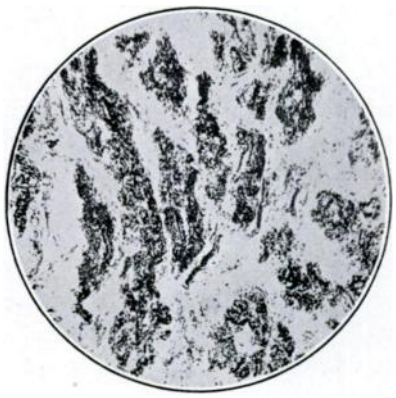

FIG. 6.

specimen which showed fibrosis, though not compressing the parenchyma to the same extent, was No. 57, from a male, æt. 5, with rickets and undescended testes, who died of a fibroid lung with terminal pneumonia after a long illness. No thymus was found. The other 4 cases are distinguished

by the density of the fibrous tissue between the separate alveoli. The least of these is shown in the microphotograph of No. 80 (Fig. 7). Particulars of these cases are as follows: No. 80 was from a male, æt. 5, with a meningocele and undescended testes. He had had bronchitis and measles and died of fibro-caseous phthisis; no trace of the thymus was found. No. 6 was from a male mongol, æt. 7, with undescended testes; he had had measles and whooping-cough and died of phthisis; his thymus could not be found. No. 34 was from a male mongol, æt. 4, whose testes were also undescended. He had had pneumonia and otitis media, erysipelas, gingivitis and necrosis of the mandible and died of generalized tuberculosis. No. 51, a female, died at 10 of broncho-pneumonia. She had had measles, pneumonia, scarlatina, broncho-pneumonia and mumps. No trace of her thymus could be found.

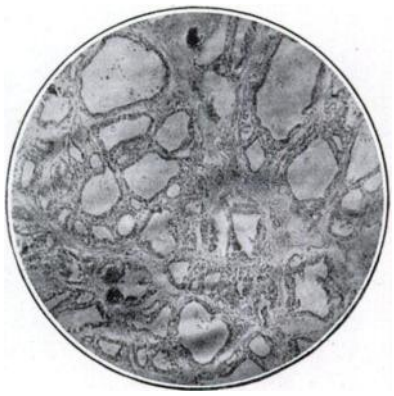

FIG. 7.

In this series of cases showing fibrosis, all the males had undescended testes, and in none could any trace of the thymus be found. Otherwise there was no common factor. One would naturally look to the past history for evidence of the cause of so slowly-developing a change as fibrosis. Yet nothing consistent emerges. For though the many serious maladies that had beset No. 34 might well have exhausted any gland, the same cannot be said for the gastritis and stomatitis of No. 14. A conspicuous feature of these cases was the absence of the thymus gland from all of them except one in which there was no record. I believe that this association was not without significance, but it will be dealt with in some greater detail in considering the thymus itself.

Blood-Supply.

The last question to be discussed from a histological standpoint is that of the blood-supply. This is probably not an indication of much significance, since the blood-supply of any organ may vary extremely within

a very short time. The condition of the blood-vessels might, therefore, be expected to give very little evidence of the activity or otherwise of the organ for any length of time before death. This view of the significance of the blood-supply is borne out by the state of the vessels in this series, for though 9 of the 11 cases which showed dilatation and congestion of the vessels also showed evidence of activity, in the other 2—in 1 of which the congestion was particularly marked—there was no hyperplasia or hypertrophy of the epithelium, and only partial exhaustion of colloid.

An associated feature, perhaps more suggestive of activity, is the presence of red blood-cells within the alveoli. This was noted in 15 cases which, like the preceding, were usually, but not always associated with hypertrophy and hyperplasia. Conversely, these evidences of activity were by no means always associated with the presence of hæmorrhages. It was thought that perhaps the cause of death might be a factor, since a condition of *status epilepticus* might well be enough to rupture capillaries. But apparently this was not so, for of 9 deaths from this cause, only 2 fell into the present group. Indeed, in this, as in the other features, a consideration of the sex, age, illnesses, cause of death and season of the year affords no indication of the cause. And this, combined with the very varying histological picture associated with the cases of congestion and hæmorrhage, suggests that these features are without significance.

