THYROIDITIS AND THYROID FUNCTION

CLINICAL, MORPHOLOGICAL, AND PHYSIOPATHOLOGICAL STUDIES

BY

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with the co-operation of

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with a special contribution on

ASSOCIATED PITUITARY PATHOLOGY

by

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Foreword by

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Foreword

THE different forms of subacute and chronic thyroiditis have always stimulated great interest among thyroid specialists and endocrinologists. In the past fifteen years the concept of autoimmunity and the application of radioactive iodine uptake and thyroid antibody tests to the investigation of goitre patients have clarified this group of diseases. It is now accepted that all forms of lymphoid thyroiditis are an expression of organ specific auto-immunization based upon a familial predisposition and possibly still unknown external agents while De Quervain's disease is more clearly virus induced and non-autoimmune. The controversy about Hashimoto's and Riedel's thyroiditis which occupied the literature in earlier years is now almost settled and it seems clear that Riedel's disease is in some way related to a group of unexplained fibrosing conditions which include retroperitoneal, mediastinal or cholangitic forms but bear little relationship to struma lymphomatosa or autoimmunity as we now know it.

One of the most interesting problems is the connection of chronic thyroiditis with the other autoimmune disorders and Paul Bastenie's 1937 monograph on this topic is one of the pioneer works. He showed not only that primary myxoedema and Hashimoto's goitre had the same underlying lesion but also that thyroiditis was found associated with pernicious anaemia, with subclinical hepatitis and several other conditions forming a spectrum of autoimmune disorders.

In subsequent years Professor Bastenie and his team at the Free University of Brussels have made important contributions to the detailed understanding of the incipient stages of hypothyroidism and have revealed important clinical connections with obesity and atherosclerosis. Their wide clinical experience is summarized in the present book which also tries to give the practising physician an overall view of iodine metabolism and pituitary thyroid relationships.

The clinical case histories given as examples for each type of thyroiditis add immediacy to the more didactic chapters, while the recent statistical research on thyroid antibodies in patients with atherosclerosis gives a foresight into future computer medicine.

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Acknowledgements

NEARLY fifteen years ago the pioneer work of Witebsky and his group and of Doniach and Roitt in the field of thyroid autoimmunity renewed interest in the clinico-pathological studies of thyroiditis performed earlier in this department and gave impetus for fresh efforts. Thanks to the new methods of thyroid investigation and the strenuous endeavours of a team of enthusiastic co-workers, material soon accumulated from which some new concepts emerged on the significance of the various forms of thyroiditis. The stimulating criticism of Dr. D. Doniach is gratefully recognized.

This work could not have been achieved without a great deal of help. In the first place the authors wish to express their gratitude to Professor P. Dustin. Not only were all ultrastructural studies performed in his department, but without his help the thyroid autoradiograph and the studies of Professors Herlant and Pasteels on the pathology of the pituitary in chronic thyroiditis would have been impossible. Moreover, many illustrations of this book are due to his kind co-operation.

The authors wish to thank Dr. J. E. Dumont, Dr. Galand, Dr. Decostre, and Mrs. Golstein who contributed with many valuable documents. They appreciate the skilful help of Mrs. Wouters, Miss Marchand, and Miss Dubois in the technical studies, of Mr. De Meire and Miss Procureur in the illustrations, and of Mrs. Delbrassine and Miss Malbrecq in the preparation of the manuscript. Great thanks are due to Mrs. Jank for her help in our struggle with the intricacies of the English language.

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P.A.B.
A.M.E.

Introduction

P. A. BASTENIE

"Chronic thyroiditis: a potentially confusing picture"[24]

THE subject of chronic thyroiditis is surrounded by many confusing concepts and denominations. The main cause of this situation is our ignorance of the aetiology of the various disorders which are included under this term.

Early clinico-pathological studies ascribed all forms of chronic lymphocytic thyroiditis to some infectious process[25,28] and blamed tuberculosis, syphilis, and non-specified infections as the pathogenic agents. Other non-specified infections were thought to invade the thyroid through the remnants of the thyroglossal duct.

It is doubtful whether, except in a few cases of tuberculous infection, any of these agents have ever played an important role in the genesis of lymphocytic thyroiditis. It is, however, most likely that certain viral infections are responsible for the development of acute, subacute, and possibly chronic reactions of the thyroid parenchyma. The description of all conditions of lymphocytic thyroiditis under the single heading of non-specific chronic thyroiditis has not helped matters.

Many years ago the study of a number of well-delineated nosological entities (myxoedema, Hashimoto's struma lymphomatosa, toxic goitre) showed that these conditions have in common identical parenchymatous and inflammatory lesions, varying only in degrees.[4]

Alongside these conditions of diffuse chronic lymphocytic thyroiditis, offering a definite clinical appearance, identical focal or diffuse inflammatory lesions were described in otherwise normal thyroids which had produced no clinical symptoms.[4,25]

The presence of the same lesions observed in such different conditions suggested that they were part of the same pathological process superimposed on different thyroid states. No evidence of an infectious origin was found, and the lymphocytes and plasma cell infiltrates were explained as inflammatory reactions to particular metabolic cell lesions leading to cell degeneration and lysis.[4,11]

At the present time, the fundamental sameness of the process, as first suggested by microscopical study, is generally admitted.[10,19,22,26] This view is based on very strong evidence. Electron microscopy has confirmed the previous observations by showing identical lesions in different variants of lymphocytic thyroiditis.[18] Biochemical studies have identified the same alterations of iodine metabolism in the hypertrophic thyroiditis of Hashimoto's disease[5] and in atrophic thyroiditis.[6,7] Finally, immunological studies have detected the same thyroid antibodies in most variants of lymphocytic thyroiditis.[10,21]

The discovery of thyroid antibodies circulating in the blood of subjects affected with chronic lymphocytic thyroiditis by Roitt *et al.*[20] and the experimental production of autoimmune thyroiditis in the rabbit by Witebsky and Rose[30] have been of capital importance in the study of this pathology. There is no doubt that the autoimmune process corresponds to important tissue alterations, possibly leading to the development of a self-maintaining destructive process.

The concept of lymphocytic thyroiditis as an autoimmune disease naturally led to the use of the general term "autoimmune thyroiditis"[9] for all the clinical entities previously described as individual variants of "non-specific chronic thyroiditis". Thus, as Wayne[27] put it so well, "the definition of the disease is switched from histological bases to an immunological aetiology". This attitude assumes that the autoimmune process is solely responsible for all forms of lymphocytic thyroiditis. It implies, as the essential cause of the disease, the existence of a primary inborn anomaly of the autoimmune apparatus.[12,14,23] However, the basis for such an attitude is not proven. A viral or metabolic anomaly may well trigger off the inflammatory process.

In many textbooks on thyroid diseases[13,17,27] or on autoimmune diseases,[3,15] the section on chronic thyroiditis is entitled "Hashimoto's disease", and in many papers the terms "chronic thyroiditis" and "Hashimoto's thyroiditis" are used synonymously. But chronic thyroiditis may occur with several variants which display different clinical characteristics, follow different courses, and require different treatments.

Further confusion arises from the assignment of an autoimmune origin to thyrotoxicosis by Adams[2] and by McKenzie.[16] This disease is claimed to be induced and maintained by a particular factor—the long-acting thyroid stimulator (LATS) discovered in the serum of hyperthyroid subjects[1] and displaying the characteristics of a thyroid

TABLE I.1. CLASSIFICATION OF THYROIDITIS (AM. THYROID ASSOC. 1969)

"Diseases characterized by euthyroidism"

5. Acute thyroiditis
   - suppurative
   - subacute non-suppurative

6. Chronic thyroiditis
   1. Lymphocytic (Hashimoto):
      - (a) variants (1) fibrous
        - (2) adolescent
        - (3) atrophic*
        - (4) focal
      - (b) with eye changes of Graves' disease
   2. Invasive fibrous (Riedel)
   3. Suppurative
   4. Non-suppurative

* This condition is further mentioned under the heading "II. Diseases primarily characterized by hypothyroidism."

antibody. Some authors consider that thyrotoxicosis and Hashimoto's disease are two facets of the same pathological process.[10] Moreover, it is believed that thyrotoxicosis might originate during the course of lymphocytic thyroiditis of the Hashimoto type, and the term "Hashitoxicosis" has even been proposed. Thus autoimmune lymphocytic thyroiditis might lead in some cases to the progressive destruction of the gland, with ensuing hypothyroidism, and in others to the development of thyrotoxicosis.

Lastly, it should be remembered that in certain types of chronic thyroiditis no serological signs of thyroid autoimmunity are observed. This is the case in invasive fibrous thyroiditis, described at the end of the last century by Riedel, and which has since been confused with the sclerotic variant of Hashimoto's thyroiditis.

It is therefore understandable that a paper describing such developments was entitled "Chronic thyroiditis; a potentially confusing picture".[24]

The classification of thyroid diseases recently proposed by the Committee of Nomenclature of the American Thyroid Association[29] goes a long way to combat these intricacies (Table I.1). Thyroiditis is mentioned under "Diseases primarily characterized by euthyroidism", and atrophic thyroiditis (a variant of lymphocytic chronic thyroiditis) is also referred to under the heading of "Diseases primarily characterized by hypothyroidism". However, chronic thyroiditis is still identified with Hashimoto's disease, although different variants are recognized. Moreover, thyroiditis is not listed under the "Diseases primarily characterized by hyperthyroidism."

These preliminary remarks underline the importance of the new concepts introduced in the study of thyroid diseases. The interest of chronic thyroiditis extends far beyond the narrow limits assigned to it by the textbooks. Study of the subject must embrace the aetiology of idiopathic myxoedema, the mechanism of thyrotoxicosis, and many important problems of diagnosis and therapy in general thyroidology.

The aim of the present monograph is to clarify this complex pathological picture as far as possible. Material for such an endeavour is provided by recent progress in morphological, biochemical, and serological thyroid studies, and by work currently under way in our own department of medicine and in the laboratories of Nuclear Medicine (Dr. J. E. Dumont), Radioisotopes (Dr. A. M. Ermans), and Pathological Anatomy (Prof. P. Dustin) of this University.

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CHAPTER 1

Structure and Function of the Normal Thyroid Gland

A. M. ERMANS, P. NÈVE, and P. A. BASTENIE

1. Introduction

The role of the thyroid is to convert inorganic iodine into thyroid hormones and to maintain a sufficient quantity of these hormones in the tissues. The gland performs this role by a complex mechanism which is at present only partially understood; the main stages are sketched out in Fig. 1.1.

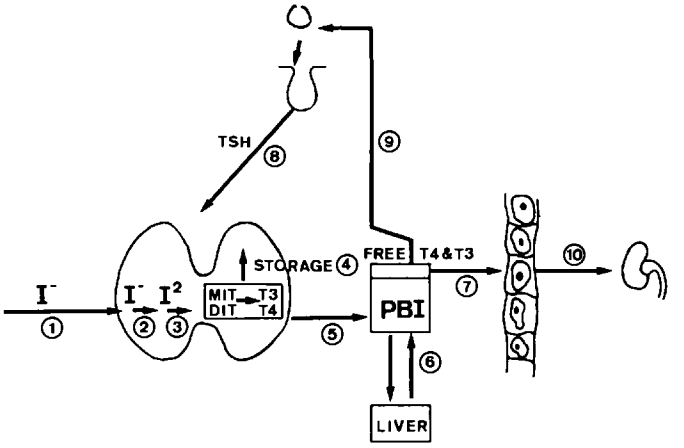

FIG. 1.1. Schematic representation of thyroid physiology.

The thyroid concentrates the iodide ion of the circulating blood during its passage through the gland (phase 1). The iodine is then oxidized (phase 2) and bound to the "tyrosyl" or "iodotyrosyl" groups of thyroglobulin. Inside this large molecule, the iodotyrosyl groups of amino acids are converted into thyroxine and triiodothyronine, i.e. into metabolically active hormones (phase 3). The thyroglobulin accumulates in the follicular lumen in the form of colloid (phase 4). The hormone compounds are released by a process of enzymatic proteolysis and secreted into the circulation (phase 5), where they are almost totally bound to blood proteins and constitute the organic iodine of the plasma (PBI). These hormones are concentrated partially in the liver (phase 6). A very

small non-protein-bound fraction penetrates the peripheral tissues by unknown mechanisms (phase 7) and there produces a characteristic metabolic effect.

The speed and duration of certain of these phases are partly governed by the hypophysial thyrotropic hormone (TSH) (phase 8), whose secretion is itself dependent on a hypothalamic centre. The quantity of thyroid hormones in the circulation controls the degree of thyrotropic stimulation through the intermediary of the hypothalamo-hypophysial axis (phase 9).

The physiological or biochemical effect of the thyroid hormones is influenced by the interference of other hormonal factors such as cortisone, epinephrine, and oestrogens.

Finally, the principal pathway competing with the thyroid iodide cycle is represented by the renal clearance and urinary excretion (phase 10).

Currently held concepts on these different stages of iodine metabolism will be briefly reviewed in this chapter: special attention is given to certain parameters which are critically altered in thyroiditis.

2. Morphology

Human thyroid tissue, even under normal conditions, displays a less uniform structure than that of thyroid glands of the usual laboratory animals. The morphological unit of the thyroid gland is represented by the thyroid follicle, made up of a single layer of cells surrounding a mass of colloid. Some controversy exists about the arrangement and the interlinking of the follicles in the thyroid gland. Certain authors hold that the follicles are always isolated whereas others maintain that they communicate with each other via a central duct.[62,78,121]

A recent study[94] using three-dimensional models reconstructed from serial sections of rat thyroid tissue seems to solve this controversy. The authors report that the follicular lumen and colloid masses are rarely connected: almost all the follicles are therefore individual, consisting of epithelial cells completely surrounding the colloid. On the other hand, epithelial contacts exist between the follicles, which thus form a chain and only retain their individuality by virtue of their own lumen.

Apart from the follicular cells proper, there are some parafollicular cells also referred to by the name of "light cells". They occupy an extrafollicular position and produce calcitonine, a factor which lowers serum calcium.[22,151,152] Finally, in rats and mice, there exists a second system of follicles alongside the classic thyroid follicles. The structure of the second series is very special, often with desquamation of the cell debris into the colloid.[93,134,208,214] These follicles, sometimes termed "ultimobranchial follicles" have also been reported in man.[208] Their significance is at present unknown.

It is possible that the peculiar cell accumulations, often resembling parathyroid tissue, which appear in thyroiditis glands, take their origin in "ultimobranchial structures".

The appearance of the follicular epithelium reflects to some extent the state of activity of the thyroid gland. In conditions of hyperactivity or intense stimulation, the usually cubic epithelium is replaced by a cylindrical epithelium with nuclei located at the base of the cells. The follicular lumen is reduced. By contrast, hypoactive glands (for instance,

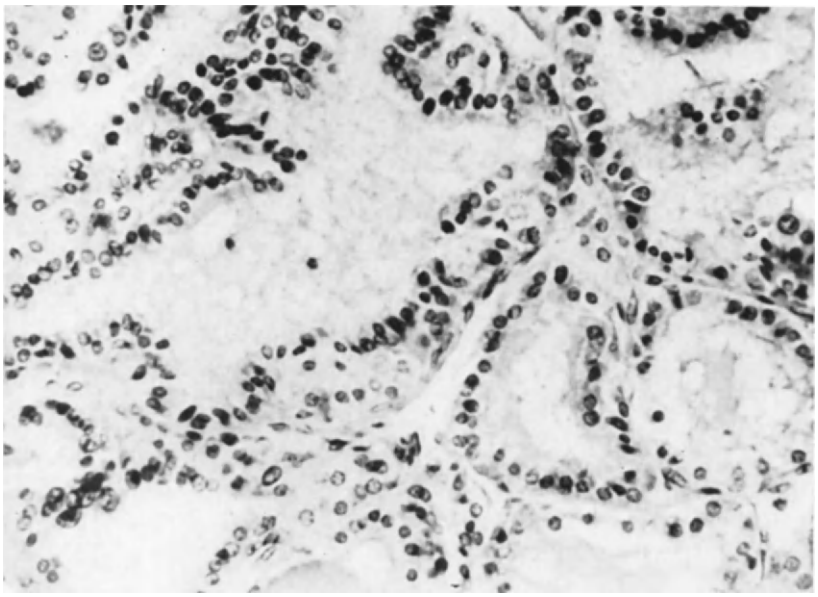

FIG. 1.2A. Cylindrical aspect of the thyroid epithelium in untreated hyperthyroidism. The colloid is foamy and scanty. Death in thyrotoxic crisis. (×200.)

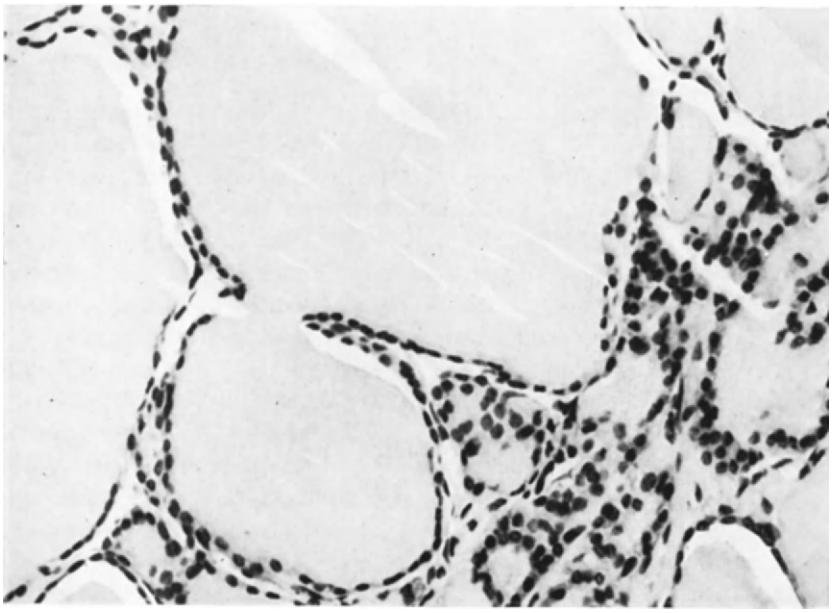

FIG. 1.2B. Flattened epithelium in thyrotoxic gland treated with iodine. Resting state. (×200.)

after hypophysectomy) are characterized by flattening of the epithelium and accumulation of colloid. Cell height is considerably diminished: the nuclei, themselves flattened, occupy a central position (Figs. 1.2A, B and 1.3).

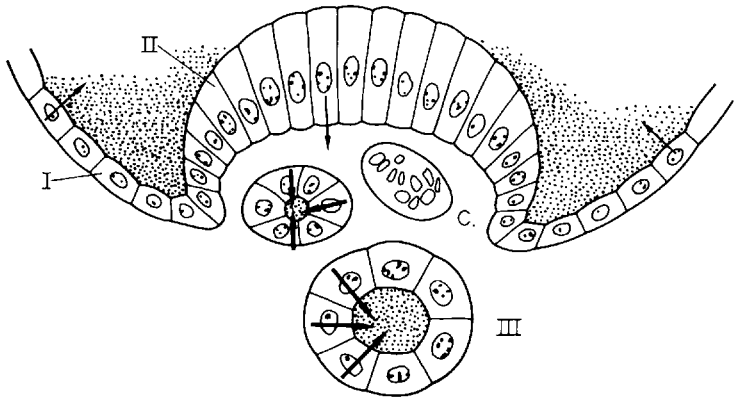

FIG. 1.3. Cellular types in the thyroid. Goormaghtig and Thomas[68] have interpreted the signification of the cellular types forming large and small follicles. The cellular types and also the size of the follicles must be considered as constantly changing. This restless morphokinesis corresponds to variations of stimulation and resting stages.

Ultrastructure of the Follicular Cells

In recent years the electron microscope has enabled the investigation of the structuer of thyroid cells in animals,[3,16,36,51,65,86,97,107,119,141,201,217,233] and in man.[85,132,136]

Figure 1.4 shows the ultrastructure of a normal thyroid follicular cell. It is characterized by polarity: microvilli at the apex, a basal membrane, a Golgi apparatus above the nucleus, and lateral "terminal bars" closing the intercellular space. The cytoplasm shows close association between the ergastoplasmic membranes and the mitochondria. Dense granules looking like lysosomes are visible here and there inside the cytoplasm.

In our understanding of thyroid function, the morphological picture cannot be separated from its biochemical aspects. Figure 1.5 gives parallel diagrams of the processes of thyroid hormone synthesis and storage and the mechanisms of secretion.

The peptide chains of thyroglobulin are synthetized in the ergastoplasmic cisternae[53,126,162] with the energy supplied by oxidative phosphorylations in the mitochondria. The carbohydrate part of the thyroglobulin (at least the galactose) seems to be linked to the peptide chain in the Golgi apparatus.[215] Subsequently, the thyroglobulin, either partly iodinated[137] or not yet iodinated, seems to be discharged into the lumen together with the amino acids (tyrosine and thyronines) trapped by the thyroid cell by an active transport mechanism.

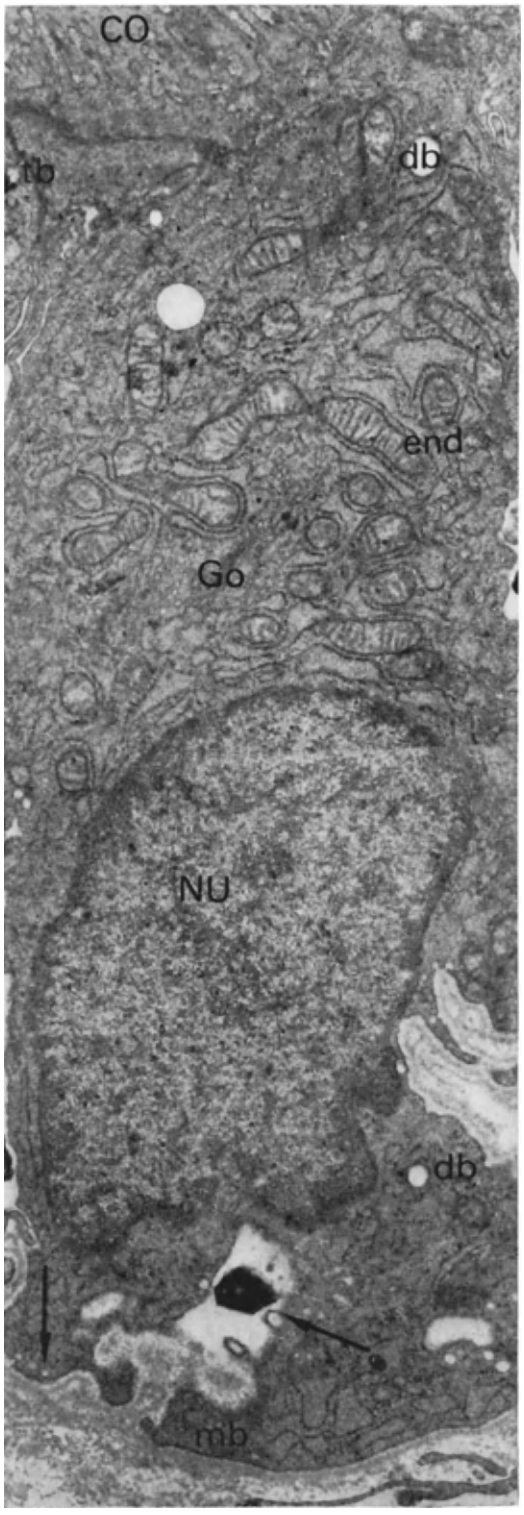

FIG. 1.4. Electron micrograph of a normal human thyroid follicular cell. Microvilli border the apex of the cell along the colloid lumen (CO). A basement membrane (mb) runs along the base of the cell; the intercellular space is closed near the apex by a terminal bar (tb). Rough endoplasmic cisternae (end) are closely associated with the mitochondria. The Golgi apparatus (Go) is above the nucleus (NU). Some dense bodies (db) are scattered thoughout the cytoplasm. Note pinocytotic vesicles (arrows) at the base of the cell. (×14,800.)

Then the iodide passes straight to the apical cell membrane, where iodide oxidation and iodination of the tyrosines of the thyroglobulin most probably take place. The thyroid hormones are thus bound to the thyroglobulin which is stored in the follicular lumen.

Mechanisms and Effects of Thyroid Stimulation by the Thyrotropic Hormone

It is well known[38,125,225] that the injection of thyrotrophic hormone of hypophysial origin rapidly induces the appearance of PAS positive droplets called "colloid droplets" in the apical cytoplasm of follicular cells. Histochemical and autoradiographic techniques applied to electron microscopy have demonstrated that most of these colloid droplets are produced by a process of colloid phagocytosis by the follicule cells; the droplets fuse with the lysosomes and are then gradually digested.[52,182,183,184,194,213]

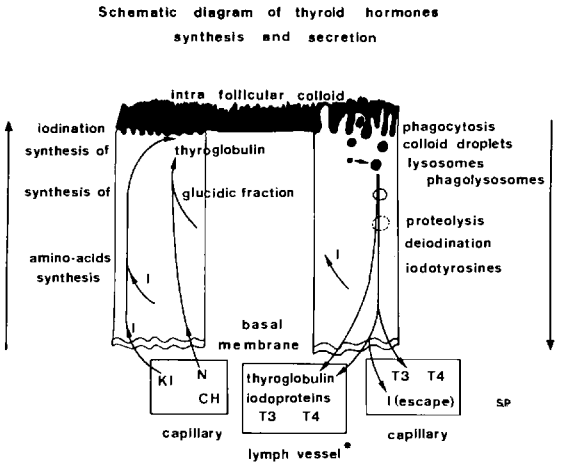

FIG. 1.5. Lymphatic drainage plays a large part in the excretion of thyroid hormones—particularly during increased stimulation. The importance of the thyroid lymphatics has been underlined in recent studies[49].

In a recent study,[133] the ultrastructural and biochemical effects of *in vivo* TSH stimulation of dog thyroid were investigated and compared (Fig. 1.6). The activity of the glands was first depressed by the administration of thyroid hormone for 3 days. At this point the rounded thyroid vesicles were made up of a flat epithelium of cells measuring 5–8 μ in height. For the first 10 min after thyrotropic hormone injection no changes were observed. Then, in a steadily growing number of cells, the colloid droplets were seen to be phagocytosed and to merge with the lysosomes. The lysosomal hydrolysis of the colloid drop led to the release of thyroid hormone. Ten to twenty minutes after the injection, prelabelled thyroid hormone was seen to pass into the thyroid veins.[44]

Two hours after the TSH injection, new morphological changes were observed: in the cylindrical cells, now attaining heights of 18–20 μ, free polysomes were present in large numbers, the ergastoplasmic cisternae were enlarged and the Golgi apparatus was developed. These morphological signs, together with the increased concentration of RNA,[100,111] suggest that this second phase of stimulation comprises increased synthesis of thyroglobulin.

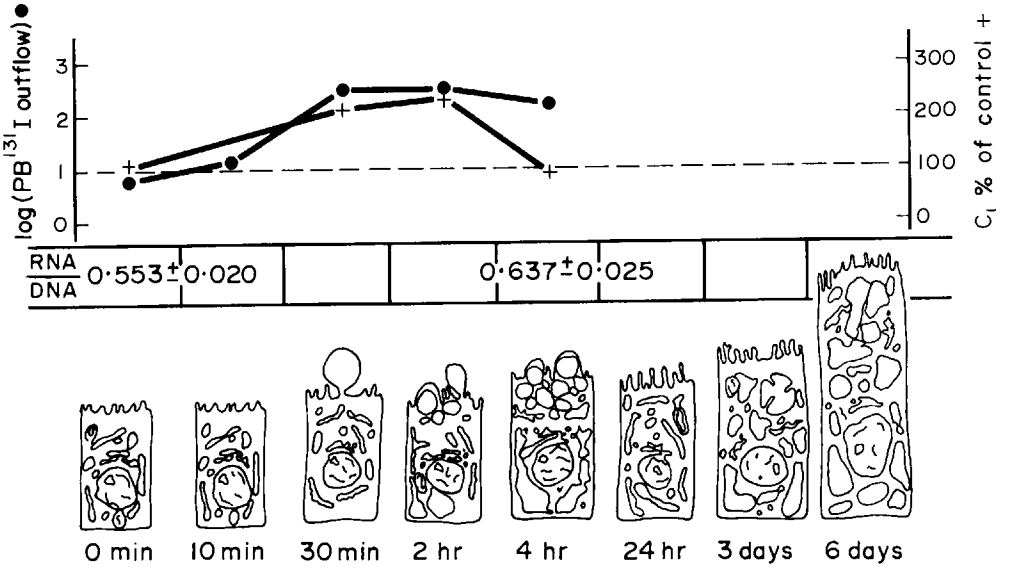

FIG. 1.6. Schematic representation of biochemical and ultrastructural changes induced by acute and protracted TSH stimulation of dog thyroid *in vivo* (unpublished documents of Dumont, Lecocq, Rocmans, and Nève; cf. refs. 44, 100, 101, 133). *Upper part*: ●—● hormone secretion; +—+ hexose monophosphate pathway. (RNA/DNA): RNA synthesis. *Lower part*: phagocytosis of colloid droplets (lysosomal digestion and growth).

Such a view seems to be confirmed by recent work.[47] The increased oxidation of 1-^{14}C glucose, observed 30 mins after the injection of TSH, probably indicates transitory stimulation of the monophosphate hexose pathway presumably related to colloid phagocytosis.[45] On the other hand, the greater glucose trapping 1½ hr after TSH administration is most likely related to the synthetic activity taking place at this time.

After 6 days of stimulation by the thyrotropic hormone, no more colloid droplets were detected in the follicular cells; at this point the colloid had virtually disappeared from the follicular lumen. The intense secretion from the cells observed at this stage is perhaps explained by a considerable acceleration of the normal process of thyroglobulin secretion and its resorption at a very rapid rate. The authors wonder, however, whether in such circumstances the intrafollicular thyroglobulin stage cannot be bypassed and the whole process of thyroglobulin synthesis—iodination and digestion—take place within the thyroid cells (cf. Fig. 1.5).

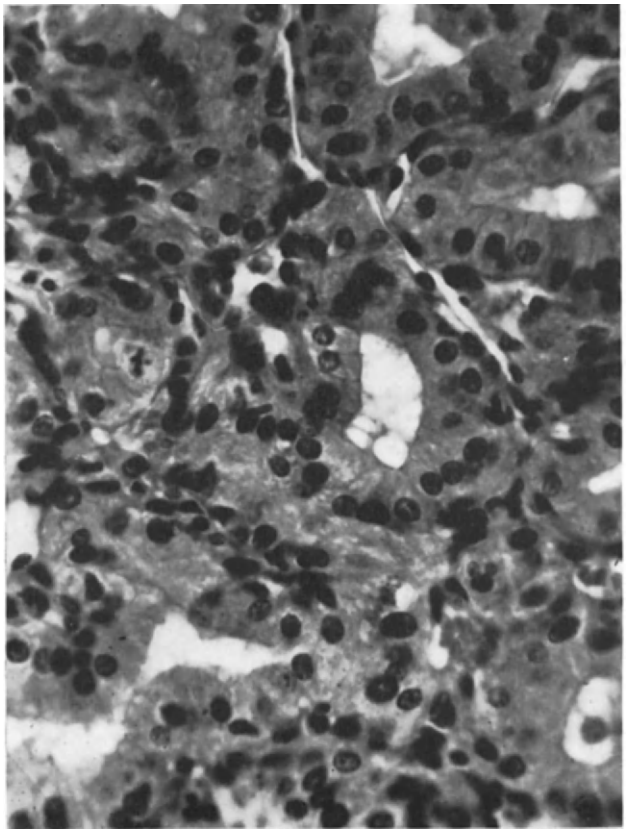

FIG. 1.7. Rat thyroid after protracted treatment with propylthiouracil (endogenous TSH secretion indicated by increased cell-height, with dome-shaped apex, and the reduction of colloid).

According to the diagram of hormone action set up by Sutherland,[200] it is currently admitted[1,21,54,95,103,175,215] that the primary effects of TSH on the thyroid gland are due to an intracellular increase of cyclic 3′-5′ adenosine monophosphate (c 3′-5′ AMP), by the activation of adenylcyclase which is presumably linked to the cell membrane.

It is through the intermediary of the c 3′-5′ AMP that the TSH would produce its primary effects, stimulating particularly 1-^{14}C glucose oxidation iodide organification and the formation of colloid droplets. Subsequently, the c 3′-5′ AMP would be transformed into inactive AMP by the intervention of phosphodiesterase formed.

A few hours after the first biochemical and morphological changes induced by TSH become apparent, numerous cell divisions can be observed in the hyperplastic cells. This mitotic process is easily demonstrated by the administration of colchicine[5] (Figs. 1.7 and 1.8). It is clearly this strong hyperplastic process that explains the evolution of the

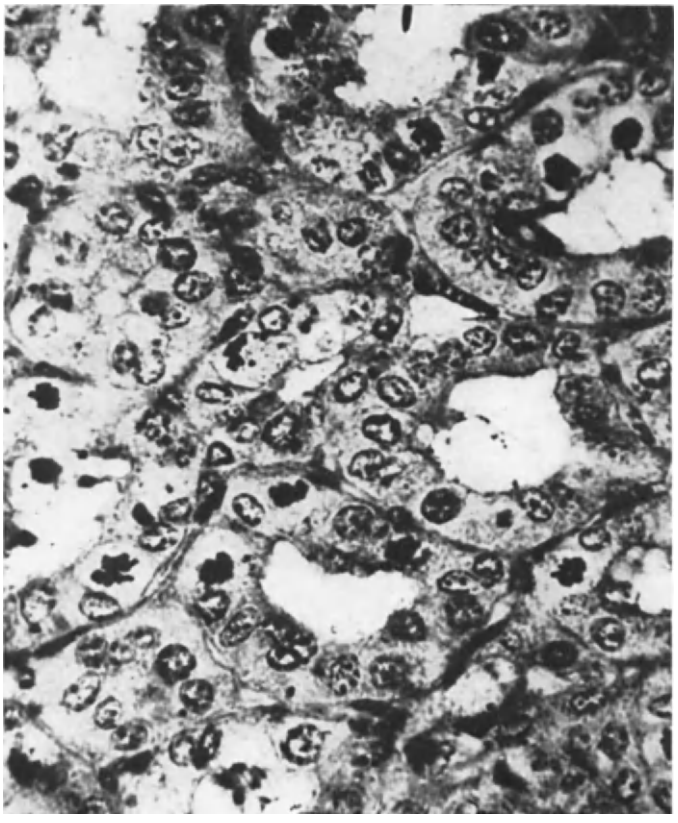

FIG. 1.8. Rat thyroid in same experimental conditions, after colchicine: a large number of mitoses blocked in metaphase are detected.

relatively homogeneous histology into very heterogeneous structures. The TSH stimulation has a marked morphokinetic effect.

Similar morphological changes may be reproduced experimentally by the administration of a low-iodine diet or anti thyroid drugs. Such treatments induce a state of chronic thyroid stimulation, characterized by colloid resorption, a high mitotic index, cell hyperplasia, and an increase of RNA per unit of cell mass.[111,199,227,228]

Morphological examination of endemic human goitre, at least in its early stages, reveals hyperplasia reminiscent of the image obtained by prolonged experimental stimulation of the thyroid.[164] Similar appearances are also found in toxic goitre.

The administration of iodine in high doses causes involution in the thyroid. Average cell height is reduced and colloid accumulates.[108,110] Pre-operative iodine treatment of toxic goitre also induces a certain degree of follicular involution for a short period of time.[85,165,167] This end picture is generally heterogeneous and difficult to interpret;

it shows small vesicles suggestive of cell hyperactivity together with large involuted follicles (cf. Fig. 1.2B).

But it must be remembered that even human thyroid glands considered to be normal show a heterogeneous morphological picture, probably accompanied by functional heterogeneity: this is a proven property of laboratory animal thyroids despite their more uniform morphological aspect. Numerous autoradiographic studies[40,99,124,184,205,224] have revealed an extremely uneven pattern of distribution of radioactivity in the thyroid after an injection of radioiodine. Shortly after injection, the smallest follicles display the

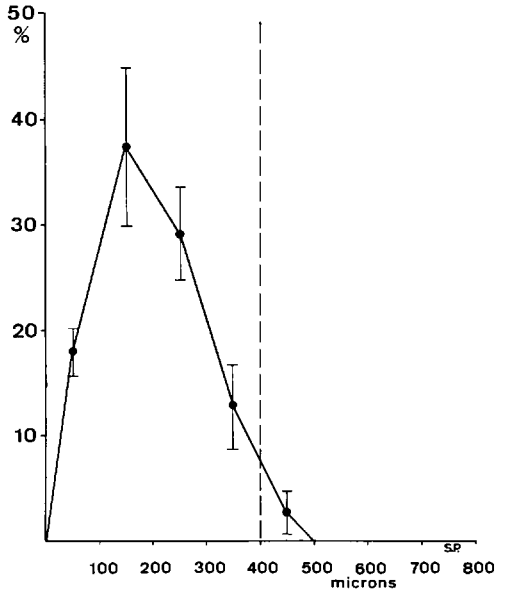

FIG. 1.9. Distribution of follicles in regard to diameter in normal human thyroid glands.

highest concentration of organic radioiodine, whereas at later intervals the concentration is highest in the large follicles.[40,125] By isotope equilibrium techniques, Loewenstein and Wollman[106] have demonstrated that the smallest follicles secrete their iodine the fastest and attain equilibrium more quickly.

In normal glands from subjects living in the Brussels area, Decostre[27] evaluated the distribution curve of the follicular diameters, by planimetry. That curve was characterized by a maximal range of 400 μ and a mean value of about 250 μ. This is in agreement with the reports of Ingbar and Woeber[90] and Means *et al.*[113] (cf. Fig. 1.9).

When colloid goitre develops, the DIT/MIT + DIT ratio drops toward very low values and is paralleled by an increase of the follicular diameters. This increase in size of the follicles induces alterations of intrafollicular iodine kinetics by a critical decrease

of their surface:volume ratio. This is associated with a lower iodination of thyroglobulin and as a consequence a slowing down of DIT and T_4 synthesis.

3. Thyroid Iodine Metabolism

Iodine trapping in the thyroid comprises two separate biochemical processes, namely transport and organic binding. In physiological conditions, and in most pathological conditions too, the two mechanisms are intimately associated; they can only be distinguished by using a drug of the thiocarbamide type which prevents the organic binding of the iodide without impeding the transport mechanism.

Iodide Concentrating Process

Iodide is concentrated in the follicular lumen by a mechanism probably involving the basement membrane of the thyroid cell.[76,156,203] The process is dependent on adequate potassium concentration and is inhibited by cardiac glucosides;[221,222] it probably also necessitates the release of energy by ATP.[206]

Even after the blocking of organification by propythiouracil (PTU), the thyroid is capable of maintaining concentrations of iodide twenty times higher than that of the plasma, or even several hundred times higher in hyperactive states.[9]

The thyroid pump is inhibited by the SCN ions and by other monovalent anions;[230] it may be saturated by an excess of iodine.

Organification of Iodide

The incorporation of inorganic iodine to the tyrosyl or iodotyrosyl radicals of thyroglobulin is preceded by the oxidation of the iodine; this reaction constitutes the initial stage of hormone synthesis.[34] The oxidation of iodine accumulated in the gland is achieved by the intervention of a peroxidase which has been identified chemically by Alexander.[2] A peroxidase-tyrosine iodinase has also been demonstrated by De Groot.[33] The ability to bind iodine in a stable manner is shared by many proteins; thyroglobulin stands out particularly because of its high efficiency in this process.

In vivo, high concentrations of iodide block the organification mechanism.[17,129,219,220] This blocking action, often called the Wolff-Chaikoff effect, may be responsible for the development of goitre in subjects receiving very high quantities of iodide.[81,150]

The process of organification may also be inhibited by thiocarbamides, the commonest of which are thiourea, propylthiouracil, and methimazol. They compete with the iodide while the peroxidase is acting.[33]

In physiological conditions the organification process is so efficient that normal thyroid glands never contain more than traces of iodide.[127,185] However, if iodination is blocked by a congenital anomaly or inhibited by PTU, large quantities of ^{131}I may be concentrated in the gland in the form of iodide;[190] they are released very rapidly after

administration of perchlorate or thiocyanate (Fig. 1.10). This release is a sure indication of a defective organification of iodine.

Iodide released by SCN or perchlorate is derived exclusively from extrathyroidal iodine newly concentrated by the gland. The iodide fraction which is liberated by the mechanisms of intrathyroidal deiodination at the expense of MIT and DIT is not discharged by SCN or perchlorate. A distinction between two functionally separate iodide compartments in the thyroid is founded on this basis. One is made up of newly accumulated iodide, and the other of iodide deriving from the deiodination of the iodotyrosines.[77,188]

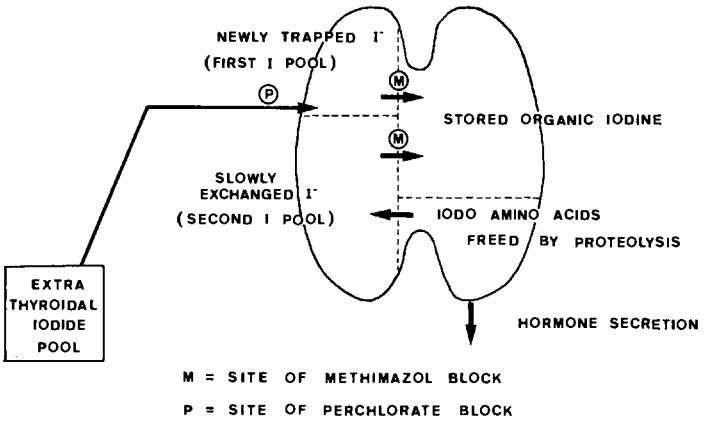

FIG. 1.10. Schematic representation of the iodine compartments in the thyroid gland, adapted from De Groot.[34]

Sequence of Hormone Synthesis

There are two fundamental stages of thyroid hormone synthesis: the first leads to the formation of mono- (MIT) and diiodotyrosine (DIT); the second to that of triiodothyronine (T3) and thyroxine (T4).[116,157]

These four end-products are obtained as a result of the following processes:

(a) Oxidation of the iodide into iodine.
(b) Iodination of tyrosyl groups and formation of MIT.
(c) Further iodination of the iodotyrosyl group and formation of DIT.
(d) Condensation of two molecules of DIT into 3:5:3′:5′-tetraiodothyronine or thyroxine.
(e) Condensation of one DIT molecule and one MIT molecule to form 3:5:3′-triiodothyronine.

The synthesis of iodotyrosines takes place extremely rapidly. In rats it can be detected a few seconds after administration of radioactive iodine.[32] In certain experimental conditions, the incorporation of radioiodine in the form of MIT is observed first, and then

labelled DIT is formed in increasing quantities.[32,157] After variable lengths of time, the distribution of radioiodine between MIT and DIT reaches a constant level which coincides with the ratio of the stable iodine contents of these two compounds.[11,32,159] This sequence is consonant with the precursor product relationship between the MIT and DIT; it has been confirmed by studies of their specific activity.[159]

In other experimental conditions, and especially when iodine supplies are less plentiful, parallel formation of MIT and DIT is observed and a stable MIT/DIT ratio is obtained almost immediately.[159] In human beings this is the general rule for both normal and diseased glands.

In physiological conditions, the MIT/DIT ratio is around 0·5 to 1 in man, the guinea-pig, and the rat.[59,60]

Rats submitted to a low-iodine diet show a marked increase in their MIT/DIT ratio.[102,161] A similar rise is observed in goitrous human glands: the quantity of di-iodotyrosine diminishes as the iodine concentration in the thyroid tissue is reduced.[55] A normal proportion of diiodotyrosine is found in glands whose iodine concentration per gram of tissue is over 400 μg. For lower concentrations, the relative quantity of DIT is inversely proportional to the iodine concentration. The factor which determines these changes in the MIT/DIT ratio is the degree of iodination of thyroglobulin.[60]

Synthesis of Iodothyronines

In contrast to MIT and DIT formation, the synthesis of T3 and T4 is a much slower process.[157,160] Although labelled iodothyronine is detected in rat thyroid during the hour following radioiodine administration,[32] in human thyroid the equilibration of the specific activity of thyroxine and triiodothyronine with that of their precursors is far from being attained even after several weeks.[59]

The hypothesis that thyroxine is synthetized by enzymic condensation of two DIT molecules was proposed by Harington and Barger in 1927[80] is still the most likely explanation particularly as thyronine—the iodine-free backbone of the thyroid hormone —is not a thyroid constituent.[34] This coupling reaction has been achieved *in vitro* under special experimental conditions, but mostly with low efficiency.[155,232] The stimulation of the coupling process by the l-amino-acid oxidase suggests the formation of an intermediate substance, namely 4-hydroxy-diiodophenyl pyruvic acid.[232]

In the normal human thyroid, *in vitro* hydrolysis by trypsin or pronase releases iodinated amino acids whose iodine contents are distributed on average in the following way: MIT 32·7%; DIT 33·4%; T4 16·2%; T3 7·6%.[59] Chromatographic data indicate that normal thyroid tissue contains 8 MIT molecules and 4 DIT molecules for each molecule of T4, which corresponds to a total of 20 atoms of iodine. It can be calculated that the simultaneous presence of these different amino acids in each molecule of thyroglobulin would correspond to an iodination level of at least 0·38%. But in Belgium the iodination level attains on average 0·23% in normal human glands. It must therefore be assumed that the iodinated amino acids are distributed unevenly over the different thyroglobulin molecules.

Thyroid Iodoproteins

Thyroglobulin (TG) is a glycoprotein with a molecular weight of about 650·000,[66,163,172] probably made up of 4 polypeptide chains; its sedimentation coefficient is 19 S. It is synthetized in the polyribosomes of the endoplasmic reticulum; it then travels towards the apical region of the cells and finally accumulates in the colloid.[126,215] Its iodination probably begins in the cytoplasm and continues in the colloid, especially on contact with the apical membrane. Synthesis and iodination of thyroglobulin take place simultaneously under physiological conditions, but they are governed by two quite distinct mechanisms.[105,137,140,202]

Other glycoproteins may be isolated in the thyroid tissue by ultracentrifugation on sucrose gradients.[178] These are glycoproteins with respective sedimentation coefficients of 3–8 and 12 S, whose molecular weights suggest that they constitute the corresponding monomer and dimer of thyroglobulin. The same methods reveal small amounts of heavier polymers—27 S and sometimes 32 S.

The relative importance of these different polymers varies considerably from one species to another also under the influence of pathological conditions and depending on protein preservation conditions.

It is generally agreed that the 4 S and the 12 S constitute the precursors of thyroglobulin, although a large part of these sub-units detected during separation is considered by certain authors to be a byproduct of 19 S degradation.[91,104,186,209] The 12 S and 19 S have identical physico-chemical properties. Part of the 4 S is made up of a lighter protein which has the properties of serum albumin.

If iodine supplies are low, thyroglobulin is insufficiently iodinated and has a sedimentation coefficient of 17–18 S.[138] This "prethyroglobulin" differs from 19 S in that it is highly sensitive to denaturing agents as freezing, sodium-dodecyl sulphate, pH increase;[48,92,186] subsequent iodination of this prethyroglobulin *in vivo* or *in vitro* gives 19 S.[28,91] The stabilization of the chemical character of thyroglobulin in the presence of iodine is often called "maturation". This maturing process is apparently not explained solely by the supply of a few atoms of iodine, but also by modifications in the quaternary structure of the protein chains together with a variation in the covalent links.[28,91]

A series of recent biochemical data have shown that the iodination level of thyroglobulin constitutes the determining factor in the quantitative distribution of various iodinated amino acids in thyroid tissue.[28,48,60,139,207] A drop in the iodination level entails a reduction in the gland's content of thyroxine and diiodotyrosine, to the benefit of monoiodotyrosine. The situation is reversed almost instantly both *in vivo* and *in vitro*, when the iodination level is increased.

Apart from the thyroglobulin, thyroid tissue contains variable quantities of a soluble iodoprotein, usually called S-1 protein or thyralbumin.[30,170,171] As regards electrophoresis, ultracentrifugation and solubility, the characteristics of this substance are similar to those of serum albumin. Only traces of this protein are found in the normal thyroid, but an iodoprotein with similar properties is present in much larger quantities in thyroid gland affected with cancer, hyperthyroidism, congenital metabolic defects, and

thyroiditis.[30,31,33,104] In the congenital anomaly called "plasma protein defect" it constitutes the main carrier in the thyroid iodination process.[30]

The origin of thyralbumin is still disputed. For some authors, it is the result of intrathyroid iodination of plasma albumin; for others it is synthetized in the gland itself.

Finally, 5–10% of organic iodine in the thyroid is bound to cell particles, mitochondria, microsomes, and cell nuclei. This protein fraction, called "particulate iodine", varies in certain pathological tissues.[10,114,138]

Under physiological conditions, therefore, thyroglobulin is virtually the exclusive substrate of iodine metabolism in the thyroid. It constitutes the principal site of iodination and the substrate of thyroid hormone synthesis; it also enables large quantities of these hormones to be stored.

Hormone Secretion

Thyroid hormones are secreted as a result of hydrolysis of thyroglobulin by a series of proteases and peptidases.[37,73,112] The characteristics of these enzymes are not yet fully known. Thyroglobulin is trapped by the apical pseudopody which isolates fragments of it and then absorbs them into the cytoplasm in the form of droplets, which are afterwards digested in the cell lysosomes.

At the end of this process of hydrolysis, the iodotyrosines and iodothyronines are liberated. The iodothyrosines are deiodinated by an iodotyrosine deiodinase in the thyroid cells.[173] The iodine thus recovered is normally re-used in the gland. Only traces of mono- and diiodotyrosines are found in the circulation under physiological conditions,[154] whereas thyroxine and triiodothyronine are secreted into the blood where they are immediately bound to specific carrier proteins.

Congenital Alterations of Intrathyroid Iodine Metabolism

Various forms of thyroid dysfunction are due to congenital disorders affecting specific stages of intrathyroid metabolism. Although exceptional, these diseases are of particular interest in that they are probably transmitted recessively. Some members of a family carry the complete anomaly, others only part of it.

The concept of a congenital error of metabolism was introduced into thyroid pathology by Stanbury;[191,192,193] it applies in cases of familial goitre associated with severe hypothyroidism and sometimes cretinism in patients carrying the complete anomaly.

Five anomalies have been described so far.[193] They affect one or the other of the following specific stages of iodine metabolism: transport, organification, coupling of iodotyrosines, deiodination of the diiodotyrosines (generalized absence of the necessary enzyme), and secretion of abnormal iodoproteins.

The metabolic alterations observed in two of these disorders are also found with significant frequency in thyroiditis. They are here briefly described.

Defective organification was the first congenital metabolic error described in thyroid pathology;[123,188] studies of thyroid tissue fragments from patients with this syndrome

agree with the hypothesis that there is a defect either in peroxidase or in iodinase necessary for the transfer of the iodine to the tyrosyl groups of thyroglobulin. Moreover, after *in vivo* administration of ^{131}I it has been observed that the only labelled iodine compound in the thyroid tissue is inorganic iodine.

This disease is to be diagnosed if administration of ^{131}I reveals the accumulation of large quantities of iodide in the gland. In the absence of organification, the iodide compartment is rapidly emptied at the same rate as the plasma iodide compartment. In these conditions the ^{131}I may be released from the gland after administration of 0·5–1 g of thyocyanate or perchlorate.

The same anomaly[153] has been observed in Pendred's syndrome which is characterized in particular by congenital deafness, in addition to hereditary goitre and hypothyroidism.[115,120,153] In such cases, the release of ^{131}I is usually incomplete. According to Stanbury,[193] the defect may also be due to a specific anomaly—albeit less marked—of the organification mechanism. But this author does not exclude the possibility that the release induced by perchlorate or thyocyanate, like that observed in patients with Hashimoto's disease, may represent a non-specific phenomenon common to different types of thyroid hyperplasia.

The second metabolic defect which resembles certain phenomena observed in thyroiditis is the replacement of thyroglobulin by other thyroid proteins as the substrate for intrathyroid hormogenesis. In this condition, part or almost all of the intrathyroid iodine is bound to a protein with the chemical and immunological properties of serum albumin.[30,104,229] The iodination of this abnormal iodoprotein has two major consequences.

In the first place, hormone synthesis is very inefficient. After enzymic hydrolysis of the thyroid tissue, only low quantities of DIT and traces of T4 are found; the main iodine compound is mono-iodotyrosine. Furthermore, whereas thyroglobulin is normally only secreted in minute amounts,[176] these abnormal iodoproteins are found in relatively large quantities in the serum.

The diagnosis is founded on the smaller-than-normal fraction of protein-bound iodine which can be extracted from the serum by butanol.[25,29] The physiological bond between plasma protein and T4 and T3 is easily broken by butanol acid, and these hormones are soluble in butanol. The normal fraction of iodine extractable by butanol (BEI) represents 90–98% of the plasma protein-bound iodine; this estimation has been checked for both stable and labelled organic iodine. Other amino acids bound to peptides found in the syndrome of abnormal iodoproteins are not extractable by butanol but precipitated with the PBI. This disparity between BEI and PBI forms the diagnostic basis of this disease.

Although the production of abnormal iodoproteins constitutes the main alteration in certain cases of congenital goitre, it is also found in other diseases and notably in Hashimoto's and Basedow's syndromes. The presence of iodoproteins other than thyroglobulin could constitute a physiological process, usually undetected because of the low concentration of the proteins or their low degree of iodination, but becoming apparent in all cases of hyperactivity of the thyroid tissue or in conditions entailing a limitation of the synthetizing capacity of thyroglobulin.[193]

4. Metabolism and Transport of Thyroid Hormones

Binding *proteins in the plasma*: as soon as they are secreted thyroxine and triiodothyronine are carried by plasma proteins until they are used by the tissues.[39,87,148,169] For thyroxine, three separate carrier proteins must be considered:

TBG (thyroxine-binding globulin).
TBPA (thyroxine-binding prealbumin).
TBA (thyroxine-binding albumin).

Thyroxine has a very great affinity for TBG which binds about 80% under normal conditions, whilst TBPA binds 10–15%.[218] Albumin only seems to bind T4 in the special conditions of *in vitro* studies. Triiodothyronine is carried mainly by TBG; it has no affinity for TBPA.[88] By adding increasing quantities of thyroxine *in vitro* it is possible to estimate the binding capacity of these proteins, i.e. the total number of sites available to the hormone. For T4 the capacity normally attains about 20 μg per 100 ml in TBG, and, depending on the techniques used, 130–210 μg per 100 ml in TBPA. A proportional relationship has been demonstrated between the concentration of TBPA and its binding capacity.[109,146,210]

Only a minute fraction of the thyroxine, about 0·05 to 0·1%, is not bound to carrying proteins.[89,197] The concentration of unbound thyroxine is the major determining factor for the metabolic activity of this hormone; it is influenced critically by the relative quantity of the carrier proteins which thus control the rate of penetration of the hormone into the cells.

Significant changes in the binding capacity of the plasma proteins are observed in pregnancy[42] after administration of oestrogens and in thyroid insufficiency. In all these conditions the binding capacity of TBG is increased. Conversely, it is diminished in thyrotoxicosis.[7,18]

Compared to T4, triiodothyronine has much less affinity for TBG; this difference of affinity accounts for the much faster speed of disappearance in the plasma of ^{131}I labelled triiodothyronine in relation to that of labelled T4. The difference in affinity also accounts for the fact that T4 easily takes the place of T3 in *in vitro* protein sites.[169] The fact that the two hormones have the same binding sites is exploited clinically by the uptake test of labelled triiodothyronine.[79,117,118,195] When serum is added *in vitro* to labelled triiodothyronine in the presence of a given quantity of ion exchange resin, the uptake of the labelled hormone by the resin varies inversely to the sites available on the binding protein. The T3 resin test thus allows an indirect estimate of the binding capacity of TBG, and is widely used in hospitals because of its simplicity.

