THE SIGNIFICANCE OF LYMPHATIC TISSUE AND ADENOMA-LIKE AREAS IN THE THYROID GLAND

THESIS

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by

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While the terms Graves' disease, Basedow's disease and Exophthalmic goiter are purely clinical expressions and their use in pathological connections perhaps questionable, no suitable pathological term exists that is descriptive of the changes seen in the thyroid gland in this disease. Parenchymatous hypertrophy and hyperplasia have been used quite properly but these expressions do not describe the most important changes seen, as we hope to show. The present clinical tendency to consider "Toxic Adenoma" as a condition separate from Graves' or Basedow's disease also lends confusion to a pathological understanding of the process in the thyroid gland.

The association of thyroid disease with a general lymphadenopathy and the idea that in some way or other it was related to changes in the thymus is by no means a recent conception, for as early as 1905 Hausemann (1) reported four cases of Basedow's disease coming to necropsy in which a general lymphatic hyperplasia was observed. At that time he suggested a relationship between thyroid and "Status Lymphaticus". In 1908 Capelle (2) also took a similar attitude and in 1911 together with Boyer (3) reported beneficial results from thymectamies on Basedow patients. Bircher (4)

in 1912 reported experiments in which he produced Basedowian symptoms in dogs by implantations of thymus glands from patients suffering from thyroid disease. Pettavel (5) writes on the pathological anatomy of Basedow's disease in four well studied cases. In two cases he found a persistant thymus; while in all he found areas of lymphoid tissue in the thyroid gland and in three cases there existed a general hyperplasis of the lymphatic tissue throughout the body. He fails, however, to place diagnostic significance on the lymphoid hyperplasia in the thyroid. Matti (6) reports necropsies on ten cases in which general lymphoid hyperplasis was a striking feature. In but one case did he fail to find lymph follicles in the thyroid. This was a twelve year old child, however, and one may properly question the existance of Graves' disease. Rautmann (7), also studying the pathological anatomy, demonstrated a general lymphadenopathy with lymphocytic infiltration in the thyroid. Pettavel (8) reports additional work in 1914, and Klose (9) in 1916 also calls attention to the general lymphoid hyperplasia existing in thyroid disease.

In this country many writers have mentioned the presence of pseudonodes, lymphatic tissue, round cell infiltration, etc, in the thyroid gland. McCallum's (10) is the only text book on General Pathology which refers to these areas. He says that

definite lymphoid nodules are found in exophthalmic goiter and but rarely if ever found in normal glands, he fails, however, to ascribe any significance to their presence. Aschoff (11), while lecturing in this country, spoke of the presence of pseudo nodes in both Basedowian and non-Basedowian glands, and observed that they are more frequently found in glands from Basedow patients. Sager (12) mentions the presence of lymphocytes, but evidently does not consider them of significance. Reinhoff(13) gives them a place in the pathological picture of thyroid disease, but evidently does not consider them to be of diagnostic importance. Broders (14) has always considered them to be evidence of thyroiditis. Menne, Joyce and VonHungen (15) also believe them to be of inflammatory origin. Warthin (16) was the first in this country to point out the pathological significance of areas of lymphatic hyperplasia. He alone at that time (1924) considered rudimentary lymphoid areas as being of diagnostic importance, thus definitely suggesting a new diagnostic criterion in Graves' disease, the essential pathological changes of which have been considered, for nearly 40 years, to rest exclusively in the acinar epithelium and amount of contained colloid. It was Warthin's observations that first engaged the writer's interest and stimulated the study in this laboratory. Elvozin (17) working

here in 1927 made a limited study of our material then available. It was Warthin's contention in 1924 and again in 1929 that the presence of lymph tissue was diagnostic of Graves' disease or Exophthalmic goiter. He gave further impetus to the idea held by the previously quoted continental observers that this tissue represents a definite pathological constitution, the so-called thymico-lymphatic type of individual or as he prefers to call it, the "Graves' Constitution". He points out that these individuals present a hyperplasia of the lymphoid tissue throughout the body and takes the position that they have a congenital predisposition to Graves' disease. In a recent survey of one hundred and eighty-one post-operative cases, Clark and Black (18) also conclude that a constitutional factor is involved. Simpson (19) also supports this view in a study of 665 resected thyroids. On the other hand, Helwig (20) in a recent article opposes Warthin's views, basing his conclusions on a study of fifty-eight surgical and seven post mortem specimens. He concludes that the presence of lymphocytes in the thyroid is the result of a simple local reaction to hyperactivity of the gland, that they are of no diagnostic importance and can in no way be interpreted as evidence of a so-called Graves' constitution. Sixty-six per cent

of his cases presented lymphocytic infiltration and he cites a group of cases without clinical symptoms in which these areas were present in 38.5% of the cases. He does not state the reasons or indications for the surgery on this latter group. One is led to believe that he assumes lymphocytic infiltration to be present in 38.5% of normal glands.

It is the purpose of this paper to present an interpretation of the significance of lymphatic tissue in the thyroid gland as gained from a study of material collected over a period of six years, consisting of (1) thyroids from stillborn infants, premature births, and very young children coming to necropsy, (2) surgically resected thyroid glands and (3) necropsy material from older subjects who died from conditions not in any way involving the thyroid gland, together with observations on the so-called adenomata of the thyroid.

If Warthin's thesis is tenable, that there exists a definite type of individual possessing a "Graves' Constitution", who is potentially a case of exophthalmic goiter, that constitution must be congenital and the significant lymphatic areas should be present at birth or even in uterine life. A routine search of thyroids of young subjects should, therefore, be rewarded with a certain

percentage incidence of the lesion. Material for this section of the study consists of thyroids from 140 full term, premature and still born infants. Further, if the lesion under consideration is a part of the "Graves' Constitution", and is of diagnostic significance, it should be present in all cases of true Graves' disease presenting the classical symptoms of the disease and it should be capable of demonstration in practically all resected glands from such cases. This material consists of three hundred and eighty-six glands removed surgically. Still another point of proof susceptible to demonstration rests in a study of supposedly normal glands obtained at necrospy.