Clinical Analysis.

The next step was to see if any common histological features could be found when the children were grouped on a clinical basis. Subsequently, various other factors which might have had an influence on the appearances of the thyroid will be considered.

It will by now be obvious from what has gone before that the histology of these specimens has varied within such extremely wide limits that no constant feature has been found which could be associated with the existence of mental deficiency. Nor is this to be wondered at when we consider that mental deficiency is merely the common outward sign of a variety of different conditions, which should be spoken of not as if they were one disease or defect —amentia—but as "the amentias" or "oligophrenias."

The classification of these conditions is complicated and, in our present state of ignorance of the subject, unsatisfactory. They are usually spoken of as primary and secondary, and Tredgold (21) says that the former provide 80% of all cases of mental defect and are due to impaired germ-cells; the latter make up the remainder and occur, not as a result of germinal deficiency, but where "the normal growth of the brain or mind is interfered with or arrested by some adverse factor acting directly on the patient". Even on this basis classification would not be an entirely simple matter, but it is further

complicated by the inclusion of "delayed primary amentia", where the defect is produced by an "illness, fright, or fall in the early years of life, such as would be incapable of damaging the nervous system of an ordinary child". Tredgold's classification is as follows—

Primary:
- (1) Simple,
- (2) Microcephalic,
- (3) Mongolian,
- (4) Sclerotic;

Secondary:
- (1) Traumatic and vascular,
- (2) Inflammatory and toxic,
- (3) Epileptic,
- (4) Endocrine;

and this is a classification to which I shall in the main adhere, though with certain modifications.

The simple primary is really the least satisfactory group in this series, since it contains those who do not fit into any other. There are 31 of them in the present series. In 4 nothing was known of the family history; in 14 nothing abnormal was elicited, but this has not much significance, since many parents resent their child's detention in a mental hospital, and are then not likely to enlarge on familial mental instability. In the other 13 there was a definite neuropathic taint; 8 of these were associated with epilepsy.

I have included under the heading of primary amentia the only case of proved syphilis in the series—that of a boy with juvenile general paralysis. No doubt there were other cases of syphilis, but the Wassermann reaction was not done as a routine at the time. Whether syphilis should be classified as a cause of a primary or secondary amentia is a debatable point since, as Tredgold points out, it may either impair the developmental potentiality of the germ-cells, or act upon the embryo after fertilization.

Microcephaly, of which there are 10 examples, is a type which is liable to misinterpretation, since some workers include under this heading all whose heads are abnormally small, while others reserve it for smallness combined with a typical configuration of receding forehead and sloping sides. The specimens in this series belong to the latter category.

The 22 mongols and one sclerotic belong to definite clinical types which do not here need further elaboration.

On this basis of classification, 65 cases fall into the group of primary amentias, giving a percentage of 72, which does not differ greatly from Tredgold's 80%. As contributory evidence that these "simple" cases are indeed due to defective development, it may be mentioned that of 13 males no less than 8, or 61%, had undescended testes; while of the other primary groups, 11 out of 20, or 55%.

The secondary amentias.—The traumatic and vascular lesions account for 8 cases. Three of these were of infantile hemiplegia, and 5 of Little's disease. I have thought fit to include these latter among the secondary cases, since the generally accepted theory is that the condition is secondary to cortical or meningeal hæmorrhage at the time of birth (Thomson (22), *et al.*), though Collier (23) has advanced the theory of agenesis or degeneration of cortical neurones from a cause that is as yet unknown.

In the second group, the inflammatory and toxic, are included 2 cases which followed meningitis, 6 of hydrocephalus, and 1 in which the mother was known to have taken ecbolics, and no familial taint was recorded.