Peripheral Metabolism of Thyroid Hormones

The proteolysis of thyroglobulin produces a constant flow of thyroxine and triiodothyronine into the circulation. The concentration of these hormones in the plasma depends on a great number of factors—their degree of affinity for plasma proteins, the

quantity of binding proteins available, and the uptake and release of the hormones by the liver,[24,82] and, finally, their catabolism in the tissues.[135,147,149]

Under physiological conditions, the average concentration of thyroxine iodine in the serum is usually considered to be 5·2 μg per 100 ml,[144,198] and that of triiodothyronine about 0·2 μg per 100 ml, but the latter figure is at present based on only a limited number of investigations.

The space of distribution of the two hormones is also very different: for a euthyroid adult weighing 70 kg it is estimated at 11 l. for T4 and 30 l. for T3.[63] Similarly, whereas the degradation rate of T4 is about 10% per 24 hr, it is as high as 50% for T3 over the same period of time.[130] On the basis of these data it has been possible to calculate the renewal rate and therefore the secretion rate of these hormones: for both thyroxine and triiodothyronine, secretion is estimated at about 60 μg of iodine per 24 hr.

Although this field of thyroid physiology is currently subject to reassessment, most recent data seem to attribute at least as much importance to the role of triiodothyronine as to that of thyroxine in the metabolic action of thyroid hormones in the tissues. The low plasma concentration of T3 in relation to that of T4 is explained by the former's much greater distribution space and, above all, by its much faster degradation rate.

5. Kinetics of Iodine Metabolism in the Thyroid

The representation of iodine metabolism in the thyroid by a system comprising three compartments was proposed almost 20 years ago by Brownell[20] and Riggs,[168] and has since been widely used by many authors.[6,35,56,189,212] The thyroid processes are reduced to the following compartments: extrathyroid iodide, extrathyroid hormonal iodine, and intrathyroid organic iodine. Despite its limitations, this representation of iodine dynamics allows easy estimation of certain essential parameters of iodine metabolism in the thyroid.

Some definite aspects of iodine kinetics have been investigated in thyroiditis. The methodologic basis of these calculations will be briefly discussed; detailed descriptions of these methods will be found in the papers of Stanbury *et al.*,[189] of De Groot,[35] and of Ermans *et al.*[23,57,58]

Kinetics of the Iodide Compartment

The extrathyroid iodide compartment represents about 75 μg of iodine distributed over a volume of 22–25 l., or about 35–40% of the body weight.[212] This space consists mainly of extracellular fluids: an appreciable quantity of iodide is concentrated by the salivary glands and digestive tract. Plasma iodide concentration is very low, around 0·2 μg per 100 ml; this concentration is too low to be detected by the usual chemical methods.

The iodide compartment is continually being cleared by two distinct mechanisms—the accumulation of iodide in the thyroid and its excretion by the kidney.

These mechanisms are defined by the constants K_{IG} and K_{IE},[35] which represent the fractions of the iodide compartment cleared per day respectively by the thyroid and by the kidney. The sum of the constants K_{IG} and K_{IE} therefore represents the overall disposal rate of the extrathyroid iodide compartment. This constant can be first calculated from the disappearance of labelled iodide in the plasma after administration of ^{131}I; it is also possible to obtain it indirectly by measuring thyroid uptake of ^{131}I during the 24 hr following administration of the tracer. The slope is obtained by deducting the uptake values at various time intervals from the maximum thyroid uptake (i.e. U_{max}).

In normal man, total disposal rate is on average 0·12 per hr, K_{IG} and K_{IE} being 0·04 and 0·08 per hr respectively. They can be worked out easily from the following formula:

$$K_{IG} = (K_{IG} + K_{IE}) \times U_{max},$$
$$K_{IE} = [(K_{IG} + K_{IE}) \times (1 - U_{max})].$$

Any interpretation of the kinetic data of inorganic iodine metabolism obtained on the basis of the three-compartment model is limited by a series of metabolic characteristics which are not considered in the model. In the first place the model postulates immediate mixing of the radioiodine in the iodide compartment. But, even after an intravenous injection of ^{131}I, its volume of distribution is observed to expand progressively over more than an hour.[142,143] Another limitation derives from the fact that under certain conditions the gland is likely to secrete relatively large quantities of iodide or a substance which is rapidly deiodinated in the circulation.[57] This mechanism probably plays only a secondary role in normal man, but assumes particular importance in certain pathological conditions, notably in endemic goitre, or when the iodine supply is very high.[57]

Intrathyroid Iodine Kinetics

The size of organic iodine stores present in the gland is another fundamental parameter of iodine kinetics. The principle of measurement is adapted from the method of Berson and Yalow,[8] which rests on the hypothesis that under equilibrium conditions the specific activities of extra- and intrathyroid organic iodine must be equal. Measurements are made a fortnight after administration of radioiodine, i.e. when plasma $PB^{131}I$ has reached a plateau.[23,57] In these conditions, let Q_g^{*eq} be the fraction of the dose of ^{131}I retained in the gland and PBI^{*eq} the level of plasma $PB^{131}I$; therefore:

$$\frac{Q_g^{*eq}\ (\%\ \text{of the dose})}{Q_g\ (\mu g)} = \frac{PBI^{eq}\ (\%\ \text{of the dose per litre})}{PB^{127}I\ (\mu g/l.)}.$$

The second member of this equation is the specific activity of the plasma protein-bound iodine in equilibrium (SA PBI^{eq}). Q_g is obtained by the following equation:

$$Q_g = \frac{Q_g^{*eq}\ (\%\ \text{of the dose})}{\text{SA } PBI^{eq}}$$

In twelve normal patients studied in our laboratory, the values of Q_g varied from 4·7 to 24·1 mg, with an average of 12·1 mg.[59] Values of the same magnitude were obtained by several authors using similar methods;[8,35,59,211] they tally with the data obtained by Heedmann *et al.*[84] using a process of *in vivo* spectrophotometry, but are perceptibly higher than the iodine contents found in normal human glands at autopsy. The estimation of the compartment of intrathyroid exchangeable iodine from the kinetic data mentioned above is open to criticism for various reasons. First, the specific activity of the iodine in the iodotyrosines and iodothyronines has not completely balanced out in the space of 15 days.[60] Furthermore, the concept of a homogeneous thyroid pool obviously clashes with the numerous morphological, biochemical, and physiological proofs of the functional heterogeneity of the gland.[158,180,204,220]

Nevertheless, certain experimental data have confirmed that it gives an acceptable approximation except in the case of glands with a very fast turnover.[55]

TSH Action on Iodine Kinetics in the Thyroid

Most stages of iodine metabolism are speeded up by thyrotropic hormone—iodide transport, organification, DIT formation, iodotyrosine coupling, and hormone secretion.[43,44,83,98,181] Study of the effects of TSH action reveals the immediate release of hormonal iodine and of large quantities of inorganic iodine deriving from the deiodination of the iodotyrosines.[177] Other effects, such as the increased activity of the iodide pump, need time before they become apparent.

(a) *TSH Effect on Iodine Uptake*

In man, the administration of a single TSH dose of 3–20 units increases thyroid uptake of radioiodine within 8 hr, with maximum effect between 18 and 24 hr. The increase is much more marked (around 25–50% above initial uptake) if the injection is repeated 3 days running.[50] This is the most frequently used test for investigating the reactivity of the gland to the thyrotropic stimulus; in the case of secondary myxoedema it furnishes conclusive proof of a pituitary deficiency.

The increased uptake induced by TSH may sometimes be masked by an accompanying increase in the release of radioiodine by the gland due to the same stimulus;[23] under these conditions it is therefore advisable to estimate thyroid pump activity by a more specific indicator than uptake at 24 hr. Einhorn,[50] for instance, measures the radioiodine accumulation rate soon after its administration.

(b) *TSH Effect on Release of Hormonal Iodine*

The gland's response to TSH may also be estimated from the changes in plasma protein-bound iodine levels.[96] A similar test has been used in this laboratory after injection of 10 units of TSH (Ambinon) in patients treated with a dose of 25 μc of ^{125}I 7 days before the test.[23,58] Figure 1.11 shows changes in PB^{127}I and PB^{125}I in the plasma observed at intervals of 2, 4, 6, and 24 hr after the injection of TSH in ten normal

subjects. At these intervals of time, the $PB^{125}I$ values were 42, 48, 61, and 98% higher respectively than the initial value. For plasma $PB^{127}I$ the initial level (6·1 μg per 100 ml) had already risen significantly by 2 hr, and had attained 8·3 $\mu g\%$ after 6 hr. It then rose less sharply, and in some patients the level noted at 24 hr was even lower than at 6 hr.

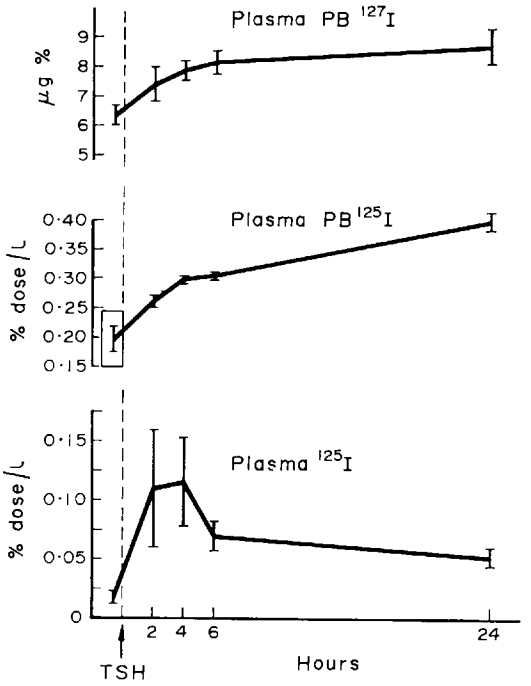

FIG. 1.11. Means and standard deviations of $PB^{127}I$, $PB^{125}I$ and of the labelled iodide in plasma after injection of TSH (10 units) in 10 normal subjects. Radioiodine was given 7 days before the injection of TSH.

Figure 1.12 shows a marked increase in the level of inorganic ^{125}I in the plasma 2 and 4 hr after TSH injection. Urine measurements show that excretion of ^{125}I is multiplied threefold in the 24 hr following administration of thyrotropic hormone. Table 1.1 summarizes the changes in the distribution of radioiodine induced by the administration of a single dose of TSH.

By comparing the measurements of labelled protein-bound iodine and stable protein-bound iodine immediately before and after TSH administration, it is possible to estimate the specific activity of the fraction of hormonal iodine released from the thyroid during stimulation.[23] We have:

$$\text{SA PBI} = \frac{PB^{125}I \text{ after TSH} - PB^{125}I \text{ before TSH}}{PB^{127}I \text{ after TSH} - PB^{127}I \text{ before TSH}}.$$

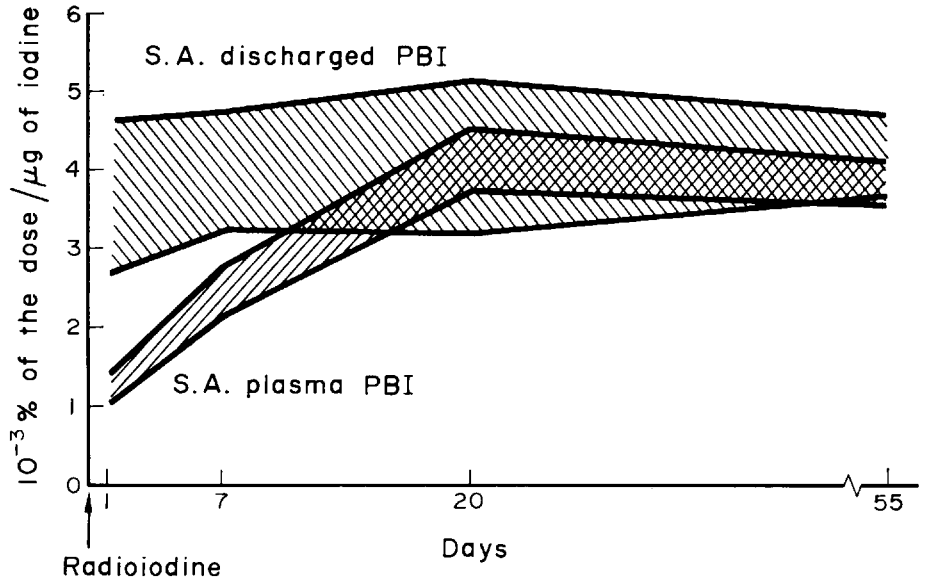

FIG. 1.12. Behaviour of the specific activity (SA) of plasma PBI and of the organic iodine discharged in blood after TSH stimulation (10 units), as a function of the time from administration of radioiodine.

TABLE 1.1. MODIFICATIONS OF THE DISTRIBUTION OF RADIOIODINE[a] INDUCED BY THE ADMINISTRATION OF TSH (10 UNITS) IN TEN NORMAL SUBJECTS

(After Ermans and Camus[58])

	Plasma PB^{125}I (% dose/l.)	Urinary ^{125}I excretion (% dose/day)	Thyroid ^{131}I (% dose)
Before TSH	0·189 ± 0·115	0·148 ± 0·068[b]	49·6 ± 7·8
Modifications after 24 hr	+0·205 ± 0·092	+0·433 ± 0·228[c]	−2·49 ± 1·78

[a] I^{131} and I^{125} were administered simultaneously 7 days before the TSH injection.
[b] Mean of 3-day collections before the injection of TSH.
[c] Twenty-four urine collections from the time of the TSH injection.

PB^{125}I and PB^{127}I are expressed in litres, PB^{127}I in micrograms, and PB^{127}I in per cent of the dose administered.

The specific activity of the PBI released after TSH was studied at different time intervals after ^{125}I administration. As Fig. 1.12 shows, the specific activity of the released iodine is already tending to become stable at 24 hr at a level approaching equilibrium.

As suggested earlier,[58] this observation indicates the prevalent role played by a very rapid turnover thyroid compartment in the regulation of hormone synthesis and secretion.

6. Regulation of Thyroid Activity

The activity of the thyroid gland is subject to several regulatory systems which will be considered here in turn.

TSH System

The regulation of thyroid function by the pituitary thyrotropic hormone (TSH) constitutes an example of the classic feedback theory: the TSH induces the secretion of thyroid hormones and the plasma content of thyroid hormones inhibits the secretion of TSH.[19,26] The process is partly controlled by the hypothalamus and the central nervous system. After stress or the action of an external stimulus, the nerve fibres of the anterior hypothalamus secrete a peptide called "thyrotropin releasing hormone" or TRH, which is discharged into the primary capillary plexus of the hypothalamo–hypophysial portal circulation.[13,71,74]

The secretion of TSH due to the action of the TRH peptide does not depend on new protein synthesis since it is not inhibited by protein synthesis inhibitors such as cycloheximide and puromycin.[15] On the other hand, the secretory effect of TRH is blocked by triiodothyronine and thyroxine, the latter being more active than the former.[14] Various experimental studies[14,179] suggest that this inhibitory effect of the thyroid hormones on the thyrotropic cells is dependent on the synthesis of a new protein which could act as a repressor of transcription. Although there are thyroxine-sensitive neurones in the hypothalamus, the anterior pituitary is, nevertheless, the main site of feedback inhibition by the thyroid hormones since inhibition continues even after destruction of the hypothalamic control of TSH secretion.

The plasma concentration of free thyroid hormones constitutes the main element in inhibition of TSH secretion: the factor involved in this feedback control is only sensitive to metabolic activity. This property has been demonstrated by the use of propylthiouracil which, by depressing metabolic efficiency and the deiodination of thyroxine, reduces T4 inhibition of TSH secretion.[61,122]

The TSH secretion time-lag is very short:[74] the plasma level of TSH increases from 15 min after electrical stimulation of the hypothalamus.[4] Similarly, the negative feedback of thyroxine is rapid since the high serum level of TSH in a patient treated with methimazole is back to normal within an hour after injection of thyroxine.[145]

Regulation of the Thyroid by Other Pituitary Factors

The existence of pituitary factors other than TSH influencing the activity of the thyroid gland is suggested by the fact that thyroid trapping of ^{131}I is depressed more in rats treated with triiodothyronine than in hypophysectomized rats.[69,70,75]

On the other hand, there is no quantitative difference in the reduction of thyroid hormone synthesis and secretion[166] whether the thyrotropic stimulus has been suppressed by hypophysectomy or by inhibitive treatment with thyroid hormone.

Several pituitary factors other than TSH have been cited as having a regulatory effect on thyroid activity. They include the heterothyrotropic factor (HTF),[64] ACTH, MSH, and vasopressin.[12,231]

The effects ascribed to these substances are open to doubt because of their lack of reproducibility and the particular non-specific way in which they are revealed.

All things considered, despite the extensiveness and diversity of the investigations, there has so far been no conclusive proof of the existence of a specific pituitary factor other than TSH capable of playing a part in thyroid regulation.

Autonomous Thyroid Regulation by Iodine

For some years it has been known that the thyroid gland possesses a self-regulating mechanism. In 1948 Wolff and Chaikoff[220] demonstrated that *in vivo* administration of a single dose of stable iodide to the rat, in a sufficiently large quantity to cause a marked increase in the plasma iodide concentration, inhibits the incorporation of iodide into the organic compounds.

The inhibition of iodide organification is overcome after a while, despite the maintenance of high plasma concentrations of iodide. This adaptation phenomenon leading to the resumption of hormone synthesis is called the "escape phenomenon".[17] It entails a reduction of the thyroid's iodide transport capacity, which causes a drop in iodide concentration and the consequent resumption of normal organification. Since *in vitro* administration of TSH does not modify escape from the Wolff-Chaikoff effect in adapted rats, it seems evident that the adaptation is an intrinsic thyroid mechanism.

This self-regulating iodine transport mechanism comes into play whatever the dietary iodine supply. Even after hypophysectomy in the rat[187] and mouse,[67] iodide trapping remains high when the animals are put on a low-iodine diet. Barakat and Ingbar[4a] have demonstrated a similar intrinsic iodine-trapping regulatory mechanism in the human gland.

The Wolff–Chaikoff effect[219, 220, 223] is of paramount importance in the study of thyroiditis. In normal subjects or in patients with non-toxic goitre the administration of a single 2 mg dose of KI reduces the radioiodine uptake by 20 to 30%.[15a] However, in patients affected with thyrotoxicosis or thyroiditis, the inhibition ranges from 60 to 90%.[23, 150, 223] This iodine-induced reduction of the thyroid radioiodine uptake is reminiscent of the perchlorate-induced iodine discharge, also observed in autoimmune thyroiditis and thyrotoxicosis.[23, 198] For this reason several authors[15a, 23, 193a] have suggested that in these diseases the excess of iodine is enhancing a mild underlying defect in iodide organification which is not detectable by conventional methods.

As the Wolff–Chaikoff effect is related to excessive intrathyroidal iodide concentration, it will be enhanced by all factors increasing the thyroid serum iodide gradient, such as high thyroidal iodine uptake, increased TSH stimulation, and low iodine pool. In

thyrotoxicosis and autoimmune thyroiditis these various factors are present. This could account for an increased susceptibility to excessive amounts of iodide without implicating defective organification. The absence of a primary metabolic abnormality is also postulated by Volpé *et al.*[210a] According to these authors, the perchlorate-induced release observed in some patients with Hashimoto's disease might represent only rapid release of organically bound ^{131}I after perchlorate has blocked further uptake. Moreover, Stanbury[193] has stressed the possibility that the iodine release induced by perchlorate and thiocyanate represents a non-specific phenomenon common to different types of thyroid hyperplasia.

The autonomous mechanism also seems to play a role in thyroid hormone secretion —at least this is the case in hyperactive glands. The iodide has an inhibiting effect on thyroid hormone secretion, which seems to be independent of the TSH supply.[70a,145a] This inhibiting effect on secretion apparently necessitates only the presence of intrathyroid iodide and not that of an iodinated protein as was demonstrated for iodide transport.[76,187]

In conclusion, then, the thyroid operates a fast homeostatic mechanism of its own, which speeds up hormone synthesis when the intrathyroid iodide content is low and slows it down when thyroid iodide rises above a critical level.

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CHAPTER 2

Thyroid Autoimmunity

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1. Introduction

The concept of autoimmunity has acquired considerable importance in many branches of pathology. It is a general notion associated with a variety of diseases in which "defence mechanisms", paradoxically directed against certain essential components of the body, may lead to the development of pathological conditions. And yet the reactions involved are identical to the immunizing mechanisms set in train to combat foreign agents invading the body. To describe these reactions, Anglo-Saxon authors often use the terms "hypersensitivity" or "autoallergy" (after Coombs and Gell).[17] The term "autoaggression" seems to give the best rendering of the nature of the pathological process. But it is the term "autoimmunity" which has now found general favour. At least it has the advantage of suggesting the similarity of the mechanisms involved with those of classic immunity.

Immune reactions may be roughly divided into three phases: a phase of information (or assimilation); a phase of cell proliferation (or induction); and a third reactive phase (or operation) (Fig. 2.1A). It is generally recognized that the macrophages play an important role in the first stage of the reaction. They transform the antigen into a much more active "immunogen" and favour contact with the immunocompetent cells.[34,88] The immunogen stimulates the immunocompetent cells, which differentiate by multiplying either into immunoglobulin-secreting plasmatocytes or into small sensitized lymphocytes carrying cell immunity.

The immunoglobulins are classified according to their antigenic specificity and their physico-chemical properties (Table 2.1). Antibody activity may be observed in one or more classes of immunoglobulins; for instance, thyroglobulin antibodies are mainly represented by IgG and to a lesser extent by IgA and IgM (cf. Table 2.3). The thymus-dependent lymphocyte, principal carrier of cellular immunity, is a small lymphocyte with a long life (1–3 years) which becomes immunocompetent under the influence of the thymus. Its role has been clearly established in delayed hypersensitivity reactions (as, for instance, the tuberculin test) and in the rejection of allogeneic grafts. The part it plays in the genesis of experimentally induced autoimmune diseases such as encephalomyelitis, orchitis, and thyroiditis, is also evident.[129,139] After antigenic stimulation the development of cell immunity has a synergic effect on the synthesis of antibodies. The distinction between humoral and cellular immunity is therefore not a clear one, especially

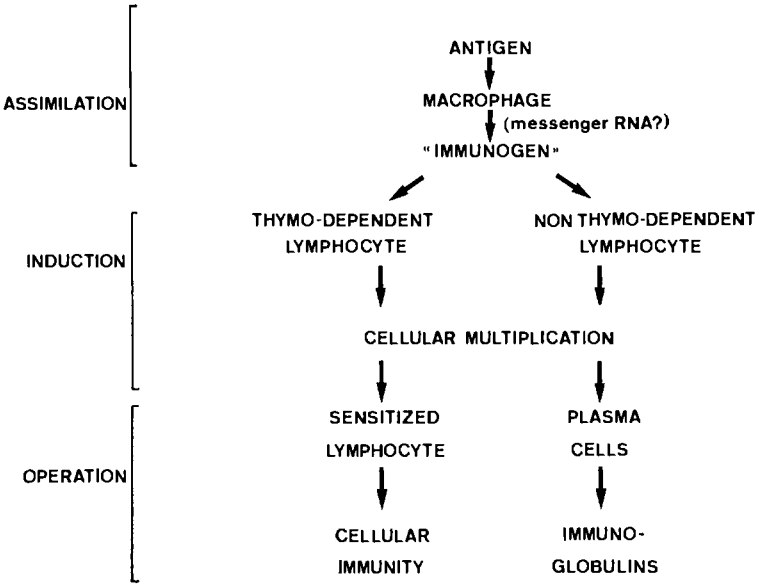

FIG. 2.1A. Schematic representation of different phases of the immune reaction.

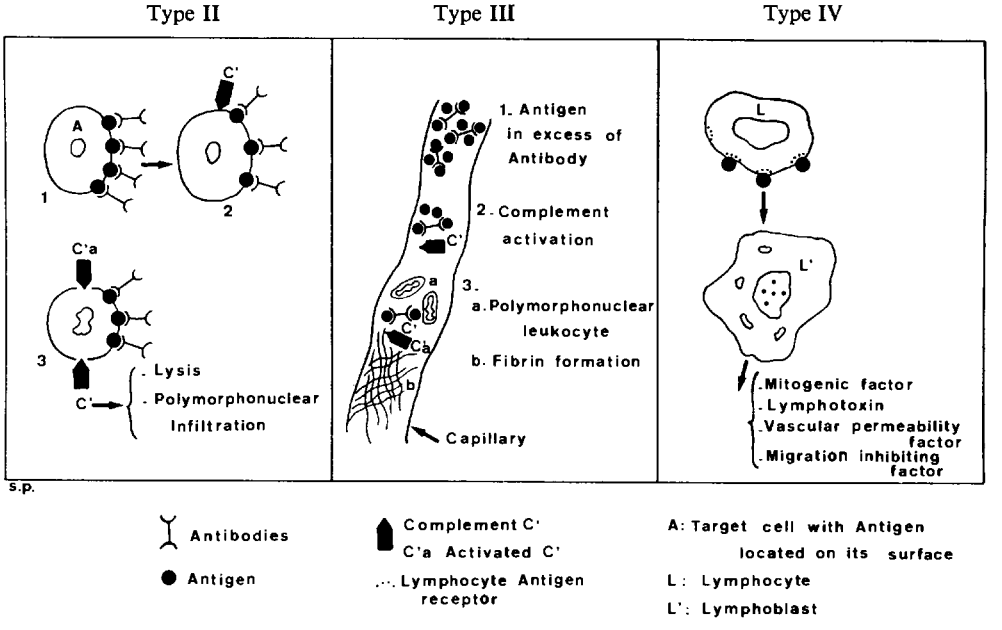

FIG. 2.1B. Schematic representation of the pathology of autoimmune reaction (after Coombes and Gell[17])

TABLE 2.1. DENOMINATION, MOLECULAR WEIGHT, AND SERUM LEVELS OF IMMUNOGLOBULINS

Denomination	Centrifugation index	Molecular weight	Serum level (mg per 100 ml)
IgG	7 S	140·000	800–1600
IgA	7 S or 9 S	160·000	140–420
IgM	19 S	900·000	50–200
IgD	—	150·000	3
IgE	—	200·000	0–05

as the specific sensitivity of these "thymocytes" could result from the coating of special antibodies to their surface.[9,28,48,93] It is probable that cellular and humoral immunity work together to produce autoimmune diseases. At any rate, this has been conclusively demonstrated in experimental autoimmune orchitis.[13]

The definition of autoimmune diseases is still often vague. For instance, McKay and Burnett[78,79] class as autoimmune "Any condition in which structural or functional damage is produced by the action of immunologically competent cells or antibodies against normal components of the body". However, stricter criteria can be drawn up from other studies.[36,147] These are summarized in Table 2.2.

TABLE 2.2. CRITERIA FOR DIAGNOSIS OF AUTOIMMUNE DISEASE

1. Increase in the level of serum gammaglobulins
2. Presence of organ- or tissue-specific antibodies in the serum or the tissues
3. Identification of a specific antigen
4. Presence of lesions with lympho- and/or plasma cell infiltrates
5. Reproduction of the characteristic lesions in experimental animals
6. Aggregation of cases of the "autoimmune disease" in the families of affected patients
7. Incidence of other autoimmune phenomena in affected subjects and/or their family.

Not all criteria are necessarily observed in every instance: the criteria 1, 6, and 7 are facultative.

The antigen has not been isolated in several conditions which are, nevertheless, admitted as autoimmune diseases.

2. Currently Held Concepts of Autoimmunity

Autoimmunity and Autoimmune Diseases

The discovery of antibodies or delayed hypersensitivity to an autoantigen in humans or animals does not necessarily indicate a pathological condition. The serum of most

normal subjects is found to contain autoantibodies in the form of anti-T-haemagglutinins directed against an antigen located on the inside surface of the erythrocytes. These autoantibodies only adhere to red corpuscles treated *in vitro* by bacterial enzymes. *In vivo* they are totally devoid of pathogenic activity.[87] Similarly, anti-muscle antibodies are found fairly regularly after physical shock, as are myocardial antibodies after the myocardial infarct. In these cases, not only are the antibodies free of pathogenic effects, but indeed they seem to help with the resorption of the damaged tissues. In many organs (thyroid, adrenal, gastric mucosa) discrete lymphocytic infiltrations are observed with a significant frequency which increases with age. These infiltrations are accompanied by nil or low rates of specific autoantibodies.

Autoimmunity in these different examples seems to be a (frequent) physiological process for purging the system of tissue residues and waste, due for instance, to ageing.[12,49,56a,87] The process only seems to become pathological when it assumes abnormal intensity; then, exceeding its useful "cleaning-up" function, it creates a self-maintained inflammatory lesion leading to the destruction of the functional tissue.[135]

Physiopathology of the Autoimmune Process

Three distinct mechanisms may play separate—usually associated—roles to spark off and sustain an autoimmune disease. They are the reaction described by Gell and Coombs[17] as Type II, Type III, and Type IV (Fig. 2.1B).

Type II reaction* is a manifestation of the "cytotoxicity" of autoantibodies. The antigen is directly accessible to the antibody either because it is on the surface of the target cells or because it is released into the circulation. This is what happens in haemolytic anaemia, leucopaenia, and autoimmune thrombopaenia: the autoantibodies adhering to the surface of these cells result in their capture and early destruction by the reticulo-endothelial system.[18]

Following the work of Dixon,[20] it is recognized that certain subacute or chronic forms of glomerulonephritis are the result of antibody action against the basement membrane of the glomeruli. In this case the lesions are caused by the interaction of different biological systems activated by the union of antibody with the basement membrane, namely the complement system, blood coagulation, and the system of lysosomal enzymes of leucocytic origin.

The role of cytotoxic antibodies in thyroid disease is discussed in section 2.4.

Type III reaction results from the deposit of antigen-antibody complexes of varying degrees of solubility in the walls of the capillaries. In this case, too, there is activation of complement, the blood coagulation system, and the leucocytic lysosomal enzymes. This mechanism occurs in the genesis of lupus nephropathy, of certain renal complications of rheumatoid arthritis, and probably also of acute post-streptococcal glomerulonephritis.[70] The importance of this reaction in thyroid pathology has not been demon-

* Type I reaction is involved in immediate allergic diseases such as allergic rhinitis, asthma, etc. and is mediated by the liberation of histamine-like substances. It has no part in autoimmune diseases.

strated, although it has been advanced in the pathogenesis of fibrous variant[25] of Hashimoto's struma.

Type IV reaction corresponds to the inflammatory and cytotoxic phenomena which result from the contact of specifically sensitized lymphocytes with the corresponding Ag (or Ag–Ab complex).

This reaction is largely explained by the biological action of "lymphokins"-soluble factors, without immunological specificity, released by the lymphocytes sensitized on contact with the antigen.[27]

At least four in number, the lymphokins are responsible for:

(1) Transformation into blast cells and multiplication of (unsensitized) lymphocytes: this is due to the *mitogenic* factor and could explain the formation of germinal centres in the affected tissue.
(2) Destruction of the target cell by *lymphotoxin*, a protein of mol. wt. 90·000–100·000 which, when released by the lymphocyte, displays cytotoxic activity *in vitro* towards mammalian cells.[50,138]
(3) Appearance of a local inflammatory reaction due to the *vascular permeability factor*.[27]
(4) The progressive accumulation of mononuclear cells mostly without immunological specificity due to the *migration-inhibiting factor*.[127]

These phenomena of delayed hypersensitivity play an important role in the genesis of organ-specific autoimmune diseases in which the antigen occupies a mainly intracellular position[106] (cf. section 5).

Aetiological Factors

Autoimmunity may be considered as the result of a failure of the body's immune tolerance to one or more of its own components. Experimental studies of induced tolerance show that it is possible to conceive this tolerance (sometimes relative) without having to imagine a genetically determined process of recognition of self and non-self by the immunizing system.[72]

Experiments on animals show that the induced tolerance to an Ag depends on several factors:

The animal species and age.
The chemical and physical properties of the Ag.
The dose and route of antigen administration.

By varying these different elements it is possible to obtain either immunization or specific immunotolerance. According to Mitchison[89] tolerance is obtained when the antigen reacts directly with its corresponding immunocompetent cells without being transformed by *macrophages*. This theory explains most of the known aspects of first immuno-tolerance. The break-down of tolerance may result either from a defect in the immunological system or from an alteration of the autoantigens, making them capable

of stimulating a normal immunological system. These two mechanisms are not mutually exclusive and, indeed, may play associated roles.

The mechanisms currently thought to play some part in the aetiology of autoimmunity are:

(A) Escape of normal tolerance to autoantigens:
  (1) immune cross-reaction;
  (2) denatured antigens;
  (3) hidden antigens (this is, in fact, not a case of tolerance because the antigens are unknown to the immunizing system).
(B) Failure of the mechanisms of immunotolerance:
  (4) genetic defect of the immunological system;
  (5) acquired defect of the immunological system.

Autoimmunity considered as a result of cross-reaction

In this case the autoantibody appears as the primary element which triggers off the disease: the antigenic stimulus which produced it is foreign to the body but possesses some antigenic determinants in common with body constituents. An immune cross-reaction thus occurs. Rheumatic fever represents the best illustration of this. Subjects who are predisposed to this disease have in their sarcolemma Ag determinants in common with certain types of beta haemolytic streptococci.[67] In such conditions a common streptococcal infection causes the appearance of anti-streptococcal antibodies (and sensitized lymphocytes). Some of the latter adhere to cardiac tissue and set off an inflammatory process which entails the release of myocardial material capable in its turn of maintaining the auto-immune response thus induced. Experiments on animals have shown that the injection of an autoantigen such as thyroglobulin, coupled to a haptene,* causes the appearance of thyroglobulin antibodies whose formation is maintained by subsequent injections of "native" thyroglobulin.[133]

Autoimmunity considered as a normal immunizing reaction to a denatured autoantigen

Many experiments show that it is possible to induce a state of autoimmunity by treating animals with native substances rendered antigenic by a minor chemical modification (cf. section 7). In human pathology there are numerous examples of autoimmune diseases following on a previous alteration of certain normal components of the system by viruses, trauma, chemical products, and bacteria. This is the case in the recurrent lymphocytic pericarditis after an attack of viral, ischaemic, or surgical origin, on the pericardial tissue. It also explains the lupus syndrome induced by various drugs[130] and autoimmune haemolytic anaemia induced by methyldopa. Recently a virus was discovered in SLE:[68] the virus located in the nucleus could act by denaturing the normal nuclear components into autoantigens. Viral infections so far undetected could induce auto-

* Haptenes are simple chemical substances incapable of provoking immunological reactions by themselves, but capable of doing so when linked with macromolecules.

immune reactions either by an alteration of the structure of the cell constituents or by the development in these cells of new antigens, distinct from the viral Ag.[29,131] The role of such viral infection in the pathogenesis of chronic lymphocytic thyroiditis has been advanced by Thier *et al.*[126] and Leboeuf *et al.*[73]

Autoimmunity resulting from the release of a sequestrated antigen

Certain antigens, because of their location in the tissues, have never been in contact with the reticulo-endothelial or lymphoid tissue. They are therefore not tolerated but ignored by the immunizing system. The only example currently accepted is that of cristallin, normally isolated from the lymphoid reticulo-endothelial cells. The release of this component into the general circulation provokes an autoimmune response.[12]

Presently, this concept is no longer acceptable for thyroid diseases since thyroglobulin has been shown to be present in the circulation of normal subjects.[5,58,107]

Autoimmunity resulting from an anomaly of the immunizing system

The possibility of a genetically determined primary anomaly of the immunizing system has been advanced by Burnett.[13] According to this author the lymphoid tissue is the permanent seat of somatic mutations entailing the constant formation of immunocompetent cells with fresh potential. In autoimmune disease, the "forbidden clones" directed against the components of the system would not normally be eliminated by a process of homoeostasis controlled by the thymus. This organ could thus play a cardinal role in the pathogeny of autoimmunity. Thymic anomalies have indeed been described in association with various autoimmune diseases,[30] and notably with Hashimoto's goitre.[50] An objection to this theory is that the multiplicity and diversity of autoantibodies observed in some autoimmune disorders such as SLE[59,115] would only be explained by "an uncomfortable number of mutations".[130]

Nevertheless, the high incidence of autoimmune diseases associated with congenital anomaly of the immunological system[43,116] may also be cited as an argument for the role of a disturbance in the immunological system in the pathogenesis of autoimmune disease. Indeed, the immunological reactivity of patients affected with rheumatoid arthritis, biliary cirrhosis, Crohn's ileitis, and sarcoidosis is abnormal.[37,124] But such anomalies could be due to viral, bacterial,[10] or chemical factors, for instance. In experimental autoimmune diseases frequent use is made of Freund's adjuvant which is known to modify immunological reactivity.

In conclusion, no single mechanism can explain on its own all the phenomena observed in autoimmune diseases. Moreover, it is probable that the mechanisms responsible for diseases as different as Hashimoto's thyroiditis and autoimmune haemolytic anaemia are also very different from each other. The high frequency of autoimmune phenomena observed in patients' families (cf. section 7) and the frequent association of autoantibodies directed against various organs in the same patient (for instance the association of thyroiditis, gastritis, adrenalitis) do not seem to offer sufficiently convincing proof that autoimmunity is due to a primary anomaly of the immunizing system. There is nothing

to show, for instance, that this hereditary trend is not the result of primary anomalies of the organs themselves.

3. Lymphocytic Thyroiditis as an Autoimmune Disease

General reviews of autoimmune thyroiditis have been published by Doniach and Roitt,[22,25] Witebsky,[141] and Hall.[54] The actual concept of autoimmune thyroiditis derived originally from the experiments of Witebsky and Rose[140] and the clinical studies of Roitt, Doniach, Campbell and Vaughan-Hudson.[101] The first authors produced lymphocytic thyroiditis in animals injected with thyroid extracts. The second group of authors succeeded in detecting precipitins against purified human thyroglobulin in the serum of patients affected with lymphocytic thyroiditis. Since these early investigations, considerable literature has been devoted to the subject and has demonstrated that immune processes play an important role in the pathology of Hashimoto's goitre, atrophic thyroiditis in myxoedema, and other forms of lymphocytic thyroiditis. Moreover, lymphocytic thyroiditis (and especially Hashimoto's thyroiditis) has often been considered as the best example of an autoimmune disease.[78] In fact, this condition meets all the criteria listed in Table 2.2. First of all, gammaglobulin levels often attaining values

TABLE 2.3. THYROIDAL ANTIGENS AND ANTIBODIES

Antigens	Antibodies	
Origin and composition	Nature	Methods of detection[a]
(1) Microsomal localized in thyroid epithelial cytoplasm from which it is obtained by ultracentrifugation; essentially formed by lipoprotein membranes of microsomal vesicles	IgG (complement fixing)	(a) Immunofluorescent method of Coons on unfixed sections (b) Complement fixation test (c) Cytotoxicity test on thyroid tissue cultures (d) Mixed haemadsorption test
(2) Thyroglobulin constitutes 75% of proteins in colloid	Mainly IgG, also a little IgA and IgM	(a) Precipitation in agar gel (for high concentrations) (b) Tanned red cell agglutination (TRC) (c) Immunofluorescence (alcohol-fixed section) (d) Latex fixation
(3) Second colloid antigen (CA_2): constitutes less than 1% of proteins in thyroid colloid, contains no iodine	IgG	Immunofluorescence on alcohol fixed sections
(4) LATS[b] antigen distinct from (1)	IgG	McKenzie method[b]

[a]Techniques: cf. Appendix, pp. 334–335.
[b]See Chapter 8.

of 2 g per 100 ml are regular in Hashimoto's thyroiditis.[25] The thyroid antibodies and the antigens to which they react are given in Table 2.3. They are organ-specific and, with the exception of the LATS, have been detected in tissues taken from Hashimoto's goitre.[25] The antibodies directed against the thyroglobulin contained in the intravesicular colloid or against cell components may appear simultaneously or separately in the serum (Fig. 2.2). Microsomal antibodies are easily detected by the Coons fluorescent technique on unfixed sections (which therefore have no remaining colloid in the vesicles)

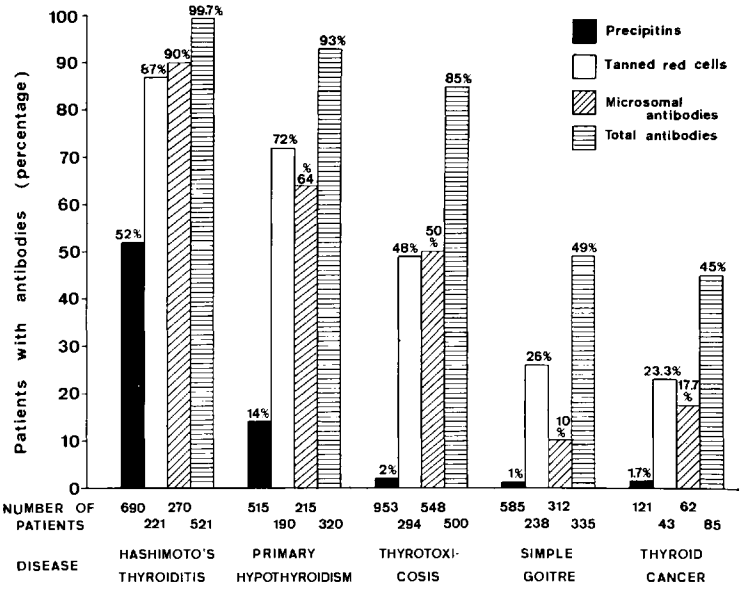

FIG. 2.2. Incidence of autoantibodies in various thyroid conditions. (After Whaley and Buchanan, with permission of the authors.)[132a]

(Fig. 2.3.). The titre of these antibodies may be measured by the complement fixation method, which is less sensitive than the Coons technique. Thyroglobulin antibodies may also show up by fluorescence technique on alcohol-fixed sections: in this the microsomal antigen is destroyed but the colloid remains (Fig. 2.4). The easiest method, however, for detecting thyroglobulin antibodies is by agglutination of tanned red cells formolized and coated with purified human thyroglobulin according to the Boyden[11] or Fulthorpe technique.[42] Latex reactions are very insensitive; the same goes for precipitation in agar gel, which is only positive for very high concentrations (Fig. 2.5). Recently, however, Feinberg *et al.*[33] described an immunodiffusion technique which is almost as sensitive as the tanned red cell (TRC) haemagglutination technique.

There exists in the colloid a second antigen (CA_2), which, in contrast to thyroglo-

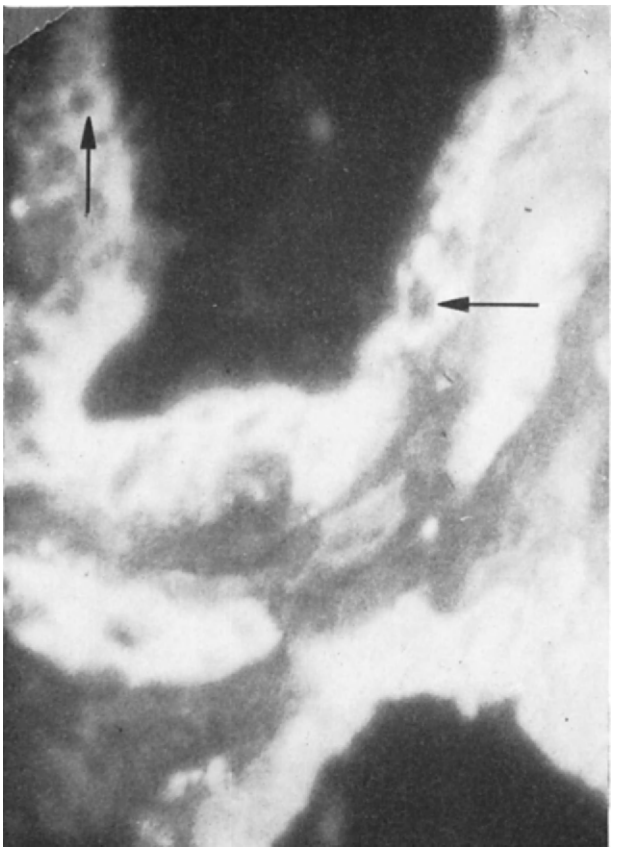

FIG. 2.3. Detection of microsomal antibody by the immunofluorescent technique. Fluorescence appears in the cytoplasm and spares the nuclei (arrows).

bulin (iodinated to 0·3%), probably contains no iodine. Its relationship with thyralbumin remains to be established. The latter substance is present in all thyroids, and its intrathyroid synthesis has been demonstrated.[95]

Finally, in the thyroid cytoplasm or plasma membranes there would seem to be another antigen distinct from the microsomal antigen described earlier and responsible for the development of a particular type of immunoglobulin called long-acting thyroid stimulator (LATS) because it has the property of stimulating the activity of the thyroid cells for long periods (cf. Chapter 8).

The reasons for the spontaneous onset of serological reactions to thyroid antigens remain surrounded by mystery. A theory admitted until recently maintained that the thyroglobulin formed a hidden antigen which, on entry into the circulation, was taken to be an element foreign to the body: hence the formation of antibodies. This concept is demolished by the demonstration that thyroglobulin is present in small quantities in the

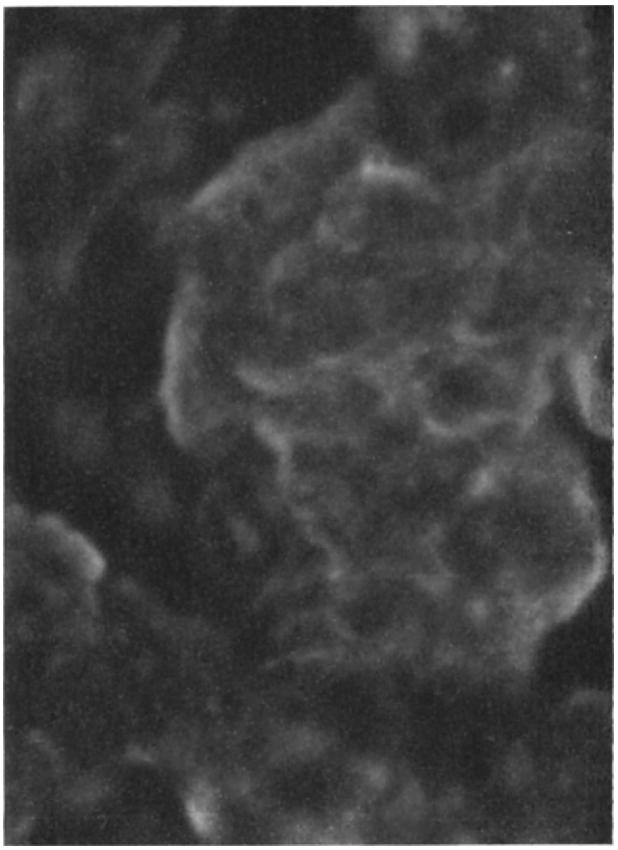

FIG. 2.4. Detection of TGA by the immunofluorescent technique. Floccular pattern of the colloid fluorescence.

circulation of normal subjects,[58] and may even pass into the lymphatic system draining the thyroid in large quantities under intense stimulation of the normal organ.[5,58,107]

4. The Pathogenic Role of Circulating Thyroid Antibodies

The pathogenic role of circulating thyroid antibodies is not yet formally established. Transfusions of large quantities of immunoglobulins taken from the serum of patients affected with Hashimoto's disease produce no thyroid alterations in Rhesus monkeys.[102] Furthermore, although thyroid antibodies pass easily through the placenta, no thyroiditis is observed in babies born of affected mothers.[96] Finally, the various attempts to reproduce thyroiditis experimentally using sera of diseased animals have always been unsuccessful.[104,123] Nevertheless, Nakamura and Weigle[92] recently managed to transfer experimental autoimmune thyroiditis from one rabbit to another with the aid of serum

or purified thyroglobulin antibodies drawn off early in the course of immunization of thyroidectomized animals. Barring this case, however, thyroglobulin antibodies, which are the most frequent and numerous in the serum, hardly seem endowed with any direct pathogenic effect. Complement fixing antibodies, on the other hand, have proved to be cytotoxic to cultured thyroid cells. This cytotoxic effect seems to result from the activation of complement whose cytolytic role is well established. This phenomenon has only been observed on cells which have been subjected to the action of trypsin and which are rich in antigens. The nature of the cytotoxic factor is still a subject of controversy. For most authors it is the microsomal antibody fixing complement; Kite *et al.* hold that it might be a distinct antibody.[69]

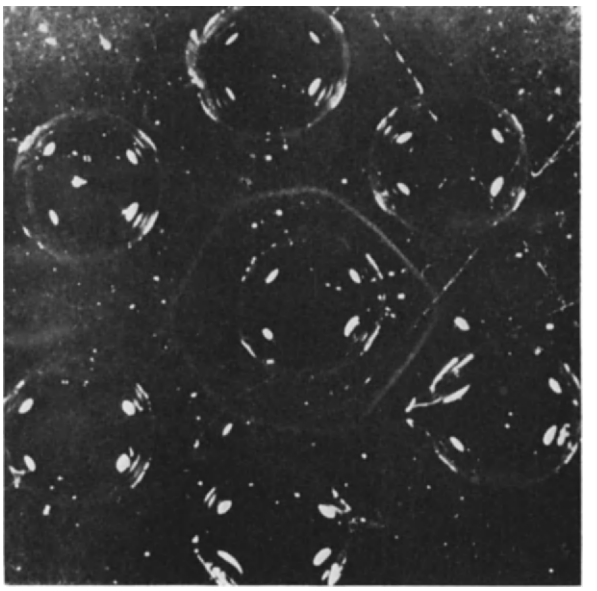

FIG. 2.5. Precipitin reactions in agar gel for detection of TGA.

5. Cellular Autoimmunity in Thyroiditis

A series of morphological and immunological observations suggest that cellular immunity plays a part in autoimmune thyroiditis. The tissue lesions observed in the various forms of this disease comprise extensive inflammatory phenomena—capillary dilatation, exudation of lymphocytes, appearance of plasma cells, and frequent development of germinal centres. These lesions resemble those accompanying rejection of an allogeneic graft,[52] in which the role of cellular immunity is evident. Figure 2.6 shows an atrophic thyroiditis in which lymphocytes are present inside degenerating cells, suggesting aggressive and destructive phenomena. Such "emperipolesis" has also been observed by electron microscopy.[94] However, although *in vitro* studies have confirmed lymphocytic penetra-

tion in cultured thyroid cells and demonstrated a preference for cells of Hashimoto's thyroiditis,[75] they have not been able to establish any destructive effect by these lymphocytes on the cells of the parenchyma.

Studies of transfer of experimental thyroiditis have shown, with the exception of the recent investigations of Nakamura and Weigle,[90] that only the lymphocytes of immunized animals are capable of producing thyroid lesions and serum antibodies in other animals of the same species.[35,55,81,90] Furthermore, although most experimental studies have demonstrated absence of correlation between circulating antibody titres and the severity of thyroiditis,[86,111] on the other hand they have shown that the disease

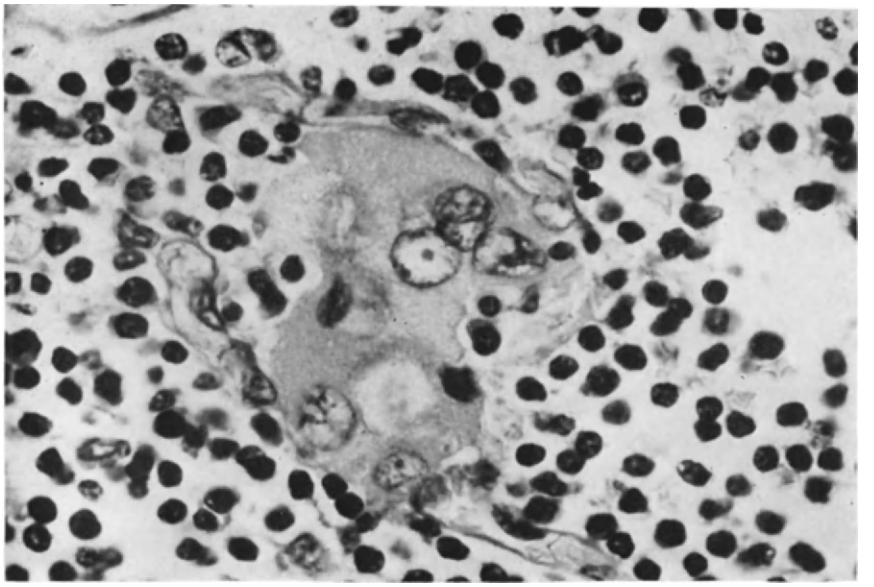

FIG. 2.6. Atrophic thyroiditis: lymphocytic infiltration—emperipolesis.

evolves parallel to the manifestations of delayed hypersensitivity established by skin tests for thyroid antigens.[21,38,80,132] Finally, the evolution in time of the appearance of thyroid infiltrations pleads in favour of an early role played by delayed hypersensitivity reactions.[71] In human pathology, the appearance of cutaneous reactions to intradermic injections of thyroid extracts[14,142] coincides with the existence of intense anti-thyroglobulin serological reactions; the skin infiltration is mainly of the polynuclear type, as in Arthus's phenomenon, but the particular induration of the lesions argues in favour of a delayed-type reaction.[106]

In vitro studies of lymphoblastic transformation and the incorporation of tritiated thymidine (or of labelled amino acids) in the lymphocytes of patients affected with thyroiditis, in the presence of specific antigens, are few in number and contradictory in their conclusions. Although the addition of phytohaemagglutinin always produces

stimulation, that of thyroid antigens yields variable results, sometimes nil,[19] and sometimes distinctly positive.[41] In animals[144] such stimulation has been observed on lymphocytes, even if sampled very early, before the serum antibodies appear. The macrophage migration inhibition test proved positive in patients affected with lymphocytic thyroiditis.[119]

Finally, the rosette formation phenomenon, which reveals the existence of receptors to thyroid Ag. on the surface of lymphocytes from subjects affected with thyroiditis or from

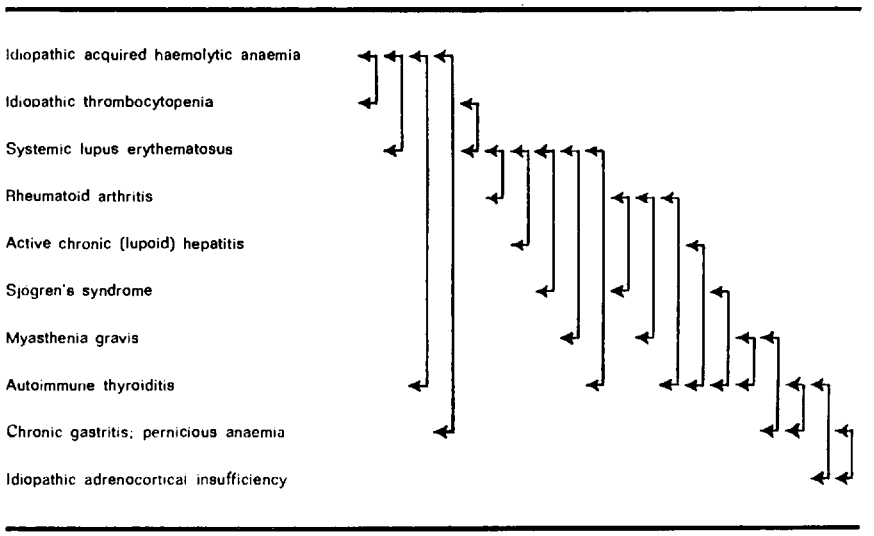

FIG. 2.7. Clinical relation between the various idiopathic autoimmune diseases. (After Feltkamp, with permission of the author.)

immunized animals, would suggest, according to Perrudet-Badoux and Frei,[97] the intervention of delayed hypersensitivity. Moreover, in Hashimoto's thyroiditis, thyrotoxicosis,[113] myxoedematous thyroiditis,[118] and asymptomatic atrophic thyroiditis,[7,53] the presence of inflammatory lesions in the thyroid very frequently coincides with thyroid antibodies in the serum. This raises the question of whether cellular immunity and humoral immunity might not play associated roles.[106]

6. Coexistence of Autoimmune Thyroiditis with Other Immune Diseases

Such associations have been established by numerous authors.[24,36,61,108] Figure 2.7 (from Feltkamp[36]) summarizes the various known combinations, especially thyroiditis and pernicious anaemia, myasthenia, systemic lupus erythamatosus (SLE), and idiopathic atrophy of the adrenals. So the associated diseases include organ-specific (Addison's

TABLE 2.4. LABORATORY AND IMMUNOLOGICAL DATA OBTAINED IN A PATIENT WITH THYROTOXICOSIS AND ADDISON'S DISEASE AND HER CHILDREN

	Patient	Children		
	Female 46 yrs.	Male 24 yrs.	Male 20 yrs.	Female 16 yrs.
$PB^{127}I$ (μg per 100 ml)	20	4·8	7·5	5·6
$BE^{127}I$ (μg per 100 ml)	20	4·1	7·2	5·6
TGA ×	pos. (1/78125)	pos. (1/125)	neg.	neg.
CFA ×	+++	+	neg.	neg.
ACA ×	+++	+	neg.	neg.
Gastric mucosa antibodies	+++	++	neg.	neg.
LATS:				
Whole serum	*R*:170/105=1·62	*R*:126/106=1·19		
LATS IgG	*R*:144/95=1·48	*R*:152/115=1·32	*R*:65/90=0·72	*R*:158/90=1·76

disease, pernicious anaemia) and non-organ-specific autoimmune diseases (SLE). Table 2.4 gives an example of such an association in a patient affected with thyroiditis superimposed on thyrotoxicosis; her children were also affected. The significance of these associations is further discussed in Chapter 11.