According to Warthin's thesis not all of those individuals possessing this "Graves' Constitution" develop clinical Graves' disease. It should, therefore, be possible to show a small incidence of the lesion in question in post mortem material from subjects devoid of thyroid history. While this incidence should be less, it should be roughly comparable with that found to be existant in the glands of infants, prematures, etc. Our material studied in this connection consists of glands from two hundred cases selected from the standpoint of a non-thyroid history.

The normal thyroid has been quite intensively studied by many workers. No attempt will be made

here to present a review of this literature. Suffice it to say, that in all the literature consulted, no mention is made of the presence of lymphatic tissue in the normal thyroid except by Marine (21), who merely says that lymphocytes do occur normally. He dismisses the subject with a single sentence and fails to state the amount of material in which it was observed.

Williamson and Pierce (22) in an extensive study of the normal gland make no mention of lymphoid tissue. Reinhoff(23) working with serial sections and using reconstruction methods says nothing of their presence in normal glands. In view of the fact that lymphoid areas failed to attract the attention of most investigators of the normal gland, one may feel safe in assuming that such tissue is not a common histological component of the normal thyroid.

STUDY OF INFANT THYROIDS.

This material, as before stated, was secured from premature fetuses, still-born infants, and infants that lived for but a short time after birth. Most of the material consisted of still-borns, but we have several specimens from fetuses as young as the fifth month of gestation. In passing, it is perhaps of interest to note that colloid was present in the acini of these fetal thyroids to a greater or less degree. This is in keeping with the observation of Murray (24) and others quoted by him. A search of the literature reveals few studied on fetal or infant glands; Murray makes no mention of lymphocytes, neither does he speak of adenomata. Rautmann(7), however, did observe small areas of lymphocytes in rare instances while studying glands from very young children. Warthin also mentions their occurrence in rare instances. Our study of glands from these cases was confined to a search of microscopic preparations for areas of lymphocytes and an attempt was also made to make observations on the presence of adenomatous areas.

The histological picture of the thyroid gland from the young subject is quite constant, maturity of the epithelial cells lining the acini is apparently established prior to birth and colloid storage is a pre-natal function of the gland, at least as early as the fifth month. Murray has shown that

post mortem desquamation of acinar epithelium is responsible for the appearance of acini filled with epithelial cells. This is also our experience. Study of microscopical sections from one hundred and forty glands from the sources above outlined revealed the presence of lymphoid areas in four cases only. Two of these were still-born infants, one was a three weeks old baby dying from hemorrhagic disease of the new-born, while the other was an infant that lived for but a few hours after birth, death being due to cerebral hemorrhage. These results give a percentage incidence of the lesion of approximately 2.8%. Had more material been available a more accurate incidence would, of course, have been established, as it is very obvious that in a matter involving low percentages a large mass of material is quite essential. These results, however, are indicative of findings that could confidently be expected in a large number of cases. A further consideration of this percentage incidence will be taken up in connection with post mortem material from older subjects. There was one case in which the lymphoid bodies were found which was not included in the series because of the other pathology present. This was a case of a nine months old child dying a so-called thymic death. This case was previously reported by the writer (25) and the observation made at that time was that no areas of

of rudimentary lymphoid tissue were found in the thyroid parenchyma. During the progress of this work a re-study of this case was made, new sections were cut and an intensive search revealed the presence of lymphoid areas. This experience points out the necessity of numerous blocks and careful search.

Of the one hundred and forty specimens examined areas of so-called "fetal" adenoma were observed in three cases. These areas are separated from the adjacent parenchyma by a thin fibrous connective tissue capsule and there is a definite difference in the appearance of the cellular structure, little or no colloid is seen in these areas, the cells are very compact and take a much deeper nuclear stain.

RESECTED THYROID GLANDS.

In a study of surgical material, the conclusions at which one may arrive are made difficult by the perplexing question of the clinical diagnosis as recorded on the patient's chart, because of the paucity of the clinical information, for it is upon these clinical records that the comparative study must be based. With the aid of experienced clinicians we have attempted to classify our material into two groups (1) those cases showing undoubted clinical evidence of Graves' disease and (2) those cases in which the data in the record did not warrant such a conclusion, or cases which were definitely diagnosed as not of a Graves' character. The criteria used for the first group were: Tachycardia, exophthalmos, tremor, increased pulse pressure, definite loss of weight and increased basal metabolic rate. Cases showing any three of the above clinical symptoms on the record were considered, perhaps liberally, as true Graves' disease. All others were placed in the second group. It is very obvious that errors in classification are certain to occur inasmuch as the information on some of the charts was meagre and incomplete, not representing in many instances, perhaps, a true picture of all the clinical signs present.

Slides from three hundred and eighty-six surgical cases were studied with the following

histological findings:

Lymphatic tissue with no epithelial hypertrophy---	123
Hypertrophy of epithelium with lymphatic tissue---	62
Hypertrophy of epithelium with no lymphatic tissue-	4
Hypertrophy, lymphatic tissue and adenoma----------	12
Lymphatic tissue and adenoma----------	59
Adenoma, iodization and degeneration----------	7
Colloid gland only----------	45
Cystic degeneration without hypertrophy or lymphatic tissue----------	28
Iodism----------	46
	386

Examination of the tabulated observations, shows the presence of lymphoid tissue in 246 cases, while epithelial hypertrophy existed in but 68 cases. There were four cases showing epithelial hypertrophy without lymphatic areas. These cases were among our earliest material and but few blocks were available in each case. We feel that had sufficient material been available the lesion could have been demonstrated in these cases. The low incidence of epithelial hypertrophy is in striking contrast to the high incidence of lymphoid areas and represents a valuable feature in the study of these glands. Were epithelial hypertrophy the only pathological change considered as indicative of Graves' disease, a marked difference between clinical and pathological findings would exist, since of the 246 cases showing rudimentary

lymphoid tissue, all but eleven had been diagnosed or showed definite clinical signs of Graves' disease, as did the four cases showing epithelial hypertrophy only. The eleven cases not classified as clinical Graves' disease were cases with a very meagre history in each instance, with the clinical diagnosis given as "Toxic Goiter", which would perhaps warrant their classification as Graves' disease since, clinically, this term is often used interchangeably with Graves' disease. Of the other one hundred and forty cases, nine had been classified according to our standards as clinical Graves' disease. The fact that these failed to show lesions of the disease is, we feel, due to our liberal clinical requirements or to having "missed" the areas because of an insufficient number of blocks having been taken. Two of these cases were classed pathologically as undergoing degeneration, four as Iodism, while in three no definite changes could be detected. The data presented emphasize the importance of recognizing the presence of lymphoid tissue and its interpretation as a pathological feature of Graves' disease, since practically all cases showing the classical clinical signs of the Graves' syndroma present the lesion in question.