The third group, the epileptics, presents difficulties. Tredgold writes: "It is easy to mistake cause for effect, and my experience is that in the great majority of cases where the two are associated in early life, both conditions are a manifestation of the neuropathic diathesis". If all the epileptics in this series were considered together, they would constitute a group of 18 cases. However, I have broken them up as follows: Three of them, being associated with paraplegia or hemiplegia, naturally fall into the traumatic or vascular group. Two more are grouped with the hydrocephalics. Eight others have already been mentioned as included with the simple primary cases. Their family histories are of interest and are briefly as follows:

No. 61. Father very nervous, father's aunt insane.
No. 27. "Family history of insanity and cataract."
No. 84. "Illegitimate child of mentally defective mother."
No. 50. "Father's mother in asylum."
No. 67. Father's brother feeble-minded, father's mother insane.
No. 15. Intemperance of father, who was mother's uncle.
No. 45. "Family history of tuberculosis and hydrocephalus."
No. 32. "Mother epileptic."

In these cases I have little doubt the epilepsy was an association and not the cause of the mental deficiency. The other 5, having no neuropathic taint, are considered as a secondary group apart.

Finally, the endocrine cases are the 3 cretins. Case 54, already mentioned as possibly an endocrine case on account of the unusual growth of hair on the face, was included with the simple primary cases, as there was no definite evidence of hormonic dyscrasia. The occurrence of congenital glaucoma and undescended testes suggested the existence of a developmental abnormality.

If any abnormality of the thyroid is to be found among the simple primary cases, it is most likely to be in the group in which a neuropathic diathesis may clearly be traced; for these are the ones in whom a congenital maldevelopment of the brain is the prominent feature. The following table, summarized on the same principle as Table IV, sets out, albeit in rather a rough way, the characteristics found in the thyroids of this group:

TABLE VII.

No.	Colloid.	Hypertrophy.	Hyperplasia.	Fibrosis.
15	+++	−	+	−
16	++	++	++	+
18	−−	++	++	+
22	++	−	−	−
27	+	−	−	−
32	++	−	+	−
45	−−	−	−	+
50	−−−	−	+	−
61	−−−	++	+++	−
67	−	+	++	−
68	−−	−	−	+
72	±	−	−	−
84	+++	−	−	−

Such a table shows quite clearly that not only is there no superficial similarity common to all these specimens, but that, even allowing for variations produced by extraneous demands, there is no fundamental abnormality common to all.

Mongolism is the only type of amentia in which I could find any reference to the condition of the thyroid in the literature. And even here the evidence is very scanty. Kauffmann (15) records that he " found the thyroid unchanged in this condition ". Brousseau (24), in a monograph on this condition, gives an account of the literature from which it appears that no extensive study has yet been made, but that, on the limited material available, most workers have failed to identify any abnormality. The few who have found any abnormality have only done so in a few cases, and even then nothing consistent has emerged in all.

In view of these divisions of opinion, and the fact that the 22 cases of mongolism in this series seem to provide a longer sequence than many previously recorded, I have summarized the features in the following table :

TABLE VIII.—*Glands of Mongols.*

No.	Colloid.	Hypertrophy.	Hyperplasia.	Fibrosis.
1	+	−	−	−
3	±	−	−	−
6	−−	−	−	++
14	−−−	−	+	+++
17	+	+	−	+
25	+	−−	−	−
26	++	−	++	−
33	−	++	−	+
34	−−	−	−	++
39	−−	+	+	+
41	−−	+	+	−
43	++	−	−	−
44	+	−	−	−
46	++	−	−	−
48	+++	−−	−	−
49	+	−	−	−
55	−−	−	−	−
66	++	−	−	−
73	−−	++	−	++
74	−−	+++	−	+
76	−	−	−	+
78	++	−	−	−

In this table, as in the preceding one, no consistent characteristics are to be seen. But the great variety of structure may be best appreciated from the description of the specimens already mentioned and from Fig. 6.

Microcephaly shows a somewhat similar sequence.

TABLE IX.