7. Family Aggregation of Different Types of Autoimmune Thyroiditis

Another particular feature of autoimmune thyroiditis (also encountered in other organ-specific autoimmune diseases) is its tendency to occur in families in a variety of clinical forms (Hashimoto's goitre, myxoedema, thyrotoxicosis). Hall *et al.*,[53] Doniach *et al.*,[23] and Hennen[57] maintain that the tendency to autoantibody production is transmitted by a dominant-gene mechanism. Hall *et al.* base this opinion on their discovery of thyroid antibodies in 50% of the parents or direct collaterals and in 25% of the uncles, aunts, and nephews of subjects affected with autoimmune thyroiditis. In a personal study, a similar frequency rate was observed (Table 2·5): more than 50% of the brothers and sisters of subjects affected with symptomatic or asymptomatic thyroiditis had significant titres of thyroid antibodies in their sera. However, these statistics are based on studies made under hospital conditions and are therefore open to criticism.[83] In the study published by Roitt and Doniach,[105] which seems to escape such criticism, 42% of the close female relatives and 30% of the close male relatives of subjects affected with Hashimoto's disease had circulating antibodies, making an average of 36% which contrasts sharply with the 14% noted in controls but does not reach the expected 50% level.

So the existence of a hereditary factor seems undeniable. However, the transmission of a defect in the maintenance of immunological tolerance does not necessarily involve the immunizing apparatus. High family incidence of thyroid autoimmunity might also be due to genetically determined anomalies in the epithelial tissues.

TABLE 2.5. INCIDENCE OF THYROGLOBULIN ANTIBODIES AMONG BROTHERS AND SISTERS OF PATIENTS WITH THYROID DISEASES

Subjects	Age	Cases studied	No. of cases with TGA	%
Normal controls[a]	35·6 (15–60)	50	3	6
Siblings of patients with thyroid diseases	27·7 (15–68)	38	17	45

[a]Physicians, nurses, technicians.

8. Experimental Thyroiditis

Experimental induction of lymphocytic thyroiditis has greatly increased our knowledge of the human pathological process. In their experiments on rabbits, Rose and Witebsky[109] have shown that subcutaneous administration of thyroid extracts in Freund's adjuvant causes the appearance of thyroid-specific antibodies and the development of extensive lymphocytic infiltrations in a third of all the animals. Similar findings have been reported in guinea-pigs and dogs,[123,141] in rats,[63] and in monkeys.[111] In the latter, the parenchymatous lesions, comprising follicular disruption, disappearance of colloid and the formation of dense parenchymatous masses with no vesicular structure, strongly resemble the tissue alterations found in human pathology. The process may develop slowly, possibly attaining its peak after 100 days or progress over more than a year to the destruction of the thyroid. The thyroglobulin antibody titre evolves at the same rate as the lesions, apparently reflecting the gravity of the process. Furthermore, in these experiments cytoplasmic antibodies have also been observed.[111]

All these immunization experiments were carried out using homologous thyroid extracts emulsified in Freund's adjuvant. Although the injection of unmodified extract proved incapable of inducing immune reactions, once the immunization was acquired, the animal became intolerant of its own thyroglobulin.

Weigle[133] managed to induce thyroiditis (with antibodies against autologous thyroglobulin) without resorting to Freund's adjuvant, by administering the animals own thyroglobulin slightly modified by haptenic groups (in this case derivatives of diazonium). The results suggest that a minor alteration of the thyroglobulin is capable of sparking off an immune reaction, which will lead the system to react subsequently against its own thyroglobulin, thus initiating the development of lymphocytic thyroiditis.

Guinea-pigs injected with homologous thyroglobulin, together with an immunosuppressive drug, no longer react to guinea-pig thyroglobulin.[112] However, if bovine thyroglobulin or guinea-pig thyroglobulin modified by picric acid is used instead of unaltered guinea-pig thyroglobulin for the desensitization test, no immunosuppression is obtained towards guinea-pig thyroglobulin. These experiments show the high specificity of the induced tolerance, and underline, as the authors say, that an animal not

reacting to its own proteins will respond to a slight alteration of one of these proteins, thus causing the changes peculiar to an autoimmune disease.

In dogs, too, lesions resembling those of Hashimoto's thyroiditis have been obtained: in addition to infiltration of the parenchyma by lymphocytes and plasma cells, the formation of eosinophilic cells has been observed.[32] In these experiments, after 2 months of treatment with Freund's adjuvant, the treatment was continued for 7 or 8 months with a saline extract of the thyroid gland and daily administration of sodium iodide in a dose of 2 mg of iodine per day. The histological picture obtained is different from the one produced earlier in dogs by classic immunity,[123] but comparable to that of spontaneous thyroiditis occurring in certain breeds of dogs.[8]

Experimental thyroiditis may also be produced without any immunization with homologous or heterologous thyroid extracts. Thus certain authors[6,77] had induced lymphocytic infiltrations and degenerative alterations in rat thyroids by keeping the animals on a diet deficient in vitamins A and B. Degenerative changes seemed to precede the inflammatory reactions. Recent studies have re-emphasized the value of these early observations. For instance, it has been found that rats may develop chronic thyroiditis after ingestion of methylcholanthrene.[44] Similarly, a high frequency of thyroiditis has been observed in rats affected with cirrhosis induced either by carbon tetrachloride[45] or by an unbalanced diet.[100] The pathogenesis of these types of thyroiditis is still not clear: a disturbance of thyroid hormone metabolism has been cited as the decisive factor. However, until now this research has not included any study of humoral autoimmune processes.

Experimental work has also thrown some light on cellular autoimmune mechanisms. The administration of two antigens produces competition between them in their action upon the antibody-producing cells. Such competition inhibits the production of circulating thyroglobulin antibodies but does not prevent the development of experimental thyroiditis.[126] This dichotomy suggests that thyroiditis may result solely from a process of cellular immunity or that under experimental conditions the production of a small quantity of immunoglobulin has not been affected by the immunological competition. On the other hand, the presence of a cytophilic thyroglobulin antibody has been described in the serum of patients affected with thyroiditis and in the serum of rabbits injected with thyroglobulin. It is not impossible that this factor might play a role in the development of lesions of lymphocytic thyroiditis.[122] Finally, by using heterologous anti-lymphocyte serum, which has the property of inhibiting delayed hypersensitivity and to a lesser extent the formation of antibodies,[62] it is possible to prevent the appearance of experimental thyroiditis.[66]

Studies of *iodine metabolism in animals affected with experimental thyroiditis* are not numerous, and the results reported are not always compatible because of the different reactions of the species of animals selected for immunization, the diverse methods of immunization, and the varying lengths of time between the induction of thyroiditis and the moment of investigation. One fundamental feature of Hashimoto's thyroiditis, namely the disturbance of iodine organification, which results in heavy iodine release after administration of perchlorate or thiocyanate, has never been observed in ani-

mals.[47,60] Another feature—the release by the gland of large quantities of non-butanol extractable iodinated proteins—has been demonstrated by Torizuka *et al.*[128] and Anderson *et al.*[2] in guinea-pigs and rats respectively. However, this anomaly has not been observed in rabbits[128] or monkeys.[3]

Other studies have thrown light on the progressive character of alterations in iodine metabolism. In guinea-pigs, after a single immunizing injection, Torizuka *et al.*[128] observed an initial phase of thyroid hypoactivity, characterized by low radioiodine uptake, a low or normal level of serum iodothyronines and iodoalbumin, in association with intense thyroid infiltration by inflammatory cells and a disruption in the follicles. Flax and Billote[39] demonstrated, by means of autoradiography, a marked drop of uptake in the follicles surrounded or invaded by inflammatory infiltrations, contrasting with normal uptake in follicles which were still intact.

After 5–6 weeks, a phase of thyroid hyperactivity could be detected by high uptake, high levels of serum iodothyronines, and iodoalbumin and generalized hyperplasia of the follicular cells. With the exception of the high level of iodoalbumin in the serum, these morphological and biochemical anomalies were all reproduced in animals only injected with TSH. It has therefore been suggested that stimulation of pituitary origin could intervene in the development of experimental thyroiditis. In rats subjected to repeated immunizations every 2 weeks for 23 weeks, Anderson *et al.*[2] demonstrated a reverse process. The first period, up to 12 weeks, was characterized by an increase in thyroid weight, in serum $PB^{127}I$ and $NBE^{127}I$, and in $PB^{131}I$, by a high titre of thyroglobulin antibodies and by clear-cut inflammatory lesions and marked parenchymatous hyperplasia; only the ^{131}I uptake remained normal. After 12 weeks, thyroid weight, $PB^{127}I$, $NBE^{127}I$, antibody titres, and histological lesions all declined despite continued immunization, and certain parameters attained subnormal values. Anderson *et al.*[2] attribute the temporary thyroid hyperactivity to stimulation by inflammation of the gland and not by TSH, whose levels they consider to be probably diminished.

The fate of circulating thyroxine in experimental thyroiditis has been studied by Premachandra *et al.*[99] who report that it can attach itself to thyroglobulin antibodies; this combination would be responsible for the prolonged presence of thyroxin in the serum and its reduced efficiency for tissue metabolism.[84]

Morphological Aspects of Experimental Thyroiditis

Focal or generalized hyperplasia of the acini in human autoimmune thyroiditis is a phenomenon which investigators have tried to explain by experimentation.[40,128] Increased TSH secretion in response to possible hypofunctioning of the thyroid in the early stages of thyroiditis is the hypothesis most often advanced to explain this hyperplasia.[40,128] It has even been said that TSH administration to rats immunized with heterologous thyroglobulin increased the severity of the thyroiditis.[63] But work of McSween and Goudie[82] and of Nève[94] make it clear that in experimental thyroiditis parenchymatous hyperplasia may develop without any pituitary TSH stimulation. The latter work, as yet unpublished, will be reviewed briefly. Guinea-pigs were pretreated

with a thyreostatic drug (methimazol) or with triiodothyronine (T3) in order to induce endogenous TSH stimulation in the first experimental group and endogenous TSH suppression in the second. This treatment was continued throughout the experiments until the animals were sacrificed. Focal or diffuse thyroiditis was induced by injections of thyroid extract emulsified in Freund's adjuvant. The chronological appearance of thyroiditis was independent of the pre-treatment.

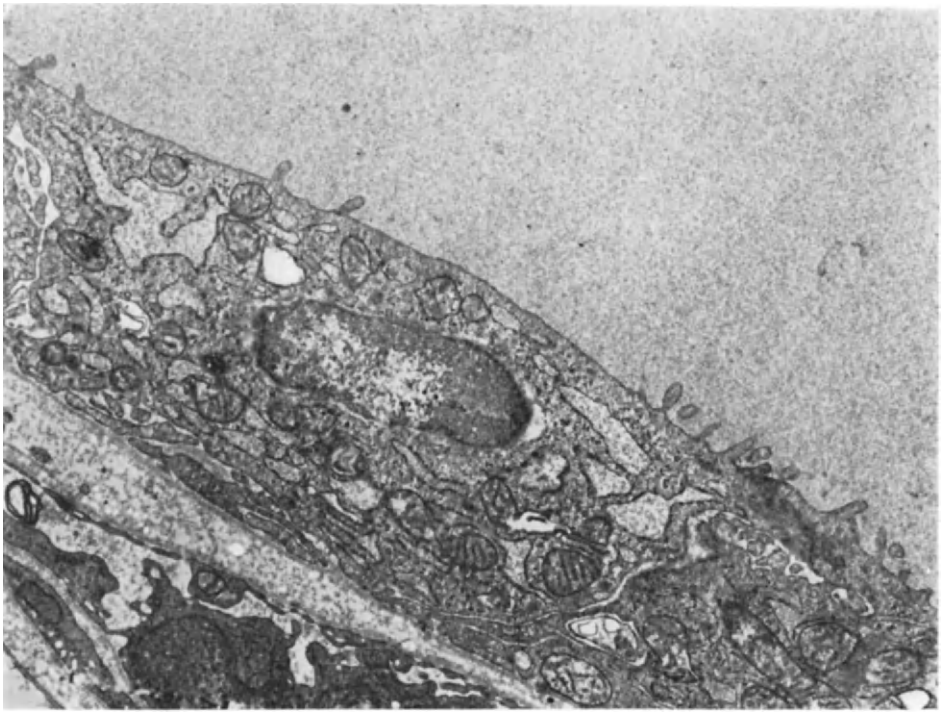

FIG. 2.8. Guinea-pig experimental thyroiditis. Control guinea-pig thyroid after treatment with triiodothyronine. The thyroid cells are flattened. (×11,800.)

The morphological lesions observed by light microscopy were similar to those described by other authors.[38,74,98,123] In accordance with other studies[91,125] no oncocytes were seen. In the areas involved with thyroiditis, definite cell hyperplasia was present in the immunized animals whose pituitary–thyroid system has been depressed by prior T3 administration. The cellular height reached 7–8 μ, whereas in the zones free from thyroiditis and in the control animals (T3-treated but not immunized) the follicular epithelium reached a cellular height of only 2–3 μ (Fig. 2.8).

Electron microscopy of thyroids in T3-treated and immunized animals confirmed the findings of previous authors concerning the types of inflammatory cells and their relations with the thyroid cells.[40,76,120,125] The hyperplastic parenchymatous cells were either cuboid or cylindrical, with rounded or cylindrical nuclei near the base of the

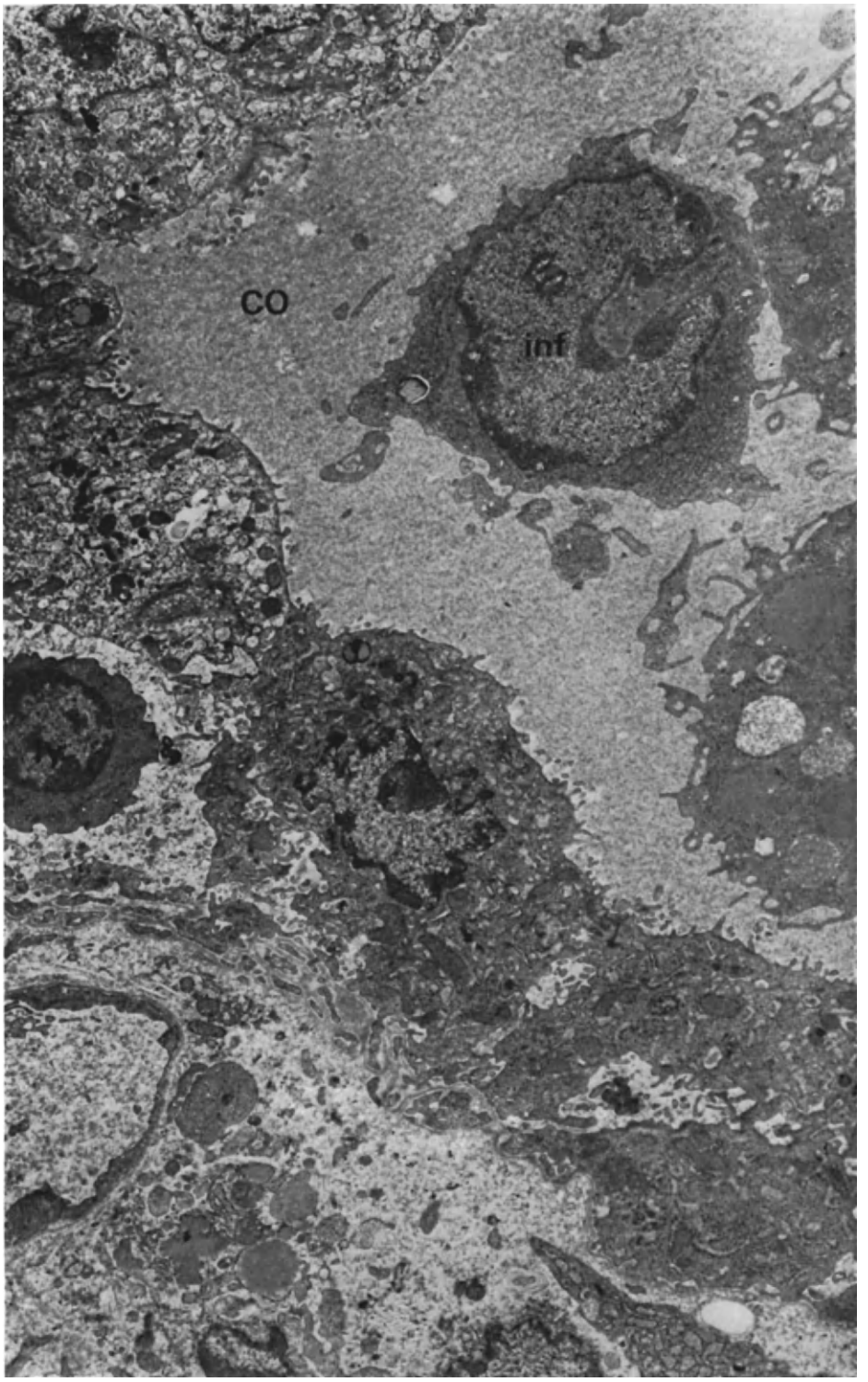

FIG. 2.9. Guinea-pig experimental thyroiditis. Part of follicle made up of cuboid or cylindric thyroid cells. Inflammatory cells (inf) invade the colloid lumen (CO). A lymphocyte (ly) is located inside the basement membrane. (×5000.)

cytoplasm (Fig. 2.9). Rounded or somewhat distended ergastoplasmic cisternae filled the cytoplasm: they were associated with a large number of polysomes. The well-developed Golgi apparatus was located above the nucleus.

A few follicular cells displayed abnormal cytoplasmic extensions projecting into the follicular lumen from the apical margin (Fig. 2.10). These cell extensions were generally free of cytoplasmic organelles. They contained some free ribosomes and sometimes an irregularly shaped vacuole with a content resembling colloid. A large number of these colloid cells were observed (Fig. 2.11) similar to those described previously in experimental thyroiditis.[16,116,121,138] These observations seem to indicate that the functional state of the thyroid, before and during immunization, plays no role in starting off the process of experimental thyroiditis. Furthermore, as the picture of hyperactivity is different from that produced by TSH and as the thyroid histology of control animals still testifies to TSH suppression, the hyperplasia observed in these experimental studies seems to result from a direct action by the inflammatory process and not from a pituitary reaction following thyroid destruction.

Finally, it should be emphasized that, as a rule, in experimental thyroiditis no oncocytes have been observed.[120,125] Rare observations to the contrary[8] are based on light histology and concern experiments in which other pathogenic factors such as iodine administration seem to be responsible.

9. Conclusions

Born less than 15 years ago, the idea of autoimmune thyroiditis has proved to be of cardinal importance. It was initially interpreted as a process following on the entry of thyroglobulin—a supposedly concealed antigen—into the circulation, or else a process deriving from a primary anomaly of the immunizing apparatus.

New ideas, mainly based on experimental work, suggest that a chemical anomaly of certain normal thyroid components or of its secretory or metabolic products may be partly responsible for the development of antigenic properties. To explain this denaturation, certain authors cite an infectious—and particularly viral—attack. A metabolic alteration of genetic origin, possibly accentuated by physiological stimuli or by tissue ageing, could also explain the appearance of the antigen. It is possible that, to a certain extent, the process corresponds to a normal function of cell homeostasis and cell waste elimination. Only its intensification by increased production of antigens and/or of antibodies would turn it into a tissue-destroying inflammation.

Whatever the aetiological mechanism, once the process is under way it may evolve towards a self-maintained and progressive state. In human pathology this evolution varies considerably, but may lead to the total destruction of the parenchyma. In animal, the artificially induced process is usually self-limited and transient. This observation by itself suggests that some constitutional disorder in the thyroid parenchyma or in the immunological system must be present in human autoimmune thyroiditis.

Furthermore, in certain conditions an immune reaction is said to be responsible for the elaboration of a special immunoglobulin having the capacity to stimulate the

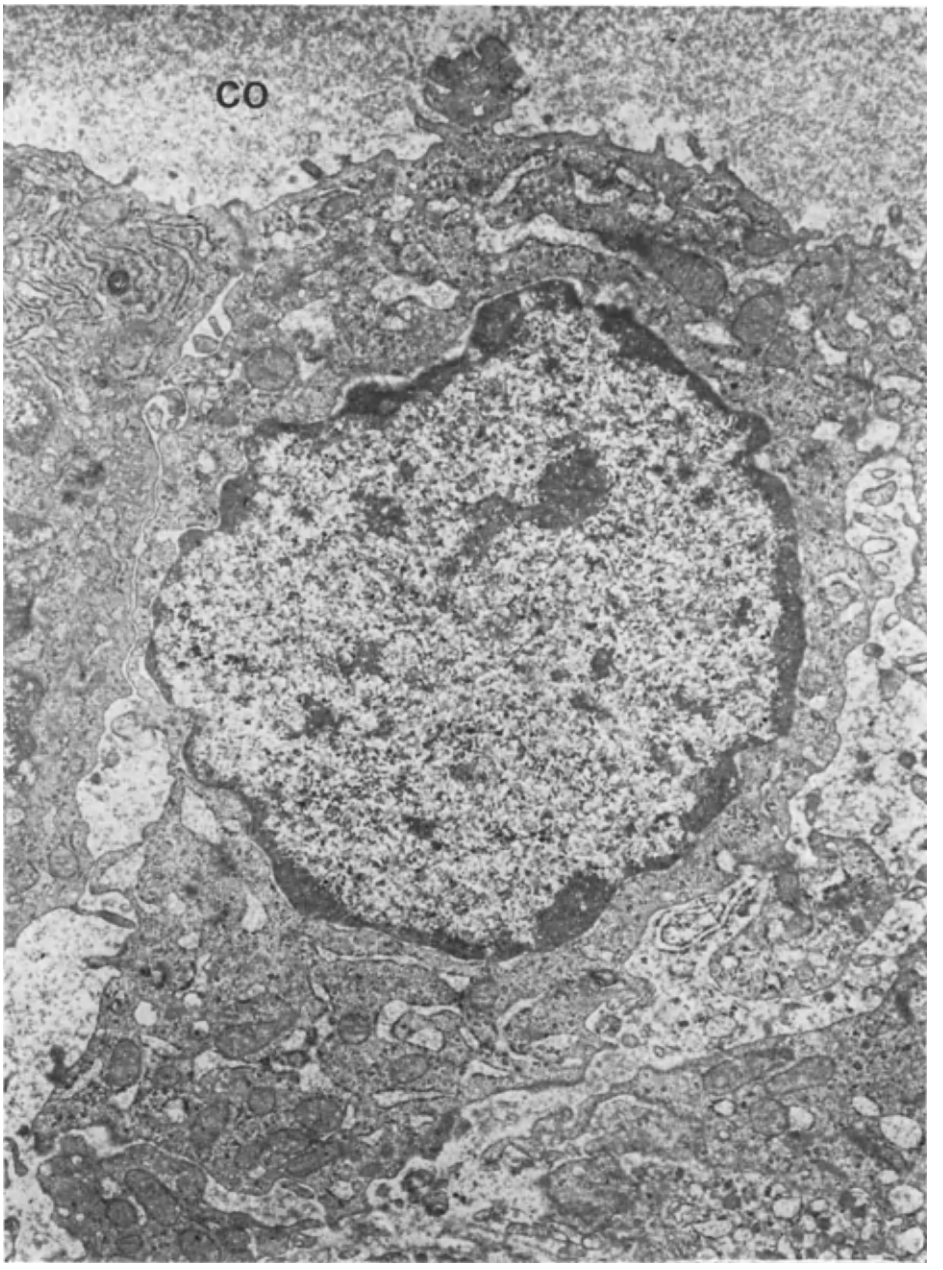

FIG. 2.10. Guinea-pig experimental thyroiditis. Cuboid thyroid follicle cell in an animal immunized and treated with triiodothyronine. The apex of the cell shows a cellular process protruding into the colloid lumen (CO). Many polyribosomes are scattered throughout the cytoplasm compared with control thyroid (Fig. 2.8 same magnification). (×11,800.)

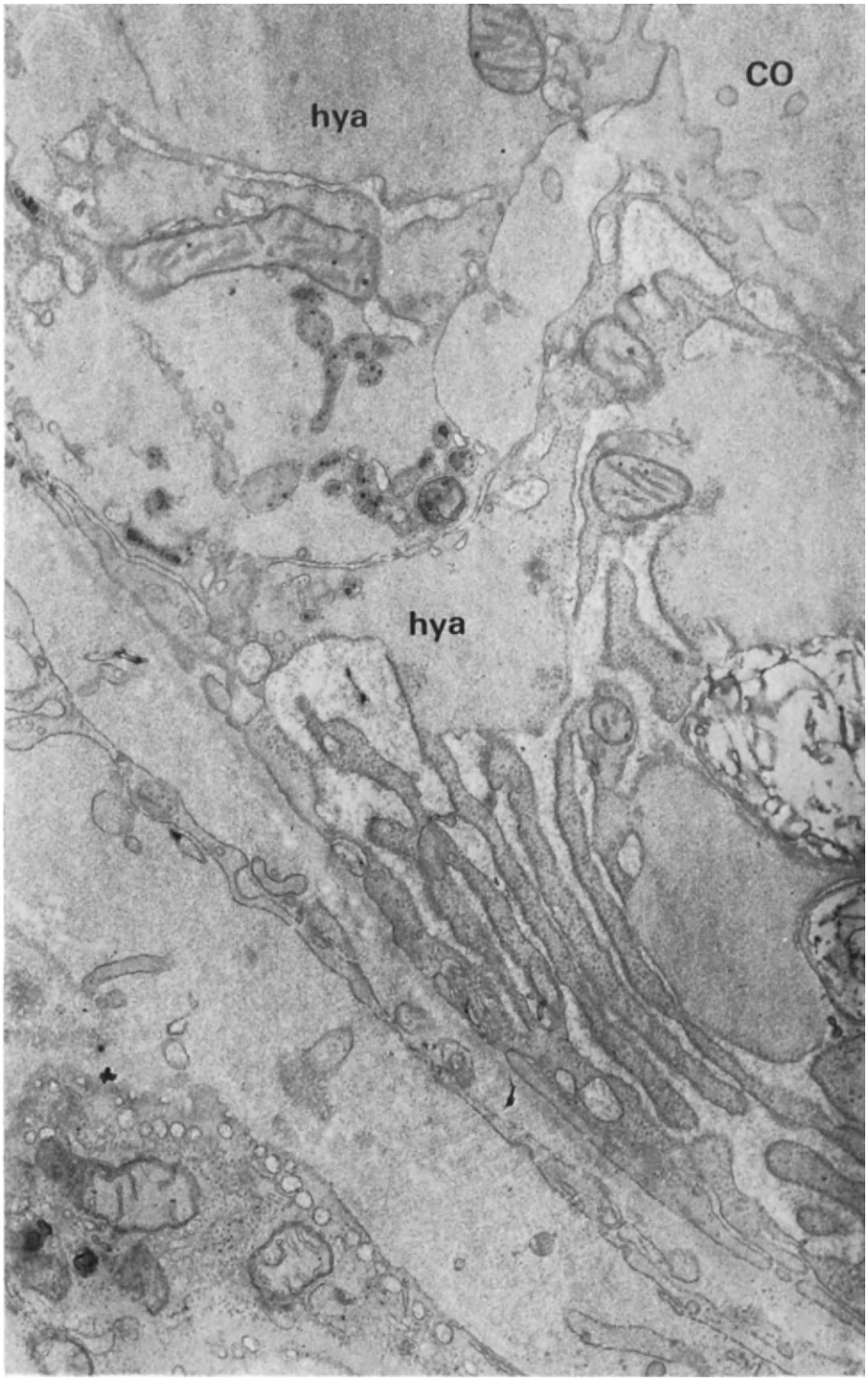

FIG. 2.11. Guinea-pig experimental thyroiditis. Typical colloid cells bordering the colloid lumen (CO) in guinea-pig experimental thyroiditis. Large homogeneous areas of cytoplasmic matrix (hya) are prominent. (×24,500.)

parenchyma to thyrotoxic levels, called LATS (long-acting thyroid stimulator); it is the subject of a separate chapter (cf. Chapter 8).

From the diagnostic point of view, the production of thyroid antibodies and the presence of immunoglobulins in the circulating blood are of great interest. The thyroid antibodies are organ-specific, and their presence in significant quantities nearly always betrays the existence of lesions of lymphocytic thyroiditis in the thyroid gland.

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CHAPTER 3

Subacute and Chronic Granulomatous Thyroiditis

P. A. BASTENIE, M. BONNYNS and P. NÈVE

Synonyms: de Quervain's thyroiditis, granulomatous thyroiditis, pseudotuberculous thyroiditis, giant-cell thyroiditis, viral thyroiditis, acute non-suppurative thyroiditis, subacute thyroiditis.

1. Introduction

Granulomatous thyroiditis, first described in 1904 by de Quervain,[23] is a distinct nosological entity with characteristic clinical, pathological, and functional signs. During recent years it has been detected with increasing frequency, and several observations point to the probability of a viral origin. In general, the condition affects a previously normal gland, runs a variable subacute or prolonged course, and, after an active period lasting between a few weeks and several months, spontaneously disappears without after-effects. Despite this self-limiting benign course, granulomatous thyroiditis raises important diagnostic and functional problems. It also deserves attention on account of its possible relationship with autoimmune processes and with chronic thyroiditis of the struma fibrosa giant-cell variant.

2. Illustrative Case Reports

CASE REPORT 3.1: SP 61,441

A 22-year-old male patient with no personal or family history of thyroid disease was admitted for pharyngitis which had lasted for 15 days, was accompanied by a temperature of 39–40°, and resisted numerous antibiotic treatments. The patient was very weak and complained of headaches, painful swelling on the left side of the neck, and painful dysphagia.

On examination the subject was found to be pale, asthenic, with a fever of 38° and to have a diffuse swelling in the left cervical region which was tender to palpation but not associated with enlarged lymph nodes. The pulse rate was 100 per minute.

The significant laboratory results are given in Table 3.1 and Fig. 3.1. The reactions of Wright, Widal Paul, and Bunnell were negative and no polio virus, ECHO, or adeno-virus were found in the stools. Treatment with 25 μg of triiodothyronine and 25 mg of cortisone acetate three times per day brought rapid regression of the subjective signs and pyrexia. After 15 days the patient left the hospital cured. A check-up 5 years later showed complete absence of after-effects.

TABLE 3.1. CASE REPORT 3.1. LABORATORY INVESTIGATIONS

	2.5.1964–16.5.1964	1.6.1964	24.9.1964	18.12.1964	Sept. 1969
Haemoglobin (g per 100 ml)	11·1				
Leucocytes (per mm^3)	12,000	7,000	5,700		
Neutrophils (%)	66	70	52		
ESR (mm/l hr)	90	3	4		
Fibrinogen (mg per 100 ml)	765				
Serum proteins (g per 100 ml)	6·7	8·3	7·5	7·6	7·3
α_2 glob. (%)	23·6	18·4	13·7	11	9·6
γ glob. (%)	14·6	16·3	11	11	8·8
$PB^{127}I$ (μg per 100 ml)	5·9	5·1	4·7		5·8
B.M.R. (%)	+8			−1	
TSH (mU per 100 ml)[a]	19				
Cholesterol (mg per 100 ml)	185				288
TGA		+(1/125)	neg.	neg.	neg.
6 hr ^{131}I uptake (%)	2	43	30	33	30
24 hr ^{131}I uptake (%)	8	49	47	58	51
Scan	Fig. 3.1a	Fig. 3.1b			Fig. 3.1c

[a]McKenzie method.

CASE REPORT 3.2: SP 69,951

A 37-year-old female patient was admitted on 8 August 1967 because of a thyroid swelling which had developed in the preceding 4 weeks, with a pyrexia of 38°C, pains in the front of the neck, and painful dysphagia. Since treatment with antibiotics and aspirin had had no effect, the patient had been admitted to a provincial hospital from 17 to 24 July, where treatment with ACTH had brought a temporary improvement. A week after this treatment was stopped, the pyrexia and cervical pains had reappeared.

On examination, the patient was thin but generally in a satisfactory condition. There was a medium-sized goitre, estimated at about 50 g, with the right lobe larger than the left, but without thrill or bruit. It was moderately tender to palpation. No enlarged lymph nodes were felt.

Investigations suggested granulomatous thyroiditis (cf. Table 3.2 and Fig. 3.2). Nevertheless, open biopsy was performed and confirmed the clinical diagnosis by revealing extensive lesions of giant-cell thyroiditis. Alongside the large-sized intact thyroid vesicles with well-stained colloid, other cells were observed in the process of disintegration (Fig. 3.3). The epithelium of the gland was broken in parts and stratified in others, and the colloid was invaded by wandering cells of the histiocytic type (Fig. 3.4). This infiltration was accompanied by resorption of the colloid and the formation of

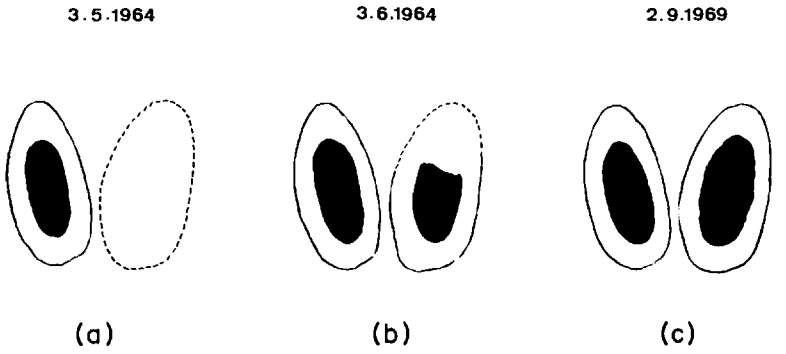


FIG. 3.1. Diagram of successive thyroid scans in case report 3.1. (a) At peak of disease. (b) After 1 month. (c) After 5-year follow-up.

TABLE 3.2. CASE REPORT 3.2. LABORATORY INVESTIGATIONS

	17.7.67 First attack	10.8.67 Second attack	26.9.67 After treatment
Leucocytes (per mm^3)	11,300	11,100	8,000
Neutrophils (%)	80	72	78
ESR (mm/2 hr)	94	62	12
Fibrinogen (mg per 100 ml)		695	350
Serum proteins (g per 100 ml)	7·3	6·6	6·1
Alb. (%)	48	50	56·5
α_1 glob. (%)	6	5·5	4·2
α_2 glob. (%)	16	14·5	11
β glob. (%)	12	10	11·3
γ glob. (%)	16	20	17
Serum iron (μg per 100 ml)	74	26	152
$PB^{127}I$ (μg per 100 ml)	11·3	9·1 9·55	4·2
$BE^{127}I$ (μg per 100 ml)		7·90	
B.M.R. (%)	+29	+23	−2
Cholesterol (mg per 100 ml)		236	345
6 hr ^{131}I uptake (%)		4	2
24 hr ^{131}I uptake (%)		5	38
PB ^{131}I (% dose per l. at 24th hour)		0·01	0·04
TGA		neg.	neg.
CFA		neg.	neg.
TSH		Undetectable	
LATS		neg.	
Scan		Fig. 3.2a	Fig. 3.2b

giant-cell granulomas around colloid masses (Fig. 3.5). In some parts there were small patches of necrosis infiltrated with multinucleated cells. In other parts, the only remains of the vesicles were cell masses with no definite architecture. Furthermore, the stroma contained a few discrete infiltrations with lymphocytes. No signs of tuberculous granuloma were observed.

The patient was submitted to a month's treatment with triiodothyronine (25 μg per day) and a short course of cortisone in low dosage. Two weeks after the cessation of treatment, follow-up examination showed the disappearance of the inflammatory signs and a return to normal thyroid function (Table 3.2).

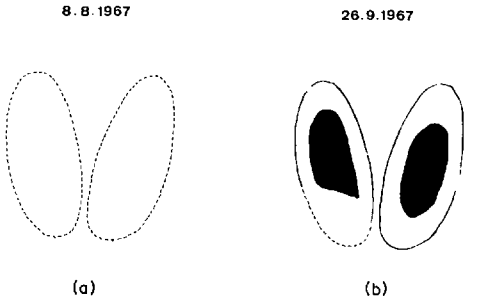


FIG. 3.2. Diagram of successive thyroid scans in case report 3.2. (a) At peak of recurrence a month after onset. (b) After a month's treatment.

CASE REPORT 3.3: SP 83,379

Another interesting case was that of a 56-year-old woman admitted on 3 February 1969 for neck discomfort, painful coughing, a temperature of 37–39°C, loss of weight, and severe asthenia. The symptoms had set in insidiously 2 months before. The main data are given in Table 3.3. Treatment with triiodothyronine and aspirin improved the condition in a few days, bringing a drop in the leucocytosis and marked regression of ESR. Despite the cessation of triiodothyronine treatment at the end of February, the patient's condition was normal at the follow-up examination on 19 March 1969. Six months later the patient had had no relapse, and the investigations furnished perfectly normal results.

CASE REPORT 3.4: E 41,971

From 1 to 17 August 1968 a 30-year-old patient was treated with antibiotics for influenza and discomfort in the neck. On 12 August the diagnosis of subacute thyroiditis was made at the Medical Clinic in Rome (Professor Cassano) on the basis of a high $PB^{127}I$ level, nil uptake, very high sedimentation rate with moderate polymorph leucocytosis. Treatment was started with cortisone in doses decreasing from 40 to 10 mg per day.

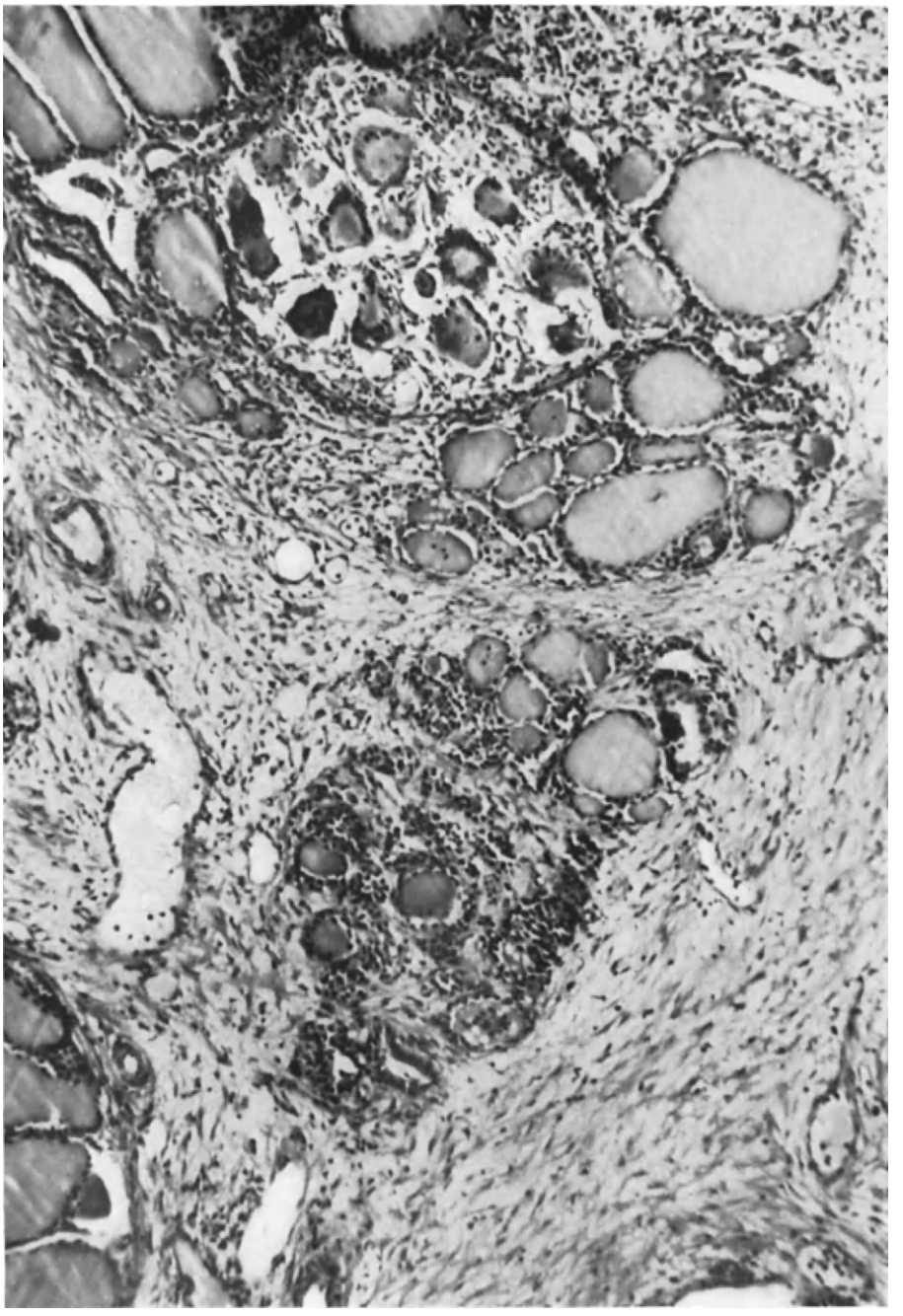


FIG. 3.3. Granulomatous thyroiditis (case report 3.2.) Disrupted follicles. Formation of giant cells—oedema of stroma—very scant inflammatory infiltration. (×130.)

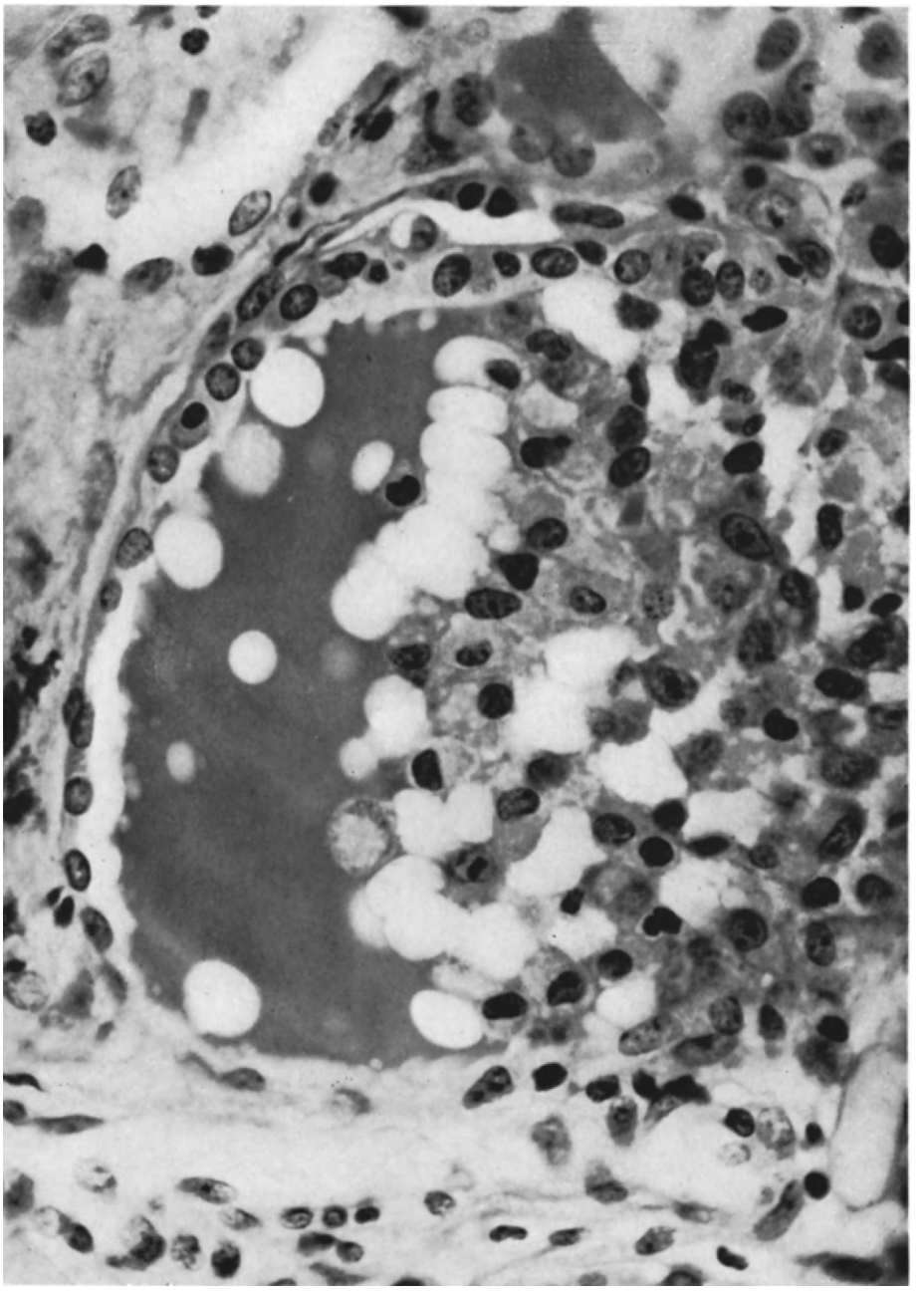


FIG. 3.4. (Same case as Fig. 3.3.) Disruption of epithelial lining, with stratification; invasion by histiocytes. (×750.)

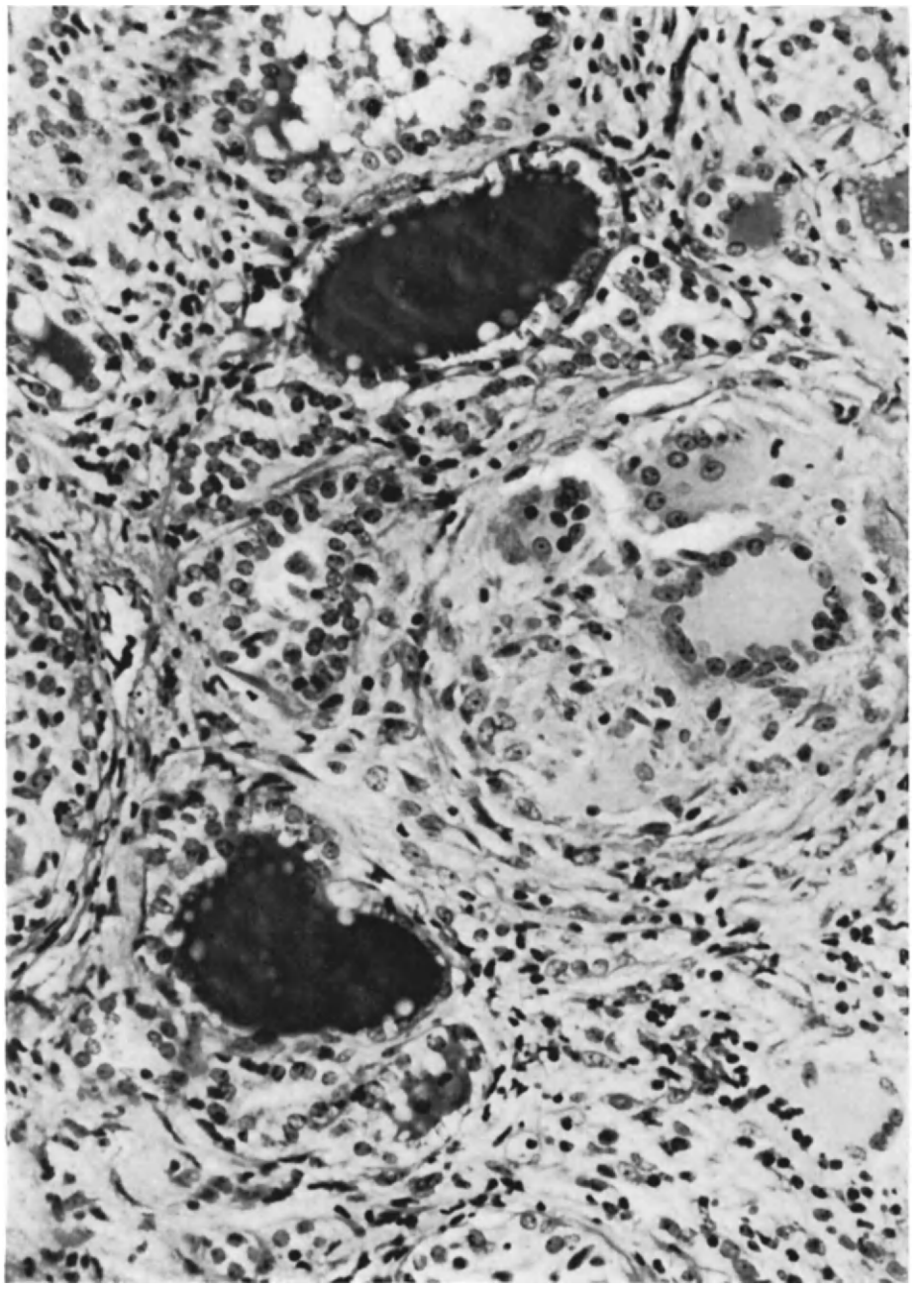


FIG. 3.5. (Same case as Figs. 3.3 and 3.4.) Nodule of PAS negative giant cells adjoining a follicle with stratification, and two normal or near normal acini with PAS + colloid content. (×300.)

TABLE 3.3. CASE REPORT 3.3. LABORATORY DATA

	3.2.69–25.2.69		19.3.69	10.69
Leucocytes (per mm^3)	18,000	9,200	7,800	8,600
Neutrophils (%)	73		51	57
ESR (mm/hr)	122	32	22	9
Serum proteins (g per 100 ml)	6·5		7·9	6·6
α_2 glob. (%)	17·4		8·8	11
γ glob. (%)	21		21·7	14·5
Serum iron (μg per 100 ml)	53		135	100
$PB^{127}I$ (μg per 100 ml)	10		5·8	
BEI (μg per 100 ml)	6·95		4·6	
NBEI (μg per 100 ml)	3·05		1·2	
Cholesterol (mg per 100 ml)	205		415	
6 hr ^{131}I uptake (%)	0		43	
24 hr ^{131}I uptake (%)	0·5		59	
T3 resin test (%)	99		66	
TGA	neg.		neg.	neg.
CFA	neg.		neg.	neg.

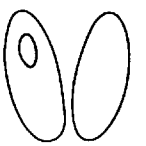
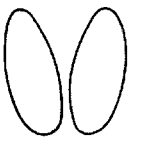
On 18 September the patient was examined in the Endocrinology Department at Brussels. She showed physical and laboratory signs of hypothyroidism with low BEI (Table 3.4). Uptake was abnormally low at 24 hr, and $PB^{131}I$ very high. The scintigram showed a uniform pattern of low uptake except in one area in the middle of the right lobe. Continuous treatment with 50 then 37·5 μg of triiodothyronine was necessary for 10 months. Whenever treatment was stopped, signs of hypothyroidism reappeared. After 10 months, uptake was back to normal and the scintigram showed no more deficit. $PB^{127}I$ had returned to the lower limits of normal. At no time were any thyroid antibodies detected.

3. Clinical Features

Incidence

Once considered as a rare disease,[12,44,75] granulomatous thyroiditis is now being reported with increasing frequency. Initial descriptions concerned only severe cases often treated by surgery.[12,24,102] But better knowledge of the illness and accurate investigation methods have made the diagnosis possible in milder cases. McWhinney[61] reported ten cases observed in a clinical practice over a period of 9 years. Recently an outbreak comprising numerous cases was reported.[41] Werner[98] estimates the frequency in New York to be about 0·5–2% of all thyroid diseases. According to Weyeneth,[100] the age incidence ranges from 30 to 60 years, and according to Means *et al.*[63] the F/M ratio is 7 to 3. In ten cases recently observed in Brussels[59] (present study), the F/M ratio was 5/2 and the age range 21–63 years.

TABLE 3.4. CASE REPORT 3.4. LABORATORY DATA

	7.8.68	19.9.68	2.1.69	27.11.69
ESR (mm/hr)	116	10	9	—
White cells	11,000	6,900	—	—
Polynuclear cells	80	50	—	—
$PB^{127}I$ (μg per 100 ml)	14	6	3·3 3	3·9
$BE^{127}I$ (μg per 100 ml)	—	3·8	2·4 —	—
6 hr ^{131}I uptake (%)	1	47		
24 hr ^{131}I uptake (%)	1	26		
$PB^{131}I$ (% dose per l., per 24 hr)	—	3.8		
T3 resin uptake (% of N)	—	74	70	
TGA	—	neg.	neg.	neg.
Cytopl. fluor. antib.	—	neg.	neg.	neg.
SCAN				

Course

The onset of the disease is sometimes slow but more often acute, with a sore throat, fever, and fatigue. Diffuse pains in the neck, dysphagia, and general malaise suggest a common viral or some other common infection of the upper respiratory tract. After some days the fever increases, thyroid swelling and tenderness become more marked, and general signs develop. The main signs and symptoms at this stage are summarized in Table 3.5.