Those glands classified as adenomatous all contained encapsulated areas of atypical thyroid tissue in different stages of development, but no

case showing adenomata as the only deviation from normal presented true clinical signs of Graves' disease. The clinical adenoma described by clinicians is not, in our opinion, an adenomatous structure at all but merely represents a nodular portion of the thyroid containing perhaps large amounts of hypertrophic tissue. We have observed in a few cases that the areas of lymphoid tissue are more numerous in these nodular structures than in tissue taken at some distance from the nodular portions. We feel that this accounts for the so-called "toxic adenoma" and the prevailing impression that removal of the "adenoma" gives clinically beneficial results. That there is some doubt as to the permanency of these beneficial results is shown by the recent survey of Clark and Black.

There were twenty-eight cases of large glands showing no evidence of Graves' disease. These all showed, grossly, areas of degeneration of various degree, some adenomatous, but consisting for the most part of colloid cysts containing old hemorrhage and softened tissue. A few were undergoing calcareous degeneration and an occasional one showed definite necrosis. It is possible that tissue dissolution products in these degenerated glands may supply a toxic amount of the thyroid hormone and thereby cause symptoms that clinically simulate the Graves' syndrome, thus being responsible for many diagnostic errors.

This point seems susceptible to experimental study and experiments embracing it are now in progress.

The forty-six cases reported as iodism demand consideration since the question of iodin-Basedow which formerly occupied a large place in the literature is now receiving but scant attention. According to Crotti (26), individual sensitivity to iodine varies widely. Many patients tolerate large amounts of iodine, while to others, very small amounts are responsible for marked disturbances. Moreover, some of those who have previously shown good tolerance to iodine preparations suddenly develop pronounced symptoms of iodine-Basedow. In this day of iodine salt (particularly in Michigan) and proprietary reducing nostrums containing iodine, when practically everyone is receiving iodine constantly or at intervals, it seems to us that the question is deserving of more consideration than ever. Warthin contends that over-iodization will produce clinical signs simulating Graves' disease. Jackson (27) also writes of a type of hyperthyroidism being caused by iodine. In one of our cases diagnosed clinically as Graves' disease by the physician, having a basal rate of Plus 30, together with a milk tachycardia and slight loss of weight, we failed to find lymphoid areas. Upon investigation it was found that this patient had previously been using proprietary goiter remedies containing iodine, and

had been further iodized by his physician. Histologically the tissue presented all of the involutional changes described as due to iodinization.

Warthin reported in 1924 an analysis of nine hundred seventy-six resected glands. Of these, two hundred and forty-seven presented areas of lymphatic tissue while one hundred and fifty-four showed both lymphatic tissue and epithelial hypertrophy. A large portion of Warthin's material was collected before the extensive use of iodine as a preoperative therapeutic procedure which no doubt accounts for the greater incidence of hypertrophic epithelium as compared to our results in this connection. The remainder of the cases studied by Warthin showed no evidence of Graves' disease and the physical findings did not warrant such a diagnosis.

The absence of epithelial hypertrophy in a large proportion of the specimens is no doubt due to epithelial involution due to iodine therapy. Many observers including Sager, Reinhof and Warthin have pointed out the involutional effects of iodine in exophthalmic goiter. At the present time practically all cases of Graves' disease coming to surgery are iodized pre-operatively, consequently a non-treated surgical specimen is rare indeed. Reinhof, in particular, studied the effect of iodine on the involution of thyroid epithelium in exophthalmic goiter. His observations were made upon seven well

studied cases in which artificial involution was studied at various stages. He describes the changes due to iodine as follows:

"(a) Increased amount and density of Colloid.

(b) Increase in size and regularity of acini.

(c) Increase in amount of connective tissue in the septum and scarring throughout the gland.

(d) Decrease in size and height and change in shape of epithelial cells from a high columnar to a cuboidal or endothelial cell.

(e) Decrease in cytoplasmic bodies or constituents.

(f) Decrease in vascularity of gland.

(g) Decrease in vacuolization of colloid and deposits of lymphocytes".

Warthin believes that over iodinization produces a "watery" colloid and that lymphocytic exhaustion of the germ centers of the lymphoid tissue results. In our experience extensive iodinization also causes marked atrophy of the epithelial cells lining the acini, the cytoplasm is decreased and the nucleus contracted and deformed. We have been unable to show a definite difference in the lymphoid areas in over-iodized and under-iodized specimens because of our inability to sur-

mount the difficulty of obtaining specimens from the same patient before and after iodinization.

SELECTED POST MORTEM THYROIDS.

In a study of the thyroids from one thousand autopsies Warthin found thirty-two showing areas of lymphoid tissue, two of these were also carcinomatous. These findings would give a 3.2 per cent incidence of lymphoid areas in a routine examination of all cases coming to necropsy. These cases were evidently not selected with reference to the exclusion of thyroid involvement and possibly included some cases which had previously suffered from Graves' disease.

As before stated we studied slides from two hundred cases without thyroid involvement, many of them in the younger age groups (early part of 1st decade). In this study we made the following observations.

Epithelial hypertrophy---------- 0

Lymphatic tissue---------- 4

Areas of adenomatosis---------- 9

The percentage incidence of lymph tissue was two per cent. While this is considerably lower than Warthin's figures it corresponds to the incidence of these areas found in infants glands, since theoretically the incidence should be higher in the case of the latter. It will be seen that the incidence of adenoma-like areas in selected necropsy and infant material is also within comparable limits.

ADENOMA.