No.	Colloid.	Hypertrophy.	Hyperplasia.	Fibrosis.
2	− − −	+ + +	+	+
5	±	+ + +	+ +	−
13	+ +	−	−	−
19	− − −	−	+ +	+
36	− −	−	+	−
47	+ + +	+	+ + +	−
59	+ + +	−	−	−
65	+ +	−	−	−
71	+	−	−	−
82	+ +	+	+ + +	−

None of the classes of primary aments have been found to have common factors, either individually or collectively. For the sake of completeness the 2 odd cases, 1 of epiloia and 1 of juvenile general paralysis, may be added.

	Colloid.	Hypertrophy.	Hyperplasia.	Fibrosis.
Epiloia 53	−	+ +	+	+
Con. G.P. 11	+ + +	−	−	−

The secondary aments may be tabulated on similar lines as follows:

TABLE X.

	No.	Colloid.	Hypertrophy.	Hyperplasia.	Fibrosis.
Vascular	20	+ + +	+	+ + +	−
	29	− −	−	−	−
	38	+	−	−	−
	42	− −	−	−	−
	51	− −	+	+ +	+ +
	60	+ + +	+ +	+ + +	−
	64	−	−	+	−
	70	+ + +	+	+ +	−
Toxic	8	+ +	−	−	−
	35	− −	+	+ +	−
	58	− −	+ + +	−	−
Hydrocephalic	12	±	+	−	−
	23	+ +	+	−	−
	52	+ + +	+ +	+ + +	−
	56	+ + +	−	−	−
	63	− −	−	+	+
	69	+ +	+ +	+	+
Epileptic	4	+ +	−	−	−
	9	+ +	−	−	−
	21	+ +	+	−	+
	87	− − −	+ +	+ +	+
	88	− −	+ +	−	−
Cretinous	62	+	−	−	+
	75	−	−	−	+ + +
	81	+	−	−	+

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Considered thus in individual groups or in their two main classes, there is a total absence of common grounds for comparison or contrast. Assuming now that either hypertrophy or hyperplasia may be taken as evidence of activity, the following percentages of activity and fibrosis may be worked out :

Primary	22	Mongols	36%	showed	activity,	41%	fibrosis,	50%	neither.
	10	Microcephalics	60%	,,	,,	20%	,,	40%	,,
	33	Others	51%	,,	,,	45%	,,	27%	,,
	65		47%			40%		37%	
Secondary	8	Little's disease	62%	,,	,,	12%	,,	37%	,,
	9	Toxic and inflammatory	77%	,,	,,	33%	,,	22%	,,
	5	Epileptic	60%	,,	,,	40%	,,	40%	,,
	3	Cretins	0%	,,	,,	100%	,,	0%	,,
	25		60%			36%		28%	

These percentage figures show no particular difference between the primary and secondary groups, and as far as the subdivisions of these groups are concerned, the numbers, at any rate in the secondary group, are too small to justify any conclusions. However, the low figure of 36% for activity among the mongols is decidedly the lowest among any group, and does definitely suggest that in this type of amentia there is a tendency for the thyroid to be less than normally active. Further support to this suggestion is given by the fact that where evidence of parenchymatous activity is found, it is less in degree, as a rule, than in the other groups.

It now remains to consider various factors that might perhaps influence the histology of the thyroid in any sequence of 90 specimens. To reproduce in full tables such as those already given for the various types of amentia would only be to add needless elaboration, and detailed particulars are therefore omitted.

The Age and Sex.

The specimens for this purpose are divided into groups for the first two quinquennia and for the subsequent ages. This system, though arbitary, was adopted because the age of 5 has already been mentioned as the time when hyperplasia begins to overshadow colloid storage as the dominant characteristic, and because it will be in the group of over 10 years of age that any changes associated with puberty will be evident. A percentage table worked out on such a basis will be as follows :

	Age.						Total.	
	Birth—5.		5—10.		10—			
	M.	F.	M.	F.	M.	F.	M.	F.
Number of cases	16	13	28	17	2	14	46	44
Percentage showing colloid storage	55	46	36	47	100	57	45	50
,, ,, activity (cellular)	44	69	54	64	50	36	50	57
,, ,, fibrosis	31	39	50	41	0	36	41	38