The severity of the illness varies both in its local signs and systemic symptoms. Woolner *et al.*[102] reported on seventy-one cases, out of which fourteen displayed a clinical picture of thyrotoxicosis. In the other cases, classified as mild, the thyroid was painful and tender but systemic signs and symptoms were either absent or slight. Volpé *et al.*[92] classified their fifty-six cases as very severe, moderately severe, and mild. Eleven patients in the first group, who underwent a thyrotoxic phase, presented "a sudden fulminating onset, severe pain with radiation to the ears, high fever and a pronounced systemic reaction with malaise, fatigue and weight-loss". At the other extreme of the clinical picture the illness may be asymptomatic. This is shown by the discovery of typical lesions in silent cold-nodules removed for suspected malignancy.[55,92,102]

The thyroid may be affected to varying degrees. In only about half the cases is the

TABLE 3.5. SIGNS AND SYMPTOMS OF GRANULOMATOUS THYROIDITIS (8, 41, 96, this book)

	Frequency	%
Local signs		
Diffuse or local swelling of the thyroid	146/146	100
Tenderness	134/146	92
Local symptoms		
Pain	90/146	62
Sore throat	22/44	50
Dysphagia	35/102	34
Hoarseness	9/44	20
General signs		
Asthenia	40/44	91
Headache	34/44	78
Fever	69/146	47
Perspiration	12/44	27
Nervousness	12/44	27
Palpitations	8/44	18

whole thyroid swollen. In the other half one lobe or part of a lobe is affected. Sometimes the creeping nature of the process is clinically apparent, a focal lesion extending to the entire lobe or possibly the whole gland. Redness of the skin and the development of adenopathies seem to be exceptional.[21]

Whatever its initial severity and the duration of the acute stage of the disease, the natural course of granulomatous thyroiditis is characterized by regression of the local and systemic signs and recovery of normal thyroid function. However, even mild cases may recur after a remission of several days or weeks or even months.[8,102] The development of chronic thyroiditis has been observed exceptionally after an attack of subacute thyroiditis,[30,46,93,98] possibly with permanent hypothyroidism.[46,56,93,102] The latter condition is extremely rare except when patients have been submitted to subtotal thyroidectomy or thyroid irradiation.[12,32,38,64,91,102]

4. Pathology

Owing to the benign course of the illness, the improvement of diagnosis and the replacement of surgery by medical therapy, recent pathological data are scant. Although needle biopsy may permit a histological diagnosis[70] and has yielded interesting information in several investigations,[70,93,102] this method is often considered of limited value.[41,56] Nevertheless, two important pathological studies[62,102] have confirmed the previous descriptions of de Quervain,[23] Wegelin,[94] de Quervain and Giordanengo,[24] and Weyeneth.[100]

Gross Pathology

Inspection during surgery usually reveals some degree of inflammatory reaction involving the capsule and perhaps some loose but never firm adhesions to the trachea and surrounding tissues.[24,100,102] However, no invasive inflammatory process is observed, and the gland can easily be separated from the adjacent tissues. Thyroid enlargement is generally moderate and may be restricted to one lobe or part of a lobe.

The affected tissue differs from normal parenchyma by its yellowish white colour and firm consistency.

Light Microscopy

In their description, de Quervain and Giordanengo[24] summarized their findings as follows:

(a) Increase in number, desquamation, and degeneration of the epithelial cells.
(b) Alterations and disappearance of the colloid.
(c) Penetration of polymorphonuclear leucocytes, round cells, and large connective tissue cells into the follicular lumen, formation of giant cells (of foreign-body type) around remnants of non-resorbed colloid.
(d) Development of a connective tissue reaction.

These features are illustrated in Figs. 3.3–3.5.

Although material for microscopical study has never been obtained before the 10th day and the initial lesions are not known for certain, it is likely that the multiform histological pattern observed in sections studied during the active period is representative of the different phases of de Quervain's "parenchymatous inflammation".

This process apparently starts with extensive cell destruction in large, previously normal vesicles,[93,102] leading to cell necrosis and desquamation. Secondly, blood-cell infiltration occurs and giant foreign-body cells are formed, usually around a central mass of colloid. There remain some giant cells and sometimes groups of abnormally small follicles. It is uncertain whether the latter are residual cells or whether they are of a regenerative nature.[56] Proliferation of fibrous tissue inside and around newly formed follicles may be very marked. In the later stages inflammation and obliteration of veins are often observed.[102]

Although morphological proof is lacking, the return to normal thyroid function and the normalization of the thyroid scan suggest that in the majority of cases the process leaves no important sequellae.

Electron Microscopy

Electron microscopic studies have not been published so far although Volpé *et al.*[93] report briefly on two cases. Material from case report 3.2 has been examined by one of the authors.[65] Marked thickening of the basement membrane in thyroid follicles is shown in Fig. 3.6.

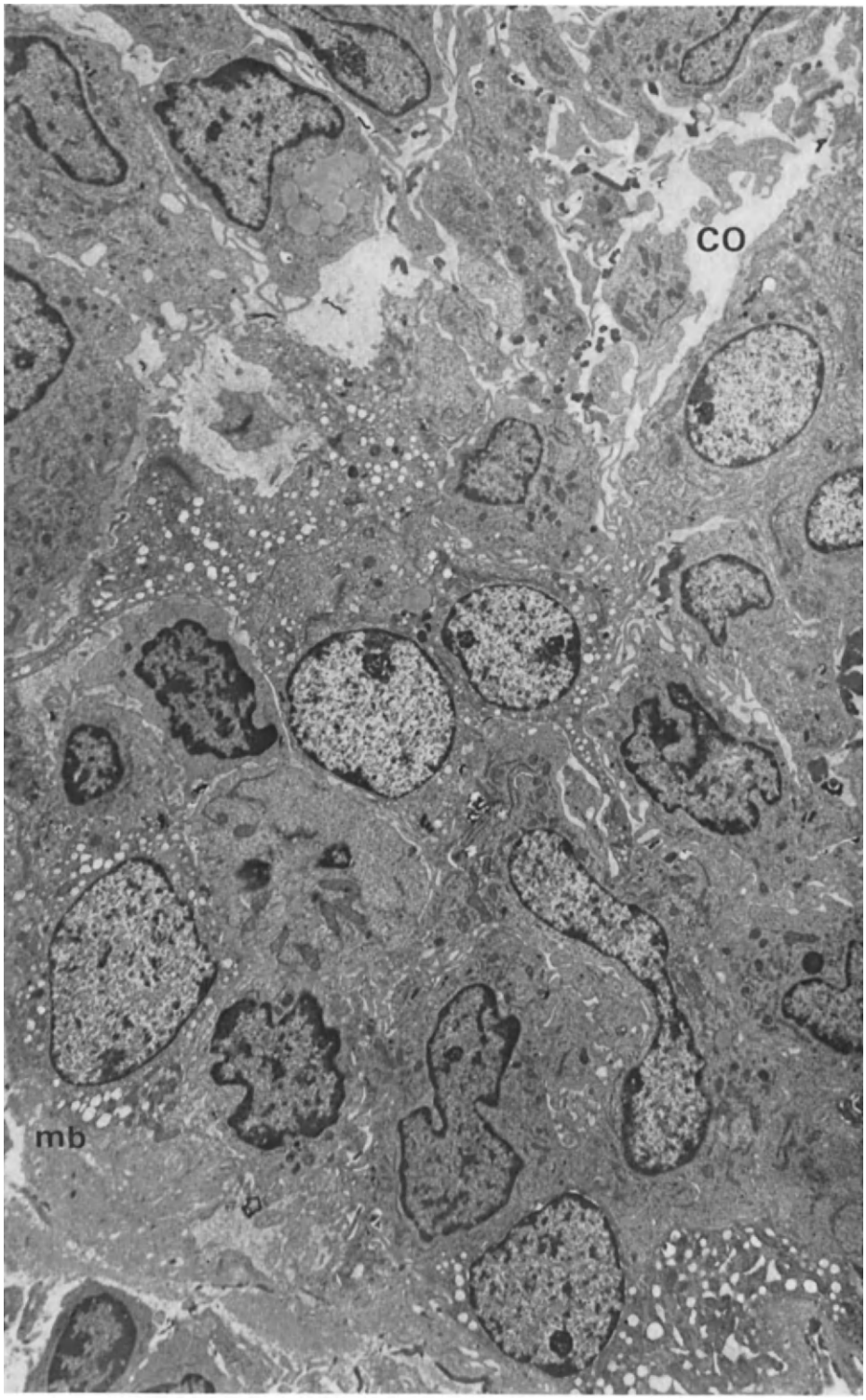


FIG. 3.6. Part of a follicle, the lumen (CO) and the wall of which are invaded by many epitheloid cells. The basement membrane (mb) appears thickened. (×4500.)

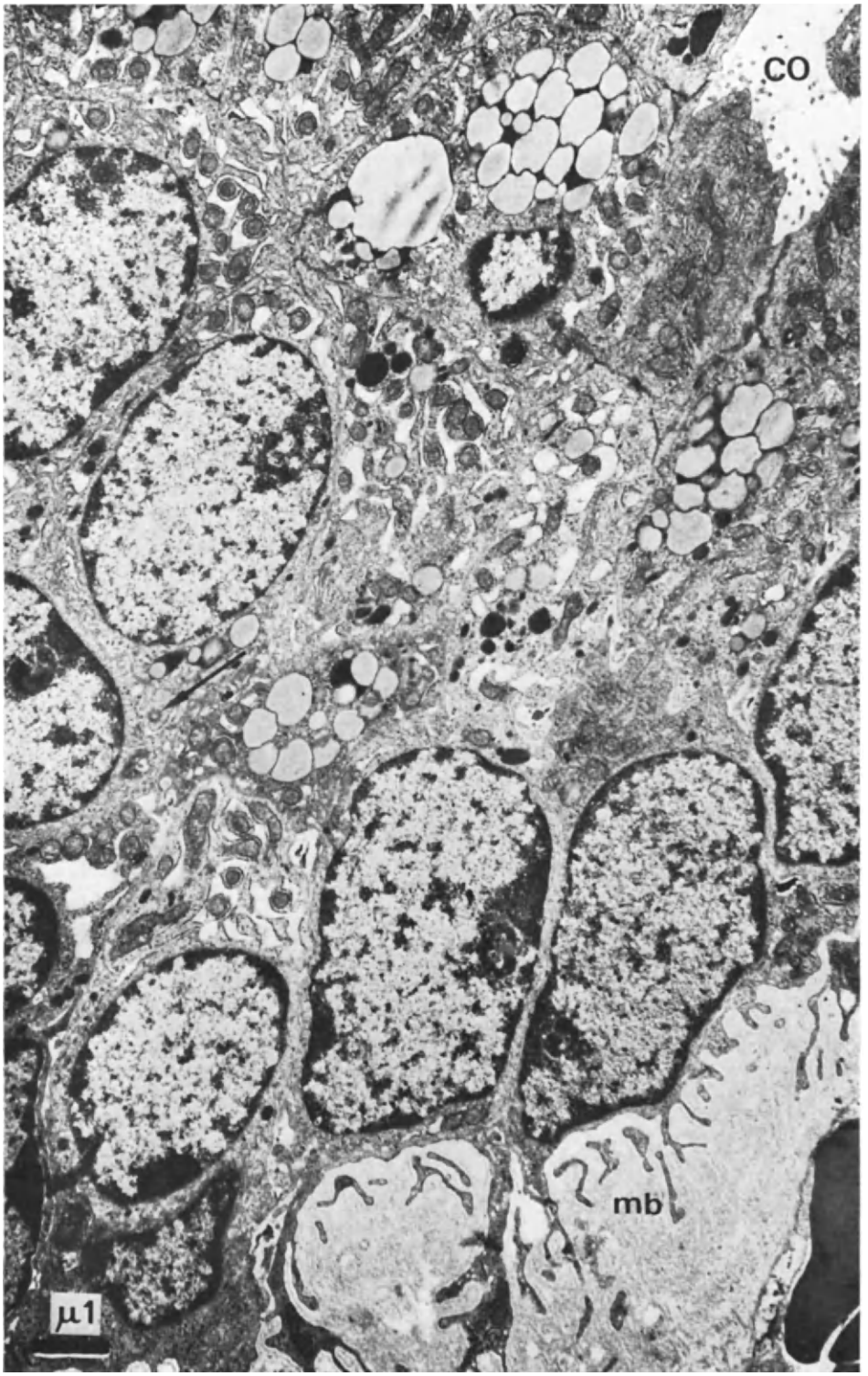


FIG. 3.7. Piling of follicle cells bordering a part of the colloid lumen (CO). The basement membrane (mb) appears thickened by deposition of material with some density. A centriole (arrow) is noticed at the bottom of a cell. (×9500.)

Some of the ultrastructural features suggest increased cellular activity: cylindrical aspect of some of the epithelial cells; apical cytoplasmic protrusions; dilated rough endoplasmic cisternae and a well-developed Golgi apparatus. This hyperactivity is different from that induced by TSH as there are no apical pseudopods with colloid droplets. The observed changes could be induced by the thyroiditis process itself, the more so that there is no definite proof of increased levels of TSH or LATS.

A large number of the epithelial cells present "lipid inclusions" which presumably correspond to the "paravacuolar granules" described by Persson[70] in his cytological study of fine needle biopsy material. These inclusions could correspond to phagolysosomes (Fig. 3.7). Some of the follicles show stratification of the epithelial cells with apparent loss of cellular polarity (Fig. 3.7). The inflammatory infiltration mostly consists of epithelioid cells or histiocytes (Fig. 3.6). The morphology of the cells that make up the giant cells resembles histiocytes more closely than epithelial cells (Fig. 3.8). These cells lose their edges and fuse into large syncytia, the centre of which is composed of amorphous material, lipid droplets, and cell debris (Fig. 3.9). Intermediate stages can be observed from simple agglomerations of individual cells to definite syncytia. No colloidophagy was observed either in inflammatory cells or in giant cells. This contrasts with suggestions derived from light microscopy.[3,35] The giant cells thus resemble those of tuberculosis or sarcoidosis. As in Volpé's cases, no viral particles could be detected in the thyroid cells or in the inflammatory cells.[93]

5. Laboratory Findings

The most important changes described in the thyroid literature are illustrated by the findings obtained in five severe or moderately severe cases (Table 3.6). Most of these changes reflect the magnitude of the inflammatory reaction.

Erythrocyte sedimentation rate (ESR) is markedly increased, often above 100 mm/hr and seemingly out of proportion to the localized inflammation. Lower rates are observed in mild cases or during regression of the inflammatory process. Although by itself non-specific, the high sedimentation rate, in contrast to the localized process, has a diagnostic value.

Leucocytosis. Leucocytosis may be inconstant and transient, never exceeding 20,000 (Table 3.6).[12,41,56] It has been related to polymorphonuclear cell invasion of affected follicles.[17,24,62,102]

A marked increase in the level of *plasma fibrinogen* was found in four severe cases (Table 3.6). This non-specific parameter of inflammatory reaction has rarely been mentioned in previous reports.[82] It may be of diagnostic interest as it is not observed, at least to such a marked extent, in common viral infections: it probably explains the unexpected rise in the erythrocyte sedimentation rate.

According to Weissman and Perlmutter,[97] all fractions of *serum globulins* may be increased, but in Werner's opinion[98] such changes may be characteristic of "any infection". However, as shown in case reports 3.1, 3.2, and 3.3, and in other reports,[21,52,82,85,90] α_2 globulins are often high in severe cases and fall as the illness recedes, whereas

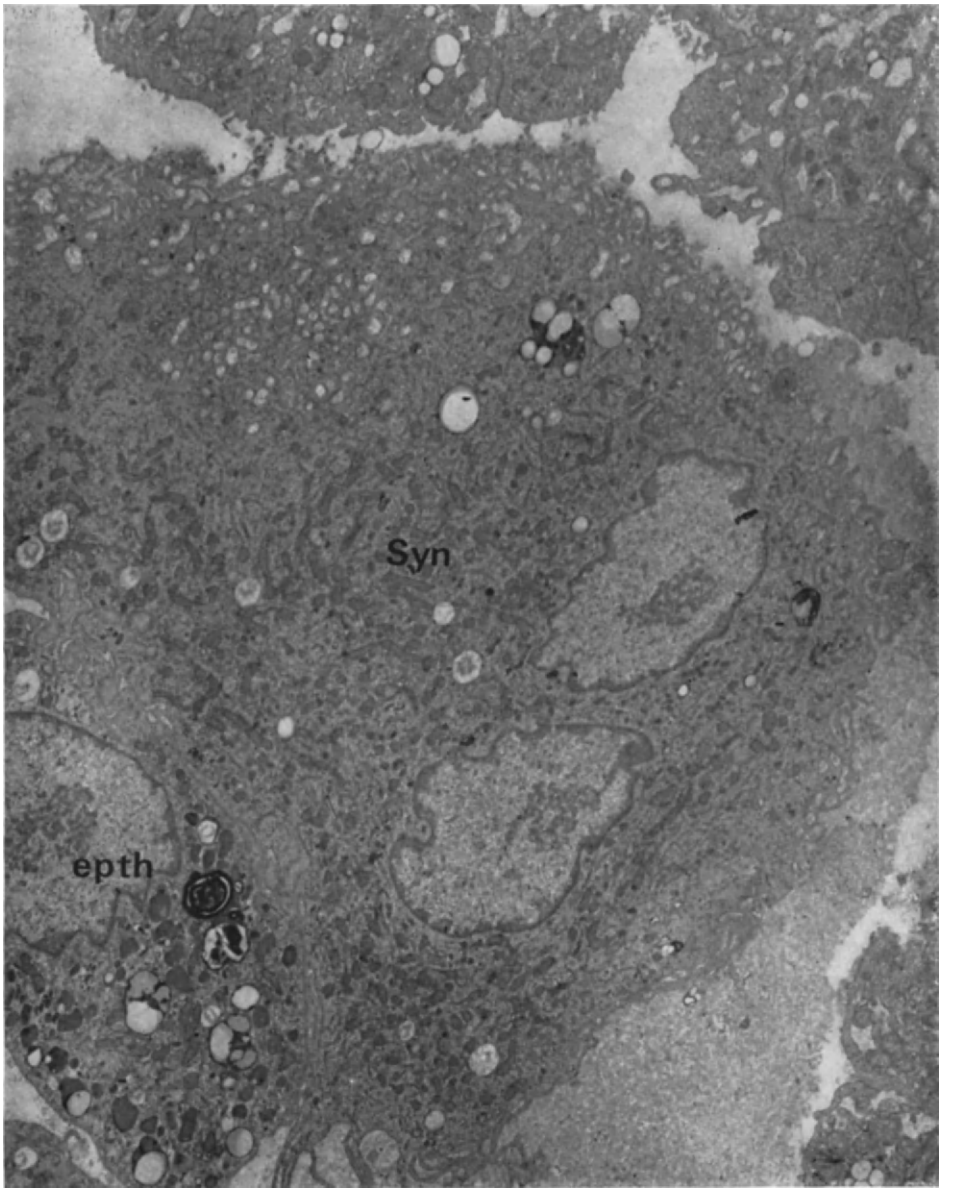


FIG. 3.8. Giant cell in de Quervain's thyroiditis. An individual epitheloid (epth) cell is closely joined to an authentic syncytium (Syn). Such intermediary stages suggest that giant cells result from fusion of inflammatory cells. ($\times$ 5000.)

gammaglobulins are much less increased in the acute phase than in autoimmune lymphocytic thyroiditis. In 21 out of 27 patients studied by Skillern and Lewis,[82] a significant *rise of* α_2 *globulins* was observed, and in 18 of these 21 subjects there was also a significant increase in fibrinogen. In contrast, only 6 out of 55 patients affected with Hashimoto's thyroiditis showed an increase in α_2 globulins.

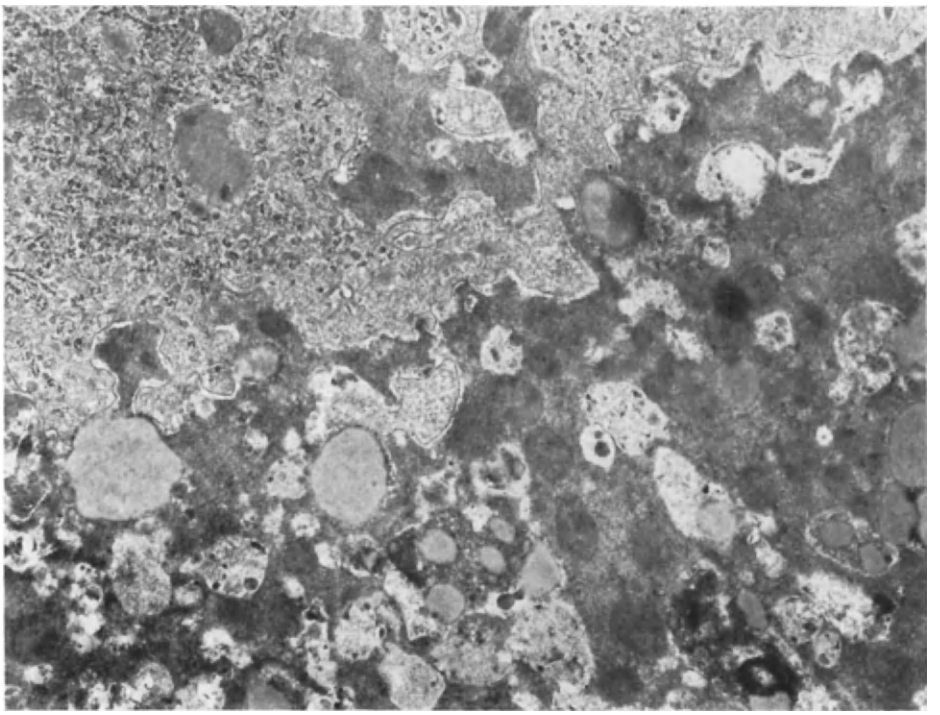


FIG. 3.9. Cellular debris in the centre of a giant cell.

A low *serum iron* level was found in the three cases studied; the patients showed borderline haemoglobulin values. Normochromic anaemia has been described as an important clinical manifestation by Skillern and Lewis,[82] who ascribe it to the fall of iron metabolism due to the infectious process. Anaemia and the low iron level disappear rapidly when the infection subsides.

Vogt[90] observed high levels of *alkaline phosphatase* in the serum of a patient with typical subacute thyroiditis and rapid regression under successful corticosteroid therapy. Parathyroid involvement was presumed as an explanation. No other case has been reported in the literature. In two of our cases studied for this phenomenon, normal values for calcium, phosphorus, and alkaline phosphatase were found.

TABLE 3.6. COMMON LABORATORY FINDINGS IN FIVE CASES OF SEVERE SUBACUTE (GRANULOMATOUS) THYROIDITIS

	Mean value	Range
Leucocytosis (per mm^3)	14,000	11,300–18,000
Polymorphonuclear cells (%)		66–80
ESR (mm/hr)	94	70–122
Fibrinogen ($n = 4$) (mg per 100 ml)	710	665–765
α_2 glob. (g per 100 ml)[a]	1·18	0·82–1·58
γ glob. (g per 100 ml)	1·14	0·93–1·37
Serum iron ($n = 3$) (μg per 100 ml)	40	26–53

[a] After clearing of the process $\alpha_2 = 0{\cdot}77$ (0·67–0·84). In this hospital the normal values for these parameters are: α_2, 0·40–0·83 g per 100 ml (6·2–10·1 % of total serum protein); γ, 0·78–1·53 g per 100 ml (11·4–19·9 % of total serum protein).

6. Iodine Metabolism and Thyroid Function

Both pathological and clinical studies indicate that subacute thyroiditis constitutes a fulminating or creeping process which runs a typical three-stage course (Table 3.7):

(1) Invasion by active inflammation and flooding of the body with extruded hormonal reserves.
(2) Regression of lesions leaving scarred tissue and an exhausted hormone reserve stock.
(3) Recovery of thyroid function.

These changes are reflected by the fluctuations of iodine metabolism. At the height of the process, *serum $PB^{127}I$* is increased in many cases and in all severe ones. If the clinical picture suggests thyrotoxicosis and the $PB^{127}I$ reaches the hyperthyroid range (Table 3.8), however, all the $PB^{127}I$ is not hormonal iodine. Owen and McConahey[67] found that a large part is composed of butanol-insoluble material. Ingbar and Freinkel[44] have suggested that the difference between $PB^{127}I$ and $BE^{127}I$ was due to the presence of thyroglobulin and iodinated polypeptides. Mahaux *et al.*[59] found the ratio of $BE^{131}I$ to $PB^{131}I$ down to 60 and 45%. In one of our severe cases (case report 3.3) the $PB^{127}I$ was 10·7 and 10 μg per 100 ml during the active phase, 3 μg of the material being insoluble in butanol. After healing, the respective values were $PB^{127}I$ 5·8 μg, $BE^{127}I$ 4·6 μg, $NBE^{127}I$ 1·2 μg per 100 ml. Ivy[46] reported values of $PB^{127}I$ 5·3 and $BE^{127}I$ 4·5 during a recovery from a severe attack.

At this stage of the process, when clinical signs suggest hyperthyroidism and $PB^{127}I$ is in the hyperthyroid range, the *radioiodine uptake* is paradoxically low or even nil. This finding, reported by Lumbroso *et al.*,[57] McConahey and Keating,[60] Seed *et al.*,[79] Tubiana[89] and Werner *et al.*,[99] has been consistently confirmed* and illustrated in case reports 3.1 and 3.2. $PB^{131}I$ is accordingly very low.

* Apparent absence of such a decline has occasionally been observed in countries where a low iodine intake normally leads to high radioiodine uptake.[41, 52]

TABLE 3.7. PATHOLOGICAL STAGES

Stage	Pathological lesions	Clinical signs	Iodine metabolism		
			$PB^{127}I$	^{131}I uptake	Scintigram
Active inflammation	Destruction	Inflammation; hyperthyroidism	> N	O or < N	O
Regression	Stores destroyed; tissue regeneration proceeds	Hypothyroidism	< N	N or > N	± N
Recovery	Normal structure restored (at least in most part of the gland)	Euthyroidism	N	N	N

TABLE 3.8. PARAMETERS OF THYROID FUNCTION IN THE ACTIVE PHASE OF SUBACUTE THYROIDITIS (SIX CASES)

	Mean value	Range
$PB^{127}I$ (μg per 100 ml)	9·4	5·9–14
$NBE^{127}I$ (n = 3) (μg per 100 ml)		1·65–3·05[a]
$PB^{131}I$ (n = 4) (% dose per l. at 24 hr)		0–0·02
24 hr ^{131}I uptake (%)	3	0–8
Blood cholesterol (mg per 100 ml)	190	135–236
Reflex-time (n = 2) (SP in seconds)		0·21–0·23
TSH[b] (n = 4)	Undetectable or normal values	

[a] In a series of 106 normal subjects the mean value was 0·75 ± 0·07.
[b] Methods used: radioimmunological and biological (McKenzie).

The *basal metabolic rate* may be increased, blood *cholesterol* lowered, and the *ankle reflex time* shortened.

One or two months after the onset of the disease, a transient decline of thyroid function may be apparent, serum $PB^{127}I$ possibly falling below 3 μg per 100 ml, blood cholesterol rising and *radioactive T3 resin uptake* dropping to very low levels (cf. case report 3.4).

This transient hypothyroidism, first described by Bergen[5] and Volpé *et al.*,[92] only occurs in cases which have shown severe initial invasion. Its occurrence fits in well with the basic pattern of the disease, as suggested by Czerniack and Harell-Steinberg.[15]

Of special interest, both for the study of the natural history of the disease and for practical diagnostic purposes, are the changes in *the thyroid scintigram.* In the early stages of the disease, the scintigram may reveal a patchy and irregularly reduced pattern

of distribution of the tracer or it may be completely negative. Next, serial scintigrams demonstrate progressive recovery.[37,52,55,59,63] This is illustrated by case report 3.1. Whereas in most cases serial scintigrams provide graphic evidence of the evolution of subacute thyroiditis, at some stages this method may erroneously suggest the possibility of thyroid malignancy,[37] which may occasionally be accompanied by pain and tenderness.[25] In such cases, as Decourt *et al.*[21] and Hamburger *et al.*[37] point out, in view of the rather high frequency of subacute thyroiditis and of the generally slow progression of thyroid malignancy, surgery may be postponed to allow for further thyroid scanning after a therapeutic trial of cortisone.

Conflicting results have been published concerning the gland's response to endogenous or exogenous *TSH stimulation.* Czerniack and Harell-Steinberg,[15] Lamberg *et al.*,[52] and Robbins *et al.*,[74] all reported responsiveness to TSH stimulation in some of their patients. On the other hand, Skillern *et al.*[83] and Jefferies *et al.*[48] observed no response. Lewitus *et al.*[55] found no increase in radioiodine uptake in the serial scans made before and after TSH administration in the unaffected areas. Dyrbye *et al.*[27] observed normal response in 3 out of 6 patients studied, but low response in 3 others, as in hypothyroid subjects.

Direct measurements of serum TSH levels have been performed in a small number of cases. High levels,[54] normal values, and undetectable levels[6,28,71] have been observed at the peak of this process. To sum up, there is no uniform response to TSH in the cases reported. Any response that is observed may be due to an increase in uptake in the unaffected part of the gland, whereas unresponsiveness in the affected areas is probably due to tissue lesions.

7. Aetiology

Since granulomatous thyroiditis was first recognized, its genesis has been associated with different infectious agents. In 1949, after an extensive review of the preceding literature, Wegelin[95] stressed the importance of the prior occurrence of tonsillitis, pharyngitis, influenza, and other infectious diseases. However, all bacteriological studies have remained negative.[32] Volpé *et al.*[92] listed the clinical aspects of the disease which they considered to resemble benign viral diseases:

(1) It is often preceded by infection of the upper respiratory tract.
(2) There is often a prodromal phase characterized by muscular pains, malaise, and fatigue.
(3) The illness may occur at the time of an outbreak of a specific viral disease.[29,41,84]
(4) After some weeks or months complete recovery is usual.
(5) There is no leucocytosis. The absence of leucocytosis alleged by Volpé *et al.*[92] conflicts with the findings of many authors (cf. Table 3.6): it is not unusual for the leucocyte count to reach 12,000 or 18,000 in the initial stage of other viral diseases.

One of the several agents cited is the mumps virus. In 1957 Eylan *et al.*[29] described eleven cases of subacute thyroiditis occurring in connection with an outbreak of mumps.

Out of 12 cases reported in 1958,[31] the mumps virus was isolated in 2 cases from the thyroid gland and in 10 cases complement fixation was positive. One case of mumps with thyroiditis was also described by Eyquem *et al.*[30] Volpé *et al.*[92] detected antibodies to various viruses during the course of proven subacute thyroiditis in seventy-one subjects.

In almost half of the subjects significant changes in antibody titres occurred during the illness, suggesting recent viral infection. The antibodies included those of influenza virus, Coxsackie, and adenovirus. Since no traces of virus have ever been found so far in sections of thyroid tissue, although mumps virus has been cultivated from thyroid tissue in two cases,[29] the authors admit that these virus antibodies may represent only

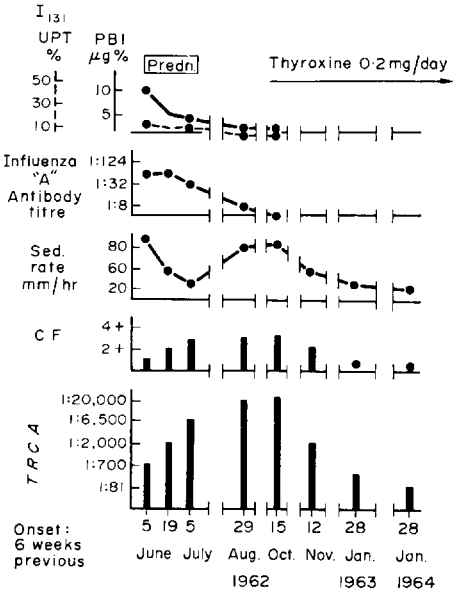


FIG. 3.10. This chart (published with permission of the authors) depicts changes in serum PBI, ^{131}I uptake, ESR, serum influenza, and thyroid antibodies titres in a case of typical granulomatous thyroiditis evolving into chronic thyroiditis. Effect of treatment with Prednisone and Thyroxine (Volpé *et al.*, *J. clin. Endocr.* **27**, 1278, 1967).

anamnestic responses and do not necessarily indicate specific viral infections. The adenovirus was also associated with cases reported in Tennessee,[86] Q-fever was reported in a well-documented case in Canada,[84] and the mumps virus again in a single case studied in Germany.[58] Finally, in the epidemic described by Hintze *et al.*[41] in 1964, there was a clear relationship between the distribution of the forty-four cases and the relative frequency of the common cold during the same period. All these data and other reports lend support to the view held by Volpé *et al.*[93] that any one of a variety of viruses could be an aetiological factor in the genesis of subacute thyroiditis (Fig. 3.10).

Thus the bulk of evidence favours the view that a normal thyroid may develop the

typical clinical and pathological signs of subacute thyroiditis under the influence of various viral agents. This idea closely approaches the aetiological concepts in other viral diseases such as hepatitis or lymphocytic chorio-meningitis.

8. Diagnosis

In typical cases, the diagnosis of granulomatous thyroiditis should present no difficulty. Although *pharyngitis* is a common mis-diagnosis in the early stages[8,34,61,91] the sequence of an acute onset of fever (usually after a cold) with dysphagia, pain in the neck, and tender swelling of all parts of a previously normal thyroid gland, together with general signs out of proportion to the local disorder, should make the diagnosis certain. Clinical signs suggestive of hyperthyroidism, increased serum PBI contrasting with low radioiodine uptake, are pathognomonic of subacute thyroiditis or *thyrotoxicosis factitia*; the former may then be differentiated from the latter by its high sedimentation rate and increased fibrinogen and α_2 globulin levels. The radioiodine scintigram and its sequential changes also follow a typical pattern for the disease.

Acute septic thyroiditis is very rare and does not have the same symptoms as subacute thyroiditis. For these reasons and absence of disturbance in thyroid function, no further mention will be made of pyogenic or fungal thyroiditis. *Tuberculosis of the thyroid*, although very rare even in the early literature,[1,94] should sometimes be considered. Goldfarb *et al.*[36] reviewed the previous literature and reported one case of tuberculosis with fever, painful swelling, and induration of one thyroid lobe. The scintigram showed a cold area suggesting malignancy. Subsequent surgery revealed an abcess containing pus with Koch bacilli. In this case, pre-operation PBI was 6·6 μg per 100 ml with low BEI (2 μg per 100 ml); post operation the non-butanol extractable iodine had disappeared. PBI was 6·9 and BEI 6·7 μg per 100 ml. Since Jaffe's investigations,[47] several authors have stressed that the discovery of giant cells in the thyroid does not indicate a tuberculous infection. For a diagnosis of the latter there must be evidence of caseous necrotic areas and of acid-fast bacilli.

Acute epidemic goitre has been described by Costa *et al.*[10] in a slightly endemic goitre area as an epidemic disturbance affecting young female patients and characterized by sudden painful swelling of a previously normal thyroid, with fever and general malaise. Histological investigations showed hyperplasia without inflammation. Radioiodine uptake was high and homogeneous throughout the gland. *Thyrotoxicosis* may coincide with granulomatous thyroiditis[102] or follow its onset[55,68] or simulate it.[67] Frid and Wynblath[33] claim that subacute thyroiditis is the commonest cause of painful thyroid enlargement after *haemorrhage into an adenoma*. Focal thyroiditis may be confused with *haemangioendothelioma*[88] and with *malignant growth*.[37,55] This is especially true of the asymptomatic form, diagnosed as *a cold nodule*.[55,102] In doubtful cases, sequential scans,[55] possibly combined with a therapeutic trial of prednisone,[13,55,64] will clear an inflammatory process. Finally, the possibility of this disease should be borne in mind when the clinician is faced with *fever of unknown origin*[102] or with *cryptogenic anaemia* with low serum iron levels (cf. case reports).

9. Therapy

As soon as it was recognized that the illness runs a self-limiting course, it was clear that *thyroidectomy* is only required[11,66] when malignancy is suspected. Treatment with *sulphonamides*, *antibiotics*, and *iodine* is generally found to be ineffective. *Radiotherapy* has been claimed by Ingbar and Freinkel,[43] de Gennes and Bricaire,[22] Osmond and Portmann,[66] and Volpé *et al.*[92] to afford immediate results, but the latter authors admit that the disease is not shortened. *Thyrostatic drugs* have also been thought to reduce the acute signs.[7,32,50,73] Werner[98] may be right in assuming that the alleged results are coincidental with spontaneous remissions. Moreover, permanent hypothyroidism has been observed in patients who received radiation or thiouracil therapy.[5] Robbins *et al.*[74] claimed successful results in 5 out of 8 patients treated with TSH. In contrast, other authors have observed enlargement of the thyroid, local heat, and systemic prostration in healthy adults treated with TSH.[18] Although, as pointed out by Keating,[49] these clinical signs are no proof of a TSH-induced "acute thyroiditis", they may explain why, except for one case,[81] no other reports of this therapy have appeared.

Most authors agree that *corticosteroids* provide the most effective therapy: the clinical response is prompt, occurring in a matter of days.[4,8,13,14,34,42,51,69,93] The recommended dosage varies in different reports. The initial dose is usually of 200 mg of cortisone or equivalent amounts of other steroids, although in some cases there should be "no reluctance to increase the dosage as needed".[5,64] However, the course of the disease is not shortened,[83] and relapses seem to occur more frequently than in untreated cases, as shown by reports of numerous authors.[5,21,40,52,58,59,63,82] This is illustrated in case report 3.2. The mechanism of steroid action is probably a non-specific suppression of the inflammatory process. According to Ingbar and Freinkel[44] the abnormal protein-bound iodine fraction is not affected by the steroids. In mild cases *acetylsalicylate* has yielded comparable results.[5,16,34,41,45,76,77,87] Roskam and Van Cauwenberge[76,77] have given evidence in favour of "an ACTH-like" or an "ACTH" stimulating effect of high doses of salicylates. Moreover, a direct effect of the drug on the thyroid has been described.[39]

Thyroid hormones have been used in the treatment of acute attacks. Cassidy[8,9] reported complete remissions in 2 out of 3 patients treated with thyroid powder (120–180 mg/d) usually within 1–2 weeks. Of the nineteen patients who proved refractory to this therapy, twelve responded to combined prednisone-thyroid administration. Recurrences were only observed in patients who needed steroid therapy. It would appear from our limited experience that *triiodothyronine* administration in 25–50 μg doses per day is of immediate benefit, strikingly reducing the acute symptoms and considerably shortening the course of the disease. This is illustrated by case reports 3.1, 3.2, and 3.3, as well as by a case described by Mahaux *et al.*[59] In five severe cases so treated, permanent remission was obtained in 1–1½ months. The reasons for applying this treatment are that the thyroid tissue is undergoing widespread destruction, that endogenous TSH secretion may be increased, and TSH by itself is capable of aggravating the signs of acute thyroidi-

tis,[40] and that the increased serum PBI is, in fact, partly due to the presence of metabolically inactive material.

To sum up, therefore, in the present state of our knowledge the most effective treatment of subacute thyroiditis is the administration of corticosteroids. Thyroid hormone therapy may be helpful.

10. Relationship of Granulomatous Thyroiditis with Autoimmune Thyroiditis and Chronic Thyroiditis (Struma Fibrosa Giant Cell Variety)

Earlier observations suggested that granulomatous thyroiditis might be an autoimmune disease.[5,31,101] Circulating antibodies to thyroid antigens, specially to the second colloid antigen,[26] have been detected in a number of cases. However, when present they tend to appear in low titres 3–4 months after the initial attack and disappear after several months.[20,26,59,75,80,84] This was also observed in case report 3.1. Volpé *et al.*[93] found antibodies present in 18 out of 71 cases (25%) tested 3–6 weeks after the onset of the disease. Over periods of 3 months to 4 years, positive results were obtained in an additional twelve patients, making up a total of thirty (43%) subjects. In some patients, who presented both CFA and TGA, the titres became very high and the patient "went from proven subacute thyroiditis into proven chronic thyroiditis", requiring substitution with thyroid hormones. This sequence of events is illustrated in Fig. 3.10. A similar transformation from subacute granulomatous into chronic autoimmune thyroiditis was described by Decourt *et al.* in 1959.[19]

In other cases, in the absence of an autoimmune phenomenon, permanent hypothyroidism may result from atrophy of the thyroid tissues as an unusual complication induced by a severe attack of subacute thyroiditis.[46] In such cases the extent of the destructive parenchymatous lesions and the secondary fibrosis[102] may explain the loss of thyroid function, whereas the scarcity of lymphocytic infiltrations is in keeping with the absence of circulating thyroid autoantibodies.

To sum up, an active autoimmune process is only occasionally observed as a complication of granulomatous thyroiditis. Serological, as well as histological evidence, points against the concept that an autoimmune process plays a pathogenic role in this disease. Conversion of subacute thyroiditis into autoimmune thyroiditis is exceptional. "Chronic non-specific thyroiditis"—with or without giant-cell granulomatous tissue—may occasionally be a late complication of subacute thyroiditis.

Wegelin,[94,95] studying de Quervain's cases, already observed the features of chronic thyroiditis and fibrosis in the early stages of the disease. Likewise, Weyeneth,[100] also studying material from Switzerland, described *non-specific chronic inflammation* differing from Hashimoto's or Riedel's thyroiditis.

Under this denomination many authors have described all forms of chronic thyroiditis (including Hashimoto's and Riedel's diseases) in which no specific pathogenic agent had been detected. Riedel's struma fibrosa and Hashimoto's lymphoid goitre are now recognized as well-delineated entities. Although their aetiology remains open to

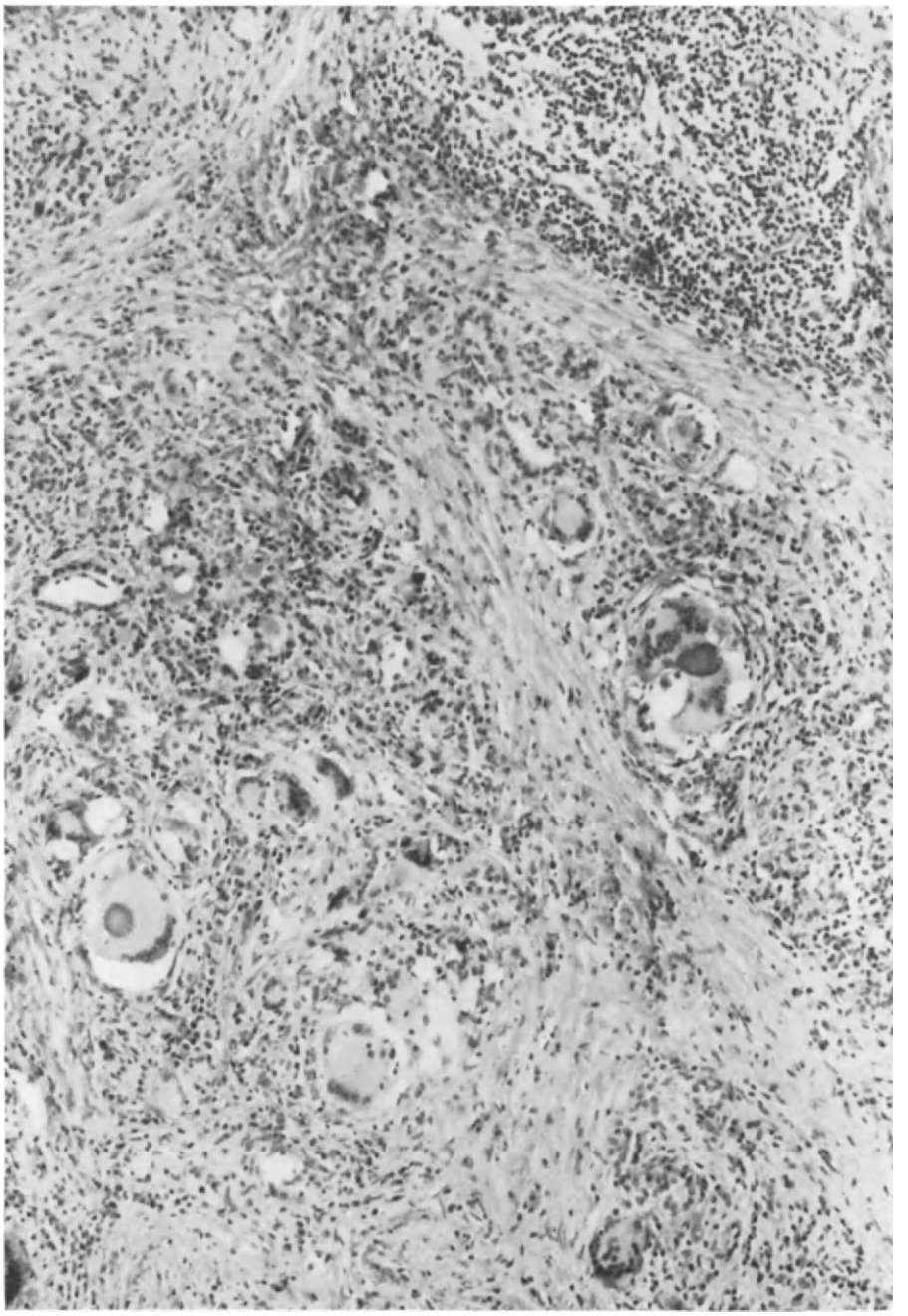


FIG. 3.11. Chronic thyroiditis with giant cells, fibrosis, and infiltration. Clinically diagnosed as "probable carcinoma". (×120.)

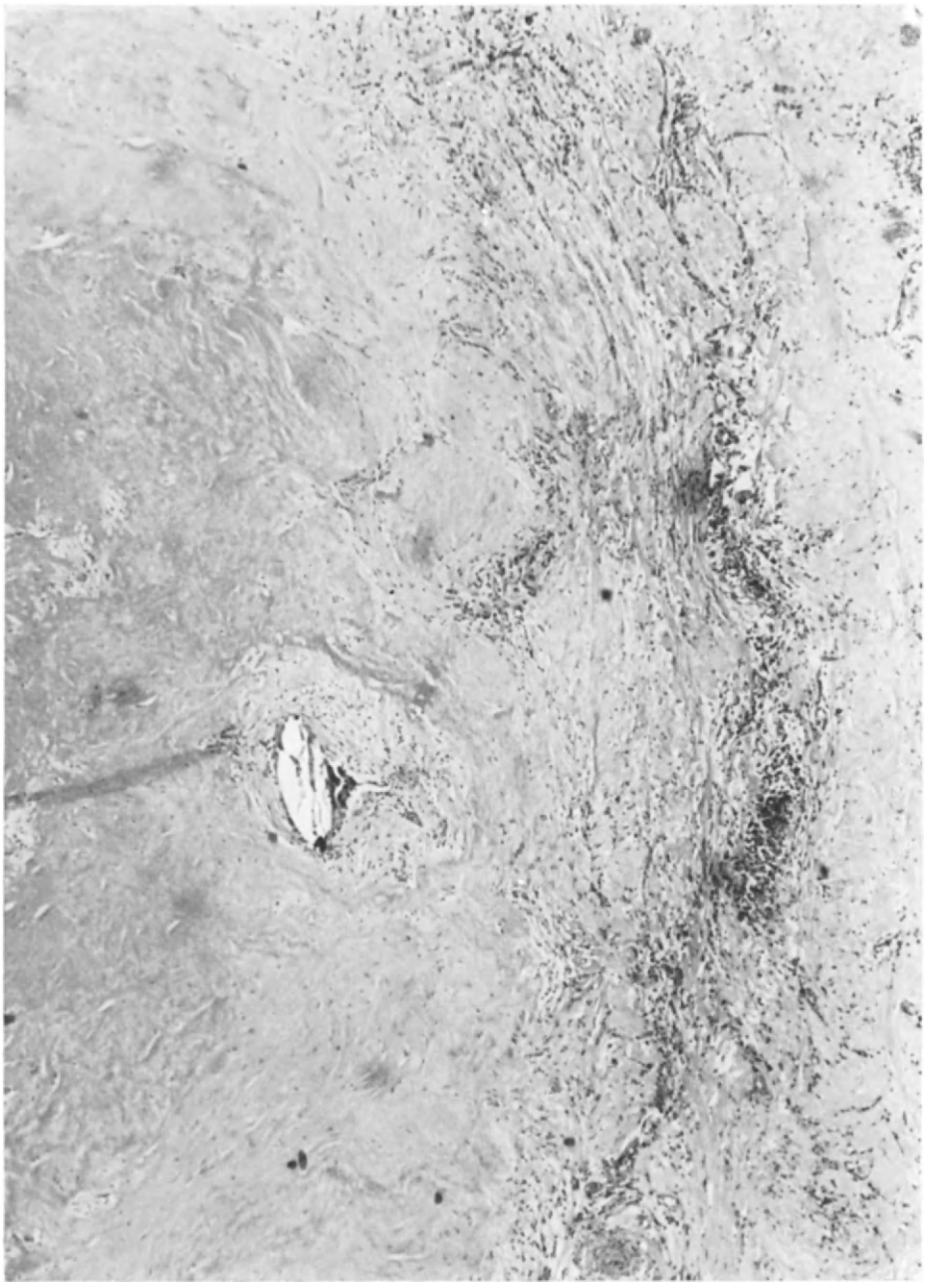


FIG. 3.12. Chronic thyroiditis with extensive fibrosis, scanty infiltrations in nodular goitre (32-year-old female with tender goitre. No thyroid antibodies in the serum. No giant cells: "non-specific chronic thyroiditis"). (×60.)

TABLE 3.9. CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF CHRONIC GRANULOMATOUS THYROIDITIS[a]

Age	21–50; peak 40	Goitre	Moderately enlarged; hard, often tender; mostly asymmetrical
Sex ratio	M = F		
Pain	Present in most cases		
Onset and duration	Usually rapid development 1–2 months; persistent for many years	Compression	Slight
		Histology	Lymphocytic infiltrations; giant cells; dense fibrosis respecting thyroid architecture
Autoimmunity	Moderate or absent		

[a] After Reist, 1922;[72] Lee, 1936;[53] Bastenie, 1937;[2] Weyeneth, 1941;[100] Schilling, 1945;[78] and Wegelin, 1949.[95]

debate, these forms of chronic thyroiditis should therefore be distinguished from the group of the so-called "non-specific inflammations". In most of the latter cases the patients at one time complain of spontaneous pain, tenderness, and increase in size of an often previously enlarged thyroid gland (Table 3.9). Biopsy frequently shows giant-cell granulomas in dense fibrous tissue with lymphocytic infiltrations (Fig. 3.11). Schilling[78] has proposed the term of struma fibrosa giant cell variety (Chapter 4).

Higgins *et al.*[40] suggest that many of the patients[101] with "chronic non-specific thyroiditis" without circulating thyroid autoantibodies would fit into this diagnosis. Analysis of earlier work by Lee,[53] Bastenie,[2] and Weyeneth[100] strengthens the concept that this form of chronic thyroiditis is a more sclerotic variant of granulomatous thyroiditis (Fig. 3.11).

The treatment of this variety of granulomatous or chronic non-specific thyroiditis (Fig. 3.12) does not differ from that of the subacute form. Surgery should be limited to biopsy and removal of compressing thyroid tissue.

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CHAPTER 4

Invasive Fibrous Thyroiditis (Riedel)

P. A. BASTENIE

Synonyms: Eisenharte struma,[35] strumitis chronica,[37] struma fibrosa, Riedel's struma, Riedel's thyroiditis, chronic productive thyroiditis.

1. Introduction

From observations of two cases,[35,36] Riedel described a "specific inflammation or mysterious nature producing an iron-hard tumefaction of the thyroid". The condition was further characterized by "strong adhesions of the gland to the surrounding tissues preventing the completion of the intended thyroidectomy". Fragments which were removed showed "the destruction of the parenchyma and sclerosis of the organ".

In the subsequent European thyroid literature, Riedel's original description was broadened to embrace other forms of "non-specific chronic thyroiditis".[3,46,48] Several studies entitled "Chronic thyroiditis" included typical cases of lymphoid goitre alongside examples of fibrous thyroiditis answering to Riedel's description. For a number of years it was commonly held that these two conditions represented extreme forms of the initial and final phases of the same process.[11] However, Graham[16] and Joll[23] furnished convincing proof that the two entities should be separated. Hashimoto[20] had in fact been the first to stress the characteristics of lymphocytic thyroiditis, differentiating it from Riedel's goitre, namely the absence of adhesions and the diffuse infiltration of the stroma by lymphocytes.

Woolner *et al.*[50] established the following morphological criteria for the diagnosis of Riedel's thyroiditis:

(1) The fibrotic process may involve the whole gland or be localized to one lobe or portion thereof. On palpation, the affected zone is found to have a woody consistency.

(2) The inflammatory fibrotic process extends well beyond the capsule into the surrounding tissues. This extension is clearly visible to the surgeon, but microscopical proof is always required.

(3) Microscopical investigation reveals that the inflammatory fibrotic process has almost completely destroyed the thyroid tissue. The affected parts no longer show either capsule or lobulation. There are no giant-cell reactions of the type observed in granulomatous thyroiditis.

Two features could be added to this picture: the paucity of lymphoid infiltrations and the almost complete absence of oncocytes.

2. Illustrative Case Report

CASE REPORT 4.1: Obs. 3785

A woman of 36 years of age without any personal or family history of thyroid disease had noticed over the previous 2 years the gradual development of a very hard, painless, thyroid swelling without any other general signs.

She underwent extra-capsular partial thyroidectomy, and a colloid adenoma was removed along with a fairly large mass of whitish fibrous tissue. The operation was very difficult because of tight adhesions and the lack of any cleavage planes. Six months later, the patient was readmitted for goitre recurrence with stridor due to tracheal compression. The thyroidal mass was very hard and firmly fixed to the skin and tissues of the neck. There were no signs of functional disturbance. The trachea was freed and with great difficulty a mass of hard tissue was removed together with a sheet of muscle and fibrous tissue.

Except for slight and temporary tetany, there were no post-operative complications. The patient was in an euthyroid condition on leaving the hospital (MB + 10%). A check-up 6 years later showed her to be in good health.

Two voluminous pieces of tissue removed were uniformly made up of yellowish-white tissue containing visible and very clearly defined brown colloid zones. Under the microscope most of the tissue showed a very dense texture. No glandular architecture was recognizable. Between the bundles of collagen tissue, small lymphocytic infiltrates could be seen, and the hyalinized fibrotic tissue enclosed isolated colloid nodules with apparently normal epithelia. No oncocytes or lymphoid follicles could be detected (Fig. 4.1).

3. Clinical Features

If the criteria defined earlier and illustrated in case report 4.1 are applied, Riedel's thyroiditis appears in practice as a very rare disease. Indeed, Riedel himself was surprised to encounter only three cases in 15 years. Woolner *et al.*[50] at the Mayo Clinic observed twenty cases out of 42,000 thyroid patients submitted to surgery. In 1964 Woolner[51] could only add five more cases diagnosed during the next 5 years. As Oberdisse[28] so rightly put it in 1967, this apparent rarity must correspond to reality since all cases of hard tumorous growth inevitably induce the subject to seek medical advice.

The preponderance of female cases is much less marked than in the majority of thyroid diseases. The ratio varies from 2:1 to 4:1. The condition is found mainly in middle-aged subjects. Woolner's cases ranged between 23–70 years of age, with an average of 50 years. Out of twenty-one cases reported in early studies and reviewed in 1937,[5] the age range of eleven male subjects was 25–65 years (average 40) and that of ten female subjects 25–59 years (average 44).