A study of this surgical material has made possible observations regarding adenoma. Many clinicians consider toxic adenoma a disease independent of Graves' disease, but as before stated, the clinical term "adenoma" has no reference to histology and is applied to nodular forms of thyroids which may or may not be involved in Graves' disease. Reinhof in his series of seven carefully studied cases of exophthalmic goiter in which involution was established by the administration of iodine comes to the conclusion that a large proportion of those areas considered adenomata are but residual areas of hypertrophy and hyperplasia which have remained refractive to iodine or because of disturbed vascular supply have not been subjected to its influence. Ewing's miliary adenoma are considered by him to be such areas. He offers as a possible explanation for the failure to secure permanent remission from iodine that these areas of persistent hypertrophy maintain a state of hyperthyroidism. Warthin considers the adenoma of the thyroid as a congenital anomaly due to altered vascular supply and therefore altered development results. Ewing considers the fetal adenoma as being embryonal. Menne et al (15), consider adenoma as a separate division in their system of classification.

Our observations have disclosed the following facts:

1. Small areas of adenoma-like structures are capable of demonstration in certain slides from infant thyroids. These areas present a cell arrangement distinct from the balance of the tissue.

2. Adenomatous areas, both the so-called "fetal" and mature types are seen in post mortem material from selected non-thyroid cases. Figure (1).

3. These adenomatous structures are quite as frequently found in non-toxic glands as in so-called toxic cases. Figure (2) shows a gross specimen of adenoma together with a photomicrograph of the encapsulated area. Figure (3) shows an area of lymphocytes in the thyroid tissue outside the encapsulated area at "A". We also have many cases in which the lymphocytes are seen within the adenomatous area.

4. A study of one hundred glands from dogs of all ages and breeds shows the presence of these adenomata in a small percentage of the glands. Figure (4).

In view of the foregoing it appears to us that "Fetal Adenoma" bears no relation to thyroid disease. We have no cases of adenoma in our material which presented clinical signs of toxicity that were not shown to be Graves' disease, as determined by the presence of lymphoid tissue. The presence of these areas of adenoma-like structure in infant glands would tend to refute the conclusions of Rienhoff (13) that they are persistent hypertrophic areas. Their

presence in post mortem material of all ages, as well as in infants lends support to the view of Warthin that they are congenital structures. Their presence in dog thyroids leads to a safe assumption that they are in no way related to Graves' disease, per se, as dogs are supposedly not subject to the Graves' syndrome.

COMMENT.

In this study of the occurrence of rudimentary lymphoid tissue and exophthalmic goiter we have included limited observations on the significance of adenomatous areas. The data presented from the examination of infant and selected necropsy material may be taken together when considering Warthin's hypothesis that these pseudo nodules are evidence of constitutional deviations from normal. The presence of areas of lymphatic tissue in infant glands is perhaps of greater significance than their presence in the glands from necropsies of older subjects, inasmuch as one is not confronted by the question of pre-existing Graves' disease, although we have tried to obviate this factor in the selection of our necropsy cases. We were unable to follow Warthin's study with reference to a general lymphoid involvement in exophthalmic goiter for the reason that but one necropsy case of exophthalmic goiter was available. In this one

case, a female fifty years of age, cervical and mediastinal lymph nodes were enlarged and hyperplastic, the thymus was mildly persistent having a weight of six grams and the liver showed marked degenerative change. Menne et al.(15) take the position that lymphocytes in the thyroid gland are the result of inflammatory absorption reactions following sustained hyperactivity of the gland and that the "prolonged activity probably leads to the necessity for more supportive stroms". While there might be some defense for this reasoning regarding the presence of this lesion in adult thyroids, it is hardly conceivable that this explanation would hold in cases of infant glands. Furthermore, a considerable number of our specimens came from children succumbing to so-called "Summer Diarrhea" and it is interesting to note that none of these showed the presence of these areas. It would be a conceivable possibility that were they the result of a true inflammatory process, one would be able to demonstrate their presence in an infectious disease of this type in which there is a marked disturbance of all metabolism, and in which a general lymphadenosis exists. Numerous other childhood diseases were represented in our material and in no case were these areas of lymphoid tissue noted. Figure (5) shows a section of thyroid from a case of miliary tuberculosis in a child eight months of

age. Diligent search of many sections failed to disclose the presence of lymphoid areas in the face of the presence of a distinctly local infectious process of acknowledged chronic type. Another case in point is our failure to find these areas after exhaustive search of many sections in a necropsy case of generalized tuberculosis in an adult even though a definite tuberculous process was demonstrated in the thyroid. Hellwig, also believes that lymphocytic infiltration is the result of a purely local response, inflammatory in nature, but the number of his cases is small and he offers no assurance of exhaustive search for areas of lymphoid tissue. We have repeatedly called attention to the necessity of many blocks and intense study. We feel that the discrepancies occurring in our work are largely due to this factor. Figure (6) shows a small area of lymphoid tissue in a gland showing extensive epithelial hypertrophy in all sections. This was the only area of lymphatic tissue found, however, in sections from many blocks. Furthermore, it is not our experience that these areas always co-exist with epithelial hypertrophy. We have seen many cases in which no epithelial hypertrophy and but an occasional area of lymphoid tissue could be demonstrated in sections from many blocks. This is illustrated by Figure (7) which is a photomicrograph of the only area of lymphoid

tissue found in sections from nine different blocks, and none of which showed hypertrophy of the epithelium. We fully agree with Warthin that epithelial hypertrophy persists longer in and about the lymphoid tissue in the face of iodinization and feel that this is the proper interpretation when the two processes are found to be co-existant. These observations, in our opinion, indicate that the production of rudimentary lymph nodes does not form a part of the picture in inflammatory processes in the thyroid gland and that the lesion in question is not of inflammatory origin.

The almost universal presence of this lesion in surgical thyroids from patients exhibiting clinical Graves' disease is the main point of interest in the entire work, since Warthin's interpretation of lymphocytic areas as a diagnostic criterion is strongly supported. To us, there is a difference in the amount of lymphatic tissue and the degree of its hyperplasia, depending on the severity of the toxic symptoms of the patient and the degree of clinical response to iodine treatment. Figure (8) is a photomicrograph of a specimen from a patient whose basal metabolic rate, before iodine treatment was plus 43, improvement under iodine was very slight, the basal rate remained high and partial resection of the gland was of but slight clinical benefit. Later a nearly total