In considering these figures the results for the males over 10 years old may be left out of account. To take the question of sex first, a comparison of total figures shows a close parallelism between the two, and this may further be seen if the respective groups are compared. Thus, that among the girls, for instance, 46%, 47% and 57% respectively should have shown some degree of colloid storage, while 51% and 36% of the boys showed the same, indicates that no particular age or sex significance can be attached to the presence of colloid. Indeed, the only contrast, and one that is of some interest, is in the question of cellular activity. In the case of boys the increase of 44% for the first five years of life to 54% in the second tends to support De Quervain's observations of the gland at this period of life, though the difference is too small to justify a definite conclusion. But the figures for the girls are rather striking. After the age of 10, only about half as many showed cellular activity as did so during either of the two preceding quinquennia. Nor is this difference due to the presence in the older group of a number of mongols in whom, as already suggested, absence of epithelial overgrowth is a common feature, for there was only 1 mongol in this group of 14 specimens. That such a lack of cellular activity should be found at this age is directly opposed to the views of the authorities already quoted, and it would be unjustifiable to deny the truth of their observations on the evidence of only 14 specimens. None the less, it is to be noted that the numbers of specimens on which these observations were based differed only very slightly, and the facts as here shown suggest at least that an increase in cellular activity is not the inevitable accompaniment of the approach of puberty.

The Cause of Death.

The fact that the specimens were all from low-grade defectives makes such an investigation as that described in this section one of unusual difficulty. In the first place, though the cause of death may be revealed by the autopsy, the duration of the fatal illness may be quite unknown. For these children, being unable for the most part to make known their complaints, may have been ill for some considerable time before this became apparent. Thus Case 39 had only one day's illness recorded, but was found at autopsy to have died of pneumococcal peritonitis, and Case 85, after only three days' recorded illness, was found to have grey hepatization of the lower lobe of the left lung, together with an empyema and pericarditis. Secondly, the actual cause of death may be incorrectly stated, for there are those obscure cases in which death can only be said to be due to " congenital brain disease " or " inanition ". Such a case was No. 36, a male microcephalic, æt. 2, who lost weight and became progressively weaker for three months, but in whom the post-mortem examination showed no evidence of disease. There were 6 such cases (including 2 who showed pyrexia). It is possible that in these the

determining factor was overlooked. But judging by one case (not included in this series), in which I performed the autopsy myself, I believe that cases do occur in which no evidence of disease can be found on naked-eye examination, though it is not unlikely that a close microscopical scrutiny might reveal some such change as toxic degeneration of the myocardium.

In view of these possible fallacies, an examination of the specimens in relation to particular general diseases would probably produce misleading results. But in any case the cause of death would probably only influence the condition of the thyroid according to whether or not it was associated with a prolonged illness. In order to put this possibility to the test, three groups in which the cause of death was known were chosen from among these specimens. Group I consists of those who died suddenly, and includes 9 cases of *status epilepticus*, 1 of "*status lymphaticus*", 2 of asphyxia and 1 of pancreatitis. Group II consists of those who died after severe illness of moderate duration, namely 9–28 days (average 15), represented by 11 cases of broncho-pneumonia, and 2 which may have been lobar. Group III consists of 14 children who died of tuberculosis. A percentage table compiled on the same lines as before is as follows:

	I. Sudden death.	II. Short illness.	III. Long illness.
Number of cases	13	13	14
Percentage showing colloid storage	39	23	71
,, ,, cellular activity	54	69	43
,, ,, fibrosis	54	54	64

It might well be expected that with an illness of some severity and duration as in Group II, the thyroid would show signs of exhaustion. This is borne out by a comparison of the figures of Group II with those of Group I, when it will be seen that colloid storage has diminished and cellular activity has increased. One might expect to see the same process carried a stage further in Group III, in which the fatal illness had been not only severe, but of longer duration. However, instead of this, the surprising fact emerges that colloid storage has increased enormously, and cellular activity has proportionately diminished. There seems to be only one explanation of such a state of affairs and that is as follows: With the onset of illness the colloid tends to be absorbed, and the epithelium will then begin to undergo compensatory hypertrophy and hyperplasia associated with increased secretory activity. These epithelial changes involve a production of secretion which is in excess of the body's increased demands, and the epithelium then tends to undergo regressive changes which may perhaps be exaggerated by exhaustion. It must be remembered, however, that the figures in these groups do not differ enough and the number of specimens available are not large enough to permit of generalizations, though as far as they go they do seem to support the explanation here given.