Clinical Features (*Table* 4.1)

In most reported cases of Riedel's goitre the patients had not suffered any previous

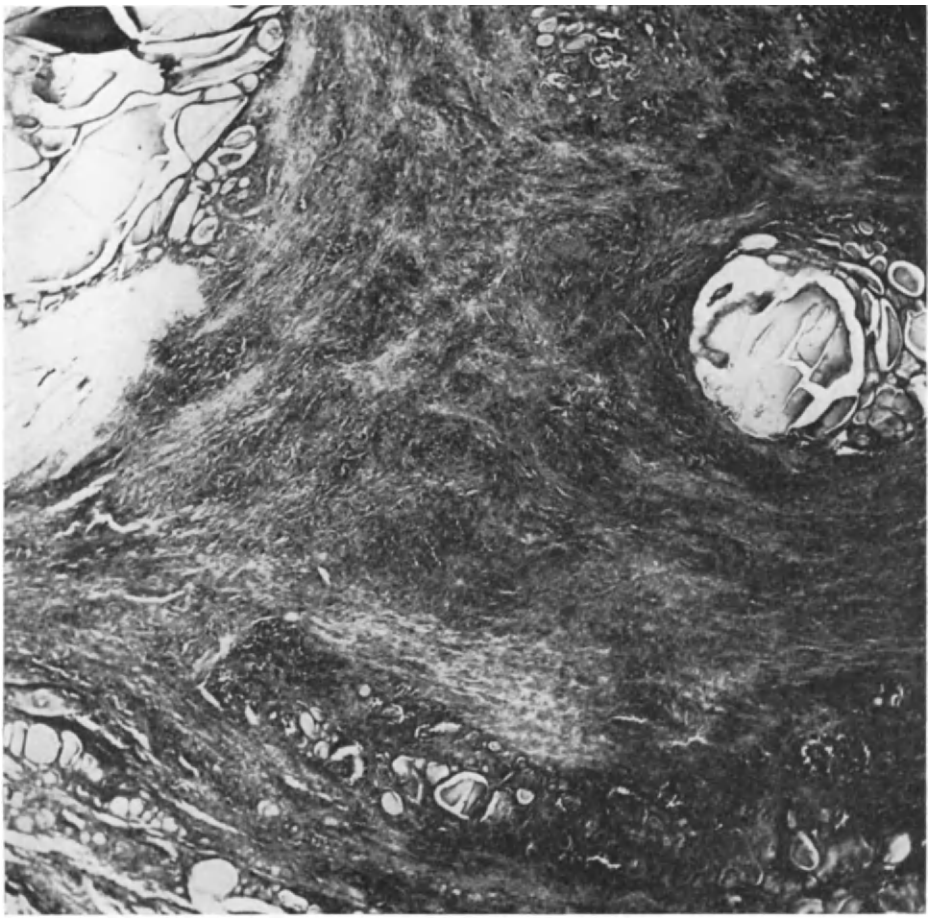

FIG. 4.1. Riedel's struma (case report 4.1). Dense fibrous tissue with sparse lymphocytic infiltrations. Adenomatous thyroid tissue in left upper corner, without oncocytes or giant cells. (×60.)

thyroid disease. In 11 out of the 20 patients described by Woolner *et al.*[50] the symptoms had lasted for 2–6 months before the patient sought medical advice. Complaints are generally related to the rapid increase in thyroid size. The swelling is of stony-hard consistency and adheres to the tissues of the neck. Pain is rarely a major complaint, but dysphagia and a sensation of pressure are reported by most patients. Pressure symptoms dominate the overall picture of the condition. The compression of the trachea[24,39] may cause dyspnoea, stridor, and attacks of suffocation[7,23,37] (cf. case report 4.1). Hazard in 1955,[21] reported several cases of unilateral paralysis of the larynx. Compression is often out of proportion to the size of the thyroid mass. The swelling may be unilateral or bilateral. It has a harder consistency than in carcinoma and is rarely tender to the touch. The regional lymph nodes are not enlarged.

TABLE 4.1. CLINICAL FEATURES

	Struma fibrosa
Age incidence	20–40 years
Sex ratio (F/M)	3–4/1
Predominant symptoms	Pressure symptoms
Duration of symptoms	6 months to 2 years
Thyroid involvement	Unilateral in 30% of the cases
Response to thyroid therapy	None
Response to steroid therapy	Inconclusive
Follow up	No myxoedema. Occasionally no relief of pressure symptoms. Possible recurrence after operation

All these phenomena develop without any general signs or fever. The patient generally remains euthyroid, although risks of hypothyroidism may occur when the gland is affected extensively on both sides.[24,50] The course of the disease, despite its often ominous beginnings, is generally benign except when the pressure symptoms are very marked and cannot be alleviated by surgery. Of Riedel's three patients, the youngest was in perfect health 15 years after partial thyroidectomy; the others died of intercurrent diseases.*[37] The same benign evolution was observed by Saint-Georges[41] in his own typical case and in two patients whom he described. This favourable course is illustrated in case report 4.1.

For an unexplained reason the disease seems to limit itself of its own accord in most cases.[7,37,39] To quote Cooke:[7] "the disease will become quite stationary or gradually disappear." But the prognosis is not always so favourable; 16% of the patients experienced recurrence of the disease (cf. case report 4.1).[10] Joll[23] reports one patient in whom pressure symptoms recurred within a year. This patient died of asphyxia 4 years later.

4. Pathology

The main characteristics have been described in the definition of the disease. Figures 4.1 and 4.2 illustrate the pathological details of case report 4.1. Table 4.2 summarizes them and contrasts them with those of giant-cell fibrous goitre.

Three further points should be added to complete the pathological picture of Riedel's fibrous thyroiditis:

(1) The first concerns the absence of giant cells, isolated or in nodules. Woolner *et al.*[50] place particular emphasis on this feature of Riedel's goitre. However, there have been a few cases in which isolated giant cells have been observed although Woolner's criteria were satisfied in every other respect.[23,38]

* One of Riedel's patients died of renal failure and this could have represented a retro-peritoneal fibrosis.

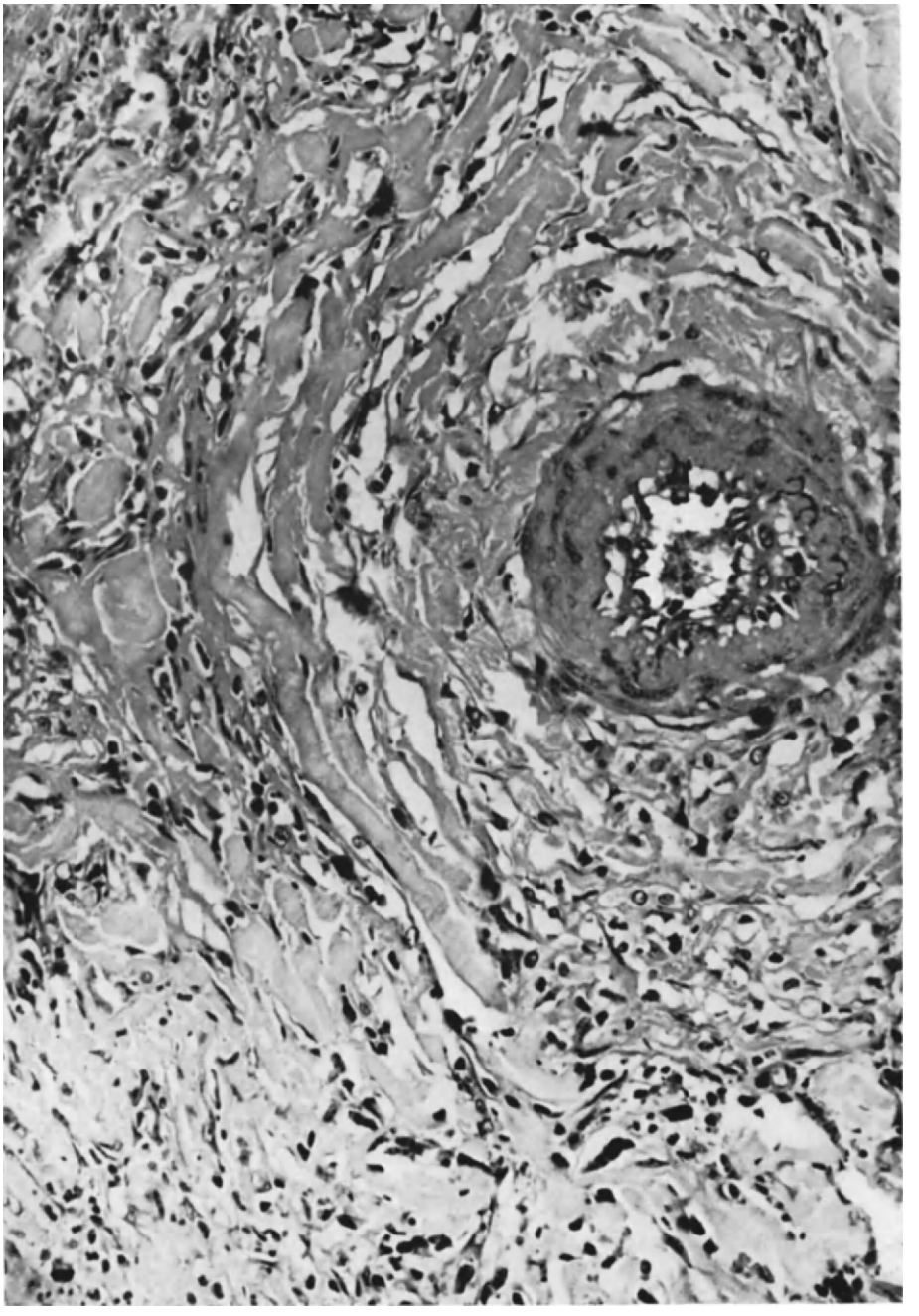

FIG. 4.2. Case report 4.1. High magnification, very dense and large collagen fibres—arteriolitis. (×320.)

TABLE 4.2. PATHOLOGICAL CHARACTERISTICS OF RIEDEL'S STRUMA FIBROSA[a]

	Struma fibrosa	Chronic non-specific thyroiditis—struma granulosa
Gross		
Surgical appearance	White, smooth	Grey-white, smooth
Bleeding tendency	Decreased	Usually decreased
Adjacent adhesions	Always present, generalized, very dense	Variable, usually none
Extent involvement	1/3 unilateral	1/3 unilateral
Consistency	Bone-like	Hard
Presence of adenomas	Occasional	Occasional
Microscopic acinar epithelium	Compressed, usually absent in involved areas; normal elsewhere	Marked acute, degeneration in involved areas; normal elsewhere
Colloid presence	Normal in uninvolved areas	Normal in uninvolved areas; intercellular in involved areas
Stroma	Marked fibrosis with hyalinization	Whorls of fibrous tissue around lobules
Cellular infiltrate	Moderate number lymphocytes and leucocytes in fibrous planes	Dense lymphocytic and leucocytic infiltrate plasma cells and histiocytes; many pseudo and true giant foreign-body cells
Blood vessels	Thickening of intima and media	Periarteriolar fibrosis and intimal thickening occasionally

[a] After Schilling, 1945.

(2) The second point is that many cases of Riedel's goitre comprise a central adenoma.[8,23,26,39] This was also a feature of the case record 4.1 quoted as an example. According to Woolner *et al.*[50] this is not a major characteristic of Riedel's goitre.

(3) A third phenomenon concerns the pathology of the vessels in Riedel's thyroiditis. In almost all cases inflammatory lesions are observed in and around the veins and arteries. Roulet[38] was the first to describe endo- and peri-phlebitis and granulomatous arteritis in three cases of chronic thyroiditis, of which the first two corresponded to the strictest definition of Riedel's disease. Similar lesions were described by Schilling[39] and may be observed in the photomicrographs published by Woolner *et al.*[50] In four cases of Riedel's disease, Hardmeier[19] and Hedinger[19] confirmed the presence of lymphocytic periarteritis and arteritis characterized by the destruction of the media and proliferation of the intima. Giant-cell arteritis was also described by Bogomoletz[5a] in a presumed case of Riedel's disease, but it is doubtful whether this case, which was characterized by granulomatous inflammation, can in fact be considered as struma fibrosa.

These different pathological details are important for the pathogenetic interpretation of the disease.

5. Laboratory Findings

There are not usually any typical changes in the behaviour and composition of the blood, although mild leucocytosis may be observed.[12] The erythrocyte sedimentation rate is often raised.[8,18,50] But it is only in exceptional cases that it reaches the high levels observed in granulomatous thyroiditis.[44,45,50]

As a rule, serum protein electrophoresis undergoes no particular changes. The levels of blood cholesterol when recorded are normal. No falsely positive Wasserman reaction has been observed.

6. Iodine Metabolism and Thyroid Function

Thyroid function is generally unaffected during the course of Riedel's struma. Basal metabolic rates remain within normal limits, although low values have sometimes been observed in cases with extensive bilateral involvement.[18,50] High BMR values or other signs of hyperthyroidism have never been found.

Plasma $PB^{127}I$ levels are normal and the radioactive iodine uptake figures are also mostly within normal limits.[27,45,47] Thyroid scintigrams, as yet few, show normal symmetrical patterns of distribution in non-affected parts and a complete absence of activity in the involved zones.[45]

Circulating thyroid antibodies are generally reported absent from the serum of patients with proven Riedel's disease. No thyroid antibodies were found in any of five genuine Riedel's cases studied at the Middlesex Hospital.[45] However, thyroglobulin antibodies were found circulating in two of the five cases studied by Witebsky *et al.*[49] and in one other case. Bansi,[3] in 1960, also described a case with thyroglobulin precipitins. It is difficult to interpret these findings due to the possibility of diagnostic confusion or coincidence with lymphocytic thyroiditis. The latter possibility is well illustrated by the very interesting case described by Thomson *et al.* in 1968.[44] Their 52-year-old patient was first treated as a clear-cut case of Hashimoto's thyroiditis, but 6 months later bore the characteristics of genuine Riedel's disease and answered all Woolner's criteria in this respect. Gammaglobulins were up to 1·5 g per 100 ml and antithyroid serological responses were highly positive from the first test right up to the final stages of the disease. This particular subject had two sisters in whom circulating thyroid antibodies were found, so it is probable that he carried hereditary autoimmune thyroiditis which was precipitated by the fibrotic process.

7. Aetiology

Despite numerous theories, Riedel's thyroiditis has retained the mysterious character attributed to it by the German author. The initial idea of an infectious origin was suggested by inflammatory histological reactions, but no supporting bacteriological evidence has ever been found.

Several authors suggested that fibrous goitre was the final phase of a non-specific chronic inflammatory process triggered off by subacute or lymphocytic thyroiditis.[11,

[34,46] This idea was still in favour with Goetsch and Kamner,[13] in whose view the process was set in action by "irritation factors residing in the hyperfunctioning epithelium of primary hyperplastic (toxic diffuse) goitre". Such a hypothesis may serve to explain lymphocytic infiltrations and fibrosis developing in thyrotoxic glands, but it does not seem valid for the aetiology of Riedel's goitre which usually has no antecedents of hyperthyroidism and whose fibrotic process is of greater magnitude than the simple sclerosis observed in commoner forms of thyroiditis.

In fact, there is no doubt that Hashimoto's goitre, thyroiditis after hyperthyroidism, and Riedel's goitre constitute three distinct entities.[14,16,39,42,43,50] Immunological studies[45] have merely served to reinforce this view. Despite observations such as those of Thomson *et al.*,[44] Riedel's goitre can no longer be justifiably considered as a variant or another form of autoimmune thyroiditis.

The relationship between subacute thyroiditis and non-specific chronic thyroiditis has been discussed since the study published by de Quervain and Giordanengo.[9] These authors had stated that the thyroid swelling may be very hard. Wegelin,[46] who studied their histological material, noted that in most cases extensive fibrosis was present. But Crile and Hazard[8b] and Hazard[21] clearly demonstrated which characteristics distinguish granulomatous thyroiditis from fibrous goitre. The same authors report that, out of 100 cases of subacute thyroiditis studied by them, no case of secondary transformation into Riedel's disease was found.

Studies of the vascular lesions found in Riedel's disease have led to an interesting development. Hardmeier and Hedinger[19] advanced the opinion that the vascular process observed in Riedel's thyroiditis resembles the one described in Takayashu's arteritis, and that the fibrosis of the thyroid is similar to that seen in the mediastinum and retro-peritoneal tissue during the course of Ormond's syndrome. In fact, Riedel's thyroiditis has been observed in association with mediastinal and retro-peritoneal fibrosis[4,14,31,51] with pseudo-tumour of the orbit[1,2,45] and with fibrosis of the lachrymal glands.[40] For these reasons it is suggested that retro-peritoneal fibrosis, fibrosis of the mediastinum, sclerosing cholangitis, pseudo-tumour of the orbit, and Riedel's thyroiditis may be different manifestations of the same disease.

As for the causes of this new pathological entity, little is known. Que and Mandema[33] reported circulating anti-nuclear factors and Raynaud's disease in a case of coincident idiopathic retro-peritoneal fibrosis and a thyroid condition; thus, as Turner-Warwick *et al.*[45] and Comings *et al.*[6] suggest, Riedel's thyroiditis could be the result of a general process, possibly related to collagen diseases but without any specificity for the thyroid.

8. Diagnosis

The presence of Riedel's goitre may be suspected from clinical evidence, but histological proof is essential for a firm diagnosis. The relevant clinical signs are the existence of a fast-growing indolent tumour of hard consistency, its early adhesion to the surrounding tissues, and the development of pressure symptoms. But all these characteristics may equally well suggest the existence of the more common condition of carcinoma.

Indeed, in the large majority of reported cases, the pre-operative diagnosis was malignancy.[50] But physicians and surgeons should bear in mind the possibility of invasive fibrous thyroiditis and obtain a pre-operative histological diagnosis in order to limit extensive, dangerous, and unnecessary surgery if no malignancy is found.

No great difficulties are encountered in differentiating between Riedel's disease and Hashimoto's goitre because of the clinical characteristics and high thyroid antibody titres of the latter disease. A cytological diagnosis is possible by needle biopsy,[8b,30] although open biopsy is often necessary. A differential diagnosis between Riedel's fibrous goitre and other forms of "non-specific chronic thyroiditis"[34,46,48] or struma fibrosa of the giant cell variety[39] may also be difficult without the aid of needle biopsy or surgery. But spontaneous pains in the neck, behind the ears, and even in the shoulders, together with tenderness on pressure, should plead strongly in favour of a diagnosis of non-specific chronic, granulomatous, or giant-cell thyroiditis.

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CHAPTER 5

Struma Lymphomatosa (Hashimoto)

P. NÈVE, A. M. ERMANS and P. A. BASTENIE

Synonyms: lymphadenoid goitre, chronic lymphocytic thyroiditis, Hashimoto's disease, Hashimoto's goitre, autoimmune thyroiditis.

1. Introduction

In 1912 Hashimoto[59] reported four cases in middle-aged women showing diffuse hypertrophy of the thyroid gland in association with lymphocytic infiltration of the stroma and the formation of numerous lymphoid centres. This disease has since been recognized more and more frequently, and is admitted as a distinct nosological entity characterized by its clinical signs, its histological lesions and, in recent years, its serological context (Table 5.1).

TABLE 5.1. INCIDENCE OF HASHIMOTO'S DISEASE IN SURGICAL MATERIAL REMOVED FROM 1920 TO 1959[23]

Years	Number of thyroidectomies	Hashimoto's disease	%
1920–9	2357	38	1·2
1930–9	3199	147	4·6
1940–9	2363	147	6·3
1950–9	937	100	10·7

However, various authors[9,24,25,45,51,74] have wanted to class together under this heading all forms of chronic lymphocytic thyroiditis involving the passage of thyroid antibodies into the circulation, irrespective of the absence or presence of goitre and the absence or presence of hyperthyroidism.

In principle, three essential criteria should be satisfied before admitting a diagnosis of Hashimoto's thyroiditis:

(1) Increase in thyroid size.
(2) Diffuse lymphocytic infiltration of the stroma with development of lymphoid follicles.
(3) High thyroid antibody titres in the serum.

Of these three criteria, the last one is at present often difficult to ascertain, but it must be established conclusively whenever clinical or serological data leave room for doubt.

Alongside the classic form, corresponding on all counts to Hashimoto's description, there are reports of three variants which respect the conditions set out above: the fibrous variant, the hyperplastic variant of adolescence, and the variant with exophthalmos.

1. *The Fibrous Variant*[61,80]

This is characterized by the development of dense fibrosis in part of the gland, or sometimes in an entire lobe, whilst the other parts retain the typical picture of diffuse lymphocytic infiltration. On account of its asymmetrical development, its localized induration, and possible pressure signs, this variant can arouse fears of tumour.

2. *The Hyperplastic Variant of Adolescence*[28,51,61,128]

Although the four patients described by Hashimoto were aged between 40 and 61 years, various authors have reported otherwise typical cases in young subjects of both sexes first of all as rare occurrences,[64,73,124] but, later, on a fairly frequent basis.[38,51,68,80,104,153] In subjects 15 and 25 years younger than patients affected with the classic form, this type of hyperplasia develops rapidly and is symmetrical. The diffuse goitre generally remains of moderate size and usually gives rise to no general phenomena or local symptoms. However, Woolner *et al.*[153] report that basal metabolism is often lowered, and Nilsson and Doniach[104] observed signs of hypothyroidism in a quarter of their thirty-four boys and girls aged between 7 and 17 years with progression towards definite myxoedema in four of them. Certain cases were operated on because of suspected neoplasm, suggested by the rapid growth of the goitre. In other cases, needle biopsy brought confirmation of the diagnosis of Hashimoto's disease, already indicated by the high antibody titre in the blood.[113] Some authors[49,62] have proposed classing this variant as a form of lymphocytic thyroiditis distinct from Hashimoto's (cf. section 4).

3. *The Exophthalmic Form*

In addition to the clinical and laboratory features of Hashimoto's thyroiditis, this variant comprises the typical ocular signs of Basedow's disease.[65,86,112,149] But other signs of thyrotoxicosis proper are missing.[45]

This condition can only be admitted as a true variant in the rare cases that satisfy the formal criteria of Hashimoto's goitre, namely a recently developed symmetrical and homogeneous goitre, the presence of very high thyroid antibody titres, and the diffuse lesions characteristic of the disease.

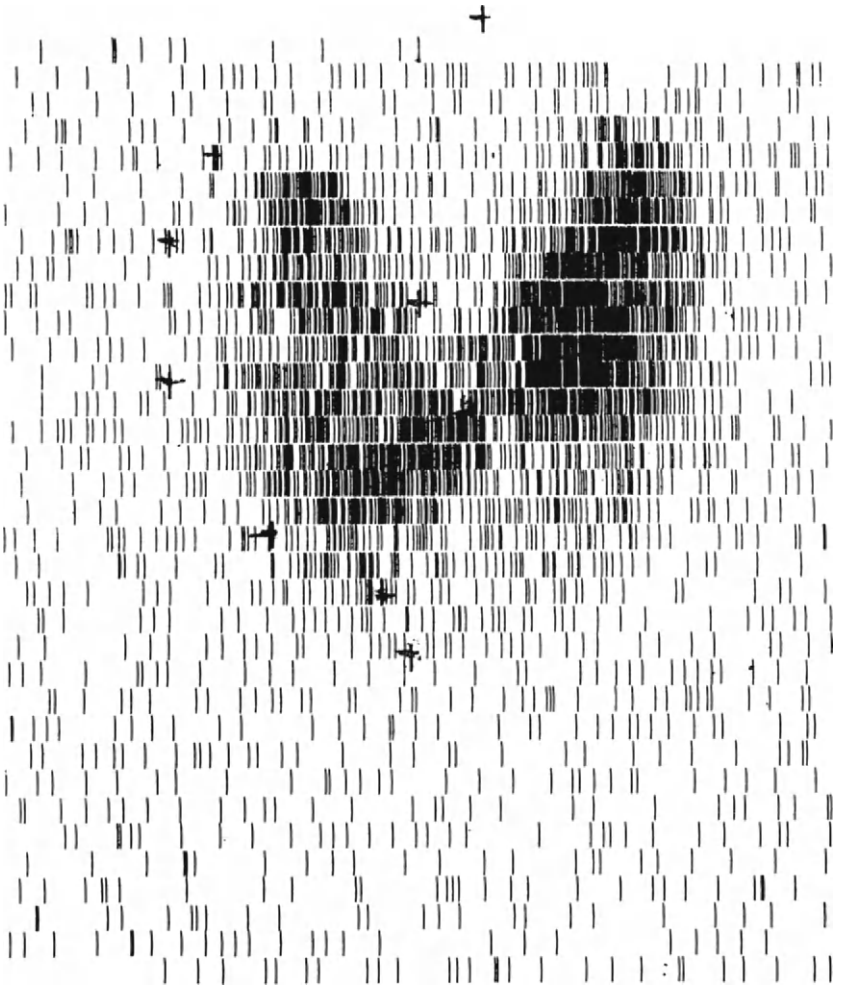

FIG. 5.1. Thyroid scan in Hashimoto's thyroiditis (case report 5.1).

2. Illustrative Case Reports

CASE REPORT 5.1: SP 65,745. *Rapid development of Hashimoto's goitre with initial signs suggestive of hyperthyroidism. Regression of the goitre under treatment with thyroid extracts. Persistence of biochemical and serological abnormalities.*

In September 1966 a 45-year-old woman developed a large goitre in 3 weeks with nervousness, palpitations, and loss of weight. In October 1966, despite subjective signs suggesting the possibility of hyperthyroidism, the examination showed this (still moderately obese) patient to be perfectly euthyroid. The goitre was symmetrical, elastic, and firm, with a finely irregular surface.

The usual examinations were unremarkable, except for a Thymol turbidity value of 9·5 U, slight anaemia, and relative lymphocytosis (35%). Plasma $PB^{127}I$ was 4·5 μg per 100 ml; serum cholesterol 210 mg per 100 ml; thyroid antibodies TGA 1/78,125; CFA (not measured); ^{131}I uptake 23% at 6 hr, 40% at 24 hr. The scintigram was very abnormal (Fig. 5.1).

After the diagnosis of Hashimoto's goitre, the patient was treated with desiccated thyroid (thyroid 60 mg/d). The result was a remarkable diminution in the size of the gland, but the protein and serum disorders remained unchanged. In November 1967, after a year of treatment, the antibodies were still TGA 1/78,125, CFA +++; gammaglobulins 20%.

CASE REPORT 5.2: B 68/3425. *Hashimoto's goitre in a male subject with intrathoracic localization, pressure symptoms, and hypothyroidism. A latent process had probably existed for* 10 *years.*

A 68-year-old patient with no personal or family history of goitre had been taking iodoquinolein for 5 years to combat diarrhoea following resection of part of the intestine for benign polypi. A year previously, blood tests carried out because of fatigue had aroused suspicions of anicteric hepatitis: sedimentation rate 28 mm/hr; positive flocculation reactions.

For the last 3 months the patient had noted an enlargement at the base of the neck, with hoarseness and occasional feelings of suffocation when he leaned forward. Physical examination revealed a heavy body frame, moderate obesity, and a plethoric facial appearance. At the base of the neck there were engorged vessels which increased when the subject leaned over or raised his arms. On palpation the upper poles of the thyroid which extended behind the sternum, were found to be very hard. The rest of the physical examination was negative. The laboratory results are given in Table 5.2.

TABLE 5.2. PROGRESS OF LABORATORY FINDINGS IN A CASE OF HASHIMOTO'S GOITRE TREATED BY SURGERY FOLLOWED BY TRIIODOTHYRONINE ADMINISTRATION (50 μg/d)

	1.6.57	5.7.67	5.6.68	29.10.68	3.9.69
Sedimentation (mm/hr)	3	28	29		13
Hanger	+	++	++		+
Thymol (U)	11	20	29		6·8
Total proteins (g per 100 ml)	7·7				7·3
α_2 globulins (%)	7				6
γ globulin % (g per 100 ml)	25 (1·94)				14 (0·90)
Cholesterol (mg per 100 ml)	278	280	320	270	274
$PB^{127}I$ (μg per 100 ml)			3·15	5·1	
TGA: titre			1/78125	1/78125	1/315
CFA: intensity			++	neg.	neg.
^{131}I uptake: 6 and 24 hr			7 and 12%		

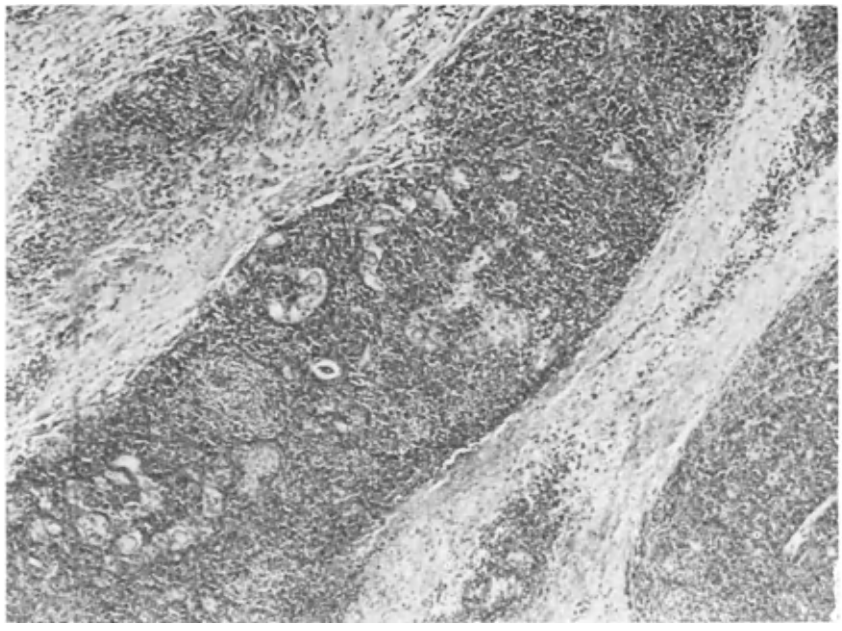

FIG. 5.2. Hashimoto's thyroiditis (case report 5.2). Infiltration and oncocytic metaplasia accompanied by localized dense fibrosis. (×50.)

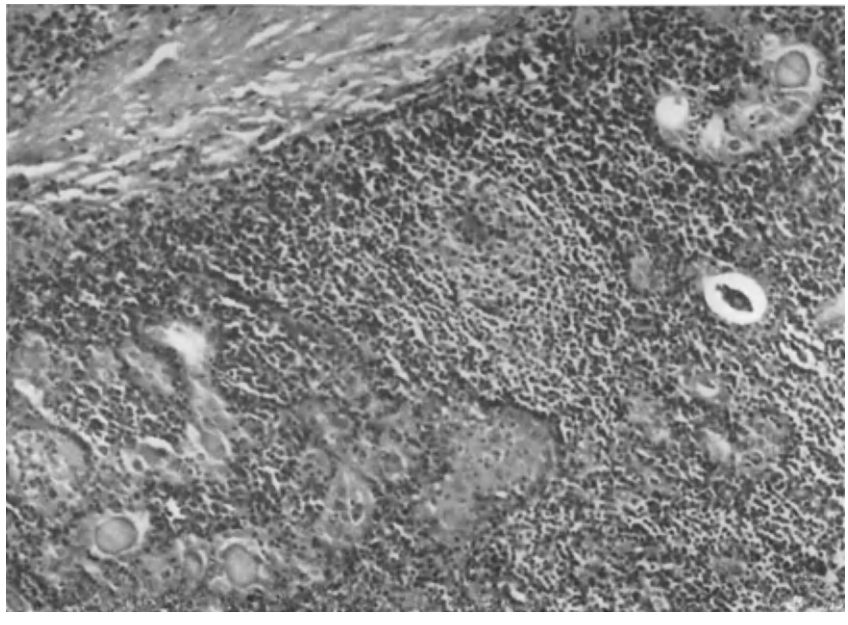

FIG. 5.3. Case report 5.2. High magnification of Fig. 5.2: lymphoid follicle, oncocytic metaplasia, and (in the centre) squamous metaplastic nodule. (×140.)

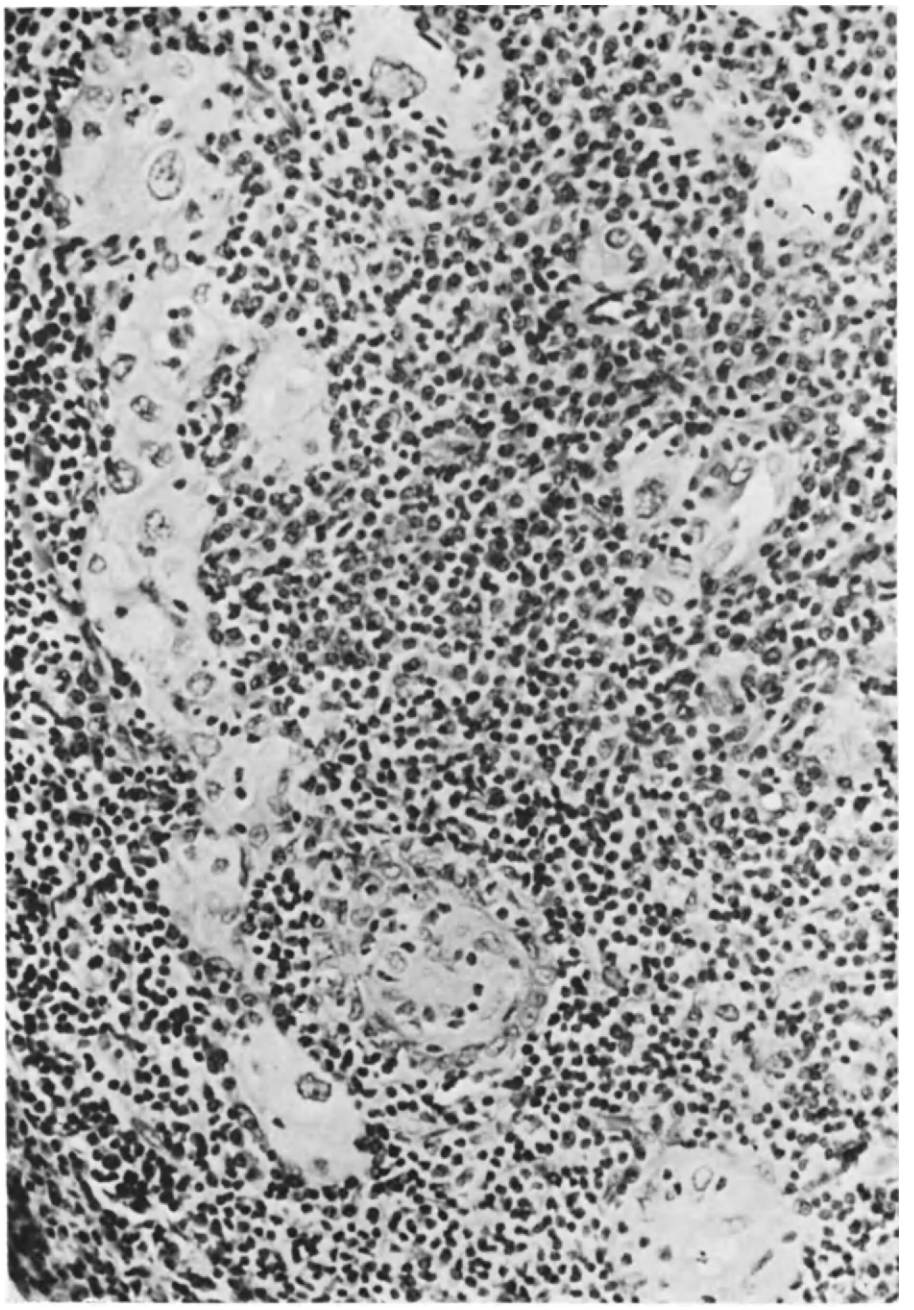

FIG. 5.4. Hashimoto's thyroiditis (case report 5.2). Clumps of oncocytes and stratified metaplasic follicle with diffuse lymphocytic infiltration. (×200.)

The X-ray film of the thorax showed a dense, well-defined opacity in the upper mediastinum. There was slight compression of the trachea producing a biconcave constriction. The hypothyroidism and intensity of the serological reactions argued in favour of a diagnosis of Hashimoto's goitre. However, due to the age and sex of the subject, the possibility of neoplasm with associated thyroiditis could not be excluded. Surgery was performed on account of tracheal constriction. Under the microscope the tumour had the appearance of a typical lymphomatous goitre (Figs. 5.2, 5.3, and 5.4).

Five months after subtotal ablation, corrected by substitution therapy, the thyroglobulin antibody titre was unchanged, but the cytoplasmic antibodies had disappeared from the serum.

3. Clinical Features

Age and Sex Incidences

In its classic form, Hashimoto's thyroiditis probably constitutes the most frequent type of chronic goitrous thyroiditis.[26,47,80,111,132] Estimations of frequency and incidence by age and sex are only valid if based on rigid criteria (Table 5.3).

TABLE 5.3. HASHIMOTO'S THYROIDITIS: AGE AND SEX DISTRIBUTION

	Number of cases	Females	Ages	
			Range	Means
Roitt and Doniach, 1960[120]		90–95		
Buchanan *et al.*, 1965[22]	42	93	28–70	
Al-Sarraf and Waller, 1967[2]	102	90	14–89	46·3 (F) 58·7 (M)
Present series (1969)	20	95	17–69	43·0 (F) 68·0 (M)

Out of 605 goitres with chronic thyroiditis operated at the Mayo Clinic between 1939 and 1956, Woolner *et al.*[153] observed histological signs of Hashimoto's goitre in 82% of the cases, signs of Riedel's disease in 2·7%, and lesions of subacute thyroiditis in 15% of the cases. Since the condition is now diagnosed clinically and surgery is advised only rarely, statistical data of this type are no longer available.

Women are affected nine times more often than men (cf. Table 5.3), mainly between the ages of 40 and 60, whereas male subjects generally develop the disease 10–20 years later. Our twenty cases comprised two men (48 and 68 years) and eighteen women (average age 43).

The growing frequency of the disease reported by several authors (cf. Table 5.1) is thought by some to be due to the increased interest of clinicians and pathologists. It is mainly due to the gradual broadening of the criteria used to define it. This is the case for

TABLE 5.4. HASHIMOTO'S THYROIDITIS: THYROID SIGNS

Authors: / Number of cases studied:	Hashimoto[59] 4	Hellwig[64] 4	Buchanan *et al.*[22] 42	Al-Sarraf *et al.*[2] 102	Brussels 20
Recent swelling	4	1	9	89	13
Trouble or pain	0	0	4	4	1
Dyspnoea	0	0	10	14	2
Dysphagia	0	0	4	21	3
Goitre: firm	4	4	38		15
hard	0	0	2		0
diffuse and bilateral	0	4	22	47	20
nodular	0	0	20	41	0

Chesky *et al.*[23] from whom Table 5.1 is borrowed; they class all cases of diffuse lymphocytic thyroiditis under the title Hashimoto's disease.

Clinical Features (*Table* 5.4)

In general the condition begins insidiously with a diffuse swelling of the thyroid. The swelling usually increases in a few months, or even 2 years, although it occasionally takes only a few weeks.[73] It gives little cause for complaint beyond nervous tension and fatigue.[27,47,60,80,111] It is rarely accompanied by pain or even discomfort.

However, Doniach *et al.*,[36] Buchanan *et al.*,[19] and Scazziga *et al.*[123] have described cases with sharp pains at the beginning of the disease. Alavez and de la Camara[1] report similar complaints in 3 of their 20 patients; Wanebo and Rawson mention one case.[144] Case report 5.1 is also an example.

When fully developed, the goitre generally attains twice or three times the norma. thyroid size,[60] although Buchanan *et al.*[22] give an average weight of 100 g and Lindsay *et al.*[80] mention glands weighing up to 331 and 616 g. The growth is usually symmetrical, firm but not woody, and with a fine granular surface.[73] The swollen gland is sometimes abnormally tender (cf. Table 5.4). Lindsay and his colleagues report tenderness in 15% of their patients. According to Williams,[152] the cervical lymph nodes may be enlarged, but this seems exceptional.

Signs of hypothyroidism are often apparent, even at the first clinical examination[22,99,120] (cf. case report 5.2), although some authors claim that hypothyroidism develops in only 10% of the cases.[47,132] Out of 36 patients studied by Skillern *et al.*,[128] 25 had low basal metabolism. Hypothyroidism is almost always present in patients who had part of the gland removed.

By contrast, the association with thyrotoxicosis remains questionable. It may happen that some signs of hypermetabolism appear during the early stages of Hashimoto's thyroiditis.[10,20,36,125] Nervous tension, insomnia, palpitations, intolerance to heat, loss of weight, and tachycardia suggest the existence of thyrotoxicosis (cf. case report 5.1).

In most cases, such a diagnosis cannot be confirmed either by clinical progress, laboratory findings, or histology. Clinical evidence may show poor response to antithyroid drugs.[36,125] Laboratory data may show a very high PBI level and radioiodine uptake rate in both Hashimoto's thyroiditis and thyrotoxicosis (cf. section 6). However, the suppression of uptake by triiodothyronine (Werner's test) reveals that in the majority of subjects the thyrotoxicosis is only spurious.[20] In operated cases, the histological picture is no different from that obtained in genuine Hashimoto's disease with no signs of toxicity.[125] At the most, a marked degree of cell hyperplasia may be observed,[20] perhaps explaining the state of hypermetabolism.

A series of cases have been described in which subjects showed proven thyrotoxicosis and at the same time serological and histological signs of lymphocytic thyroiditis.[19,35,36,125] Certainty of genuine thyrotoxicosis may be obtained from histological evidence[125] and by Werner's test demonstrating that the administration of triiodothyronine does not reduce radioactive iodine uptake. It has long been known that lymphocytic thyroiditis may develop intensely in toxic goitres.[60,73] However, this form of more or less diffuse lymphocytic thyroiditis clearly constitutes a secondary phenomenon grafted on to thyrotoxicosis. By its clinical, serological, and morphological characteristics it must be distinguished from Hashimoto's goitre proper (cf. Chapter 8).

The possibility of a relation existing between Hashimoto's thyroiditis and thyrotoxicosis is also suggested by the association of lymphocytic thyroiditis of the Hashimoto type with protrusion of the eyeballs, as in Basedow's disease, but without signs of hyperthyroidism. A combination of non-toxic goitre and exophthalmos was reported a long time ago.[7] Werner[147,148] showed that in subjects thus affected the administration of triiodothyronine did not inhibit radioiodine uptake. Furthermore, LATS has been found in such subjects.[89,106,114,129,154] So this condition has been considered as a "Graves's disease" without hyperthyroidism[79] or Ophthalmic Graves's Disease.[54,54a] Several authors[3,86,92] have reported the association of severe exophthalmos with goitre invaded by autoimmune thyroiditis, apparently resembling Hashimoto's thyroiditis. Eversman *et al.*[45] and Wyse *et al.*[154] studied fifteen and ten such cases respectively. But in the majority of the cases the diagnosis of Hashimoto's thyroiditis was far from being proved. Certain authors[45] make no distinction between Hashimoto's thyroiditis, myxoedematous thyroiditis, and focal thyroiditis. In many reports, such as that of Wyse *et al.*, the antibody titres are much lower than in lymphomatous goitre. Histological data, generally obtained by needle biopsy, may well show lymphocytic thyroiditis but furnish no proof that it corresponds to true Hashimoto's goitre. What is more, cystic and haemorrhagic lesions are reported in some cases and characteristic appearances of thyrotoxic hyperplasia in others. Some even report a past history of thyrotoxicosis.

Most of these data are compatible with the development of thyroiditis on a latent state of thyrotoxicosis. It is possible, as Mahaux[86] suggests, that the hyperthyroidism is neutralized by the early development of thyroiditis. At all events it is difficult to see this process as a particular aspect of Hashimoto's goitre.

Jayson *et al.*[72] have shown the presence of LATS at the same time as thyroid antibodies in the serum of twin sisters, one with thyrotoxicosis and the other with Hashi-

moto's goitre. These findings are considered by some[39] as an indication that thyroiditis and Basedow's disease represent two aspects of the same autoimmune process. Be that as it may, treatment of the two cases demands careful differentiation.

The progress of untreated Hashimoto's thyroiditis is variable and often difficult to forecast. There is no spontaneous remission.[27] In a number of cases,[80] the pressure signs become alarming. This was true of case report 5.2 concerning a man with intrathoracic Hashimoto's goitre. Fear of neoplasm may also be aroused by the asymmetrical induration in the fibrotic form.[30] In other cases the goitre remains stationary for many years or regresses moderately, whilst the signs of thyroid insufficiency often become more marked. In still other cases, submitted to repeated biopsies, the clinical and histological signs remain unchanged for long periods[140] of up to 2 years,[93] 4 years,[73] or even 9 years.[64]

Finally, some treated or untreated cases may eventually progress from an initially diffuse goitre into a nodular structure. The transformation of a genuine Hashimoto's goitre into a malignant tumour is never observed (according to Crile and Hazard[28]) or is, at all events, rare.[39]

4. Pathology

Macroscopic and Histological Appearances

The appearance of Hashimoto's goitre is striking to the naked eye; it is characterized by a diffuse swelling of the gland and a whitish,[80] fine, granular surface of the thickened capsule;[60] there are no adhesions or enlarged lymph nodes. In cross-section, the fine lobulation, the yellowish-white colour of the whole parenchyma, and the absence of surface glossiness due to the disappearance of the colloid[80] recall the appearance of a hypertrophied thymus. On histological examination, the lesions are characterized by:

(1) Parenchymatous anomalies occurring in various degrees throughout the gland.
(2) Diffuse and extensive inflammatory infiltrations.

Lesions of the parenchyma

Most, and sometimes all, of the thyroid parenchyma undergoes major changes, which may vary in intensity from one part of the gland to another. The parenchyma is broken up into lobules, often in irregular groups of vesicles, themselves altered to varying degrees and submerged in the inflammatory infiltrate.

Sometimes an appreciable degree of hyperplasia is apparent in parts of the parenchyma: the cells are fairly high, cylindrical, and arranged in vesicles with normal architecture. However, these vesicles are small and contain little colloid. *In vivo* immunofluorescent studies have revealed antibodies in the dense colloid.[96] It would seem that the hyperplastic appearance predominates in the initial stages of the process, sometimes many years before the "florid" stage of the disease is reached.[10]

Many juvenile cases also take on a hyperplastic aspect.[61] But the extreme cell hyperplasia characteristic of thyrotoxicosis is never found in Hashimoto's goitre.

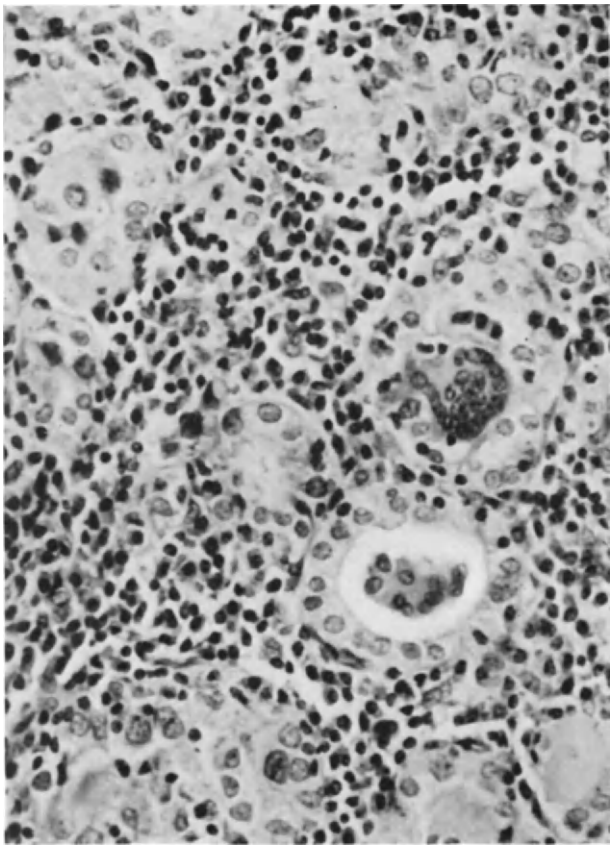

FIG. 5.5. Hashimoto's thyroiditis (B 69/2544). Giant cells in lumen of a slightly hyperplastic follicle and in another with oncocytic changes. Oncocytes and dense lymphocytic infiltration. (×200.)

In the more advanced stages, the colloid becomes rarer and the cell masses lose the vesicular architecture characteristic of normal thyroid parenchyma. The cells themselves are swollen and choked with acidophilic granules.[6,55,77]

In the lumen of the small vesicles it is not rare to see giant cells appear. These multinucleated cells differ from those of de Quervain's thyroiditis in that they are less frequent, irregular in shape, small in size, and contain small, dark nuclei (Fig. 5.5).

At an even more advanced state of disintegration, the parenchyma is arranged in formless masses of swollen cells, with vacuolized, clear, and very eosinophilic cytoplasm, often containing hyperchromatic nuclei (Fig. 5.6). The cell edges are ill defined. The inflammatory elements often seem to penetrate inside the cells undergoing lysis.

In a general way, by analogy with the elements observed earlier by Hürthle[69] in certain goitres and by Askanazy in thyrotoxic glands,[4] the eosinophil cells are called either granular or clear. For most early authors, no doubt exists as to their degenerescent

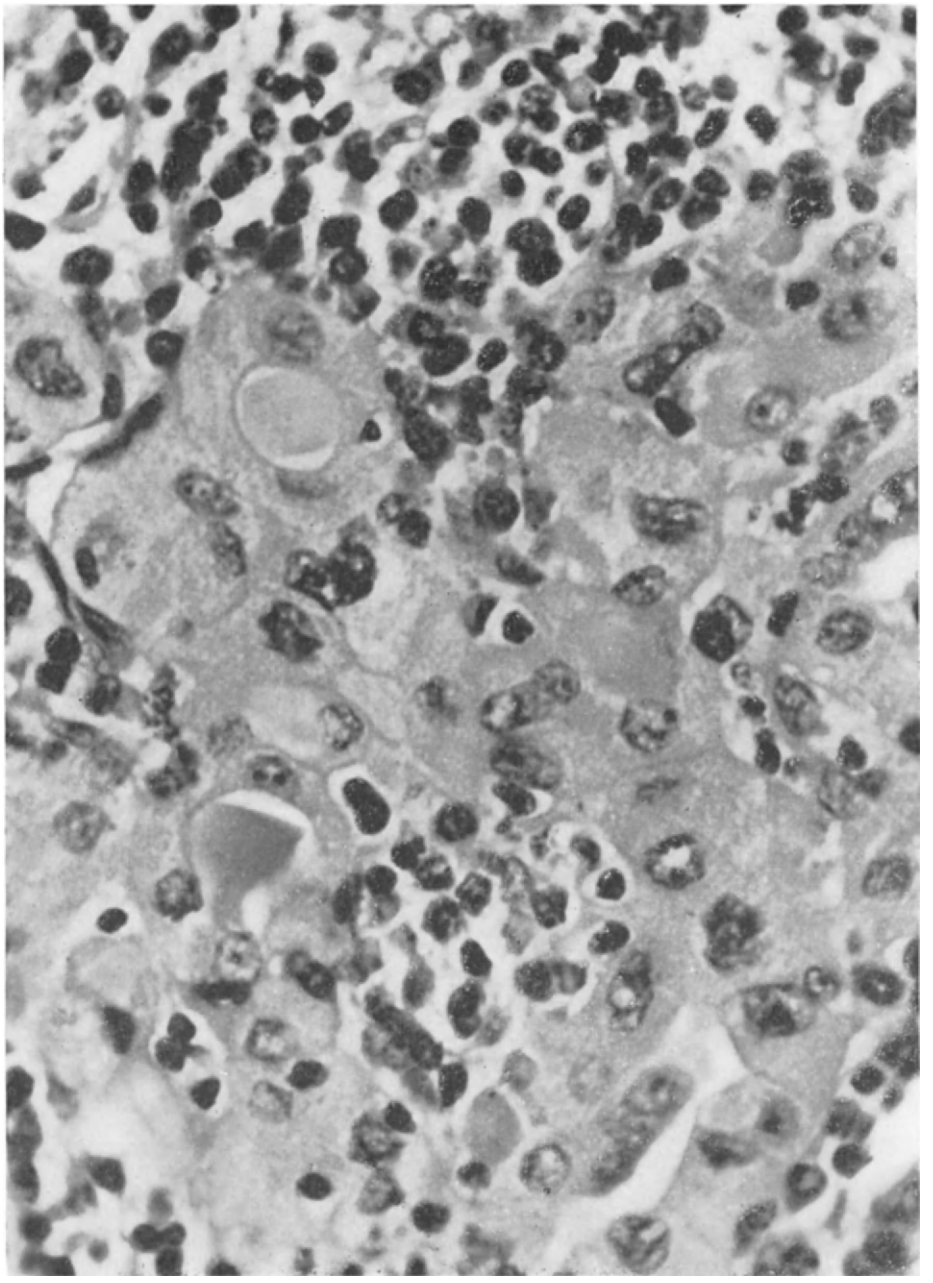

FIG. 5.6. Typical oncocytes with remnants of thyroid follicles. (×800.)

or even necrobiotic state.[146] However, Tremblay and Pearse[137] have demonstrated the existence of large quantities of enzymes in these granular eosinophil cells, which would suggest intense physiological activity.

These contradictory ideas are well explained by observations made under the electron microscope.[100,101]

Ultrastructural studies of thyroid cells in Hashimoto's goitre reveal three types of cells:

(1) One type shows marked dilatation of the ergastoplasmic cisternae with a strongly developed Golgi apparatus (Fig. 5.7). Some such cells, cylindrical in shape and located inside the follicles, have their apical parts full of colloid droplets mixed with dense bodies, probably phagolysosomes.

(2) Another type contains cytoplasm full of mitochondria, rarefied ergastoplasm, and a discreet Golgi apparatus (Fig. 5.8). The usually swollen and often longer-than-normal mitochondria contain no dense granules of the type generally observed in the mitochondrial matrix.[67]

(3) A third kind of cell is characterized by the appearance of large areas of cytoplasmic matrix free of organelles but occupied by a homogeneous substance looking like colloid. This hyaloplasm contains a very underdeveloped Golgi apparatus and, here and there, some dilated ergastoplasmic cisternae associated with sparse mitochondria (Fig. 5.9). The nucleus seems to be normal, but the apical plasma membrane is very thin, sometimes appearing broken and severely denuded of microvilli.

The three types of cell, between which transitional stages may be observed, are thus very different from normal thyroid cells in their ultrastructure.

The first type, with marked dilatation of the ergastoplasmic cisternae and sometimes numerous colloid droplets, is reminiscent of the ultrastructure of stimulated thyroid cells. Similar appearances are found in hyperthyroidism[63] and in dog thyroid after repeated stimulation.[102] The PAS+ material observed under the light microscope corresponds to colloid droplets. This first type of cell is probably preponderant in the hyperplastic stages of Hashimoto's goitre.

The second type, characterized by the extraordinary abundance of mitochondria, most likely corresponds to the granular eosinophilic cells observed under the light microscope. The histochemical analysis of these cells reveals that they contain a large quantity of oxidative enzymes.[137] Furthermore, in these cells, Harcourt-Webster and Stott[57] also observed high activity of intra-mitochondrial enzymes with reduction or absence of iodine peroxidase and phosphatase.

These characteristics and the rarity of the ergastoplasmic cisternae imply a lack of balance between the respiratory activities and other cell activities, suggesting that protein, and therefore hormone, synthesis is probably severely compromised.