extirpation was considered necessary. The microscopical picture of the two specimens of thyroid gland were essentially identical, though nearly two months elapsed between the two resections. Lymphatic nodules were numerous throughout all sections and epithelial hypertrophy is persistent particularly adjacent to the lymphatic tissue. On the other hand, Figure (9) is from a case with few symptoms, basal rate of plus 21, and showing microscopically but an occasional area of lymphatic tissue, though many blocks were examined. While we have several such comparative instances we realize that definite conclusions would necessitate a painstaking study of a great number of cases with carefully taken histories. We have also observed that in those cases of infant and selected necropsy glands showing lymphatic tissue, definite hyperplasia is lacking, the tissue not showing very distinct germ centers. Figure (10). Continuing this line of reasoning it would follow that symptoms of Graves' disease manifest themselves only when these congenital areas become hyperplastic and further, that the more extensive the hyperplasia the more severe are the symptoms. As said before it is our observation, as well as Sager's, that these areas persist in the face of evident adequate iodine therapy. We do not know, however, that they are not reduced in number, size and degree of

hyperplasia. Reinhoff, who has studied glands before and after involution makes the statement that "The areas of lymphocytosis were much less frequent during and after involution and the areas that were present seemed to be markedly reduced in size". One must recall, however, that this observation is based upon seven specimens only. The futility of too enthusiastic generalization on so limited a number of cases is too obvious to require comment. Warthin, also considers them to be affected when iodine treatment is first instituted, but that they later become increased in size. From this, one's line of thought might lead him to conclude that the transitory or partial benefit derived from iodine is in halting further hyperplastic processes in the lymphoid tissue as well as in the epithelial elements of the gland. We have previously called attention to the fact that the use of iodine as a therapeutic agent oftentimes so changes the appearance of the gland of exophthalmic goiter as to make the recognition of a definite pathological process next to impossible were one to consider the epithelial elements only. While there is no question in our mind regarding the definite pathology exhibited by the thyroid epithelium, we are forced by our own experience as well as by the evidence presented in the literature, to recognize its instability as a pathognomic lesion of Graves'

disease in the presence of iodine treatment.

We have shown a remarkably close agreement in the clinical diagnosis and the pathological picture when the presence of lymphatic tissue was considered an essential lesion of Graves' disease. Were this lesion to be ignored, and conclusions drawn only from the epithelial hyperplasia and hypertrophy exhibited, a regretably poor agreement between clinical and pathological findings would result. The presence of lymphatic tissue in practically all glands removed surgically from patients exhibiting undoubted clinical signs of the Graves' syndrome, forces one to consider it a lesion of this disease. We feel that the few cases in which the lesion was not demonstrated represent clinical diagnostic errors or cases in which the lesion was missed because of insufficient search. In this respect this lesion can be compared to infiltrating malignant cells in the prostate, for instance, where it is oftentimes necessary to section many blocks before carcinamatous areas can be found. Certainly failure to demonstrate these areas of lymphatic tissue in a few blocks does not warrant a conclusion that they are not present in other portions of the gland. Their persistence after iodine medication confers upon them a major role as a diagnostic lesion inasmuch as we have shown them to be a much more trustworthy indication

of hypertrophic and hyperplastic processes than changes in the epithelium.

In the course of a study such as this, one is impressed by the futility of attempting the solution of many of the questions involved by drawing conclusions from a study of dead pathology. The problems which are involved and which are necessary of solution for a clear understanding of thyroid disease must, in our opinion, be attacked by experimental methods for any reasonable hope of success. Such methods are yet to be devised.

CLASSIFICATION OF THYROID DISEASE.

There are many classifications of thyroid disease suggested in the literature, few of which permit both clinical and pathological application. Menne et al. have proposed perhaps the most extensive workable classification, although it does not coincide with our view that there exists but one process involved in hyperthyroidism, that symbolized by the clinical syndrome of Graves' disease. Warthin proposed a simple classification as follows:

"1. Simple colloid goiter without Graves' Constitution.

2. Nodular colloid goiter without Graves' Constitution.

3. Simple adenoma with Graves' Constitution.

4. Exophthalmic goiter (Graves' Constitution).

5. Adenoma with Graves' Constitution (so-called Toxic adenoma)".

This classification is applicable clinically and is based on the presence or absence of the "Graves' Constitution". It recognizes and dignifies the adenomata in a manner that is to us confusing and not warranted since it is our contention that the presence of adenomatous areas have no significance in hyperthyroidism. As has been often stated, no classification of any disease is of value that can not be of clinical as well as pathological application. If the symptoms exhibited by the patient, be they ascribed to Graves', hyperthyroidism, toxic adenoma, or what not, fit a given syndrome, and there is a constant pathological lesion, one is warranted in assuming the unity of the process. In view of the findings in our study, the practically universal presence of the lesion described as lymphoid hyperplasia, we suggest the following classification and diagnostic scheme.

1. Hypertrophic-lymphoid goiter - Graves' disease.
    1. Epithelial hypertrophy in non-iodized gland.
    2. Lymphoid hyperplasia.
    3. If iodized.
        1. Stroma increased
        2. Colloid increased, thin and watery.

3. Epithelial hypertrophy may be patchy or lacking.

2. Nodular colloid goiter.
   1. Large vesicles containing colloid occurring in pseudo-encapsulated areas.
   2. No lymphoid tissue or epithelial hypertrophy.
   3. May show degenerating colloid cysts.
3. Simple colloid goiter.
   1. Large vesicles, comparatively uniform.
   2. No lymphoid tissue or epithelial hypertrophy.
   3. May show degeneration, cysts, calcification.
4. Normal thyroid with adenomata.
   1. Encapsulated areas of "fetal"-like acini or
   2. Areas of more developed adenoma.
5. Inflammatory processes.
   1. Definite pyogenic infections.
   2. Tuberculosis, etc.
6. Malignant new growths.

If any thyroid would otherwise fall in the last five groups it will be seen that the presence of lymph tissue necessitates placing it in group 1. All the groups become modified by iodinization and all may contain adenomatous areas, and in addition there will

be the rare specimen usually obtained at necropsy from the potential Graves' patient which will present small areas of lymphoid tissue. These latter cases must necessarily be considered as potential exophthalmic goiter in the absence of clinical signs.

CONCLUSIONS.

1. It has been shown that areas of lymphatic tissue occur in the thyroid gland in 2.8 per cent of infants.

2. This tissue is also found in two per cent of thyroids from patients dying from diseases or accidents not involving the thyroid gland.

3. Areas of lymphatic tissue occur in practically all thyroid glands removed surgically from cases of undoubted Graves' disease.