The season of the year may be considered *pari passu* with the cause of death, since the same factor of increased metabolism due to increased thyroid activity may be at work in both. But in those who died of disease, external influences are likely to have a comparatively small effect compared with internal influences; however, a comparison of the 30 who died in warm weather between the beginning of April and the end of September shows some difference from the 60 who died during cold weather. For the difference between the 63% of cellular activity in the first group and the 44% in the second, though not very great, seems to suggest increased activity of the gland during the summer months.

	Summer.	Winter.
Number	30	60
Colloid storage	50%	48%
Cellular activity	63%	44%
Fibrosis	40%	38%

The State of Nutrition.

This again was thought to be a factor which might have an influence on the state of the thyroid—or perhaps it would be truer to say that some relation might be expected between the two. But as a matter of fact no such relationship could be discovered. In 21 cases the child was recorded to have been "well nourished", 7 of these being fat. Twenty-five were said to have been "wasted". In the case of the others, there was either no note or, more commonly, the body was said to be "fairly" or "poorly" nourished. A comparison of the two extreme groups on the same lines as before shows—

	Well nourished.	Wasted.
Colloid storage	62%	48%
Epithelial activity	71%	56%
Fibrosis	43%	32%

The wasted seem to show less colloid storage and less activity, but the differences between the two are not pronounced enough to suggest that they were associated with the state of nutrition rather than with any of the many other possible influences.

The Diet.

All these children were on a standard diet except those who, as already noted, were liable to be fed chiefly on bread and milk. This diet consisted in the main of porridge, milk, bread and margarine (or butter on two days a week); meat and potatoes, with "greens" twice a week, and suet or milk puddings. The most conspicuous defect is the low content of vitamins, the significance of which has already been described. But as no constant feature appeared in the series, the diet, as the prime factor in those variations which occurred, may be ignored; though in the light of McCarrison's researches, its contributory influence is probably considerable.

The Thymus.

One of the most striking features in studying the post-mortem records of these children is the number of cases in which the thymus seemed to be atrophied. And the fact that the endocrine glands were all being collected for microscopical examination makes it fairly certain that, in every case in which a note was made, evidence of thymic tissue was carefully looked for. Such records were to be found in 71 autopsies, and on this evidence the thymuses can be divided into three groups as follows:

Group 1: Thymus absent or "vestigial". These terms seem to be used more or less synonymously, since no note of the evidence of thymic tissue was recorded in the "vestigial" cases. This group includes for 49 cases, or 69% of the total.

Group 2: The thymus was recorded as "small" or "very small", and where the size was recorded it was referred to as "half an inch across", or the "size of a bean" or "cobnut." To this group must be added three which were recorded as "large", since they weighed 14 grm. But this weight is shown by reference to Crotti's (25) table of normals to be below the average for the age. This group of small but definable thymus glands numbers 15 specimens, or 21% of the whole.

Group 3: This group of normals or larger includes 1 normal, 1 "fairly large" (size unspecified), and 5 in which the gland, as judged by Crotti's table, was definitely enlarged. These 6 represent only 10% of the whole.

The association of mental deficiency with thymic hypoplasia or atrophy is already well recognized. Tredgold (26) writes, " . . . in a series of 292 mentally defective children the organ was absent in 74%, while autopsies performed at Bicêtre on 408 non-cretinous idiots, ranging in age mostly from 1 to 5, showed the gland to be present in only 104. As against this, Katz, in performing autopsies on 61 mentally normal children, varying in age from 1 month to 13 years, who had died of various diseases, found the gland present in every case".