In conclusion, the thyroid cells described under the various names of Askanazy's, Hürthle's cells, oncocytes, or oxyphil cells, are characterized by increased cell size and by the accumulation in their cytoplasm of eosinophilic granules which correspond to

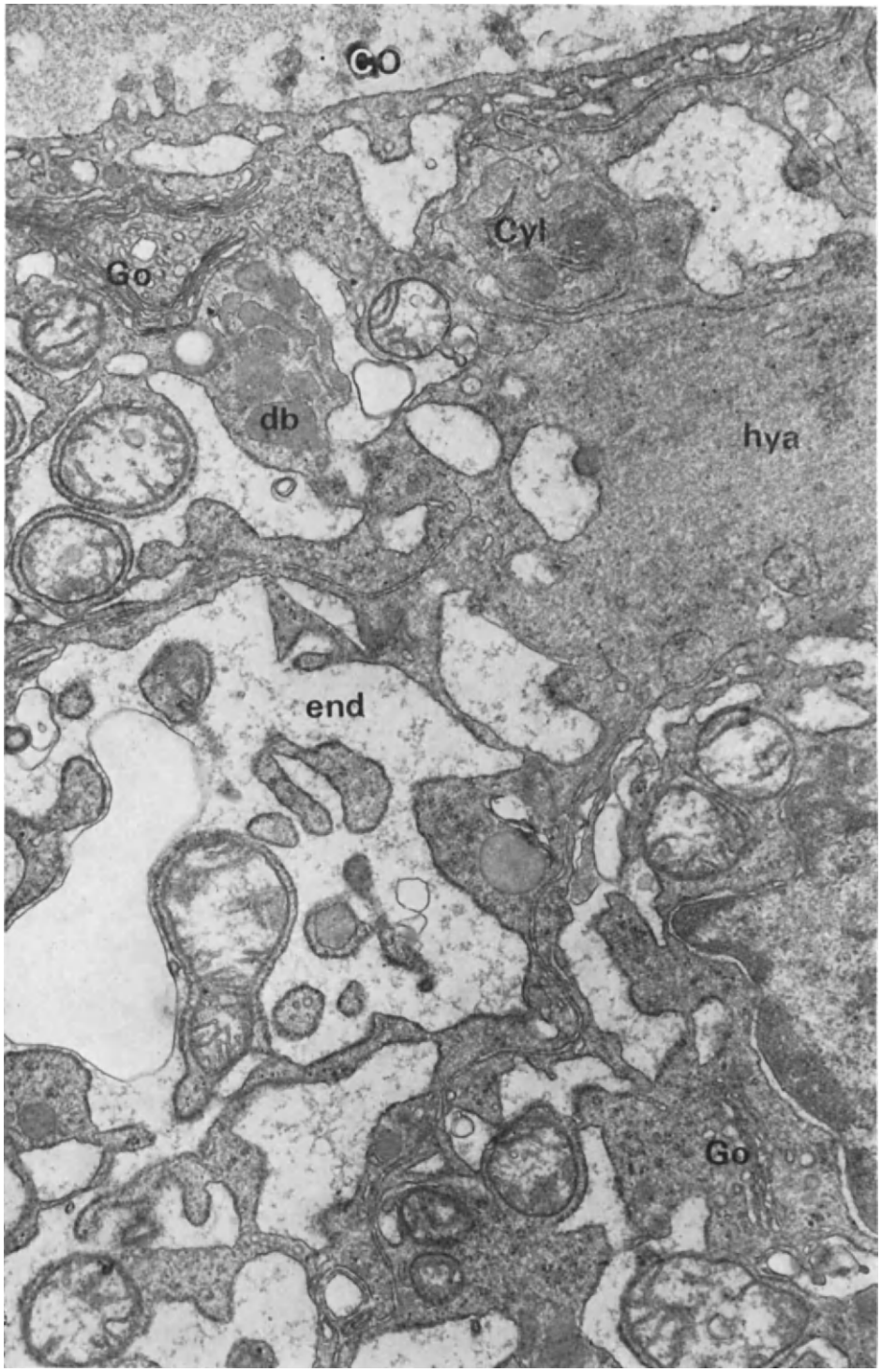

FIG. 5.7. Portions of follicle cells bordering the colloid lumen (CO). The cytoplasm is characterized by large, rough endoplasmic cisternae (end). Ergastoplasmic membranes remain associated with mitochondria which are swollen. Between such wide ergastoplasmic sacs, there are large homogeneous hyaloplasmic areas (hya), where only free ribosomes are seen. In the remaining cytoplasmic matrix, Golgi cisternae (Go), dense bodies (db), cytolysosomes (Cyl), and numerous polysomes are observed. (×18,500.)

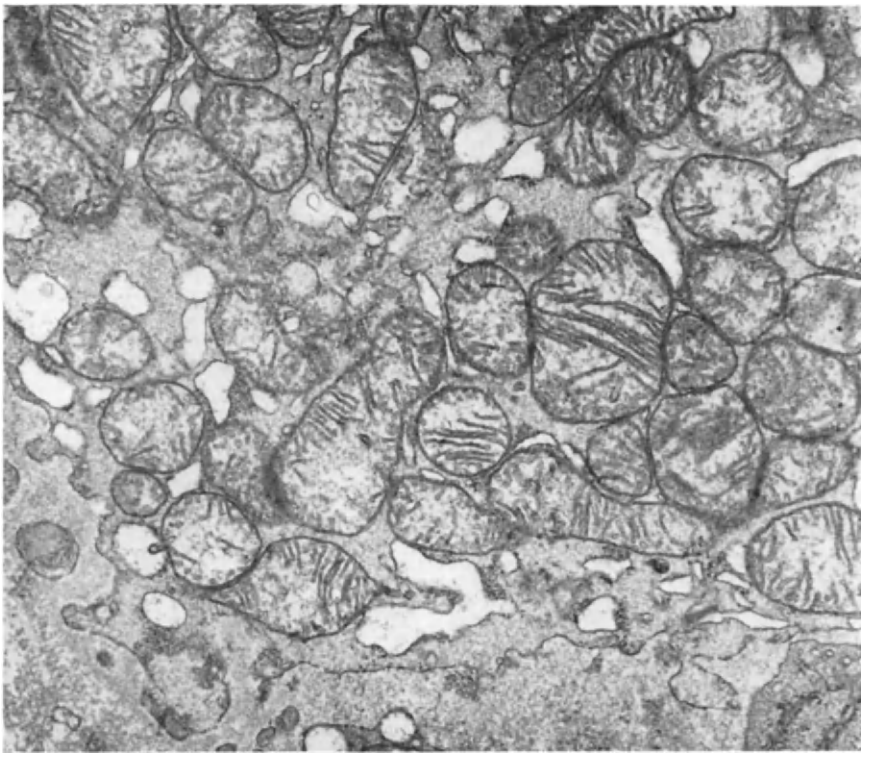

FIG. 5.8. Oncocyte in Hashimoto's goitre: mitochondria-rich cell. (×16,000.)

mitochondria, increased in number, and size. These cells are not typical of thyroiditis or even of the thyroid gland. They have been found in several other organs, more particularly in the salivary glands and in the parathyroids. The ultrastructure of salivary tumour cells is similar to that of the oncocytes described in thyroiditis.[66,122]

In these different organs concordant observations indicate that these cells are the site of increased oxidation and energy production but lack the enzymes necessary for protein synthesis. Several observations suggest that their condition may be related to ageing or to over-stimulation.

The third type, with its large areas of homogeneous cytoplasmic matrix, sparse polysomes, and swollen mitochondria, corresponds undoubtedly to the degranulated—or "colloid"—eosinophil cell detected under light microscopy.

First described in the dog,[69] these cells were later found in human[56,100,101] and other animal thyroids.[135] They have also been observed recently in the normal thyroid of the rat, mouse, hamster, and guinea-pig.[103] They are probably cells with severely reduced vital potential. Perhaps they represent for the thyroid cell a non-specific way of dying.

Table 5.5 compares the morphological and functional characteristics of the various

types of cell encountered in Hashimoto's thyroiditis. This recapitulation covers cytological and ultrastructural studies of recent years and the important observations made earlier by Wegelin[146] and Hamperl.[55] The former author gave a perfect description of the sometimes finely granular sometimes vacuolar aspect of the eosinophil cells found in various pathological thyroid conditions. He considered that these transformations indicated a phase of involution preceding cell disintegration. In Hamperl's opinion,[55,56] the granular eosinophil elements appear in the normal parenchyma of numerous organs.

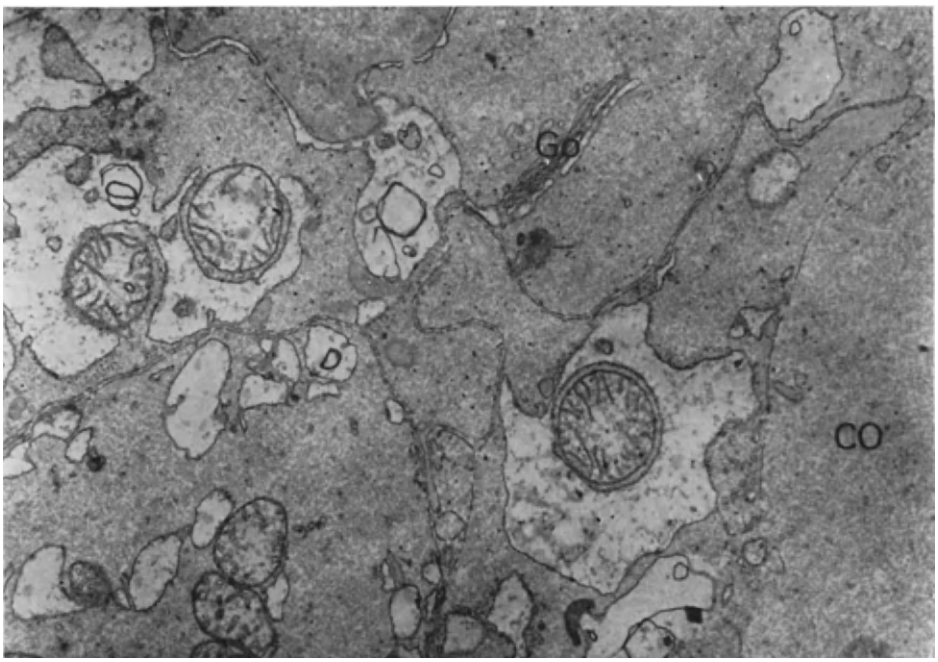

FIG. 5.9. Colloid cells. The colloid lumen (CO) is bordered by portions of two follicular cells, the cytoplasm of which is characterized by the existence of large homogeneous hyaloplasmic areas. Some swollen mitochondria remain associated with ergastoplasmic cisternae. Golgi apparatus (Go) and ribosomes appear isolated in the cytoplasmic matrix. (×14,800.)

But they are absent from juvenile tissue, only developing after sexual maturity and increasing with age. They do not necessarily evolve towards destruction but, nevertheless, constitute irreversible metaplasia probably associated with the ageing of the cells and definitely limiting their functional capacities.

Several articles on the pathology of Hashimoto's thyroiditis dwell in detail on changes in the basement membrane of the thyroid follicles. Beierwaltes[10] and Sommers and Meissner[130] report that the reticulum carrying the follicular cells grows thin and tends to break up. Irvine and Muir[70] claim to have observed actual gaps in the basement

TABLE 5.5. SIGNIFICANCE OF THE MORPHOLOGICAL CHANGES IN THYROID CELLS OF HASHIMOTO'S GOITRE

	Denominations	Electron microscopy	Light microscopy	Suspected activities
Type 1: Non-specific	Hyperplasic cells	Normal mitochondria; dilated ergastoplasmic cisternae; well-developed Golgi; colloid droplets	Cylindrical cells with positive PAS inclusions; slightly eosinophilic	Stimulated cells; increased secretion; increased synthesis?
Type 2: "Specific of autoimmune thyroiditis"[a]	Hürthle and Askanazy cells; Oncocytes (Hamperl)	Increased number of swollen mitochondria;[b] reduced ergastoplasm; poorly developed Golgi	Uniformly granular eosinophilic cytoplasm (eosinophil granules)	Increased respiratory enzymatic activities; decreased secretory activities?
Type 3: Non-aspecific	Colloid cells	Large homogeneous hyaloplasmic area; persistence of dilated ergastoplasmic cisternae	Clear and eosinophilic cytoplasm without granulations and with transparent vacuoles	Reduced; cellular agony

[a] Thyroid cellular type specifically altered in thyroiditis. Nevertheless, this cellular type is also described under the denomination "oncocyte" in several other tissues.

[b] The existence of an increased number of abnormal mitochondriae is the most marked morphological character of the oncocytes.

membrane by electron microscopy. These observations were said to confirm the autoimmune theory of the release of a hidden antigen into the circulation.

At the most it may be definitely asserted that the connective tissue web of the organ is broken up by the inflammatory infiltrations. The basement membrane of cells affected by oncocytic metaplasia does not seem to undergo particular changes and is certainly not thin. In most forms of Hashimoto's thyroiditis, masses of a very particular tissue may also be detected: the tissue is very different from normal glandular tissue, and is composed of clear cells with well-defined nuclei, resembling clear parathyroid cells. These masses vary in volume, sometimes forming small, rounded nodules and sometimes irregular formations (Figs. 5.3 and 5.4); they have long been noted in atrophied myxoedematous glands.[6,143] They are usually interpreted as being proliferations of ultimobranchial vestiges[52,53,138] or as metaplastic formations developing in areas with severe epithelial damage.[80,153] In some Hashimoto goitres the formations may assume impressive dimensions (Fig. 5.10), suggesting neoplastic proliferation. So far there is no electron microscopical evidence to specify the nature of these elements.

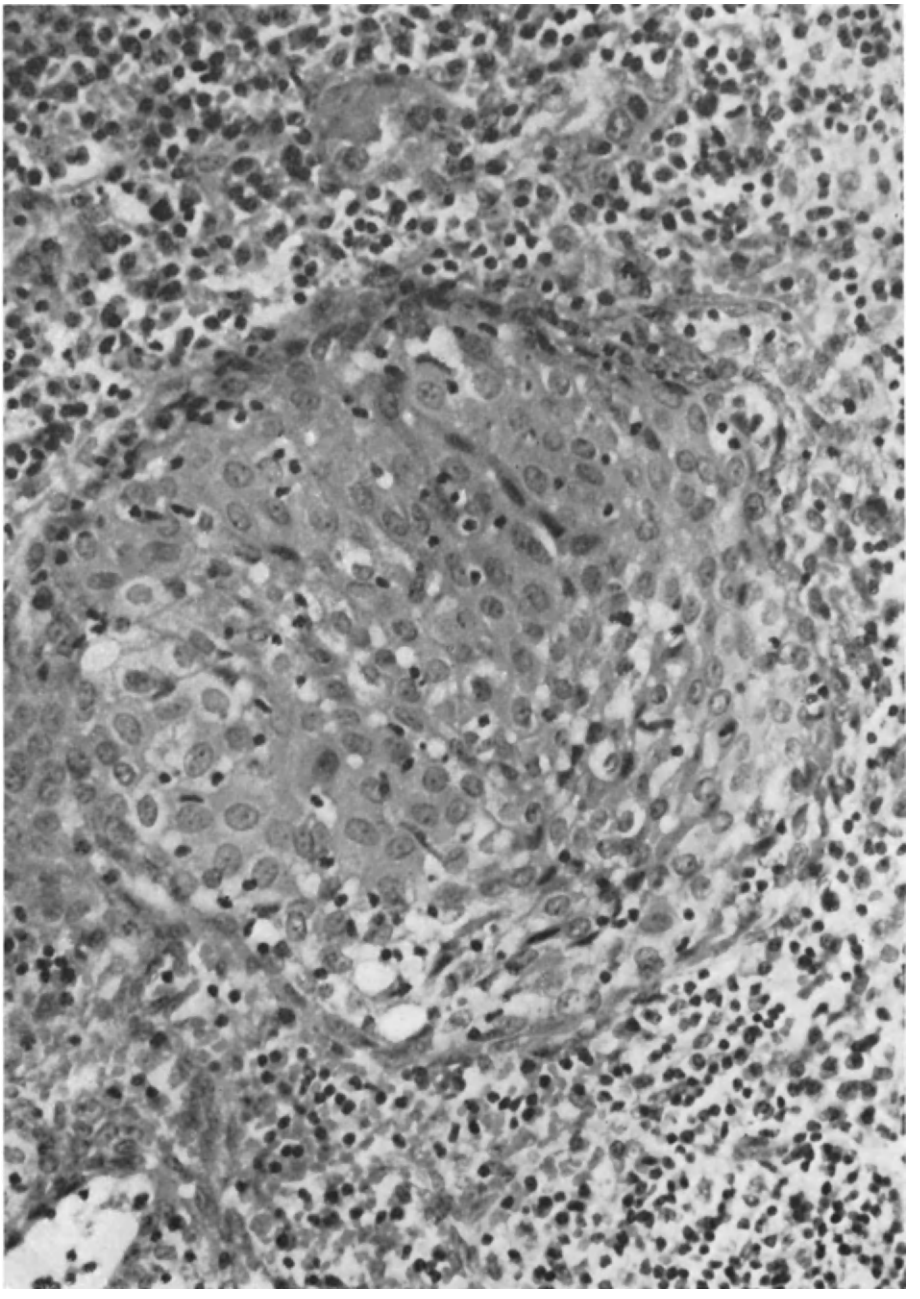

FIG. 5.10. According to Vickery and Hamlin[140] half of the cases of Hashimoto thyroiditis with intensive cell destructions show similar squamous metaplasia. (×800.)

Inflammatory infiltration

Electron microscopy has confirmed that the inflammatory infiltrations are composed mainly of lymphocytes, plasma cells, and macrophages.[11,58,70,100,101] The infiltrations are remarkably dense;[110] lymphoid follicles with germinal centres are often formed. Ultrastructural cytochemical investigations reveal intense acid phosphatase activity in the macrophages on contact with phagocytic vacuoles. These appearances are interpreted[18] as representing the lysosomal degradation of antigenic material absorbed by

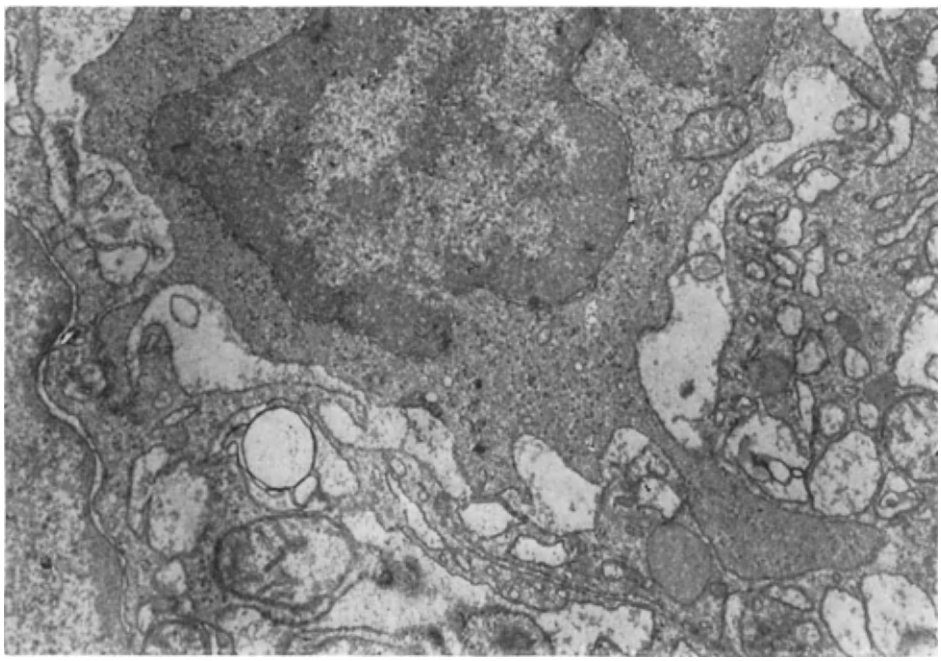

FIG. 5.11. Pseudopod of an inflammatory cell invaginating into the cytoplasm of a thyroid epithelial cell. (×18,000.)

the macrophages and the transfer of the antigenic signal to the immunocompetent cells. Indeed, many contacts exist between the macrophages and lymphocytes or plasma cells. Although it is dangerous to put a dynamic interpretation on a static appearance, it is, none the less true that such an interpretation of ultrastructural observations agrees with currently held theories on immunity which attribute the changes of autoimmune thyroiditis to delayed hypersensitivity.

As regards relations between thyroid cells and inflammatory elements, electron microscopy has also furnished a more accurate picture than it was possible to obtain with the light microscope.[18,100,101]

Not only are the small lymphocytes in close contact with the parenchymatous

elements, but it has been proved that the inflammatory elements actually penetrate inside the cytoplasm of the epithelial cells. Figure 5.11 shows a lymphocyte throwing pseudopods across the cell membrane of a much modified thyroid cell. Figure 5.12 shows the actual presence of an inflammatory cell inside a parenchymatous cell at the presumed necrobiotic stage, demonstrating well the phenomenon known as emperipolesis.[75,117,119,121,126] Intracell penetration had been observed by microcinematography in thyroid cells cultivated from a Hashimoto goitre.[81] It is of cardinal interest to note that in these studies the cells taken from normal thyroids resisted the penetration of lymphocytes, even when the latter were taken from subjects affected with thyroiditis. So it may well be, as suggested by electron microscopy, that it is the cell change which allows the "killer" lymphocyte to pass through the plasma membrane.

Discussion on the morbid anatomy of Hashimoto's goitre cannot be closed without a few words on the juvenile form and a brief mention of the role played by the thymus in this disease.

Juvenile Hashimoto's Goitre (Hyperplastic, Lymphocytic Thyroiditis)

The clinical and laboratory features of this variant have already been described (cf. section 1); they indicate a form which is more benign in intensity but otherwise similar on all accounts to Hashimoto's thyroiditis. Nor are there any pathological arguments to distinguish it as a separate entity. The lymphoid infiltration is diffuse. Some cell hyperplasia is observed, as in many goitres of the Hashimoto type. The parenchyma is considered to be less eosinophilic than in the classic form. Serial biopsies[32,140] in young subjects show that a hyperplastic phase may precede the typical picture of Hashimoto's disease. But the hyperplasia is unaccompanied by hyperthyroidism.[32] The appearance of eosinophil cells seems to increase with age,[113] although typical Askanazy cells have been reported by Hellwig[64] and Joll[73] in young subjects. Otherwise, most juvenile cases show characteristic changes of Hashimoto's disease.[49,68]

Role of the Thymus

In recent years, the role of the thymus has been cited in the pathogenesis of Hashimoto's disease. Lindsay *et al.*[80] report an extremely hyperplastic thymus in one subject affected with Hashimoto's goitre. Irvine and Sumerling,[71] studying pneumo-mediastinum aspects of 17 Hashimoto patients, found hypertrophied thymus glands in 13 of them. Similar results are reported by Michie *et al.*[97] However, Al-Sarraf and Walter[2] were unable to confirm these findings.

5. Laboratory Findings and Immunology

From the laboratory point of view, Hashimoto's thyroiditis is characterized by three phenomena:

(a) Blood protein changes, especially a rise in gammaglobulins.

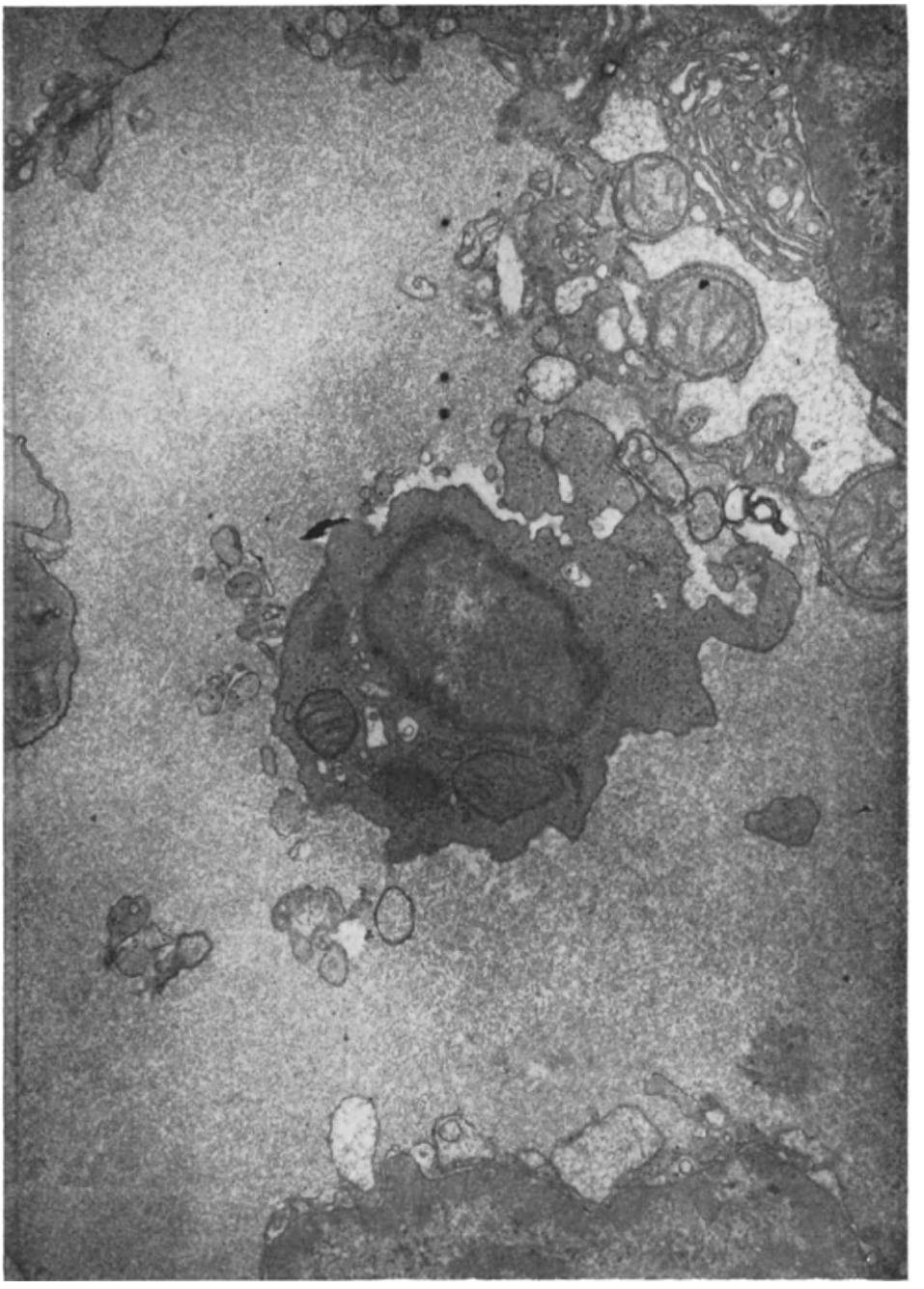

FIG. 5.12. Characteristic phenomenon of emperipolesis-penetration of a lymphocyte into the cytoplasm of a parenchymatous cells (×20,700.)

(b) High erythrocyte sedimentation rate.
(c) Constantly high thyroid antibody titres.

1. *Blood Protein Changes*

Luxton and Cooke[84] underlined the importance of flocculation reactions for the diagnosis of Hashimoto's lymphomatous goitre. McConahey *et al.*[95] reported that in the sera of 101 cases of Hashimoto goitre encountered at the Mayo Clinic, 51% had abnormally low values of albumin, 37% had high α_2 globulins, and 21% high gamma-globulins. In our own experience, limited to the study of six confirmed cases, the α_2 globulins were 8·5% (varying between 7 and 10%) and the gammaglobulins were up to 24% (between 19 and 30%). This has also been the experience of other authors. Skillern *et al.*[128] found high α_2 globulins in only 6 of their 55 Hashimoto patients.

As illustrated in Table 5.6,[85,88] the globulin changes clearly reflect the intensity of the condition; this explains the divergences of various data covering either all cases of lymphomatous goitre or only progressive cases. The increase in erythrocyte sedimentation in severe cases is clearly due to the changes in globulin levels; the latter may be associated with falsely positive Bordet–Wasserman reactions.[62,127]

2. *Presence of Thyroid Antibodies*

As shown by the Fig. 2.2 from Whaley and Buchanan,[150] almost all cases give a positive serological response; either to thyroglobulin (tanned red cell test) or to cytoplasmic antigens (complement fixation or immunofluorescent method). The agglutination reaction in half the cases merely indicates the intensity of the serological response (Fig. 2.2). Circulating thyroid antibodies persist (albeit in smaller quantities) for many years after medical or even surgical treatment of the disease (cf. case reports 5.1 and 5.2).

In the fibrotic variant of Hashimoto's thyroiditis, the thyroglobulin antibody titres are extremely high. Doniach and Roitt[39] attribute the phenomenon of intense interstitial fibrosis to the precipitation of antigen–antibody complexes in the interfollicular stroma by a mechanism identical to that described in certain cases of nephropathy with glomerular sclerosis.[34]

Finally, testing for LATS proved negative in the Brussels material.[15] Doniach and Roitt[39] also obtained negative results, even after using fifteenfold concentrations of IgG from subjects with large Hashimoto goitres.

6. Iodine Metabolism and Thyroid Function

Different studies[21,51,98,136,142] have drawn attention to various anomalies of iodine metabolism (Table 5.7).

Low $PB^{127}I$ values are often found in the serum.[21,122,142,153] Our own observations generally agree with these findings (Fig. 5.13). However, as first noted by Gribetz *et al.*,[51] high levels of $PB^{127}I$ may be found (varying between 8·8 and 9·6 μg per 100 ml),

TABLE 5.6. PROGRESS OF THYROIDAL, BIOCHEMICAL AND IMMUNOLOGICAL SIGNS IN A CASE OF HASHIMOTO GOITRE FOLLOWED FOR 10 YEARS[85,88]

	1957		1958						1969
	October	December	February	March		July	October	December	January
Goitre	++++	+++	++	+	+				
Neck circumference (cm)	41	40	38	38	38	38	37	37	
Scan (cm)		(10·5×8·5)					(9×6·5)		
ESR (mm/hr)	91	95	38	34	30	41	26	21	
Reactions:									
Hanger intensity	++++	+++	+++	++++	+++	+++	+++	+++	neg.
Thymol units	13·7	13·9	7·4	9	8·9	5·2	5·8	6·8	5·2
Takata intensity	+	+++	±	±	neg.	neg.	+	neg.	
Total proteins (g per 100 ml)	9·40	9·25	8·00	8·20	8·80	8·70	8·40	8·50	7·60
Albumin	3·29	3·42	3·18	3·49	3·58	4·09	3·81	3·95	3·56
Globulins:									
α_1	0·31	0·35	0·53	0·29	0·43	0·26	0·37	0·34	0·23
α_2	0·86	0·53	0·61	0·58	0·53	0·48	0·42	0·5	0·61
β	0·89	1·06	0·96	0·81	0·71	0·82	0·97	1·02	0·91
γ	4·05	3·89	2·72	2·99	3·55	2·91	2·83	2·68	2·27
Precipitins:									
Oudin	+1/256			+1/64			+1/64		
Quantitative (mg/ml)	18·9			6·6			3·2		
Haemagglutination ($1/1\times10^6$)	$1/2{\cdot}5\times10^6$			$1/2{\cdot}5\times10^6$			$1/2{\cdot}5\times10^6$		$1/40\times10^3$
Complement fixation:									
Intensity				+			neg.		+
Titre	>1/200			1/5					1/8
ACAT:									
Colloid immunofluorescence									++
Cytoplasm immunofluorescence									++
Gastric parietal cells' antibodies: Immunofluorescence									++

TABLE 5.7. PARAMETERS OF IODINE METABOLISM IN HASHIMOTO'S DISEASE

	No.	Mean ± SE	Extreme values	Normal values
PBI (μg per 100 ml)	39	2·5 ± 0·2	0·5 –5·3	3·2–7·2
$PB^{131}I$ (% per l.)	40	0·42 ± 0·07	0·05–2·74	0·0–0·4
^{131}I uptake, 48 hr (% dose)	40	40·7 ± 3·0	10·3 –798	20–60
Intrathyroid iodine (mg)	11	1·2 ± 0·2	0·1 –3·8	2–18

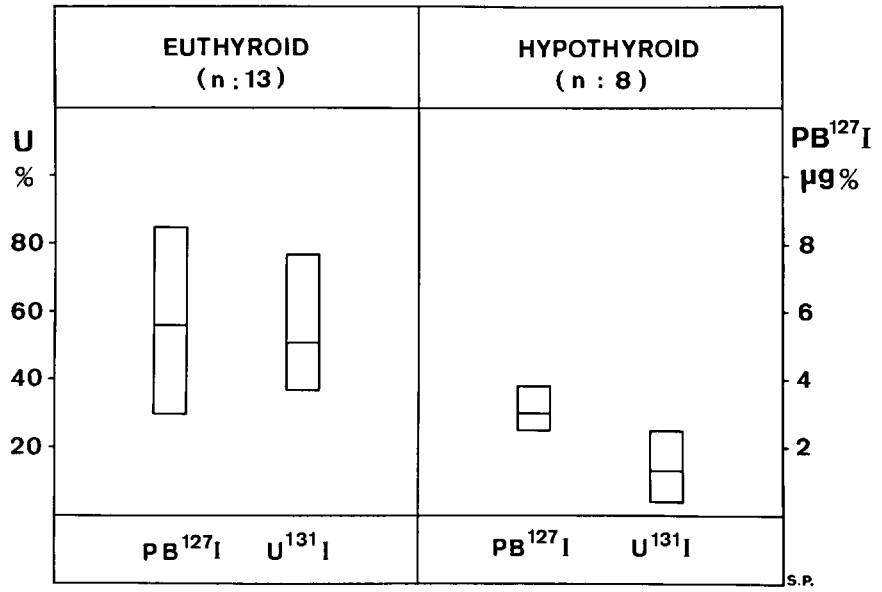

FIG. 5.13. Serum PB ^{127}I and radioiodine uptake in twenty-one patients with Hashimoto's struma.

whilst the butanol extractable fraction (BEI) is low (3·7–4·2 μg per 100 ml). In these cases, the increase of PBI is thus due to non-butanol extractable, and therefore non-hormonal material. Other authors[42,95,128,145] have confirmed the existence of variable quantities of abnormal iodinated proteins in the serum of many patients affected with Hashimoto's goitre (Table 5.8). The abnormal proteins are measured by the difference between plasma PBI and BEI. Such proteins are also found in other thyroid diseases (cf. Chapter 1): congenital goitre;[31,83] nodular goitre;[50,82] carcinoma;[118,134] and hyperthyroidism.[131] In all these cases, hyperplasia is a common denominator and the circulating iodoproteins are always different from thyroglobulin. Their amino-acid composition, their molecular weight, and their behaviour on immunoelectrophoresis are the same as those of iodoalbumins.[32,107,108]

TABLE 5.8. DISTRIBUTION OF NBEI VALUES IN SIMPLE GOITRE AND HASHIMOTO'S DISEASE
(Calculated from data of McConahey *et al.*[95])

NBEI (μg per 100 ml)	0–1	1.1–2	2.1–3	3.1–8
Simple goitres (%)	90	10	0	0
Hashimoto (%)	50	15	15	20

Radioactive iodine uptake varies greatly from one subject to the next.[142] Although often hovering between normal limits, it may be very high in some cases,[21,35] and abnormally low in others.[25] The quantity trapped at 4 or 6 hr is frequently higher than that recorded at 24 hr.[35] The inhibition of thyroid uptake by triiodothyronine enables a clear distinction to be made from thyrotoxicosis. There is often an increase of plasma $PB^{131}I$ which is in keeping with a marked reduction of the intrathyroid exchangeable iodine pool. This reduction accounts for the positive results obtained for the *iodide test* in most cases of Hashimoto goitre.[16,109]*

Iodine metabolism in Hashimoto's disease is also characterized by defective organification (of the iodine). It has been demonstrated[21,98,104,142] that the administration of potassium perchlorate an hour after a tracer dose of radioiodine entails a partial release of thyroid radioactivity in patients affected with Hashimoto's goitre. This indicates that a part of the trapped radioactive iodine is still in the form of radioiodide at this point, and that organification is defective.[21,98,105] Furthermore, chromatography of thyroid tissue labelled with radioactive iodine has shown an increase in the MIT/DIT ratio in Hashimoto's goitre, i.e. a decrease in the rate of production of DIT.[142] Similar anomalies have been found in non-toxic goitre.[33,43,44]

Thyroid scans have revealed asymmetrical uptake in 19 out of 32 Hashimoto patients[17] (Fig. 5.1 illustrates this finding).

The administration of TSH produces no further rise in uptake of ^{131}I[128,145] (Table 5.9). This observation has been interpreted as indicating maximum hypophysical thyrotropic stimulation.[42] The absence of any increase in thyroid radioactivity, or even its reduction, at 24 hr after TSH administration (Table 5.9) could be explained by the fact that the additional stimulation steps up the release of radioactive iodine accumulated in the gland. This hypothesis has been checked in the case of asymptomatic chronic thyroiditis (cf. Chapter 10). However, a rise in serum TSH is only observed in hypothyroid patients.[14,42,49,76]

Although thyroid insufficiency is chiefly explained by the destruction of the thyroid parenchyma, it has been suggested that the adherence of some thyroid hormone to the circulating thyroid antibodies might play a role in its mechanism.[116]

All things considered, the metabolic anomalies encountered in Hashimoto goitres

* After administration of potassium iodide (2 mg), the uptake of radioiodine is markedly depressed in thyrotoxicosis and thyroiditis.

TABLE 5.9. EFFECT OF TSH (15 U.S.P. UNITS) ON RADIOIODINE UPTAKE (U) IN SIX PATIENTS WITH HASHIMOTO THYROIDITIS

Sex	Age	Radioiodine uptake			
		Before TSH		After TSH	
		6 hr	24 hr	6 hr	24 hr
F	70	36	43	38	52
M	22	48	66	24	36
F	37	31	44	46	40
F	27	27	39	—	35
F	62	25	41	39	55
F		19	34	17	29

may be explained by the reduction in the exchangeable iodine pool with increased turnover and the release of abnormal iodoproteins.

7. Aetiology

The aetiology of Hashimoto's thyroiditis is still unknown despite numerous hypotheses. Recognition of the autoimmune nature of the process partly explains its evolution but not its genesis: positive information concerning the initial factor is lacking.

Clinical evidence suggested that it was perhaps a constitutional disorder,[73] frequently associated with the presence of other thyroid diseases in close relatives.[72] Reports of the disease occurring in families, or even monozygotic twins,[65,155] argue in favour of such a view.

Histological evidence showing cell hyperplasia, especially in the initial stages, has suggested the existence of hyperactivity followed by secondary degeneration in the small vesicles, whose cells are apparently unable to resynthesize colloid. The hypothesis of the release of cytolytic products from degenerating oncocytes in degenerescence has been advanced on several occasions[6,46,77,80] in order to explain the development of inflammation. But it is extremely rare to find the disease preceded by proven hyperthyroidism.[48,128] Most observations to the contrary relate to cases of secondary thyroiditis rather than authentic Hashimoto's disease.[60,73]

Virological studies have proved negative, even in the early stages of development.[136] Moreover, it is known that the types of thyroiditis which are probably of viral origin (like de Quervain's thyroiditis) almost never lead to autoimmune lymphocytic thyroiditis.

Biochemical data have revealed several anomalies of iodine metabolism of which the most important seems to be the passage of abnormal iodinated proteins into the blood. Although this anomaly may be secondary to thyroiditis, it has been observed fairly often in the absence of antibodies in offspring and siblings of subjects affected with other forms of autoimmune thyroiditis.[2,136,139] So this disorder could indicate an innate

defect,[141] which would give rise to difficulty in producing thyroid hormones. This is, however, only a hypothesis to account for the advent of an antigenic factor. Excessive immunological activity must also be cited to explain the enormous lymphoid response that characterizes Hashimoto's thyroiditis.

8. Diagnosis

The diagnosis of Hashimoto's thyroiditis should in principle be based on histological evidence. But the disease may be safely diagnosed on the basis of a typical clinical picture: a firm, diffuse, and symmetrical goitre; a high sedimentation rate; a high gammaglobulin level; and a high thyroid antibody titre. Surgical biopsy is only performed in the event of suspected cancer. In experienced hands, a needle biopsy is of valuable help, but it can fail to reveal a tumour.

In addition to a malignant growth, the differential diagnosis must take into account nodular goitre and toxic goitre. In all three conditions the antibody levels are usually much lower than in Hashimoto's thyroiditis. The diagnosis of Riedel's disease sometimes suggested by the fibrous form of Hashimoto's goitre is excluded by clinical evidence and the presence of antibodies.

9. Treatment

Surgery, which was the only treatment in the first part of the century, is now no longer indicated except in rare cases, either when concomitant neoplasm is suspected,[12] or if there are pressure signs.[90] Case report 5.2 illustrates both these conditions: Hashimoto's thyroiditis is rare in men; the intrathoracic location of the goitre is exceptional and the constriction of the trachea heightened the suspicion of tumour. Surgery may perhaps be envisaged for treating certain forms of Hashimoto's goitre evolving into nodular goitre.

In the classic cases, treatment with desiccated thyroid rapidly reduces the swelling. This treatment has the advantage of also reducing the laboratory and clinical signs of hypothyroidism, which may often be present.[13,29,47,94] The rapid diminution in the size of the goitre is clearly due to the decrease of lymphoid tissue. The epithelial lesions regress perhaps less.

Serological abnormalities may become less marked but often remain positive even after several years of treatment. In case report 5.2, a year after the removal of the greater part of the lymphomatous goitre and the start of substitution therapy, the thyroglobulin antibody titre was still found high on numerous occasions (cf. Table 5.1).

The same treatment has proved of value in the juvenile form of Hashimoto's goitre (in childhood or adolescence). The drop in the antibody titre in these cases seems to derive from the depression of thyroid activity and the disappearance or decrease of antigens produced in the gland.

Treatment of the exophthalmic form probably often requires the addition of delta-cortisone to the thyroid powder treatment.

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CHAPTER 6

Focal Lymphocytic Thyroiditis in Simple Goitre

P. A. BASTENIE, A. M. ERMANS and P. NÈVE

1. Introduction

The term "simple goitre" is used to describe a benign diffuse or nodular enlargement of the thyroid unaccompanied by signs of hyperthyroidism.

This type of hypertrophy, whether sporadic or endemic, is always the result of stimulation due to a qualitative or quantitative, temporary or persistent defect in thyroid hormone production.[27,38] It seems probable that in most cases the stimulation is achieved by activation of the anterior lobe of the pituitary and increased secretion of thyrotropic hormone. The hyperplasia of the parenchyma which follows such stimulation may in turn be followed by colloid involution. Successive phases of hyperplasia and colloid involution are eventually responsible for the formation of nodular goitre.[44]

Nodular goitre with lymphocytic infiltrates constitutes a pathological condition whose specific character has long been recognized.[44,45] When the lymphocytic infiltrations are limited to small exudates situated under the capsule and on the periphery of the adenomatous or colloid nodules, these infiltrations may correspond to a relatively insignificant local reaction. When they occur deep in the parenchyma, these infiltrations apparently have the same significance as the focal lesions of autoimmune thyroiditis observed in other thyroid conditions.

By their focal appearance and by the maintenance of extensive areas of normal or adenomatous thyroid tissue, these anomalies are quite distinct from the diffuse lesions of Hashimoto's lymphocytic goitre.[34,47] More recently, thyroid antibodies have been revealed in a large number of nodular goitres apparently in correlation with thyroiditis lesions.[2,34]

In nearly all these cases, the clinical picture is dominated by the signs of the goitre, and the presence of thyroiditis remains asymptomatic.

2. Illustrative Case Reports

CASE REPORT 6.1: SP 67,922. *35-year-old female patient presented with rapid growth of a goitre dating back to adolescence. The goitre was firm and nodular. Thyroid antibodies were present at high titres but without increase in sedimentation rate or in serum gamma-globulins. Focal lymphocytic thyroiditis was found in the nodular goitre.*

A woman 35 years of age had for some months a steady increase in size of a goitre, dating back to adolescence. On examination the goitre was nodular and of firm consis-

tency. The results of laboratory studies were as follows. Red blood cells: $4{\cdot}6 \times 10^6$ per mm^3. White cells; 3200 per mm^3 with 48% lymphocytes. Erythrocyte sedimentation rate, 11 mm/hr. Serum proteins, 7·3 g per 100 ml. Electrophoresis, A 55, 6%. Globulins: α_1, 3·7%; α_2, 8·6%; β, 9·7%; γ, 22·4%, i.e. 1·6 g per 100 ml. BMR + 15%. Serum cholesterol, 232 mg per 100 ml. Serum TGA, +1/78,125. Radioiodine uptake (24 hr), 48%. On thyroid scintigram a cold nodule was present in the centre of the gland which remained unchanged after TSH administration (Fig. 6.1).

As the goitre remained unchanged after 4 months of triiodothyronine therapy (75 μg/d), the right lobe and the isthmus were removed. Pathological diagnosis was "Nodular goitre with follicular adenoma". The thyroid parenchyme was mostly composed of small follicles; numerous lymphocytic infiltrates were observed around groups of abnormal thyroid follicles, the epithelium of which was often swollen and undergoing oncocyte metaplasia (Figs. 6.2A and 6.2B).

CASE REPORT 6.2: SP 67,996. *A woman* 48 *years of age had for* 2 *years a steady increase in size of a goitre dating back to adolescence. Age, sex, the presence of antibodies, and sedimentation rate suggested Hashimoto's goitre. Compression of the trachea and larynx made surgery advisable; the operation revealed the existence of a multinodular goitre with superimposed thyroiditis.*

A woman of 48 was admitted for discomfort in the neck, hoarseness of the voice, and pains in the nape of the neck. Her grandmother, two maternal aunts, and one daughter had been affected by goitre. She herself had over the past 2 years noted an increase in the size of a goitre she had since adolescence. At the same time she had gained weight and become sensitive to the cold.

On examination, the goitre appeared large (estimated weight 150 g), diffuse, not firm, and no lymph nodes were felt. The trachea was moderately compressed.

Erythrocyte sedimentation rate was 18 mm/hr. Gammaglobulins, 19% of total serum proteins. Thymol, 3 U. Serum cholesterol, 306 mg per 100 ml. Plasma PBI, 5·2 μg per 100 ml. Radioactive iodine uptake, 49% of the dose at 6 hr and 64% at 24 hr. Conversion rate, 30%. $PB^{131}I$, 0·02% of the dose per litre per 24 hr. Thyroglobulin antibodies, 1/78,125. The scintigram showed low-uptake areas (Fig. 6.3).

On account of the effects of compression and the scanning results, the patient underwent subtotal thyroidectomy. Histological examination showed a nodular goitre with superimposed thyroiditis.

3. Clinical Features

The frequency of thyroiditis lesions in nodular goitre was noted in early pathological studies[5] (Table 6.1). Of low frequency in diffuse parenchymatous or colloid forms of goitre which generally correspond to recent hypertrophy, these lesions occur with much more frequency in nodular goitres. Lymphoid infiltrations complicate nodular goitre in both sexes at all ages, but they affect, in particular, women after the menopause.

Except in rare cases, these infiltrations of thyroiditis are not betrayed by any local or

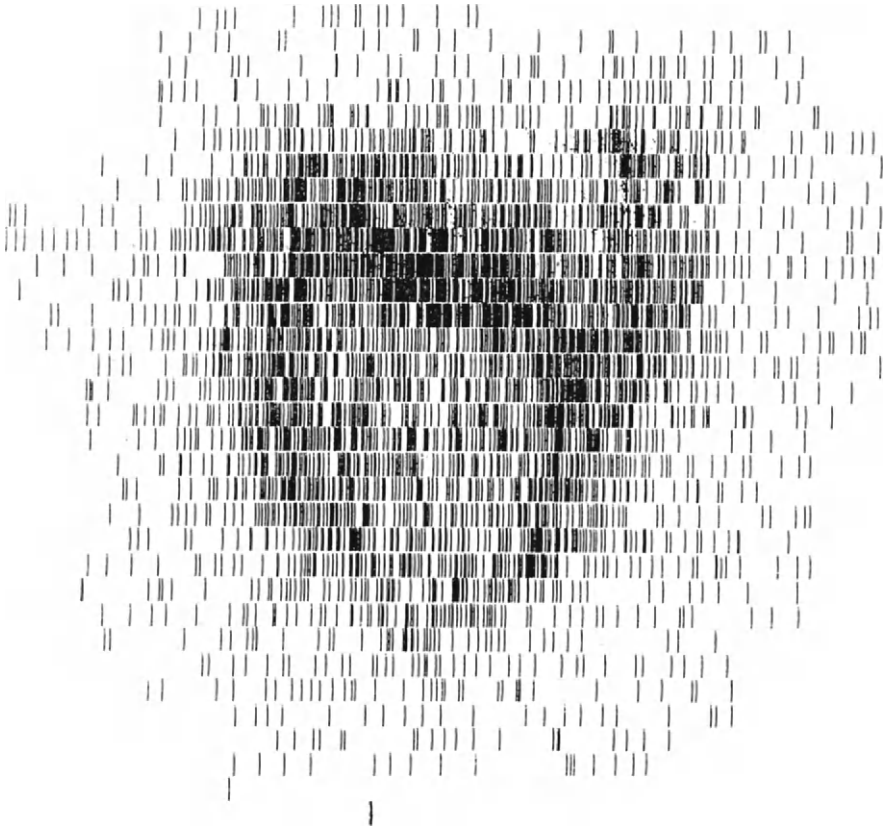

FIG. 6.1. Case report 6.1. Thyroid scan: cold nodule corresponding to a follicular adenoma.

general clinical symptoms. The goitre appears to be innocuous, and the presence of thyroiditis is only revealed by the discovery of thyroid antibodies or by histological examination after surgery. Table 6.2 shows the frequency of antibodies circulating in the blood of subjects affected with nodular goitre. Serological and histological data correspond well. The absence of perfect superposition of the lesions and antibodies[34] is doubtless attributable to the diversity of criteria used.

Among the cases of simple goitre treated at this clinic, twenty-five have been studied in more detail because at one time a diagnosis of Hashimoto's thyroiditis had been considered. The mean age of these patients was 60 years (range from 17 to 69). The goitre was diffuse in 9 cases, nodular in 6 others; in 8 cases there were some signs of tracheal compression; in 5 of these cases (1/5) signs of hypothyroidism were present (with increased serum cholesterol values) (Table 6.3).

Recently attention has been drawn to the frequency of lymphocytic thyroiditis in

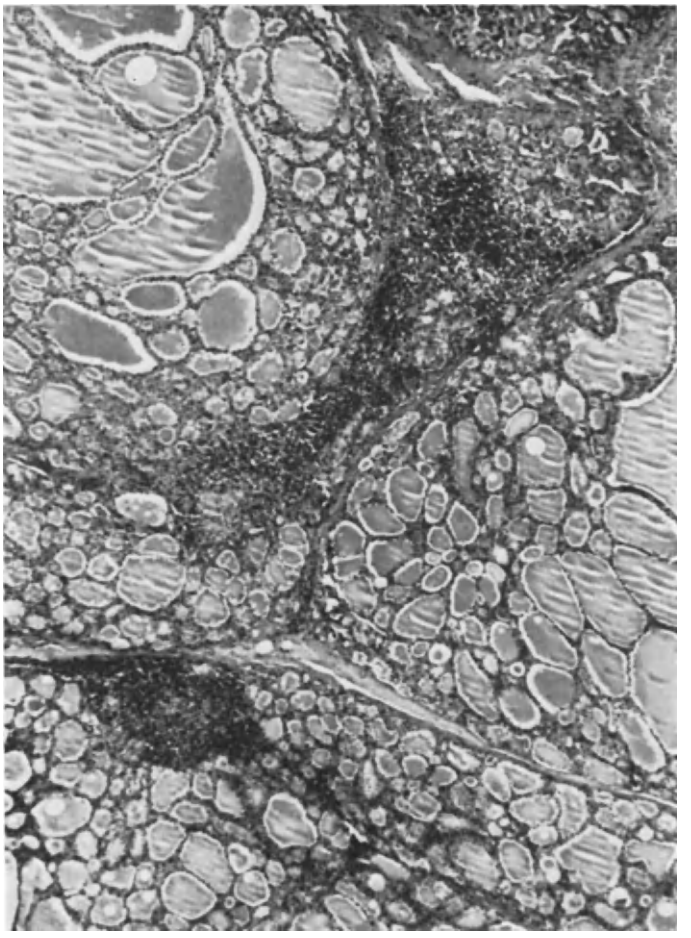

FIG. 6.2A. Case report 6.1. Thyroiditis in nodular goitre (×50.)

children and adolescents affected with euthyroid goitres.[23,25] In these cases superimposed chronic lymphocytic thyroiditis should not be confused with Hashimoto's thyroiditis. In sixty-six children with euthyroid goitre, 65% had thyroiditis lesions in their goitre (at needle biopsy), and in most of them circulating thyroid antibodies were found.

4. Pathology

On macroscopical and microscopical examination the prevailing anomalies are those of the goitrous tissue (parenchymatous or colloid, diffuse or nodular). The signs of thyroiditis do not dominate the pathological picture; although usually focal, they can be diffuse throughout the gland. The adenomatous nodules are generally spared.

When examined at high magnification, these lesions may be difficult to distinguish from those of Hashimoto's thyroiditis: the same epithelial lesions with eosinophilic cells, and the same type of lymphoid infiltrations are seen.[5] Moreover, the formation of germinal centres is sometimes observed.[34] Furthermore, the electron microscope reveals parenchymatous alterations and inflammatory cell reactions identical to those observed in Hashimoto's thyroiditis[30] (Figs. 6.4, 6.5, and 6.6). Some forms of thyroiditis with diffuse lesions, superimposed on a pre-existing goitre can only be distinguished

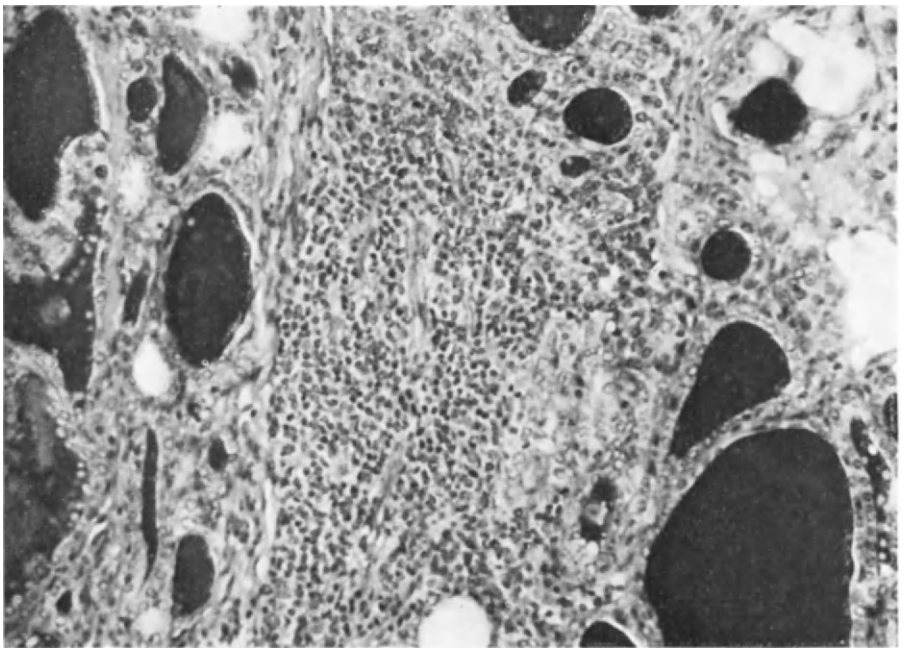

FIG. 6.2B. Case report 6.1. PAS shows normal colloid-filled follicles. Inflammatory infiltration around oncocytes in the centre. (×340.)

from Hashimoto's goitre by the maintenance of adenomatous regions and areas of normal tissue unaffected by any infiltration (cf. Figs. 6.2a and 6.2b).

These characteristics can clearly be observed in the photo-micrographs of many cases described in the literature under the ambiguous term "chronic lymphocytic thyroiditis" (cf., for instance, Ling *et al.*[25]).