4. The lesion described is not the result of a local inflammatory reaction.

5. The presence of lymphatic tissue in infant and selected necropsy specimens supports Warthin's contention of the existence of a "Graves' Constitution", that exophthalmic goiter is the clinical manifestation of a congenital constitutional anomaly.

6. Warthin's conclusion that this lesion is diagnostic for Graves' disease is vigorously supported.

7. Adenomata have no causal relationship to the symptoms of thyroid disease since they occur with equal frequency in normal and pathological glands. The use of the term should be abandoned in connection with the clinical diagnosis of hyperthyroidism.

8. A simple classification and diagnostic scheme of thyroid disease that is clinically and

pathologically compatible is suggested.

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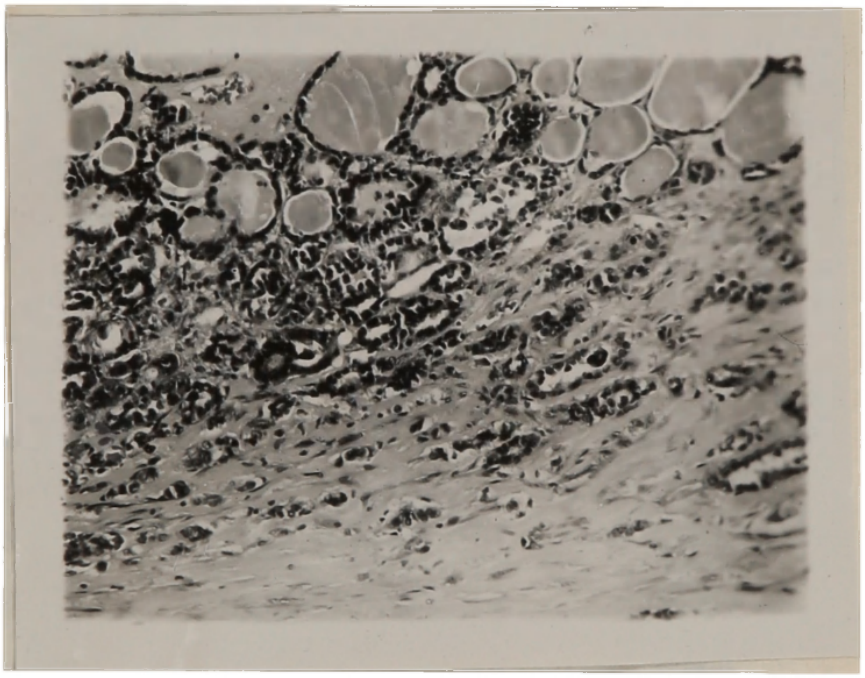

Figure 1. Photomicrograph showing an adenomatous area from a selected post mortem case with a history of no thyroid disease.

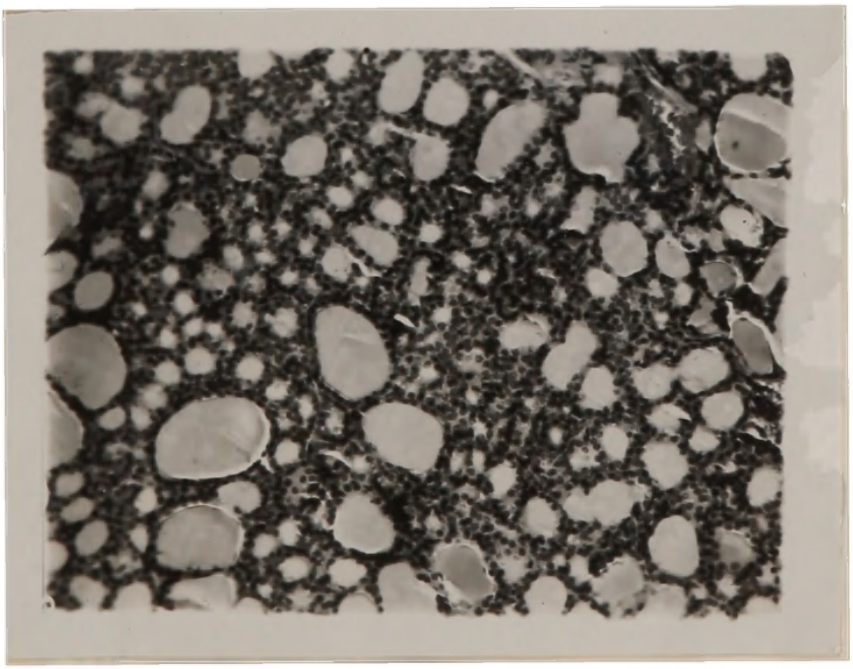

Figure 2. Photograph of gross specimen of adenoma with photomicrograph showing the encapsulated area.

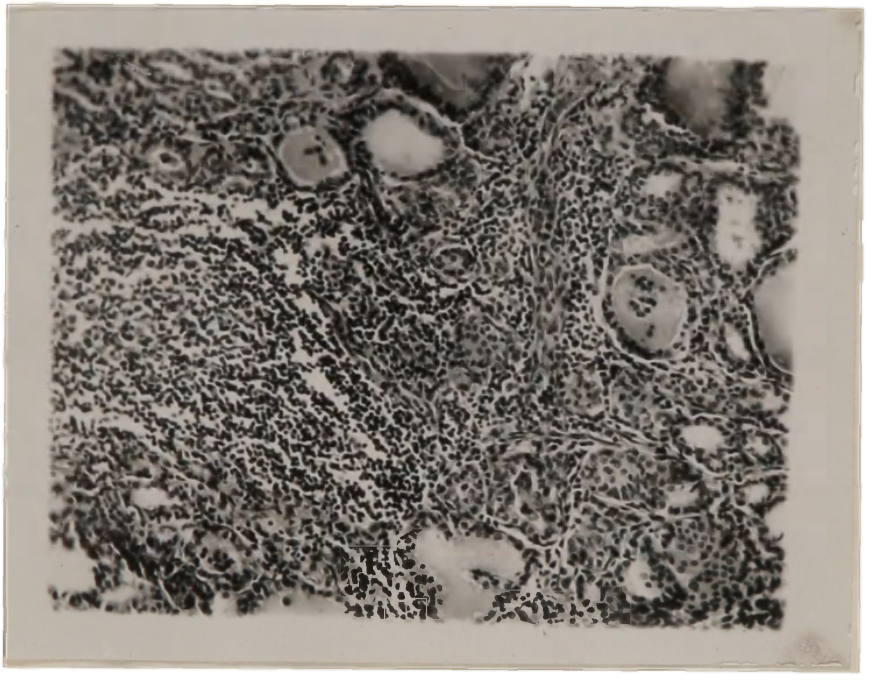

Figure 3. Photomicrograph showing an area of lymphocytes in the non-adenomatous tissue taken at "A" shown in figure 2.