Now another well-known association is that between the thymus and thyroid. Biedl (27) writes—"of the pathological anatomical findings in Graves' disease, hypertrophy of the thymus is among the most frequent", and quotes seven corroborative authorities. After thyroidectomy the thymus undergoes hyperplasia, and after total excision of the thymus the thyroid undergoes hyperplasia—the colloid entirely disappears and the height of the epithelium is greatly increased (Crotti (25)). In myasthenia gravis "the thymus is often the seat of morbid changes. The abnormalities are not specific and may be divided into three classes: (1) Simple hypertrophy, (2) hypertrophy with proliferative and degenerative changes, and (3) new growth. The thyroid has been found to be the site of lymphorrhages, interstitial fibrosis, colloid degeneration of the fibrous stroma and proliferation of the epithelium with

the formation of new vesicles" (Buzzard and Greenfield (28)). Finally, Pennachietti (29) found an early hypoplasia of the thymus in 2 cases of congenital athyroidism.

This evidence seems at first sight to be somewhat contradictory. Athyroidism is associated with thymic hypoplasia; in primary thyrotoxicosis and in myasthenia gravis, thyroid hyperplasia is associated with thymic hyperplasia. On the other hand, surgical removal of one is followed, not by atrophy, but by hyperplasia of the other. Perhaps the contradiction is only apparent, and the explanation of the latter cases is that what is left of either gland after the excision undergoes compensatory hyperplasia, and it is this hyperplasia that is associated with the hyperplasia of the other gland.

In view of this interaction between the two tissues and the considerable abnormality of the thymus in defectives, one might well look for an associated thyroid abnormality. Take first the thyroid in the 5 cases in which the thymus was definitely enlarged.

CASE 9.—Female, æt. 9, a secondary ament with epilepsy. Past history: Influenza; died of *status epilepticus*. The thymus weighed 43 grm., and microscopically there was some distinction between the cortex and medulla. There was apparently no fibrosis, eosinophil cells were moderate in number, but not conspicuous, and Hassall's corpuscles were numerous. The thyroid showed smallish regular vesicles, mostly filled with colloid, which was generally pink and hyaline, but sometimes mauve and granular, and occasionally both; the epithelium was cubical or slightly flattened and the stroma normal.

CASE 30.—Male, æt. 2; simple primary ament with evidence of rickets; his tonsils were enlarged and he died of *status lymphaticus*. His thymus was found to weigh 42 grm., and microscopically the cortex was very clearly defined from the medulla. There were few Hassall's corpuscles or eosinophil cells and scarcely any fibrosis. In the thyroid the colloid is mostly exhausted, and what remains is stained with the hæmatoxylin. The epithelium is cubical without evidence of reduplication and the stroma is increased.

CASE 67.—Female, æt. 4; a simple primary ament, who had had measles and died of *status epilepticus*. The thymus weighed 42 grm. The thyroid was less than half full of colloid, which was stained mauve and much vacuolated. The epithelium was low, columnar, and occasionally infiltrating the colloid. There was a good deal of desquamation and the stroma was normal.

CASE 70.—Male, æt. 6; secondary (vascular) ament. He had had rickets, whooping-cough, scarlet fever, measles and broncho-pneumonia, and died of diphtheria. His thymus measured 12 cm. (normal average 8 cm.). The thyroid follicles were all full of pale eosinophil colloid. The epithelium was cuboidal or low columnar, with some desquamation and some hyperplasia infiltrating the colloid.

CASE 55.—A male mongol, æt. 3, who had had measles twice, and died of lobar pneumonia. The thymus weighed 28 grm. The thyroid showed scarcely any colloid. The epithelium was much shrunken from the stroma and was cubical, but without hyperplasia, and the stroma was normal.

Beyond the fact that in each case the thymus was enlarged, there seems to be nothing in common to these cases or to their thyroid glands. Indeed, one is rather impressed by the differences between them. But perhaps the most striking thing is that the thymus of No. 70 should have been enlarged

at all. For if "accidental involution" is the outcome of disease, he, with his six illnesses in as many years of life, might well have been expected to have had a small rather than an enlarged thymus.