5. Laboratory Findings and Immunology

Laboratory tests rarely reveal the anomalies characteristic of a progressive form of Hashimoto's goitre: according to the study of twenty-five cases summarized in Table 6.3, erythrocyte sedimentation rate is generally normal or moderately increased, and the

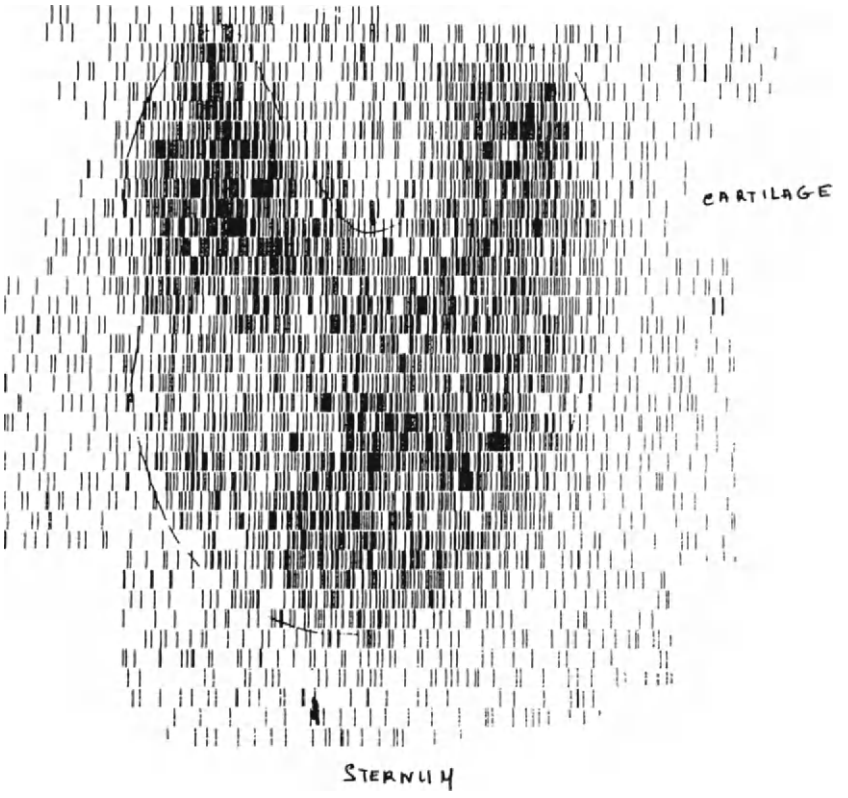

FIG. 6.3. Thyroid scan of case report 6.2.

TABLE 6.1. INCIDENCE OF THYROIDITIS IN SIMPLE GOITRE
(Pathological material from Freiburg[5])

	Diffuse goitre			Nodular goitre		
	Paren-chym.	Colloid	Total	Paren-chym.	Colloid	Total
No. of cases studied	36	28	64	23	23	46
No. with oncocyte metaplasia	6	1		12	12	
No. with lymphocytic infiltrates	3	1	4	4	10	14
Incidence of thyroiditis (%)			6			30

TABLE 6.2. INCIDENCE OF THYROID ANTIBODIES (TGA AND CFA) IN THE SERUM OF PATIENTS WITH SIMPLE GOITRE

Authors	Normal subjects		Patients with simple goitre	
	No. studied	Incidence (%)	No. studied	Incidence (%)
Roitt and Doniach, 1958[33]	148	6	198	27
Doniach and Roitt, 1963[15]			335	49

TABLE 6.3. LABORATORY FINDINGS AND IODINE METABOLISM IN TWENTY-FIVE SUBJECTS WITH SIMPLE GOITRE AND AUTOIMMUNE THYROIDITIS

	Range	Mean values
ESR (mm/hr)	3–27	11
Ser. globulins (% of total ser. proteins)	16–26	21
Serum cholesterol (mg per 100 ml):		
Hypo ($n = 5$)		299
Euthyr. ($n = 20$)		249
$PB^{127}I$ (g per 100 ml)	3–10·3	6·4
Thyr. ^{131}I uptake (% dose):		
6 hr		40
24 hr		56
$PB^{131}I$ ($n = 6$) (% dose per litre	0·05–0·26	0·11

flocculation tests are usually negative. Protein electrophoresis is barely changed. The Kahn reaction or the Bordet–Wasserman are always negative.

In general, the serological reactions are of lower intensity than in Hashimoto's thyroiditis,[2,11,15,33] although high titre of thyroglobulin antibodies may be observed in some cases. It is, however, exceptional to obtain precipitation in agar-medium.[2,15] The fact that Blizzard *et al.*[9] observed positive precipitation tests in 3 out of their 8 cases is doubtless due to the inclusion of cases of Hashimoto goitre in their study.[2]

Cytoplasmic antibodies are present in 10% of the cases.[2,11] Cytoplasmic and thyroglobulin antibodies have been reported with great frequency in a goitre endemic in Argentina.[35] The conclusion reached by the Argentine authors, who cite the autoimmune phenomenon as having an essential pathogenic role in endemic goitre due to iodine deficiency, seems to be contradicted by the negative observations made in other goitre endemics.[6,26]

Screening for LATS in endemic goitre has consistently given negative results, even when concentrated serum gammaglobulins were tested.[1] A recent review of the literature by Bonnyns[10] detected 15 positive results in 147 cases of simple sporadic goitres tested for LATS. This 10% incidence is also found in studies on normal subjects.[10]

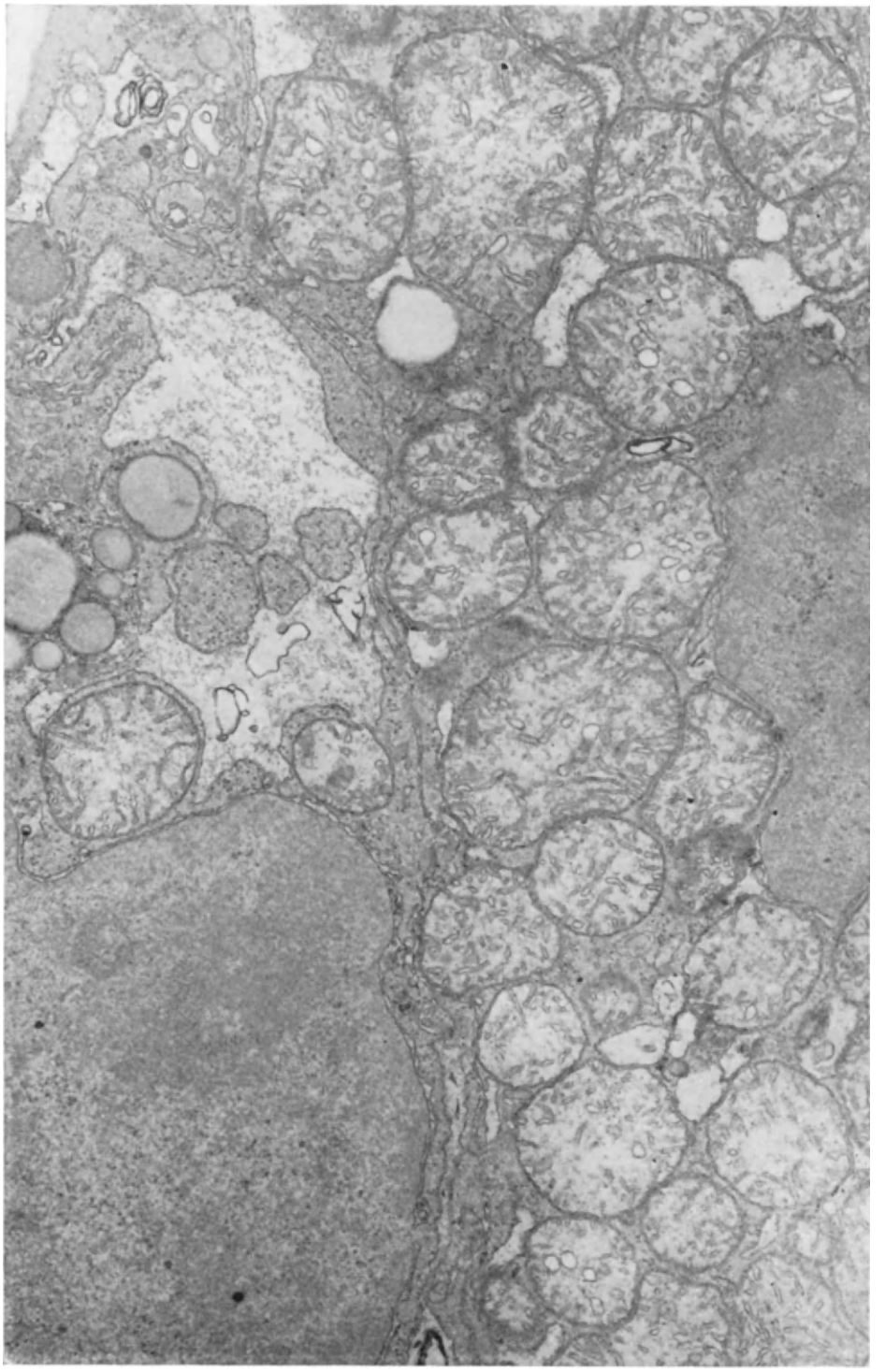

FIG. 6.4. Oncocyte in nodular goitre with thyroiditis.

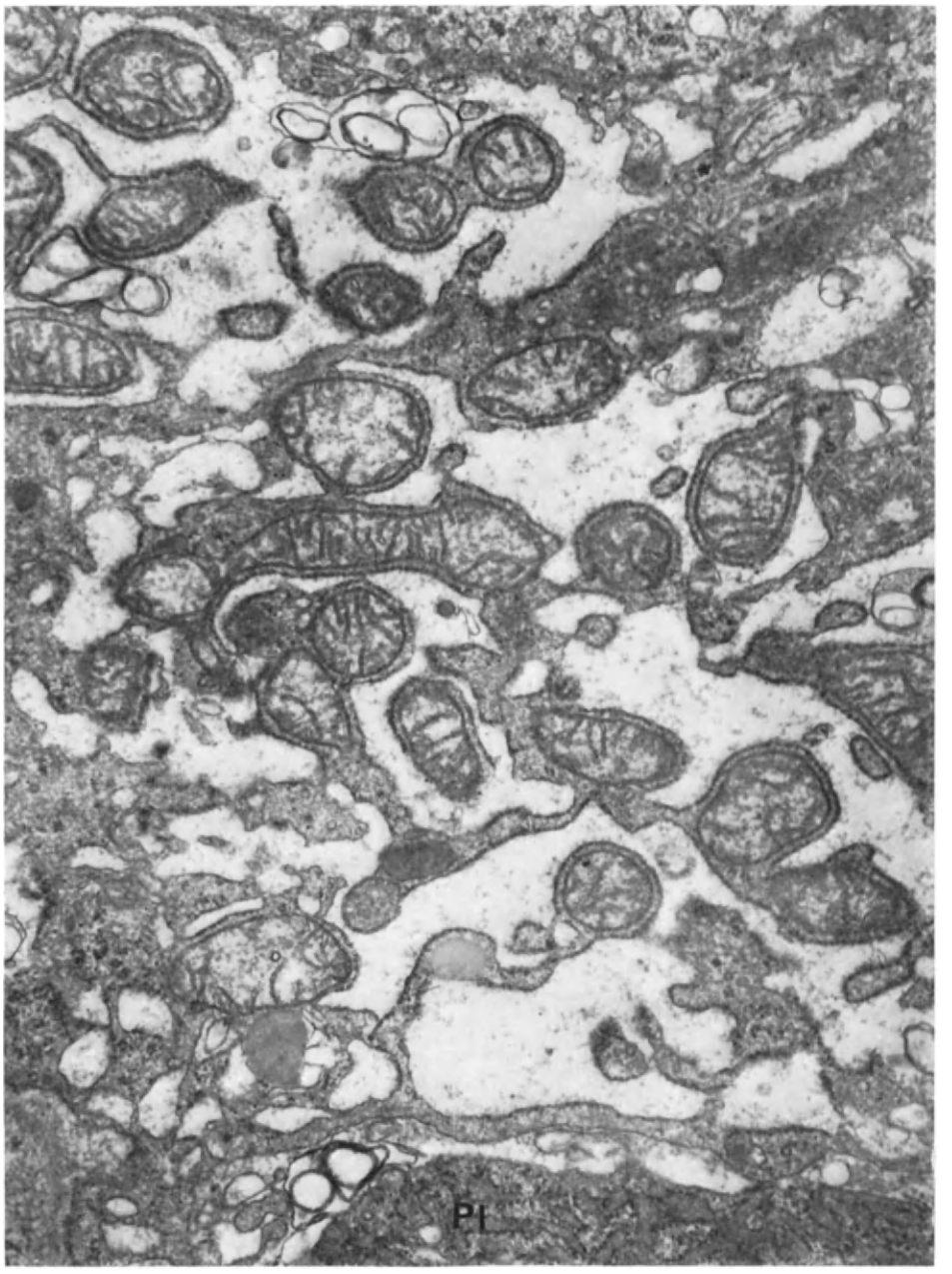

FIG. 6.5. Dilatation of the rough endoplasmic cisternae in thyroid cell of nodular goitre with thyroiditis. Part of a plasma cell (Pl) is seen at the bottom of the micrograph. (×17,800.)

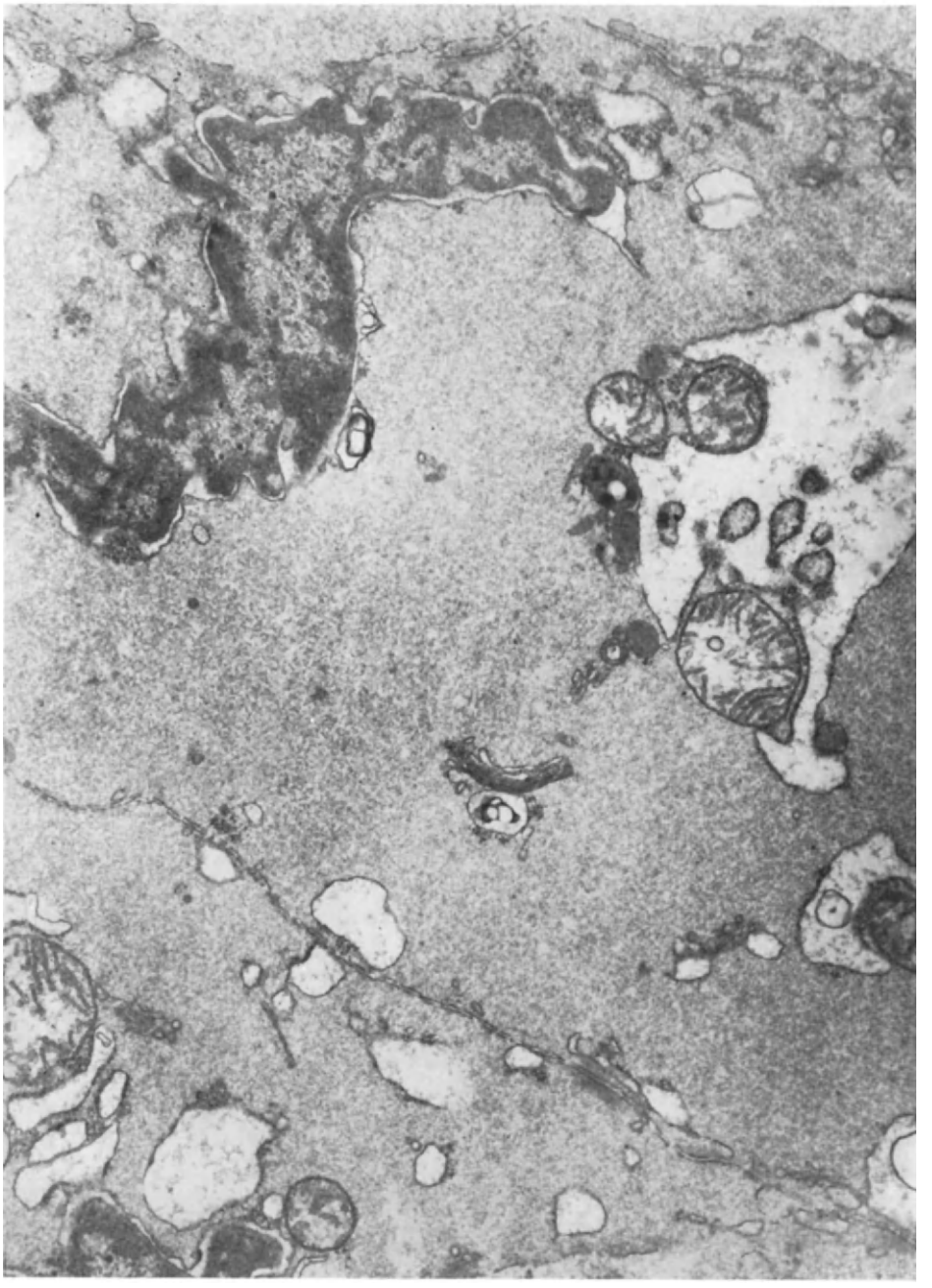

FIG. 6.6. Nodular goitre with focal thyroiditis: "colloid cells". (×16,300.)

TABLE 6.4. THYROID IODINE STORES IN SIMPLE GOITRE
(Arranged after Ermans[18])

Country	Thyroid gland		Urinary excretion (μg/d)
	Qg[a] (mg)	^{127}I concentration (mg/g)	
		Normal	
Belgium	12·1	0·62	59
Colombia	17·5	0·70	229
Sweden	12·9[b]		
United States	9·4		221
	6·3–14·7		80–225
		Simple goitre	
Belgium	22·0	0·17	
Sweden	20·9[b]		
United States	4·7–55·6		31–262

[a]Exchangeable organic iodine determined by kinetic methods.
[b]Estimation by spectrophotometric method of Heedman *et al.*

6. Iodine Metabolism and Thyroid Function

Anomalies of hormone synthesis, increase in size of the thyroid exchangeable iodine pool, fairly frequent increase in radioactive iodine uptake, and leakage of inorganic iodine from the thyroid are all well-known anomalies of sporadic or endemic goitre not complicated by superimposed thyroiditis.[17,18,40] Table 6.4 gives further details on iodine content and distribution in goitrous and non-goitrous glands. It may be very difficult to evaluate the part played by the thyroiditis in affecting the changes in iodine metabolism already present in the goitrous gland. In view of the possible spread of the thyroiditis process, a reduction of the exchangeable iodine pool is to be expected. Indeed, in the patient with goitre and thyroiditis the uptake of radioiodine is sometimes increased, and the plasma $PB^{131}I$ may be abnormally high due to the reduced pool of exchangeable iodine.

In our investigations (cf. Table 6.3) radioiodine uptake was on average high (56% at 24 hr compared to 40% in control subjects). $PB^{131}I$ was up to 0·14, 0·20, and 0·26 in three of the cases investigated.

As a rule, TSH administration in patients with simple goitre induces a normal activation of the thyroid gland. This is in contrast to the results observed in Hashimoto's and in asymptomatic thyroiditis (cf. Chapters 5 and 10). In none of the three affected subjects with simple goitre and superimposed thyroiditis did TSH administration raise the thyroid uptake of radioiodine to a normal extent (Table 6.5).

Thyroid scintigrams are of particular interest in that they can reveal isolated nodules

TABLE 6.5. TSH STIMULATION TEST IN THREE CASES OF SIMPLE GOITRE WITH THYROIDITIS

Patient	Sex	Age	TAB titre	^{131}I Uptake			
				Before TSH		After TSH	
				6 hr	24 hr	6 hr	24 hr
1. An	F	62	1/125	25	41	39	55
2. Lek	F	37	1/78125	31	44	46	40
3. Wei	F	54	1/125	13	23	8	22

or irregular areas where the thyroid tissue does not trap radioactive iodine. But considerable difficulties of interpretation arise from the fact that these appearances may correspond to adenomatous regions, seats of thyroiditis, or neoplasm (Fig. 6.7).

The study of serum TSH has yielded contradictory results. In many cases of endemic goitre an increased level of serum TSH has been detected.[1,13,37]

In simple goitre without proven thyroiditis, the values recorded are generally normal,[7,31] although in nodular goitre increased values have been found.[24] This may be explained by the existence in these cases of asymptomatic thyroiditis and of more or less marked hypothyroidism, as demonstrated in our own patients (cf. Table 6.3).

In most cases of simple goitre without thyroiditis the values for NBEI are said to be normal[28] (cf. Table 5.8). However, in a few patients with familial goitre the coexistence of thyroiditis, thyroid antibodies, and NBEI has been described.[39,42]

Moreover, two groups of authors[20,46] reported on families in which certain members affected with non-toxic goitre presented with abnormal iodoproteins in their serum. In both studies the familial distribution of this defect suggested inheritance on a genetic basis.

Excessive production of iodoproteins is a disorder which has been observed as a definite congenital defect of thyroid metabolism.[12,36,41] In this severe form it may represent an accentuation of a slight defect present in adenomatous colloid goitre.[40] This is the more probable since in the genesis of simple goitre, as in that of other thyroid diseases, a constitutional factor is involved (cf. Chapter 14). Other slight defects have been observed in families with simple goitre.[22] A special mention should be made of iodide goitre, i.e. goitre developing after prolonged ingestion of iodide.[8,16,21,29] Most authors attribute iodide goitre to the presence in the thyroid of an underlying defect of iodine organification[29] masked by an excess of iodide. A similar defect has been detected in Hashimoto's goitre (cf. Chapter 5). Hall *et al.*[21] found that thyroid antibodies occurred more frequently in patients with iodide goitre than in control subjects, and suggested that iodide administration may lead to goitre and hypothyroidism in patients in whom latent thyroid autoimmunity is present.

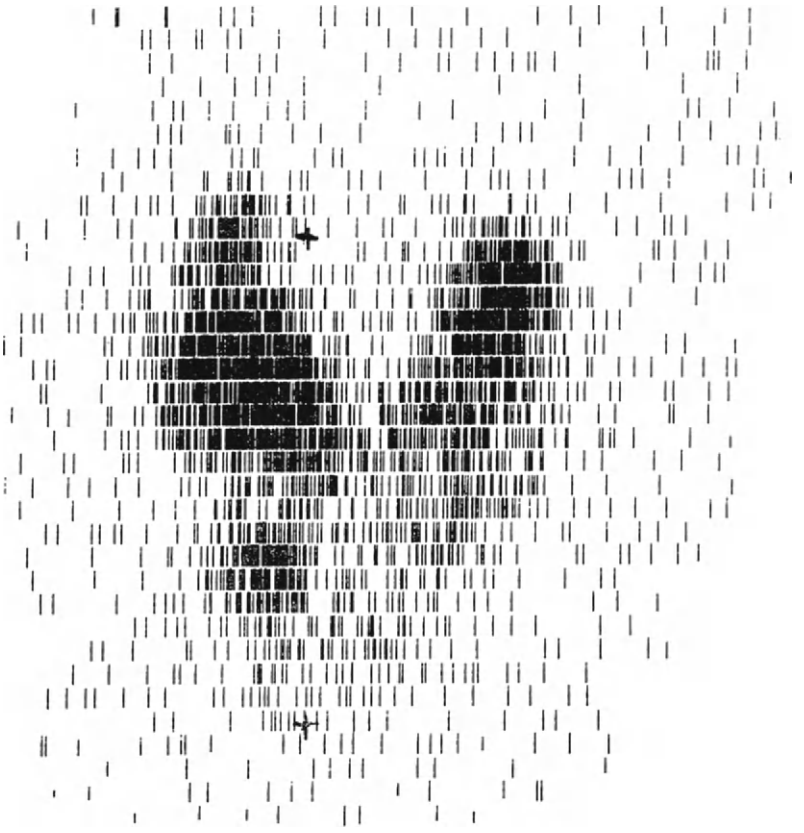

FIG. 6.7. Thyroid scan of thyroiditis superposed on multinodular goitre. Suspicion of cancer was raised in this 72-year-old woman with long standing nodular goitre (TGA, 1/78125; CFA, ++; ESR, 30 mm/hr; ^{131}I uptake at 24 hr, 40%).

Conversely, it may be that subjects with a masked metabolic defect are prone to develop thyroiditis when they are given high doses of iodine.

7. Diagnosis

In the presence of a non-toxic goitre accompanied by a significant level of thyroid antibodies, the diagnosis of Hashimoto's thyroiditis must be envisaged first.[11,14] This was excluded in our cases by one or more of the following points: (1) the age of the patients; (2) the existence of an asymmetric goitre detected several years beforehand; (3) the normal erythrocyte sedimentation rate and the absence of a distinct rise in gammaglobulins; (4) the low titre of thyroglobulin antibodies; (5) in doubtful cases the histological picture showing the absence of diffuse inflammatory lesions characteristic of

Hashimoto's thyroiditis and the persistence of adenomatous structures. According to Doniach and Roitt[15] it is the demonstration of cytoplasmic antibodies which is the best guide for a differential diagnosis "because of the high levels observed in Hashimoto's goitre and the rarity of positive results in nodular goitre". However, in a series of cases the diagnosis is only possible with the aid of a needle biopsy.[14,32] Moreover, the latter may lead to a diagnosis half-way between goitre with focal thyroiditis and Hashimoto's disease. This condition appears to be more frequent in young women with moderate quantities of antibodies.[15]

Cancer of the thyroid is often complicated by thyroiditis (cf. Chapter 7). Thus if a goitre is fast growing or is hard on one side, even in the presence of significant levels of thyroid antibodies, surgery is distinctly advisable to secure diagnosis.

Finally, the diagnosis of iodide goitre should be considered, as this particular variant of goitre may often be accompanied by autoimmune thyroiditis.[21]

8. Treatment

Once the correct diagnosis is established, the treatment of goitre complicated by thyroiditis is no different from that of nodular goitre.[3,4,19] In some cases the administration of thyroid hormones is sufficient. In others, where the goitre is a nodular one dating back some time, this treatment often has little effect, and surgery is the only resource against the compression of organs.[3] The extent of the thyroiditis lesions may dictate limited resection to avoid post-operative hypothyroidism.

In most operated cases, moreover, it is best to prescribe moderate substitution treatment with the twofold object of preventing the recurrence of goitre and avoiding the development of thyroid insufficiency.

Iodine administration should be avoided: it proves deleterious in thyroiditis, may lead to or aggravate iodide goitre, and induce myxoedema.[8,16,21]

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CHAPTER 7

Chronic Lymphocytic Thyroiditis and Cancer of the Thyroid

P. A. BASTENIE, A. M. ERMANS and G. DELESPESSE

1. Introduction

Processes of lymphocytic thyroiditis occurring inside thyroid tumours as well as in the normal tissue surrounding the cancer were first described some considerable time ago.[7,13] Lymphocytic infiltrations are particularly common and extensive in cases of follicular or papillary carcinoma.[9,14,19,26] Furthermore, immunological studies have revealed the fairly frequent presence of thyroid antibodies in the serum of patients affected with thyroid cancer. According to Stuart and Allan,[36] there is a close correspondence between circulating thyroid antibodies and inflammatory infiltrations in thyroid cancer patients. The antibodies are no different from those usually accompanying lymphocytic thyroiditis; so far no special antigens have been brought to light by the analysis of cancerous thyroid tissues.[9,11]. There is good evidence that thyroid autoimmunity is common in thyroid cancer.[12,36]

It therefore seems well established that a thyroid tumour may be affected with thyroiditis although Anderson *et al.*[1] wondered whether the selection of patients has not created a false impression of association.

On the other hand, it has been suggested that a tumour may arise in the course of lymphocytic thyroiditis, perhaps preferably in cases of Hashimoto goitre.[19,36] Such tumours are mainly of the malignant lymphomatous type, or occasionally papillary.[20]

2. Illustrative Case Reports

CASE REPORT 7.1: Obs. 70,855. *Development of thyroid cancer in a patient previously treated by radiotherapy for nodular goitre.*

The pathological diagnosis of papillary epithelioma with lymphocytic thyroiditis corresponds to pre-operative high levels of circulating TGA.

A 56-year-old woman had developed a nodular goitre in adolescence, although there was no known goitre in her family. When she was 22 years of age, the goitre was treated by external radiotherapy. At the age of 42, she was operated on for fibroma, and thereafter treated for obesity and essential hypertension. In December 1967 she was admitted for investigation of the goitre, which had become very hard, particularly in the left lobe. The estimated weight of the goitre was 70 g, and it was tender to pressure over the right lobe. Radiography showed calcifications; the ^{131}I scintigram showed no uptake. Otherwise the patient was euthyroid and her thyroid function proved normal.

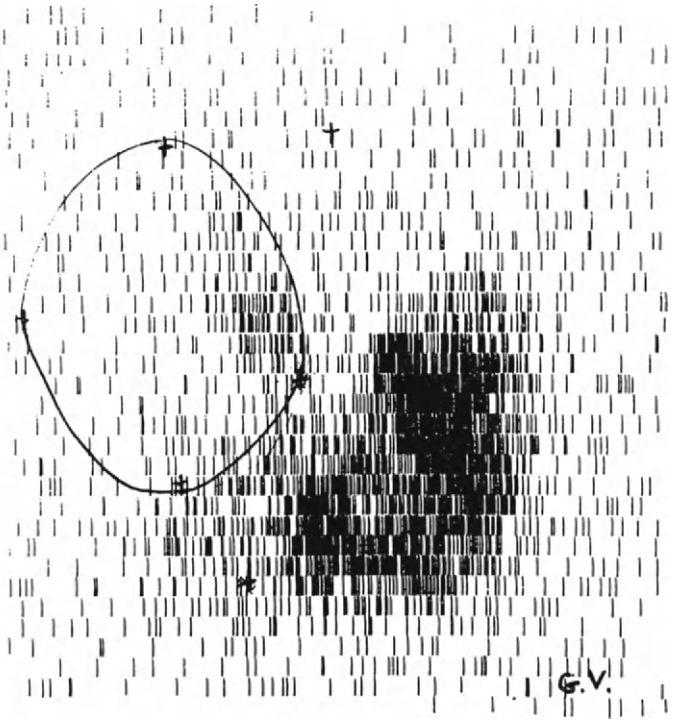

FIG. 7.1. Case report 7.1. Thyroid scan.

Laboratory findings

ESR	6 mm/hr
Leucocytes	6800 per mm^3 with 41% lymphocytes
Total serum proteins	6·1 g per 100 ml
	A = 49·4%; α_1 = 5·9%; α_2 = 12·8%; β = 16·4%; γ = 15·5%
$PB^{127}I$	5·2 μg per 100 ml
^{131}I uptake	41% of dose per 24 hr
$PB^{131}I$	0·55% of the dose per litre per 24 hr
TGA+	1/78125
BMR	+7%
Cholesterol	322 mg per 100 ml

Scintigram (Fig. 7.1)

Total lobectomy, hitherto refused, was carried out in March 1968. The histological diagnosis was "Lymphocytic thyroiditis. Vesiculopapillary epithelioma composed of Hürthle cells." After ablation of thyroid remnants by 50 mc ^{131}I, in August 1968, body

scanning was negative. On 7 September 1968, hypothyroidism was treated with triiodothyronine (37·5 μg/d).

CASE REPORT 7.2: Obs. 58B66 4437. *Medullary cancer with lymphocytic thyroiditis*

In 1958 this 34-year-old woman, who had been treated for goitre in adolescence, reported a thyroid swelling causing pain in the back of her neck.

Although there were no signs of thyroid dysfunction, the subject was treated with anti-thyroid drugs at another hospital. Still under this treatment in 1963, the patient noted a marked increase in the size of the left thyroid lobe and complained of shooting pains around her left ear. Basal metabolism, plasma PBI, and radioactive iodine trapping all yielded normal values. A scintigram showed a cold zone in the left lobe. The thyroid antibody titre was moderately high: 1/625. Since surgery was refused, T3 treatment was applied with the diagnosis of possible focal thyroiditis.

In 1966 the local signs were more pronounced, but the patient's general condition was still excellent. ESR, 3 mm/hr; BMR, +1%; serum cholesterol, 250 mg per 100 ml.

Scintigraphy at this point revealed complete absence of uptake in the left lobe. Radiography showed deviation of the trachea but no constriction.

Total thyroidectomy following operative biopsy was carried out in October 1966.

Pathological diagnosis: "Malignant tumour with strands of undifferentiated cells; part sclerous, part myxoid stroma with amyloid deposits; adjacent thyroid tissue containing vesicles arranged in lobules surrounded by fibrous stroma with intensive lymphocytic infiltration."

In 1968, when the patient was given thyroid substitute treatment, she was found to be in excellent general health. A series of tests for TGA were negative.

CASE REPORT 7.3: Obs. E 2939. *Mixed papillary and follicular cancer with thyroiditis*

A 46-year-old woman had developed a fast-growing goitre in 2 years which was causing breathing difficulty.

Examination revealed a firm, large goitre (estimated at ±120 g), with harder nodules in the left lobe.

There were clear signs of hypothyroidism: weakness, weight gain, puffy face.

Laboratory findings

ESR	9 mm/hr
Lymphocytes	36%
Thymol	12 U
TGA+	1/78125
$PB^{127}I$	3·4 μg per 100 ml
BMR	+15%
Serum cholesterol	284 mg per 100 ml
Radioactive iodine uptake:	
6th hr	35% per dose
24th hr	50% per dose

The scintigram showed an extensive cold area in the left lobe.

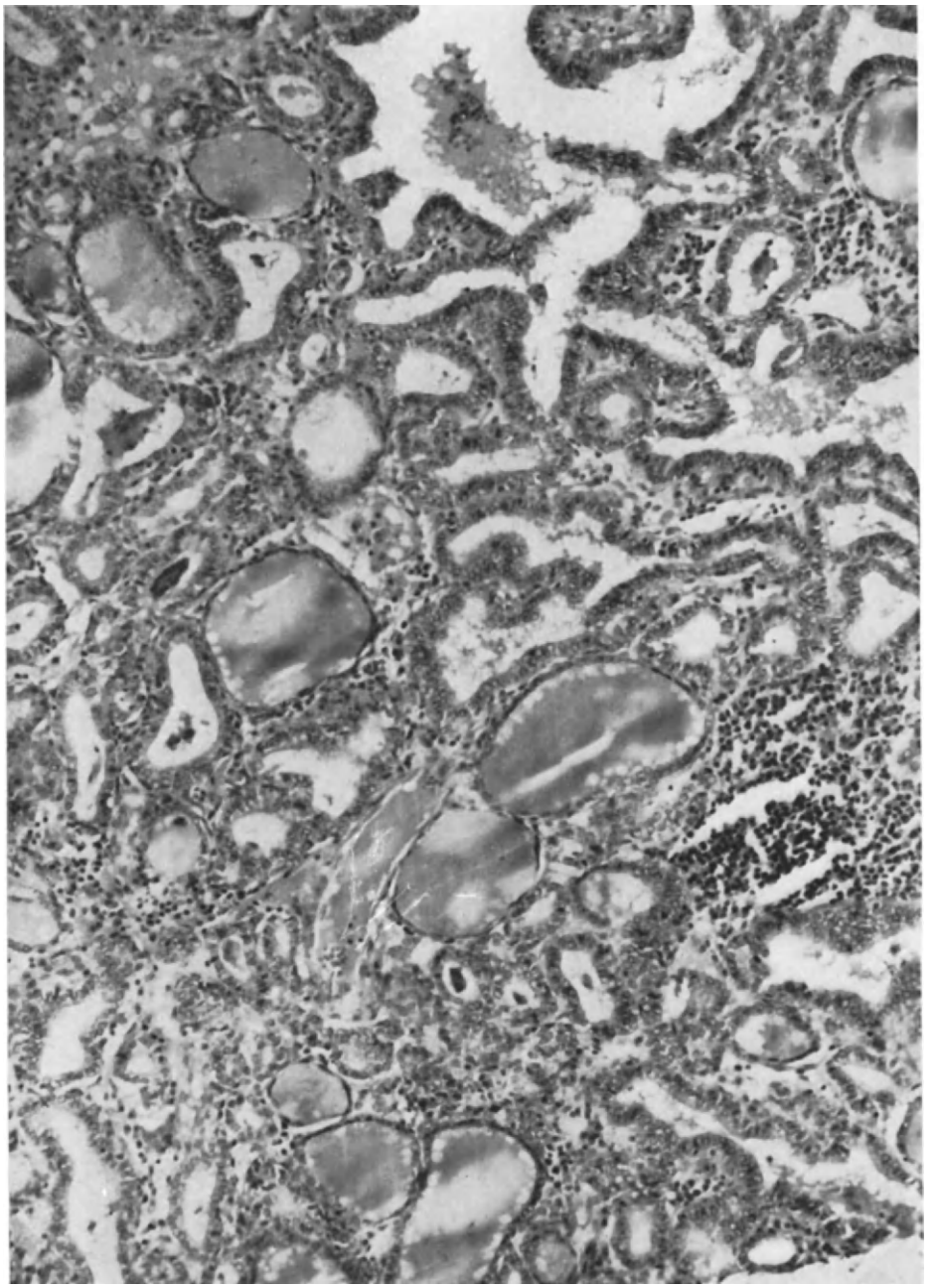

FIG. 7.2. Case report 7.3. Papillary adenocarcinoma invading thyroid tissue. Remaining thyroid follicles are lined with a low epithelium and filled with dense colloid. Smaller hyperplastic vesicles surrounded by lymphoid infiltrates are hardly distinguishable from neoplastic tissue. (×140.)

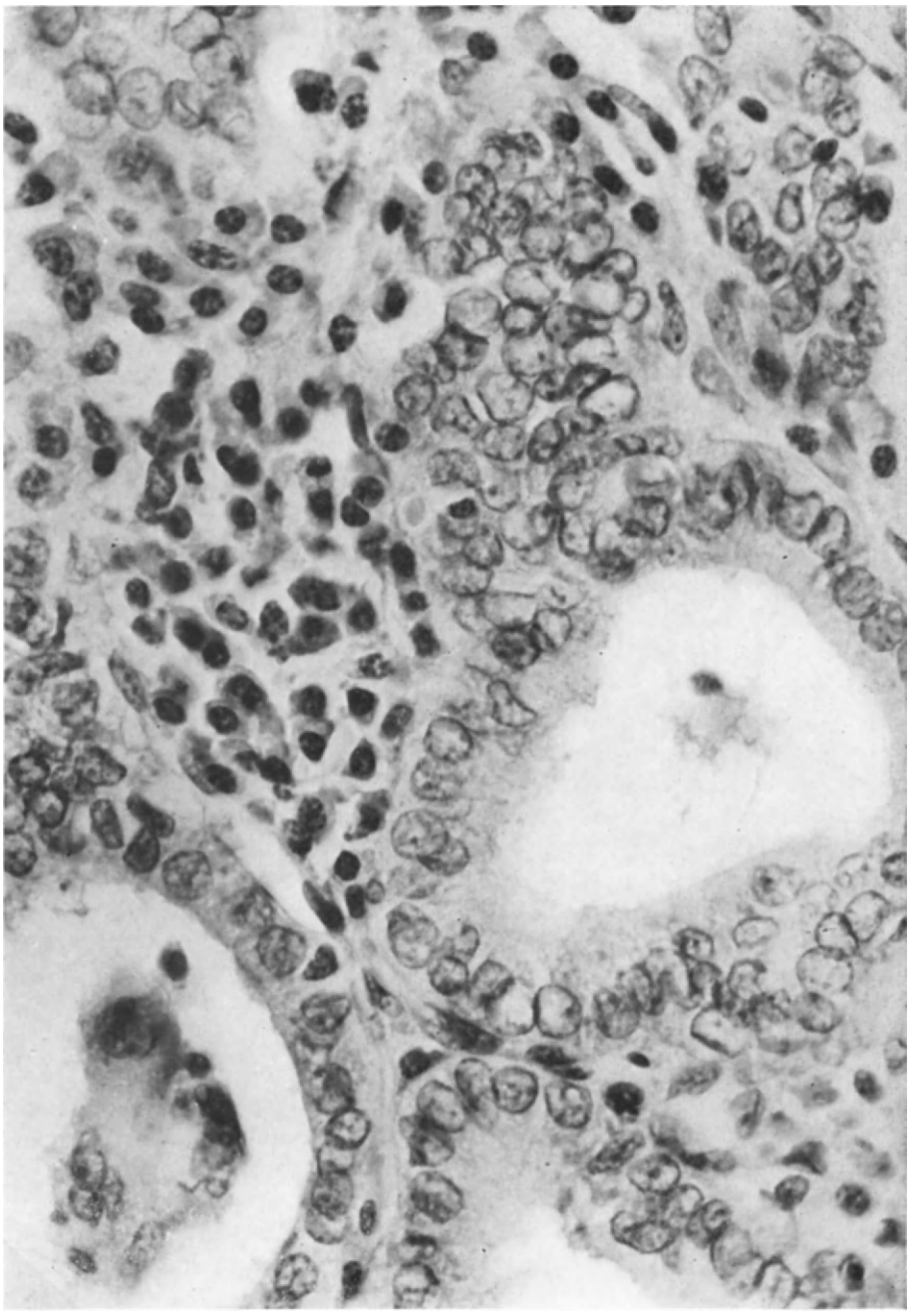

FIG. 7.3. Case report 7.3. The neoplastic tissue is characterized by typical clear nuclei. Lymphocytes and plasma cells are present in the stroma of the neoplastic tissue. (×900.)

TABLE 7.1. CLINICAL DATA ON PATIENTS WITH THYROID NEOPLASMS AND HASHIMOTO DISEASES (After Dailey *et al.*[7])

	Hashimoto's disease without neoplasm (110 cases)	Carcinoma with Hashimoto's disease (35 cases)	Carcinoma without Hashimoto's disease (85 cases)
Sex	96% F	89% F	76% F
Age at onset (years)	6–73 (m = 38·3)	20–69 (m = 37·5)	6–68 (m = 36)
Age at operation (years)	14–75 (m = 46·2)	9–66 (m = 41·4)	8–88 (m = 44·1)
Family history (%)	24	24	10
Pressure effects (%)	60	20	50

A therapeutic trial with T3 for a month had no effect. Surgical removal of the entire left lobe revealed a mixed papillary and follicular cancer and lymphoid infiltration of the thyroid tissue (Figs. 7.2 and 7.3).

For the past 6 years the patient's condition has been excellent; the TGA titre dropped from 1/78125 in 1967 to 1/15625 in 1969.

3. Clinical Features

The development of lymphocytic thyroiditis in a gland carrying a malignant tumour is by far the most frequently encountered problem in cancer–thyroiditis investigations. Lindsay *et al.*[17] and Dailey *et al.*[7] looked for lymphocytic infiltrations and cell changes (including focal lesions) in a large number of goitrous tissue samples, generally removed because of pressure symptoms. Their main findings are given in Table 7.1. The authors make no distinction between true Hashimoto's thyroiditis and other forms of lymphocytic thyroiditis.

Meier *et al.*,[19] when re-investigating the pathology of 256 cases of thyroidal cancer, found that only 10% of the cases were accompanied by thyroiditis. But if focal infiltrations are taken into account, this percentage rises to 35%.

These different studies furnish no guide for making a clinical distinction between primary lymphocytic thyroiditis and cancer complicated by thyroiditis. At the most they suggest that when a goitre is fast growing the absence of signs indicating thyroiditis pleads strongly in favour of a diagnosis of malignancy. On the other hand, the possibility of malignancy is not excluded by the discovery of thyroid antibodies or lymphocytic infiltrations discovered by needle biopsy.[23]

The other condition in which thyroiditis and cancer are associated is the result of a malignant tumour developing in a gland already affected with thyroiditis. Meier *et al.*[19] report two cases (out of 256 cancer patients) in which tumours had developed in glands invaded by a typical process of struma lymphomatosa. They also observed 8 cases of

malignant lymphoma of which 6 had developed in glands displaying lymphocytic infiltrations. From the studies published by Cox[5] and Woolner *et al.*,[43] it emerges that the majority of intrathyroid lymphomas occur in elderly women with large goitres of recent onset. Progressive tracheal obstruction is common in advanced cases. It may be very difficult to determine the exact nature of the association between these malignant lymphomas and thyroiditis: out of 605 cases of Hashimoto's thyroiditis studied by Woolner *et al.*, 5 showed such dense lymphocytic infiltrations that the possibility of lymphosarcoma was considered in the differential diagnosis.

However, no recurrence was observed in any of these five female cases, whose progress was followed for periods ranging between 4 and 16 years.

Fujimoto *et al.*[10] described six cases of malignant thyroid lymphoma observed in Tokyo between 1960 and 1962. In all the cases (three men and three women, age range 48–69 years) the main complaint concerned the rapid development of a goitre. In three cases, enlarged cervical lymph nodes were found.

The erythrocyte sedimentation rate was moderately high (15–35 mm); serum proteins were normal. High titres of thyroglobulin and microsomal antibodies were discovered in three of the four patients.

Finally, Ayala *et al.*[2] report one 64-year-old female patient who developed a goitre with thyroid adenocarcinoma and lymphoma. Her thyroid gland weighed 95 g; the very enlarged left lobe consisted of a lymphoma composed of immature lymphocytic cells enclosing a follicular carcinoma. The rest of the thyroid tissue showed the classic features of Hashimoto's goitre—oxyphil cells, diffuse infiltrations, and germinal centres.

4. Pathology

If lymphocytic thyroiditis is defined in Hashimoto's clinical and histological terms, as given in Chapter 5, the problem resolves itself to the two following points.

1. In about a third of epithelial thyroid tumours, lymphocytic infiltrations develop in the non-involved tissue around the tumour and sometimes in the actual neoplastic tissue.

The infiltrations form small foci of thyroiditis which cannot be differentiated in their essential pathology from the processes of focal thyroiditis encountered in other thyroid disease: nodular goitre (Chapter 6); toxic goitre (Chapter 8); non-goitrous thyroiditis (Chapter 10). The lesions comprise (i) alterations of the parenchyma, deformed into small vesicles poor in colloid and affected with oncotic changes, and (ii) lymphoid infiltrations breaking up the altered vesicles and sometimes forming lymphoid germinal centres.

In the majority of cases the infiltrations are small; in 10% of the cases they are of more marked intensity, and very exceptionally they may attain the degree observed in Hashimoto's goitre.[19] It is, above all, in women aged between 50 and 70 years that the inflammatory reactions are the most frequent,[19] i.e. in the subjects who show the greatest predisposition to spontaneous focal lymphocytic thyroiditis (Chapter 10).

Lupulescu *et al.*[18] investigated by electron microscopy fifteen cases of thyroid

cancer of the follicular or papillary type. Particularly in the latter they demonstrated large-scale disorganization of the mitochondria and reduction of the ribosomes in endoplasmic reticulum. The authors relate the disturbances of iodine metabolism especially to the ultrastructural anomalies.

2. There is little conclusive anatomo-pathological evidence of a malignant tumour in a gland already affected with true Hashimoto's thyroiditis.

However, some investigators claim that this happens very frequently, to such an extent that Hashimoto's goitre should always be treated by total thyroidectomy.[25] Chesky *et al.*[4] report the detection of malignant tumorous tissue in 48 out of 432 operated cases of Hashimoto's goitre (i.e. 11%). Such claims would seem to be based on an inadequate distinction between reactional lymphocytic thyroiditis and true Hashimoto's thyroiditis (cf. Chapter 5) and on the use of insufficiently exacting histological criteria for the diagnosis of malignancy.

Hashimoto's thyroiditis may comprise phases of hyperplasia involving the epithelial tissue and the infiltrated tissue, which may lead to confusion with a condition of malignancy.

In the very rare cases when a tumour does seem to be engendered during the course of true Hashimoto's disease, the growth is almost always a lymphoma. In general, the pathologist experiences no great difficulties in making the diagnosis if the cells have an immature appearance and if he finds that the surrounding tissues are invaded. But in many cases it is impossible to distinguish between lymphocytic thyroiditis and tumour. The terms of pseudolymphoma, lymphoma-like tissue, or non-invasive malignant lymphoma[43] have been used to designate these conditions in which the apparently tumorous process does not seem to be spreading. In five cases reported by Woolner *et al.*[42] the authors underlined three points which pleaded in favour of a diagnosis of thyroiditis rather than of lymphoma:

(1) The mature appearance of the lymphocytic infiltrations.
(2) The preservation of the general structure of the gland.
(3) The considerable degree of activity of the germinative centres.

It is nevertheless true that in other cases the development of a malignant lymphoma from the lymphoid tissue in the thyroid seems an undoubted possibility.

5. Iodine Metabolism and Thyroid Function

The dedifferentiation of the cancerous tissue is accompanied by a loss of the specific metabolic functions of normal thyroid tissue, namely the trapping and organification of iodine and the synthesis of thyroid hormones. This explains the appearance of cold areas on the scintigrams of cancerous thyroid glands.

However, out of all types of thyroid tumour the two most often found associated with thyroiditis are also the ones that do not entirely lose the functional activities characteristic of normal thyroid tissue, i.e. papillary carcinoma and follicular carcinoma.

These two types of tumour are distinguished by marked anomalies of iodine metabolism which give rise to disturbances of intrathyroid metabolism and the release of abnormal iodinated products in the serum.[15,16]

Disturbances of Intrathyroid Iodine Metabolism

Two major abnormalities of intrathyroid iodine metabolism are found in human thyroid cancer: a failure to organify iodine despite active iodide transport[31,41] and the production in considerable quantity of an iodinated protein which is unrelated to the gland's normal product thyroglobulin.[3,28,29,32] This iodoprotein (compound *x*) shows greater solubility than thyroglobulin in phosphate buffer, and after hydrolysis yields mainly monoiodotyrosine and very small amounts of thyroxine.

Ultracentrifugation of soluble proteins shows a slow-sedimenting compound and a decreased 19 S peak. Milcou *et al.*,[21] in their investigation of twelve cases of adenocarcinoma, found considerable disturbances of hormone synthesis in the actual tumorous parts but also signs of disturbed synthesis in the surrounding tissue.

Release of Abnormal Iodine Products

The circulating blood has been found to contain appreciable quantities of thyroglobulin[22,27,30,35] and an abnormal protein.[29] This latter substance resembles a seric albumin in that it has the same electrophoretic mobility, the same sedimentation coefficient, and the same characteristics of solubility in increasing concentrations of a buffer solution. Pochin *et al.*[24] studied 100 cases of histologically differentiated forms of cancer and confirmed the increased rate of iodine turnover and the steady release of highly anomalous iodine compounds in the blood. In more than half of these patients, iodothyronine represented 0–10% of the organic iodine concentration, 50% of which was in non-extractable form.

When hydrolysed, the abnormal iodoprotein yields mainly iodotyrosines, and particularly MIT.[28,37] It does not have the same antigenic properties as thyroglobulin.

These different anomalies of iodine metabolism have been related to the intracellular disturbances detected by electron microscopy.[18] They obviously reflect disturbances of normal thyroid hormone synthesis, but perhaps also of the hydrolysis that normally governs the release and secretion of thyroid hormones.

6. Immunology

According to Anderson *et al.*[1] and Doniach and Roitt,[8] the presence of antibodies is observed in less than half the subjects affected with thyroid cancer, and very intense reactions (resulting in precipitations) are only encountered in 2% of cancer patients. Out of 85 cases studied by Buchanan *et al.*,[40] 45% were found to have one or more circulating thyroid antibodies. All in all, these frequency figures are close to those for

nodular goitre. They would be undoubtedly higher if only follicular or papillary tumours were considered.*

The antibodies generally disappear from the serum fairly quickly when the tumours are destroyed (cf. case reports 7.2 and 7.3).[10]

The appearance of thyroid antibodies during the course of histologically differentiated thyroid tumours is fairly well explained by reference to the findings of experimental thyroiditis studies, namely that thyroiditis can be triggered off by the denaturing of a tissue component or secretory product which was not immunogenic in its original state. Compared to other thyroid diseases, differentiated and functioning cancer is a condition in which it is relatively easy to demonstrate the disturbances of synthesis, the release of abnormal substances, and the disorganization of cell architecture.

The prognosis of papillary carcinoma seems to be good in cases accompanied by thyroiditis in the peri-neoplastic thyroid tissue,[19] and, perhaps better still, according to Anderson *et al.*,[1] when the tumour itself is the seat of inflammatory reactions. The same idea is suggested by the discovery of similar immune reactions in other cancer cases whose prognosis proves favourable.[34]

7. Diagnosis

It is difficult to assess the risk of a malignant tumour developing in a true Hashimoto's thyroiditis. Although this possibility seems exceptional at the classic age for Hashimoto's goitre, the rapid development of a large goitre in women over 60 years of age should point to a diagnosis of neoplasia, and maybe malignant lymphoma, particularly in the presence of pressure signs, and even more so if enlarged lymph nodes are detected. But, generally speaking, this condition is rare.

By contrast, the development of autoimmune lymphocytic thyroiditis in a case of primary thyroid tumour (papillary carcinoma or solid tumour composed of Hürthle cells) is quite a common finding, and may, indeed, give rise to a mistaken diagnosis of primary thyroiditis.[33] Thyroid antibody titres are generally low. The best way of distinguishing between this condition and Hashimoto's thyroiditis seems to be by the screening for complement fixing antibodies. According to Doniach and Roitt,[8] these investigations yield positive results in 85% of the cases of diffuse goitrous thyroiditis and in 2·5% of other types of thyroiditis. But Anderson *et al.*[1] report microsomal antibodies in 17·7% of the sixty-two cancer cases which they investigated.

Thus high antibody titres do not exclude a diagnosis of malignancy. Any case that is not proved should be submitted to open biopsy.

8. Treatment

The development of a tumour in a genuine case of Hashimoto's goitre is extremely rare. The latter disease should not be considered as a pre-cancerous condition.[6,9] Consequently, if Hashimoto's thyroiditis is definitely diagnosed, the treatment will be as indicated in Chapter 5.

* Furthermore, LATS has been reported in some patients with thyroid cancer.[39]

In the event of a primary tumour being accompanied by autoimmune thyroiditis, surgery is the obvious choice of treatment whatever the kind of cancer. Subsequent treatment (radiotherapy, administration of radioactive iodine) will depend on the type of cancer detected and on how far it has developed. The administration of thyroid hormones is a useful treatment for thyroiditis and for the prevention of further tumorous growth.

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CHAPTER 8

Lymphocytic Thyroiditis and Thyrotoxicosis

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1. Introduction

Thyrotoxicosis is a syndrome limited to the human race in which the body is inundated with an excess of thyroid hormone. The cause of hyperthyroidism is unknown.[22] From the clinical and pathological point of view, three different conditions may be distinguished.[159,320] The first entity, commonly known as Graves' disease,[129] concerns about three-quarters of the thyrotoxic cases, affects subjects of both sexes before the age of 50, and is classically accompanied by the virtually simultaneous appearance of a diffuse goitre, a characteristic ophthalmopathy,[314,321] and a clinical picture of hyperthyroidism. The essential thyroid lesion is a parenchymatous diffuse hyperplasia with loss of colloid. The second condition occurs almost exclusively in women over 50; it is not accompanied by ocular signs; the goitre, usually of long standing, is nodular with hyperactive areas, whilst the rest of the parenchyma shows no signs of hyperplasia nor of hyperactivity. This condition is known as Plummer's disease[258] or toxic multinodular goitre. Since thyroid scans have been used, a third form of thyrotoxicosis has been identified, occurring in younger subjects (30–40 years of age) and characterized by the gradual development of a single hyperactive and autonomous adenoma of the thyroid gland. This disorder is sometimes referred to as a hyperfunctioning solitary nodule or toxic adenoma. In all three forms the excessive production of thyroid hormones escapes physiological regulation by the hypothalamus and the pituitary gland.