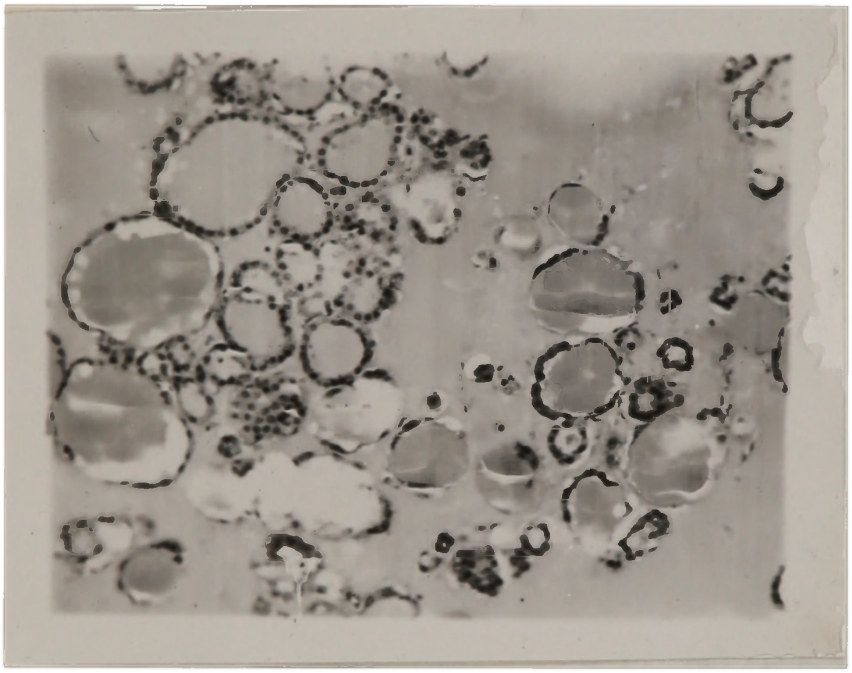

Figure 4. Photomicrograph of adenomatous tissue from thyroid gland of a dog.

Figure 5. Photomicrograph showing a tubercle in thyroid of a young child.

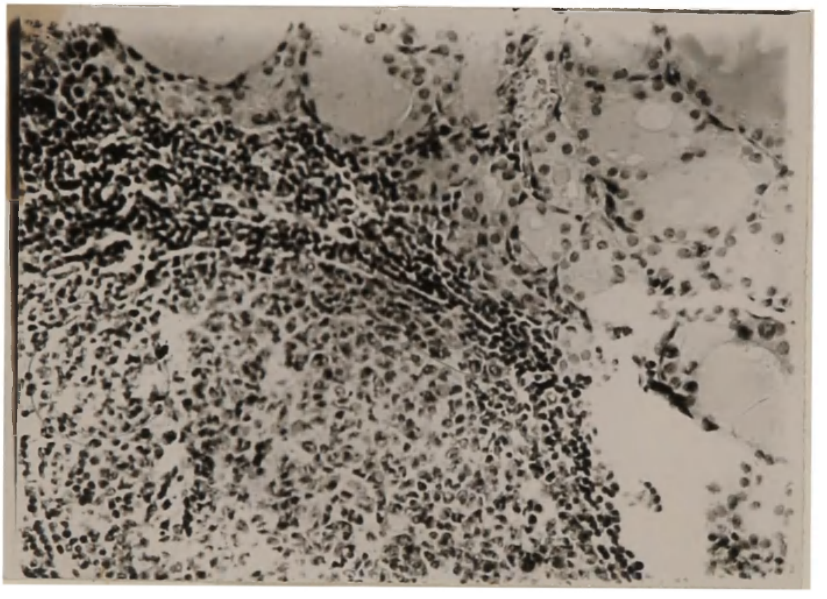

Figure 6. Photomicrograph showing the only area of lymphoid tissue found in numerous sections from a gland showing extensive epithelial hypertrophy.

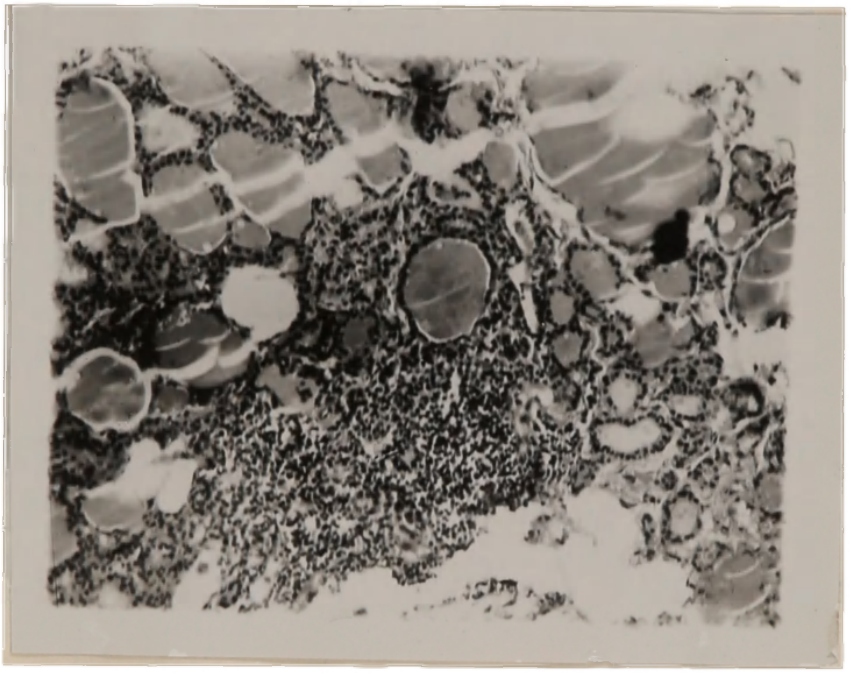

Figure 7. Photomicrograph showing the only area of lymphoid tissue found in sections from nine different blocks, epithelial hypertrophy being absent.