For an interaction between the thyroid and thymus to be proved, there must be absolute constancy in the appearances. No allowance need be made for extraneous factors, since if the glands work in association, what affects one will also affect the other. Such a close association has been shown to be absent in the group of large thymuses, and it is equally absent in those with no thymus. These latter show a greater diversity in age than the former, but, like them, show great variety in all other respects. Their thyroids are no exception to this rule; 45% showed colloid storage, 51% evidence of cellular activity and 35% fibrosis.

As has already been mentioned, there seemed at first to be an association between fibrosis of the thyroid and absence of the thymus. The state of the thymus was recorded in 6 of the 10 cases in which the fibrosis of the thyroid was most marked, and in all of them it was absent. That this might point to a connection is possible without the converse, namely, that absence of the thymus is always associated with fibrosis of the thyroid, being true. But doubt is thrown on the possibility of such an association by the fact that in No. 30, where the thymus was large, there was increase in the stroma of the thyroid. No definite association, therefore, can be demonstrated between the thyroid and thymus in this series of specimens.

Summary and Conclusions.

The thyroid is a tissue on which the demands may vary almost from moment to moment. Moreover, the factors, both internal and external, which are already known to affect it are very numerous, and it is not unlikely that others may yet be found. Apart from actual disease, the possible combinations of these factors are likely to lead to a good deal of variation in the appearances of the tissue, and consequently, any concept of a "normal" thyroid is likely only to prove misleading, no less in the child than in the adult. This view, based on theoretical grounds, receives in this series some practical support from the fact that, though parenchymatous activity has been said to be the usual accompaniment of the approach of puberty, such changes were here found to be rather uncommon than otherwise.

The variations in the appearances of these glands are extraordinarily wide. No constant findings could be established to connect mental deficiency with histological abnormality of the thyroid. Nor was it possible to find any feature which would distinguish the primary from the secondary amentias, nor were the appearances of the thyroid in any of the sub-types of these groups consistent, save only in the case of the mongols. And here

all that can be said is that evidence of a qualitative and quantitative lack of parenchymatous activity suggests a diminution of thyroid function in this condition. This absence of any general agreement among the specimens from the point of view of the various clinical types, suggests that in investigating other possible factors these glands may be considered as an ordinary sequence, and that a comparison with a control series from children of normal mentality is unnecessary.

These specimens then, considered simply as series of children's thyroids, show that a type of hyperplasia is found which is not seen in the adult. In it the epithelial cells grow syncytially and infiltrate the colloid, and the process may advance to such a degree as entirely to obscure the original alveolar structure of the tissue. Another feature of the gland of childhood, and one to which in the past much significance has been attached, is the so-called " cell masses ". From the evidence here available it seems that these masses are of no more significance in the child than in the adult, and they are therefore of no value as a histological criterion. Finally, some increase may be found in the fibrous stroma of the glands of quite young children in whom, on clinical grounds, there has been no reason to suppose that the thyroid had been the subject of excessive functional demands.

The colloid may vary greatly in its appearance and its staining reactions, being hyaline, granular or apparently mucoid, and either acid or alkaline in its staining affinities. As far as consistency is concerned, these specimens throw no light on the causation of the different varieties. The acid and alkaline, however, seem to represent two different secretions, and the reaction appears to be independent of the activity of the tissue as postulated by previous observers.

The state of nutrition of the patient seems to have no connection with the histological appearances of the thyroid. The effect of the season of the year is slight, hot weather tending to produce increased cellular activity, but no change in the amount of colloid. Fever, on the other hand, at first leads to absorption of colloid and increased activity on the part of the epithelium. But if the fever is continued, over-compensation is the result, and the gland then reverts towards a condition of colloid storage with diminished cellular activity.

Though an association between the thyroid and thymus has been established in many abnormalities of the former, and though the thymus tends to atrophy prematurely in the amentias, no close correlation could be found between the two glands. But the more considerable degrees of fibrosis in the thyroid were associated with absence of the thymus.

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