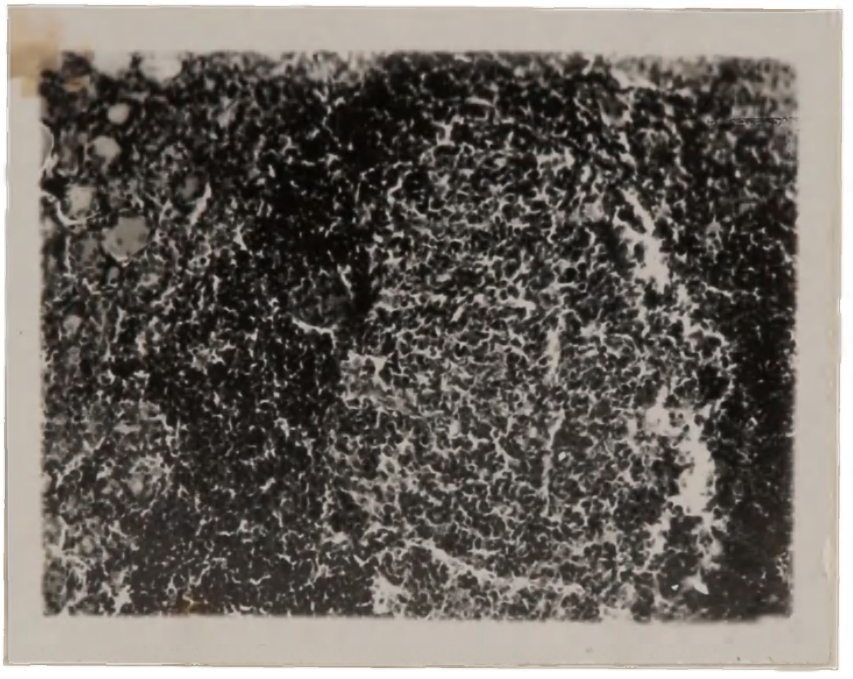

Figure 8. Photomicrograph of thyroid of severe case of exophthalmic goiter.

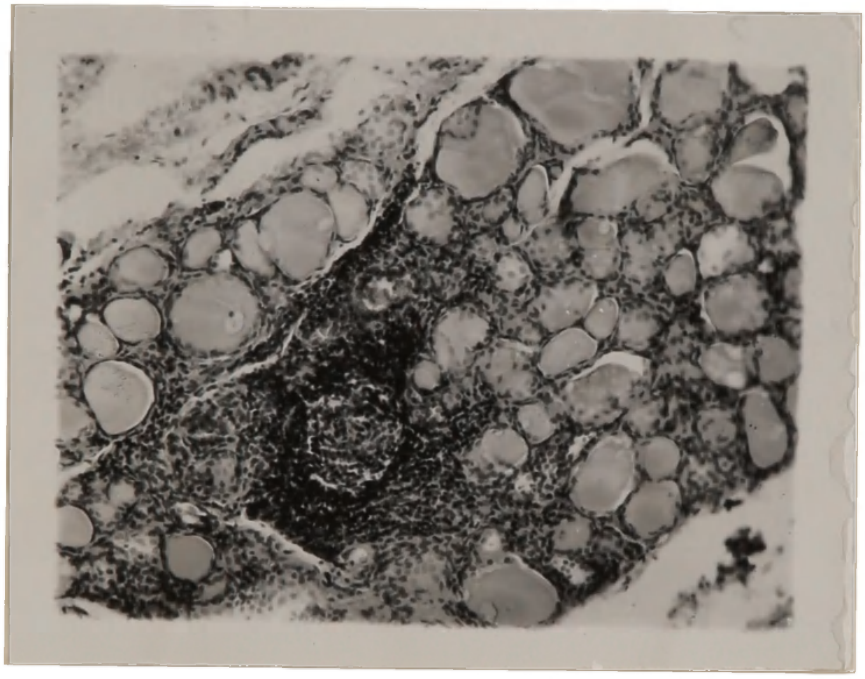

Figure 9. Photomicrograph from a mild case of exophthalmic goiter.

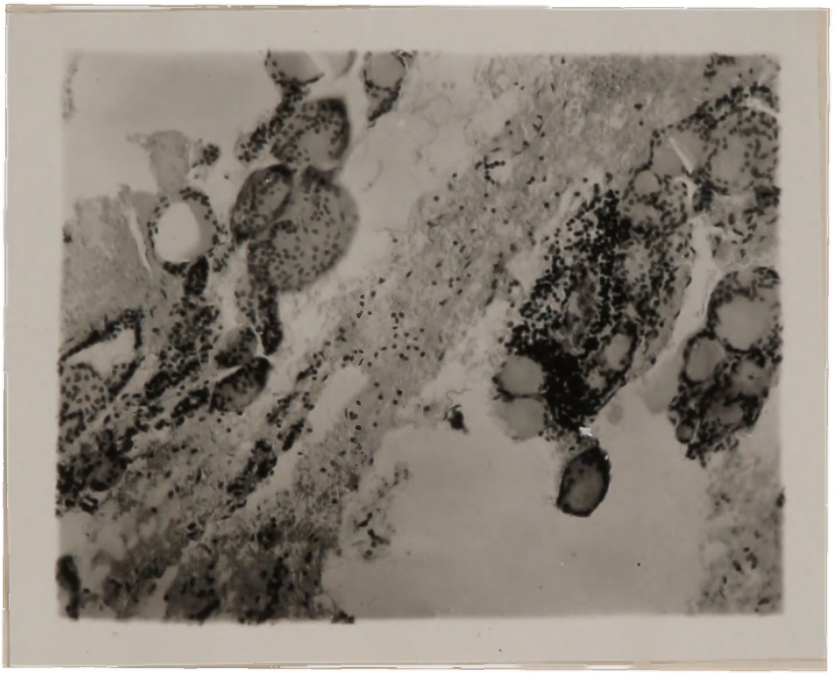

Figure 10. Photomicrograph showing a small area of lymphoid tissue in a gland from an infant.