It has long been known that in Graves' disease the thyroid gland may contain patches of lymphocytic infiltration[62,108] alongside the parenchymatous changes. The autoimmune character of this thyroiditis is indicated by the passage of thyroid antibodies into the blood. Such processes correspond to a certain degree of destruction of the parenchyma, and a number of observations suggest that they can explain the spontaneous cure of certain toxic goitres[15] or even their evolution towards a state of hypothyroidism.[109]

It has nevertheless been suggested that Graves' disease is in itself an autoimmune disease (cf. p. 192) and some authors[100,267] consider that Hashimoto's thyroiditis and Graves' disease probably constitute two facets of a single immune disorder. These ideas have arisen chiefly as a result of the discovery of an IgG globulin called long-acting thyroid stimulator (LATS) in the serum of many patients suffering from thyrotoxicosis.

This globulin is endowed with both the character of an antibody and the capacity to stimulate the thyroid parenchyma.

In this chapter two problems will be considered: first, the development and significance of thyroiditis which is often present in toxic goitre; and secondly, whether autoimmune thyroiditis might play a role in triggering off and maintaining thyrotoxicosis.

2. Illustrative Case Reports

CASE REPORT 8.1: Isot. 1091. *Classic Graves' disease with temporary presence of thyroglobulin antibodies and LATS, regressing at the same rate as the signs of thyrotoxicosis and exophthalmos after treatment with antithyroid drugs.*

In December 1964 an 18-year-old girl showed progressively severe exophthalmos and then a goitre with signs of severe thyrotoxicosis (radioiodine uptake, 78% at 6 hr, 51% at 24 hr; $PB^{131}I$, 2·45% of the dose per litre at 24 hr). Thyroglobulin antibodies were positive at a titre of 1/78125. LATS response was positive: R (20 hr/2 hr) = 468/195.

Treatment with Neomercazol ® from December 1964 to September 1966 brought the patient back to a state of euthyroidism but with residual marked exophthalmos. The LATS response remained positive (R = 349/192), although thyroglobulin antibodies fell to the titre of 1/25. A few weeks of treatment with 12·5 mg of Prednisone per day reduced the exophthalmos and induced the disappearance of the LATS (R = 147/141). From 1967 onwards the patient took no drugs and remained in a euthyroid state. Testing for antibodies and LATS remained negative.

CASE REPORT 8.2: SP 70,830. *Thyrotoxic crisis in an addisonian patient. Detection of thyroglobulin, cytoplasmic, gastric, and adrenal antibodies and LATS in the serum of the patient and some of her children.*

A 46-year-old woman was admitted to the department on 6 December 1967 for asthenia and loss of weight. Her past history was unexceptional apart from the existence of a goitre since the age of 14. During the past 3 years her skin had become increasingly pigmented. In recent months she had complained of nervous tension and anorexia; her fatigue had become extreme; loss weight had attained 8 kg. In the last few weeks the goitre had increased in size.

On examination the patient was found to be thin, apyrexial, very asthenic, and vomiting frequently. Her skin was slightly moist and tanned, with more marked pigmentation in the creases of the hands. The gingival mucous membranes carried clay-coloured patches. There was a multinodular goitre of about 50 g. Blood pressure was 120/70 mm Hg in the supine position and 100/60 mm Hg when standing. Pulse rate was 120 per min. This clinical picture suggested the diagnosis of Addison's disease. Laboratory tests revealed urinary 17-hydroxysteroids at 7·8 mg per 24 hr, 17-ketosteroids down to 3·9 mg per 24 hr, strongly positive adrenal antibodies.

In view of the danger of acute addisonian crisis, it was decided to treat the patient without waiting for investigations and without first performing an ACTH stimulation test. From 9 December 1967 she received intravenous perfusions of glucose and saline

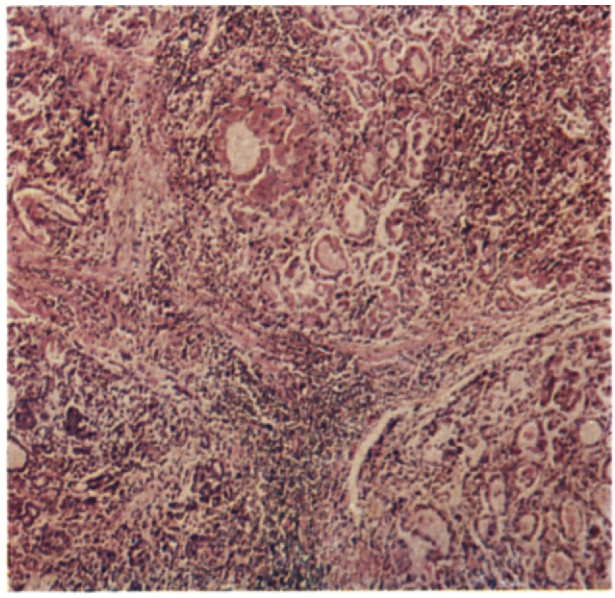

FIG. 8.1. Case report 8.4. Chronic thyroiditis with marked sclerosis and extensive destruction of thyroid tissue. (× 135).

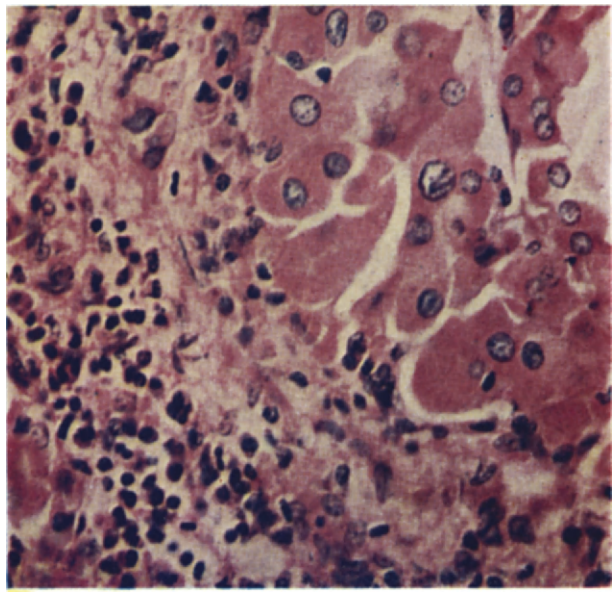

FIG. 8.2. Case report 8.4. Oncocytes surrounded by inflammatory tissue. (× 700).

solutions, 100 mg of cortisone acetate per day, and 25 mg of desoxycorticosterone twice a week. Although with this treatment blood pressure rose again to 140/90 mm Hg, the patient remained lethargic, had a tachycardia of 130 per min, and continued to vomit. After 3 days she had a fever of 38·5C; the face and upper thorax had become red and shining; the eyes were bright and the skin moist. These features led to the diagnosis of thyrotoxic crisis on pre-existent but undiagnosed hyperthyroidism. The patient was treated with intravenous iodine (2 mg/d), intramuscular reserpine (4 mg/d), methyl-mercapto-imidazole (40 mg/d), and antithermic drugs.

From then on the improvement was spectacular: the fever subsided, the pulse slackened, the redness disappeared from the face and upper trunk, vomiting ceased. The results of the thyroid tests confirmed the diagnosis of hyperthyroidism: cholesterol was at 80 mg per 100 ml; $PB^{127}I > 20$ μg per 100 ml; $BE^{127}I > 20$ μg per 100 ml; triiodothyronine resin uptake test at 148% of the normal value; thyroid uptake of ^{131}I, 70% at 6 hr, 73% at 24 hr; LATS response was positive. Two ACTH stimulation tests were performed 2 and 20 weeks after the acute crisis: the absence of any significant rise in urinary steroids confirmed Addison's disease. In April 1968, because of persistent signs of hyperthyroidism, the patient received a therapeutic dose of 8 mc of ^{131}I. Since then she has been euthyroid.

CASE REPORT 8.3: E 3210. *Hyperthyroidism in long-standing nodular goitre. Absence of thyroiditis. Presence of LATS which declines then disappears 2 years after total thyroidectomy.*

A 50-year-old woman, affected with goitre for many years, developed exophthalmos and signs of thyrotoxicosis in 1966. After treatment with antithyroid drugs, the exophthalmos increased. Surgical resection of the thyroid showed a nodular goitre with a region of hyperactivity but no thyroiditis lesions. After administration of several doses of ^{131}I to destroy all the thyroid residues, the patient still showed moderate exophthalmos. The LATS response, still strongly positive in 1966, had disappeared by 1968 (Table 8.1).

CASE REPORT 8.4: SP 67,875. *Former case of thyrotoxicosis treated with radioiodine. Diffuse lymphocytic thyroiditis with antibodies. Hypothyroidism. Presence of LATS.*

A 78-year-old woman treated for thyrotoxicosis with radioactive iodine 3 years previously was admitted in 1966 for cardiac insufficiency and hepatic cirrhosis with ascites. The laboratory tests showed the following results: Hanger, ++; thymol, 7·5 U; serum cholesterol, 136 mg per 100 ml; erythrocytes, 3,000,000 per mm^3; Hb, 9 g per 100 ml; PTT, 31%; total serum proteins, 6·2 g per 100 ml; gammaglobulins, 51·6% = 3·2 gm per 100 ml; TGA, + at 1/78125; $PB^{127}I$, 2·2 μg per 100 ml; LATS + ($R = 258/164$). After a few days the patient died of gastric (or gastrointestinal) haemorrhage. Histology showed post-hepatic cirrhosis, lesions of atherosclerosis, and a thyroid of 15 g with diffuse chronic thyroiditis (Figs. 8.1 and 8.2).

3. Clinical Features

More than two-thirds of thyrotoxic cases are affected with autoimmune thyroiditis.[100,266] The thyroiditis sometimes appears well after the onset of hyperthyroidism[165],

TABLE 8.1. EVOLUTION OF SERUM TGA, CFA, AND LATS IN A CASE OF THYROTOXICOSIS WITH SEVERE EXOPHTHALMOS (case report 8.3)

	Exophthalmos	$PB^{127}I$ (μg per 100 ml)	TGA	CFA	LATS	
					Total serum	LATS-IgG
1966	+++	4	neg.	neg.	+ (R = 252/131)	
1967	++	1,3	neg.	neg.	neg. (R = 114/103)	+ (R = 227/112)
1968	++	[a]	neg.	neg.	neg. (R = 175/120)	neg. (R = 160/128)

[a]Treatment with T3 since 1967.

TABLE 8.2. ASSOCIATED DISEASES IN UNTREATED THYROTOXICOSIS WITH AND WITHOUT THYROGLOBULIN ANTIBODIES

Associated diseases	Patients with TGA		Patients without TGA	
	No. of patients	No. of diseases	No. of patients	No. of diseases
Other autoimmune disorders	23	0	17	0
Familial thyroid history	23	8	17	2
Exophthalmos	24	13	18	6
Goitre	24	23	18	12
Pretibial myxoedema	24	2	18	0

(Brussels material. The frequency of inflammatory phenomena increases with the duration of the thyrotoxicosis as the following observations show: (1) the presence of thyroid antibodies in 28% of the recent cases of hyperthyroidism and in a higher number of longstanding cases under treatment;[20,30] (2) the existence of lymphoid infiltrations in 72% of thyroid glands removed after prolonged iodine treatment, before the introduction of modern treatments.[28,297] The frequent association of thyroiditis and exophthalmos[30,135,266] (Table 8.2) has been reported specially in young subjects.[56]

The presence of thyroiditis does not generally alter the clinical picture of hyperthyroidism, either in Graves' disease (cf. Table 8.2) or in toxic multinodular goitre, and does not prevent the development of a thyrotoxic crisis[110] (case report 8.2). Out of six cases of hyperthyroid crisis tested for antibodies in Brussels, thyroid antibodies were found five times at high titres of up to 1/78125. In these five cases, the process of thyroiditis apparently had left intact an appreciable quantity of hyperactive tissue. Andreani *et al.*[20] reported high titres more frequently in toxic multinodular goitre than in Graves' disease. For Doniach and Roitt,[100] high titres are encountered in severely affected patients in whom the disease is liable to recur. In other cases, extensive tissue destruction has been invoked to explain the spontaneous remission of the hyperthyroid-

ism[15] or even its evolution into hypothyroidism[109] (case report 8.4), and also to explain the euthyroid state of subjects with all the ocular signs of Graves' disease.[12,192] Certain authors[221] have endeavoured to explain the normal thyroid state of these subject by the binding of thyroid hormone with TGA.[259] However, measurements of $PB^{127}I$ and ^{131}I uptake before and after a TSH test in some of these subjects show that there exists a normal thyroid reserve despite the presence of thyroiditis.[138,139] The destruction of the thyroid parenchyma has also been cited as an explanation of hypothyroid states not preceded by thyrotoxicosis and accompanied by either exophthalmos[121] or pretibial myxoedema and the presence of LATS.[228]

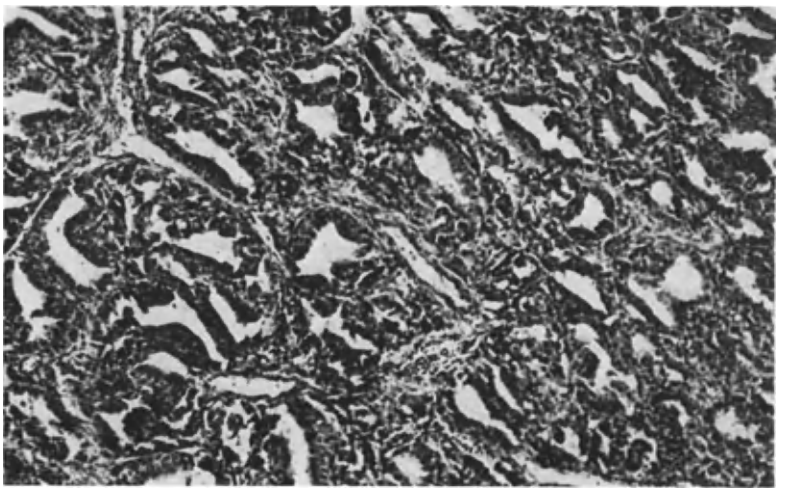

FIG. 8.3. Hyperplasia of thyroid tissue, characteristic of thyrotoxicosis, folding of follicles, almost completely devoid of colloid. Antithyroid drugs increase these characteristics. (×150.)

4. Pathology

The Thyroid

The changes occurring in the thyroid gland of hyperthyroidism are not, properly speaking, lesions, but morphological manifestations of intense hyperactivity, both in the function of thyroid hormone synthesis and secretion. Similar images are obtained experimentally by intense stimulation of the gland, for instance by the thyrotropic hormone. These changes are most marked in thyrotoxic goitre of Graves' disease due to diffuse hyperplasia of a hitherto normal gland (Fig. 8.3).

In such cases the parenchyma is very dense and the colloid pale staining and rarefied; the vesicles are pleated and evenly bordered by a high cylindrical epithelium. The latter shows nuclei in a basal position, developed mitochondria, and a very hypertrophied Golgi apparatus. Some early authors,[269] and also more recent ones,[142] describe as an integral part of this picture the appearance of centres of lymphoid infiltrations around

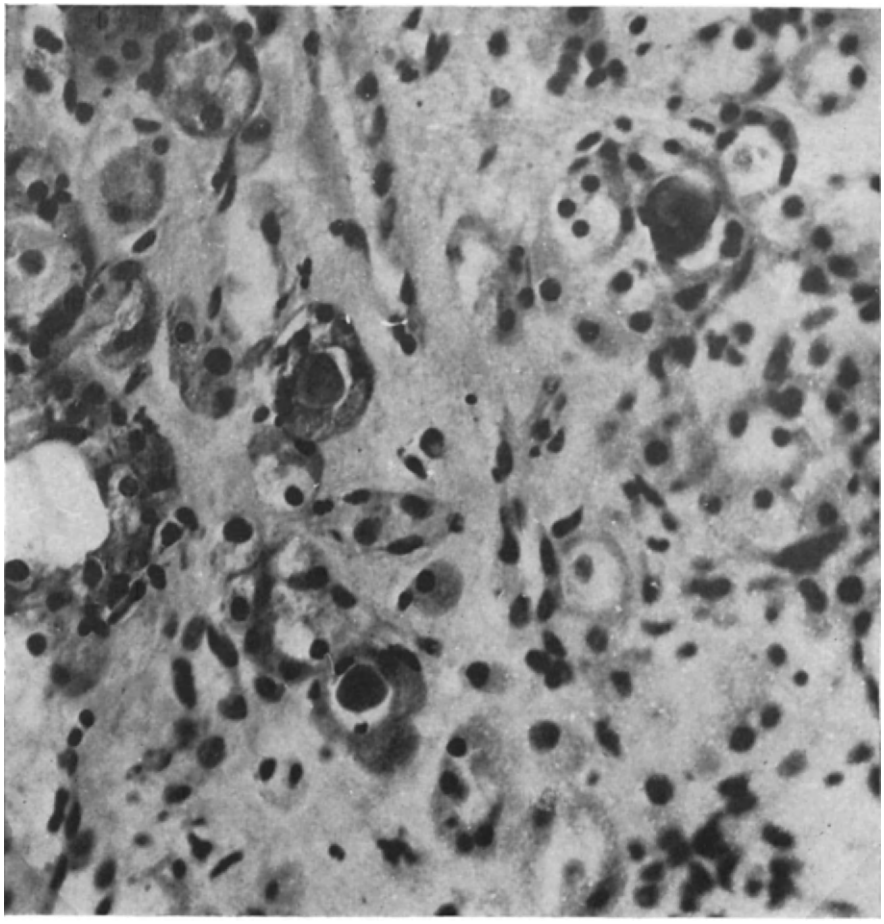

FIG. 8.4. Isolated Askanazy cells or oncocytes in an untreated thyrotoxic goitre. Note the very scant inflammatory reaction.

cells in oncotic metaplasia (Fig. 8.4). In fact, these alterations constitute an additional disease in glands that have been hyperactive for some time. They are not generally observed in cases of recent hyperactivity.

Under the influence of pre-operative iodine treatment, an extraordinary distension of the vesicles is seen. The diffuse parenchymatous goitre changes in a few days into a diffuse colloid goitre with very large vesicles filled with deeply staining colloid and bordered by a flat epithelium (Fig. 8.5). Pre-operative administration of antithyroid drugs accentuates, by contrast, the histophysiological signs of cell hyperactivity (Fig. 8.3) which give way to colloid involution after iodine therapy to complete the antithyroid treatment.[264] Thyrotoxic glands that have been evolving for some time often contain areas with small vesicles in which iodine therapy fails to induce normal colloid involution.

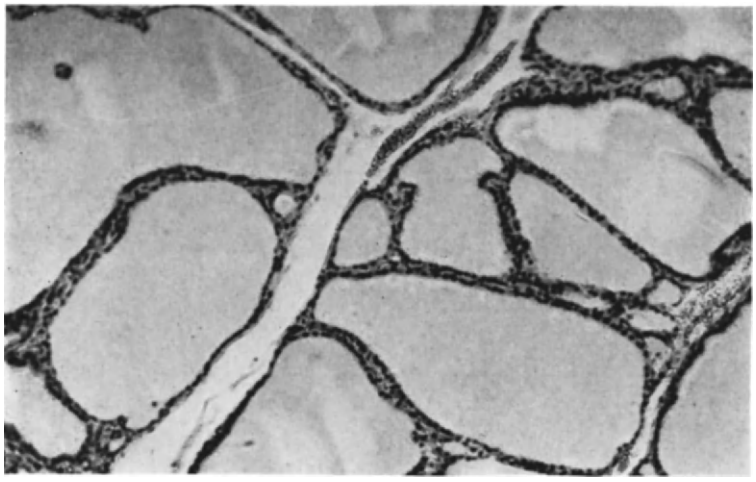

FIG. 8.5. Colloid involution of thyroid hyperplasia after iodine treatment. (×150.)

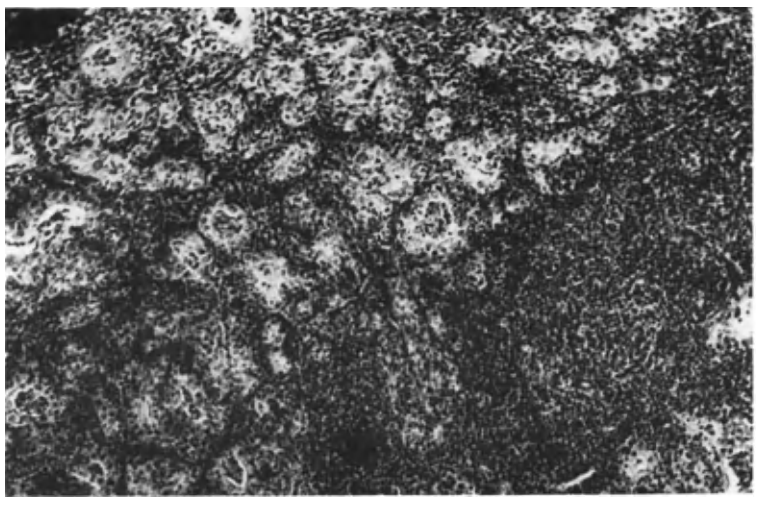

FIG. 8.6. Area of "degenerative involution" with lymphocytic infiltration around small follicles devoid of colloid. (×150.)

Patches of thyroiditis develop in these parts of the gland (Fig. 8.6) and contain parenchymatous elements affected with oncocytic degeneration.

In the absence of treatment, the process of thyroiditis may spread and give rise to the development of diffuse lesions with the formation of germinal centres. Under high-power these lesions resemble the features of Hashimoto's thyroiditis. However, alongside these "zones of degenerative involution" there usually persist some zones of hyperplasia

characteristic of thyrotoxicosis. Different authors[19,63,274] have demonstrated a close relationship between these thyroiditis lesions and the presence of thyroid antibodies in the serum. Examinations of ten cases in Brussels have confirmed this relationship.

By immunofluorescence it has been possible to demonstrate the fixation of IgG in the thyroid tissue and to detect thyroglobulin inside the inflammatory cells.[326] The claims of Stuart and Allan[299] that immune reactions entail alterations of the basement membrane remain unconfirmed.

The idea that in thyrotoxic goitre the hyperactive tissue may undergo progressive destruction, and functional regression is based more on histological comparisons than on direct evidence. First, in atrophic thyroiditis, the whole range of lesions may be encountered, from the normal parenchyma to total destruction (cf. Chapter 10). Furthermore, in Hashimoto's thyroiditis the hyperplastic parenchyma may evolve to oncocytic metaplasia with the development of hypothyroidism (cf. Chapter 5). Finally, in toxic goitres, recent stages of hyperplasia are unaccompanied by lymphocytic infiltrations; lesions of thyroiditis with oncocytes are observed in conditions dating back some time,[28,132,190,276] and lesions of advanced thyroiditis with extensive sclerosis are found in the thyroid gland of certain subjects treated with radioactive iodine (Figs. 8.1 and 8.2). It is probable that the fundamental process consists in a particular type of degeneration in the small vesicles.[28,121a,287] But it is erroneous to try, as some authors have done,[190] to establish a continuous evolutive sequence from hyperplasia to sclerosis, passing through the stage of Hashimoto's goitre. Spjut *et al.*[297] have published the best documented study in this respect. They were unable to establish any transition from hyperplasia to authentic lymphomatous goitre from their study of fifty-seven well-documented cases of thyrotoxicosis in which two or more operations were performed at intervals of between 3 months and 25 years. The authors consider, like Hellwig,[144a] that the accumulation of lymphoid tissue constitutes a secondary phenomenon to the abnormal functioning of the thyroid epithelium. In only one case had the gland acquired the appearance of a lymphomatous goitre by the second operation. These observations agree with those of authors who, from studies of a long series of Hashimoto patients, conclude that this condition is not preceded by thyrotoxicosis.[168]

A detailed description of the ultrastructure of follicular cells in thyrotoxicosis has been given by Heimann[143,144] and Lupulescu and Petrovici.[196] Most cells have a columnar appearance and carry numerous microvilli. The cytoplasm contains many mitochondria, a well-developed endoplasmic reticulum with large cisternae, and dense bodies. The apical surface is often irregular, dome-shaped, and bulging into the follicular lumen. In many thyrotoxic cells a large number of vesicles of varying density and size are found in the apical part of the cells, and broad-based projections into the colloid can be seen. These observations have been interpreted as morphological signs of hormone release, whereas the richer development of the endoplasmic reticulum and the increased size of the Golgi apparatus is considered as indicative of increased protein (especially thyroglobulin) synthesis. Some cells are particularly rich in mitochondria. In accordance with observations made in Hashimoto's thyroiditis,[162,241] they are interpreted as oncocytes. The significance of these oxyphil elements has been discussed in Chapter 5. Their ultrastructure

seems to indicate the existence of a major disequilibrium between the energy-giving respiratory function and protein synthesis.

Like some earlier authors,[28,140,327] Heimann[144] suggests that in the thyrotoxic gland certain cells are very active and others are undergoing necrosis and being broken down by lysosomes. The cellular infiltrate has been interpreted as a reaction to the breakdown products. Lymphocytes, plasma cells, and macrophages occur in and around the thyroid follicles.[144,196] Some authors interpret these findings as having a bearing on the aetiology of thyrotoxicosis.[144] However, as the infiltrates are observed in only a certain percentage of the material, and more rarely in cases of recent onset, it seems more likely that the infiltrates are secondary to the increased cell turnover and cell destruction.

The Pituitary

In contrast with the swollen and degranulated appearance of the thyrotropic cells encountered in myxoedema, the pituitary of the hyperthyroid patient is characterized by a reduction in number and an involution of thyrotropic cells and an increase of classic acidophil cells.[146,240,263,309] These observations fit in with the recent findings of very low TSH levels in the serum.[48,186,188,246] However, cases of thyrotoxicosis have been noted in subjects with pituitary tumours. This is true of several cases of acromegaly[84,185] and in other apparently chromophobe tumours.[194,242a,322] Herlant was able to demonstrate in a remarkable case[194] that a tumour formed of thyrotropic cells and secreting TSH was the cause of thyrotoxicosis.

The Thymus and Lymphoid Tissue

In autopsy material, significant hypertrophy of the thymus and an increase in size of the lymph nodes and spleen are often observed.[226a] Recently, Gunn *et al.*,[133] Irvine and Sumerling,[163] and Michie *et al.*[229] reported the development of large lymphoid follicles in the thymus of several patients operated for Graves' disease (Table 8.3). Similar lesions have only been observed in Hashimoto's goitre and severe myasthenia. According to Michie *et al.*,[229] the cases of thyroiditis with true thymic hyperplasia all had a previous history of thyrotoxicosis. These modifications in the lymphoid system are

TABLE 8.3. LYMPHOID FOLLICLES IN THE THYMUS
(After Gunn *et al.*, 1964[133])

Thyroid disease	No. of cases	Lymphoid follicles	
		Absent	Present
Thyrotoxicosis	49	33	16
Non-toxic goitre	44	43	1
Hashimoto's thyroiditis	2	1	1

considered by several authors as of great interest in relation to the possible immune aetiology of thyrotoxicosis.

Exophthalmos

The macroscopical lesions have been described in detail in several studies.[29,205,270] They are characterized essentially by an increase in the orbital content due to the swelling of the extra-ocular muscles, to oedema, and to an increase in fatty tissue. From the histological point of view, the oedema and lymphoid cells infiltrate the muscles and connective tissue. Certain muscle fibres lose their striation and merge into hyaline masses. The oedema is due to an accumulation of mucopolysaccharides. At this stage the lesions are still reversible. If the disease continues, sclerosis renders the lesions irreversible.

Pretibial Myxoedema

Optic microscopy studies have all shown in pretibial skin the intradermic accumulation of acid mucopolysaccharides (including hyaluronic acid) taking Alcian blue.[59] Electron microscopy has revealed in two cases[59] the presence of numerous microfibrils of 50–70 Å in diameter, in the close vicinity of collagen fibres. These microfibrils could represent the younger collagen fibres. Furthermore, the fibroblasts have a developed endoplasmic reticulum containing a finely granulous substance suggesting that a state of cell hyperactivity probably intervenes in the elaboration of pre-fibrillar material. In the endothelium of the capillaries there are numerous vesicles of micropinocytosis which would support the hypothesis that the vessels play a role in the constitution of mucopolysaccharide deposits. No morphological argument permits to envisage the intervention of the mastocytes in this process.

5. Laboratory Findings

Anaemia, leucopaenia, and relative lymphocytosis are reported in thyrotoxicosis.[85] Serum albumin is often low and gammaglobulins raised.[20,183] It is possible that some of these changes are related to the presence of lymphocytic thyroiditis. The occasional rise in the erythrocyte sedimentation rate is probably also explained by these changes.

Other changes classically described in thyrotoxicosis such as those of the calcium, potassium, and cholesterol levels, result from the catabolic action of thyroxine. The NEFA may be increased, probably through the effect of thyroxine and catecholamines. All these changes are probably unrelated to the presence or absence of thyroiditis.

Thyrotropic Hormone

Whatever the clinical form of thyrotoxicosis—Graves' disease, toxic adenoma, or toxic multinodular goitre,[8,13,48,82,186,188,201,246] with or without exophthalmos,[48,186] TSH level is below normal or undetectable in the majority of cases (Table 8.4). High values

TABLE 8.4. SERUM TSH LEVELS (mU per 100 ml) IN NORMAL SUBJECTS AND IN THYROTOXICOSIS

(After McKenzie,[209] Lemarchand-Béraud *et al.*,[186, 188] Odell *et al.*,[246] and Bonnyns[48])

	McKenzie bioassay (I. B-TSH)	Radioimmunoassay (Stand. H-TSH)
Euthyroidism	10–30	< 0·15–2[a]
Hyperthyroidism	< 10–20	< 0·45[a]

[a]In both groups the TSH level is frequently undetectable.

reported by a bioassay method[170,209] could correspond to the presence of a thyrotropic factor other than TSH. The cure of hyperthyroidism brings TSH back to normal.[8,176,186] There have been reports of two or three cases of pituitary tumour which could be responsible for hyperthyroidism with hypersecretion of TSH;[185,194,273] it seems that in these particular cases, the remission of the hyperthyroidism was obtained at the same time as a return to normal secretion of the thyrotropic hormone after destruction of the pituitary tumour. Studies of the half-life of TSH in hyperthyroid subjects have shown that its peripheral metabolism is more rapid than usual.[23]

It has been reported that the anterior pituitary content of TSH is qualitatively normal and quantitatively reduced[50a,180,181,201,211] although a high TSH concentration was found in one case.[24] However, according to Kumahara *et al.*[181] pituitary thyrotropic activity in thyrotoxicosis is immunologically different from that of normal TSH.

6. Immunology

A. Conventional Thyroid Antibodies

Thyroglobulin antibodies (TGA)

TGA are detected in one-third to two-thirds of thyrotoxic cases,[19,30,62,161,266,288,310,311] whether the clinical form is Graves' disease, toxic multinodular goitre,[20,77,169] or single toxic adenoma[77,86] (Table 8.5) and also in Ophthalmic Graves' disease.[137,138,139] In the latter cases there is no relation between the presence of the TGA and the positive or negative results of Werner's test;[312] nevertheless, certain of these subjects later develop hyperthyroidism.[138] The average titre of TGA is higher in untreated than in treated Graves' disease, especially in patients who have been hyperthyroid for over a year.[19] Higher titres are associated with large goitres and with higher levels of $PB^{127}I$ but not with the presence of exophthalmos or high basal metabolic rate.[19] In childhood thyrotoxicosis, the incidence of TGA seems higher than in adults.[157,272] Hjort[150] has studied the relative antigen neutralizing capacity ("avidity") of TGA in Hashimoto's goitre and in Graves' disease by a haemagglutination-inhibition test with antibody-coated cells. Sera from thyrotoxic patients yielded relatively weaker inhibition reactions

TABLE 8.5. FREQUENCY OF THYROGLOBULIN AND MICROSOMAL ANTIBODIES IN UNTREATED THYROTOXICOSIS AND TOXIC ADENOMA

	Thyrotoxicosis			Toxic adenoma		
	No.	+	%	No.	+	%
TGA	42	18	43	10	3	30
CFA	10	7	70	10	0	0

and were of a significantly lower avidity than sera from patients with Hashimoto's disease. This difference in avidity for the same antibody could be explained either by "a low affinity" or by "a narrow specificity of the antibodies, covering only a few of several possible antigenic determinants".[150]

The intensity of serological phenomena is generally moderate, although precipitation reactions, indicating extensive thyroiditis lesions, are observed in almost 5% of the cases in all three forms of hyperthyroidism.[20,100,128,265] During the evolution of thyrotoxicosis, serial measurements of the antibody titre over a period of 2 years showed constant stability compared to cases of Hashimoto's disease in which the antibody titre increased steadily.[20]

Thyroidectomy may entail the temporary appearance of low titres of antibodies.[18] Einhorn *et al.*[111] report a drop in the frequency of thyroglobulin antibodies one year after surgical treatment. The administration of anti-thyroid drugs[179,257] or radioiodine[111] have no major effect on serological reactions. However, Blagg[46] observed an increased frequency of TGA after therapy by radioiodine.

Microsomal antibodies (CFA)

The frequency of microsomal antibodies is similar in the three forms of hyperthyroidism,[77] ranging between 48%[63] and 65%.[52,99] However, in a series of sixty-seven cases of toxic adenoma, Decourt *et al.*[86] obtained only one positive complement fixation response. In Ophthalmic Graves' disease, Hall *et al.*[138] report 4 positive reactions out of 26 performed tests. An important study by Buchanan *et al.*[63] reveals that the frequency of the CFA is independent of sex, the duration of the hyperthyroidism, and the ocular signs of the disease; it is directly proportional to the volume of the goitre, and increases between 30 and 60 years of age as does thyroiditis. The incidence of CFA is higher in the active form of thyrotoxicosis than when the disease is in remission.[52] Antithyroid drugs do not influence the CFA titres.[63] The therapeutic administration of ^{131}I brings a temporary increase of frequency.[63,111,161]

Second colloid antibody (CA_2)

Balfour *et al.*[25] have observed the CA_2 in 41% of their thyrotoxic cases.

Cytotoxic factor

This was found by Irvine[160] in 67% of hyperthyroid cases and by Pulvertaft *et al.*[260] in 64%.

B. Long-acting Thyroid Stimulator (LATS)

In 1956 Adams and Purves[6] observed that the injection of serum from a hyperthyroid subject to guinea-pigs prepared for measurement of thyrotropic hormone[5]

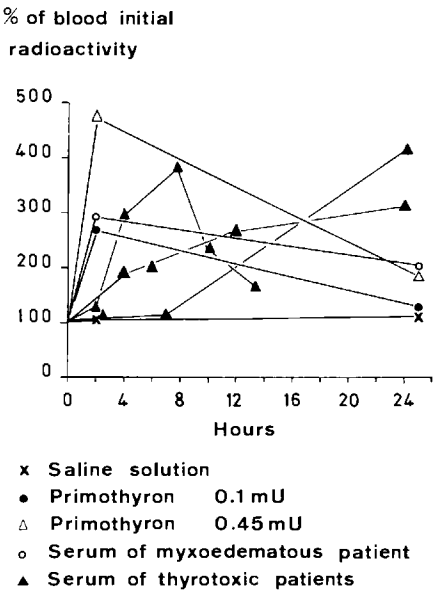

FIG. 8.7. Comparison between the time-response curves obtained with standard TSH (Primothyron ®) at two dose levels, the serum of a myxoedematous patient, and the serum of three thyrotoxic patients.

caused an abnormal response in the animal at a later time and for a longer period than with the usual thyrotropic stimulus (Fig. 8.7). First, qualified as abnormal TSH,[1] the factor responsible for the prolonged thyrotropic activity was later called an abnormal thyroid stimulator,[261] then long-acting thyroid stimulator (LATS).[2]

Biological properties of LATS (*Table* 8.6)

Only in the mammalian species,[189] in animals,[201,207,208,235,252,283] and in man,[21] LATS increases the trapping and secretion of iodine by thyroid glands whose histological appearances are comparable to that of a hyperthyroid gland[208,280,302] without lymphoid infiltrates[281] or parenchymatous alterations.[245] *In vitro*, the stimulating action

TABLE 8.6. CHEMICAL, BIOLOGICAL, AND IMMUNOLOGICAL CHARACTERISTICS OF TSH AND LATS

Characteristics	TSH	LATS
Molecular weight	± 28·000	± 150·000
Structure	Glycoprotein	7 S gammaglobulin
In vivo thyrotropic action	Early	Delayed
Mediator of biologic activity	Cyclic AMP	Cyclic AMP
Half-life in man	54 min	6 days
Action of antithyrotropic antiserum	Inhibition	No inhibition
Action of antigammaglobulin antiserum	No inhibition	Inhibition
Origin	Hypophysis	Lymphocyte
Nature	Hormone	Antibody (?)

of LATS on the intermediary metabolism of the thyroid, is hardly any different, qualitatively, from the action of TSH.[72,219,238,245,252,277,284,285] LATS does not act through the pituitary.[10,235] Its action, like that of TSH, seems to be initiated in the cell membrane;[73,218,219,247] through the intermediary of a chemical mediator, cyclic AMP (c 3',5'-adenosine monophosphate), LATS would appear to inhibit a hypothetical repressor of thyroid function.[115,123,216,221] The prolonged action of LATS, due to its longer half-life compared to TSH,[300] seems to be related to its molecular structure.[70,238] According to Emrich *et al.*,[116] LATS increases the proportion of radioactive T3 in relation to labelled T4 in the blood and thyroid tissue of animals; these authors report a similar phenomenon in hyperthyroid subjects with LATS in their serum.

Nature of LATS (*Table* 8.6)

By electrophoresis, precipitation, ultracentrifugation, and chromatography it has been demonstrated that LATS activity of a serum is related to its gammaglobulin fraction (IgG).[7,103,105,174,227,230,256,290] Chemical methods designed to disrupt the various types of binding within protein molecules[33,175,212] and enzymatic processes of globulin fragmentation[14,105,175,213,216,227,238] have been unable to dissociate LATS activity of a serum from the IgG. LATS is therefore an IgG with a molecular weight of 150·000. Human IgG antisera[14,101,104,174] and specific antisera against the kappa and lambda chains of the immunoglobulins[172,243] neutralize LATS activity of a serum without modifying its TSH activity.

Like an antibody, LATS is completely destroyed by temperatures over 70°C.[206] Its half-life in the newborn is 6 days.[300] It is partially inactivated when bound to thyroid subcellular fractions, in particular the microsomal fraction,[32,34,41,42,64,65,106,112,174,252,255,282,330,331] the cell sap, and the soluble fraction,[41,42,45,275,289] which notably contains thyroglobulin. However, the neutralizing activity of this fraction is not related to the thyroglobulin[38] but to a 4 S fraction.[286,289] In certain cases, this neutralization

is prevented by the presence of a globulin called the "LATS protector" in the serum of hyperthyroid subjects[9] although Munro *et al.*[239] failed to find this globulin in their investigations. The binding between the LATS and thyroid extracts is partially reversible in an acid medium, which argues in favour of its immunological character.[32,42] However, in the absence of reactions of passive cutaneous anaphylaxis,[64,243] passive haemagglutination[64,243] and complement fixation[64,171] between LATS and thyroid extracts, Burke[64] considered that LATS was not an antibody.

Experimentally, a thyrotropic-like factor has been produced with a varying degree of success after injection of thyroid extracts into animals.[35,37,68,94,218,219,220,223,225,253,293,294] But the exact nature of this thyrotropic factor has not yet been established: (1) in the monkey it possesses the characteristics of TSH;[37] (2) in the rabbit it behaves biologically as if it were midway between the TSH and LATS in that it produces a thyrotropic response later than that of TSH but earlier than that of LATS;[293] immunologically it is neutralized by microsomes and by an IgG antiserum, but also partly by a TSH antiserum.[293] These data support the hypothesis advanced in 1964 by Kriss *et al.*[174] that LATS is an antibody. It is now known that in the IgG molecule of LATS the portion responsible for the prolonged thyrotropic activity corresponds to the Fab fragment of an antibody,[70,104,175,227,291] and that thyrotropic activity of shorter duration is found in the heavy chain of the IgG.[227,291] LATS would be the first example of an antibody stimulating an endocrine gland, although there are other antibodies with stimulatory properties—antilymphocytic serum, which stimulates small lymphocyte,[166,279] and anti-sea-urchin serum, which stimulates the differentiation of this animal.[98]

Origin of LATS

LATS is definitely not produced in the pituitary: it has not been extracted from the pituitary.[211] Furthermore, it is known that thyrotoxicosis may appear in patients submitted to a prior total surgical hypophysectomy[40,67,81,117,122,131,134,156,204,211] which has been anatomically proven in some cases.[40] In all these cases the incidence of LATS is the same as in classic Graves' disease (literature in ref. 49). Although no LATS has been extracted from the thyroid gland,[224] the ferritine-labelled LATS-IgG has been located in the vicinity of the basement membrane and in the cytoplasm of the thyroid follicular cells.[113] McKenzie and Gordon[224] and Miayi *et al.*[231] cultured white blood cells from patients with Graves' disease in the presence of phytohaemagglutinin and observed a LATS response from proteins of the medium. However, no LATS response was obtained with an extract of lymphoid tissue removed from a thyrotoxic patient whose serum contained LATS.[251] Pimstone *et al.*[250] are the only investigators to have extracted LATS from pretibial myxoedema. Neither Pinchera *et al.*,[252] Benoit and Greenspan,[43] nor Bricaire *et al.*[59] succeeded in doing so.

Incidence of LATS

A. IN TOTAL SERUM (Table 8.7)

Untreated hyperthyroidism in adults. The frequency of LATS in patients who

TABLE 8.7. INCIDENCE OF LATS IN THYROID DISEASES

Diseases	No. of cases[a]	No. of LATS responses	%
	Results with total serum		
Neonatal thyrotoxicosis	11	11	100
Pretibial myxoedema	69	64	93
Thyrotoxicosis with exophthalmos	290	203	70
Ophthalmopathy of Graves' disease	52	27	52
Untreated Graves' disease	779	338	43
Thyrotoxicosis without exophthalmos	397	168	42
Childhood thyrotoxicosis	11	3	27
Non-thyroid disease	33	8	25
Toxic multinodular goitre	51	10	20
Other thyroid diseases[b]	487	44	9
Normal subjects	342	26	8
Toxic adenoma	78	2	3
	Results with LATS-IgG		
Graves' disease	?	?	80–85
Toxic multinodular goitre	20	0	0
Euthyroid relatives of thyrotoxic patients	43	9	21
Hashimoto's disease	1	1	

[a]From reports of the literature until 1969.
[b]Spontaneous myxoedema, cretinism, Hashimoto's goitre, asymptomatic thyroiditis, simple goitre, thyroid cancer.

have never been treated varies from one author to another, ranging from 17% to 68%.[27,56,156,176,182,242,252] The average incidence is below 50%.[49]

Neonatal hyperthyroidism. In recent years there have been several reports of positive LATS response in mothers and children.[11,114,124,125,126,141,152,153,154,200,214,268,300,301,318] The evolution of the disease follows a characteristic pattern: the LATS response in the child disappears in less than a month and the thyrotoxicosis regresses at the same time.

Thyroid diseases, other diseases, and normal subjects. Lipman *et al.*[195] report a 9% frequency of LATS in thyroid diseases other than hyperthyroidism. According to a review of the literature,[49] LATS responses are observed with a frequency of less than 15% in spontaneous myxoedema, Hashimoto's goitre, asymptomatic thyroiditis,[30] nodular goitre, and cancer of the thyroid.[107,303] In Ophthalmic Graves' disease,[313] LATS incidence is almost the same as in thyrotoxicosis[12,187,192,195,201,210,252] except in the series of Bowden and Rose[57] and in that of Hall *et al.*[139] who offer no explanation for this discrepancy. Lamberg *et al.*[184] obtained a LATS response in cases of toxic multinodular goitre and toxic adenoma although other authors have never observed a LATS response in the latter disease.[12,27,187,217,252,315] In a review of the literature, Bonnyns[49] finds an average LATS incidence of 8% in normal subjects, with extremes of 0%[1,242] and 28%.[201] This may explain the occasional reports of

LATS in miscellaneous diseases: mongolism,[233] acromegaly,[156,201,249,250] and gigantism.[249]

B. LATS-IgG

The use of certain recent IgG extraction methods for isolating the LATS-IgG have allowed an increase in the sensitivity and specificity of the McKenzie technique. Thus some authors report an incidence of LATS in 80–85% of thyrotoxic cases[75,261,262] but never 100%. Carneiro *et al.*[76] and Bonnyns and Vanhaelst[53] have shown that different IgG extraction methods can reveal the LATS-IgG factor in subjects whose total sera give no LATS response. The same procedures also eliminate certain positive responses either because the reactions were falsely positive or because these techniques may eliminate one of the IgG fractions containing the LATS-IgG.[290]

Applying the LATS-IgG extraction technique to the serum of normal subjects showing a positive LATS response, Carneiro *et al.*[75] failed to obtain any reaction. On the other hand, Wall *et al.*[307] report 9 positive responses in 43 euthyroid relatives of thyrotoxic subjects. Another family study of LATS was published recently[83] (cf. Chapter 2). Finally, Jayson *et al.*[167] observed a positive response in monozygotic twins, one of whom had Graves' disease and the other Hashimoto's goitre.

Clinical relations

Some authors consider that there is no relation between LATS and tachycardia[151] or between LATS, the age and sex of the patients, and the volume of the thyroid gland.[201] Others have found direct proportionality between the volume of the thyroid and the intensity of the LATS response[76,151] or its frequency.[156]According to Lipman *et al.*[195] the course of hyperthyroidism is not parallel to that of LATS, whereas for Hoffman and Hetzel[151] the intensity of the LATS response is significantly greater after treatment in patients who will have a recurrence of the disease. For Bonnyns *et al.*[56] 50% of the LATS responses in untreated hyperthyroidism are observed in subjects under 30 years of age.

Certain authors find no clear relation between LATS and the *eye signs of Graves' disease*.[187,201,210,226] Nevertheless, most of the studies of hyperthyroidism and progressive exophthalmos mention a high frequency of LATS.[250,261,314] Furthermore, from a systematic study of the literature,[49] it emerges that the incidence of LATS is higher in cases of thyrotoxicosis with progressive exophthalmos even in subjects who become euthyroid or hypothyroid after treatment. The persistence of LATS after treatment appears to be an unfavourable prognostic sign for the progression of the ophthalmopathy.[195] Generally speaking, high LATS values are found in severe exophthalmos.[93,151,187,201,210,242,249] Nevertheless, a quantitative study of the two phenomena reveals no correlation.[56,252] For Kriss *et al.*,[176] after treatment with radioiodine, the appearance of LATS coincides or closely follows the first signs of exophthalmos.

In *pretibial myxoedema*, with or without simultaneous thyrotoxicosis, the frequency of LATS attains 80–100% of the cases.[56,59,76,174,177,195,250,252] It is also in these cases that the highest LATS responses are reported. For Pinchera *et al.*[252] there is a

quantitative relation between the LATS response and the extent of the lesions of pretibial myxoedema. The disappearance of LATS under the effect of treatment is not directly linked to the improvement of the lesions.[43]

To sum up, as Lipman *et al.*[195] state, LATS is more closely related to the number of principal manifestations of Graves' disease (hyperthyroidism, exophthalmos, pretibial myxoedema) than with any of these manifestations taken individually.

Relation to thyroid function tests

Major and Munro[201] and Carneiro *et al.*[76] have found a relation between the LATS response and ^{131}I turnover expressed by the difference between the level of ^{131}I uptake at the 4 and 48 hr[201] and by the $PB^{131}I$ level at 48 hr.[76] The last result was only found in positive LATS subjects. For other authors, there is no relation between LATS and the parameters of thyroid function assessed by basal metabolic rate,[252] cholesterol,[56] $PB^{127}I$[56,252] (Fig. 8.8), ^{131}I uptake[56,120,151,252] (Fig. 8.9), and $PB^{131}I$ at the 24 hr[56] (Fig. 8.10).

Immunological relations

Some authors consider that there is no qualitative relation[120,201] or a quantitative one[36,90,91,151] between LATS and thyroglobulin (TGA) or microsomal (CFA) antibodies[36,90,91,254,311] even after treatment with ^{131}I.[66,176] However, other authors found a significant association between LATS, TGA,[30,48,191,254,310] and/or CFA.[52,120,333] In the Brussels material, 94% of thyrotoxic patients with serum LATS presented with either one or both antithyroid antibodies. This relation is not due to the identity of LATS and TGA[30,254,310] or CFA.[52,53,304] Indeed, CFA and LATS show different incidences in subjects taken individually, and evolve differently under steroid treatment. Furthermore, contrary to some opinions,[47,74,174] LATS has not been detected by the Coons immunofluorescent method[39,102,118,304] used to detect CFA.

Histological correlations

In animals, LATS induces appearances of thyroid hyperactivity.[219,302] Noguchi *et al.*[242] attribute the characteristic hyperplasia of human thyrotoxicosis to the effect of circulating LATS. No study has been published showing a correspondence between LATS and lesions of lymphocytic thyroiditis. Case report 8.3 illustrates a dissociation between these two phenomena (cf. Table 8.1).

7. Iodine Metabolism and Thyroid Function

Iodine metabolism in thyrotoxicosis is chiefly characterized by acceleration at each stage, i.e. iodine uptake and organification, synthesis, secretion, and degradation of thyroid hormones.[308] $PB^{131}I$ is extremely high, and the uptake curve of radioactive iodine in the thyroid reaches its peak before 24 hr. The acceleration of iodine metabolism entails a considerable increase in the quantity of hormones released into the circulation; this is partly reflected in the rise of $PB^{127}I$. The production of hormonal iodine is esti-

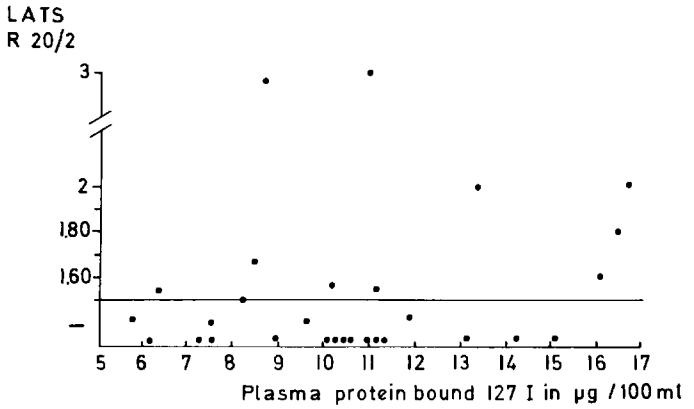

FIG. 8.8. Relationship of LATS to the PB ^{127}I in twenty-nine cases of active thyrotoxicosis.

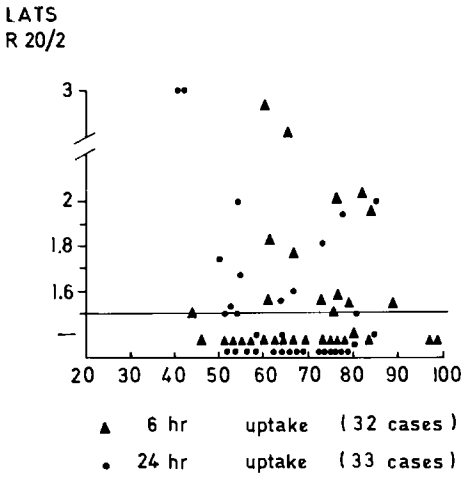

FIG. 8.9. Relationship of LATS to the ^{131}I uptake in cases of active thyrotoxicosis.

mated at between 600 and 900 µg/d,[44,158] or 10–15 times more than the normal value. In the total amount secreted, the proportions of T3 and T4 are often changed as indicated by the higher proportion of T3 frequently observed in the PBI of thyrotoxic subjects.[305] An abnormally large amount of this protein-bound iodine may, however, be non-hormonal. It is constituted in fact by an iodinated protein resembling serum albumin[298] (cf. Chapter 1). Furthermore, recent investigations[178] show that the blood of hyperthyroid subjects contains a level of free T4 of 12·20 ± 6·64 µg per 100 ml instead of the normal level of 2·13 ± 0·48 µg per 100 ml.

It is classically held that the thyrotoxic gland escapes physiological control by the hypothalamic-pituitary axis. Owing to this autonomy of the hyperthyroid gland, its activity continues unchecked on administration of triiodothyronine. However, the administration of TSH is still capable of increasing, even further, the hormone secretion of the thyrotoxic gland.[324]

The similarities and differences of iodine metabolism in thyrotoxicosis and in lymphocytic thyroiditis are summarized in Table 8.8. In some cases the diagnostic tests may yield ambiguous results. Two tests offer conclusive evidence: the T3 suppression test and the radioactive T3 red cell or resin test.

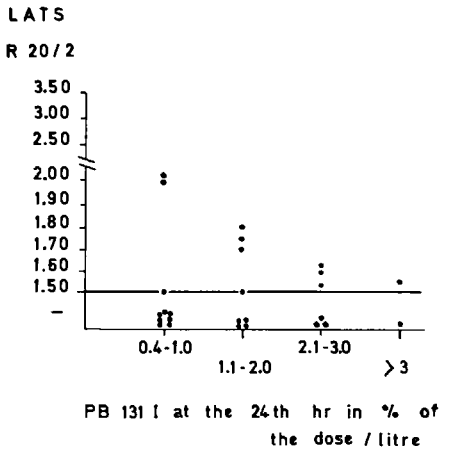

FIG. 8.10. Relationship of LATS to the PB ^{131}I in twenty-seven cases of active thyrotoxicosis.

The influence that thyroiditis superimposed on thyrotoxicosis may have on iodine metabolism and thyroid function obviously depends on the extent of the degenerative and inflammatory process. In most cases not treated with iodine, surgery, or radiotherapy, the process is not capable of reducing the hyperactivity of the pathologically stimulated gland to any marked degree. In these cases, the release of radioactive iodine from the gland will be even more intense than in hyperthyroidism without superimposed thyroiditis (Table 8.9). On the other hand, if the process is extensive, or if treatment has limited the active parenchyma, iodine trapping and hormone production may be expected to fall considerably, even if LATS values in the serum are high. This is observed in postoperative cases or in patients treated with radioactive iodine (cf. Fig. 8.1). It is possible that the prolonged administration of iodine could have a similar effect, perhaps by accelerating the degenerative process which probably lies at the root of the autoimmune mechanism. At all events, the extension of thyroiditis and destruction of the parenchyma have been cited as the explanation of the spontaneous cure of thyrotoxicosis, or the

TABLE 8.8. COMPARISON OF THYROID FUNCTION TESTS IN THYROTOXICOSIS AND LYMPHOCYTIC THYROIDITIS[a]

	Thyrotoxicosis	Lymphocytic thyroiditis
6 hr and 24 hr ^{131}I uptake	Increased	Often increased
$PB^{131}I$ (% dose per litre at 24 hr)	High >0·2	High >0·1
$PB^{127}I$ (μg per 100 ml)	Often high >10	Sometimes high; 8–10
NBEI (μg per 100 ml)	Sometimes >1	Often high
TSH test	No increase of ^{131}I uptake	No increase of ^{131}I uptake
IK test (2 mg)	Inhibition	Inhibition
T3 test	No suppression	Suppression
T3 resin test	Increased	Often decreased

[a]Hashimoto's goitre or simple goitre with extensive lymphocytic infiltration.

occasional reported cases of toxic goitre proceeding to myxoedema. The morphological evidence for such a hypothesis is discussed in section 4 of this chapter.

8. Pathogenesis of Thyrotoxicosis

Since the nineteenth century numerous theories have been advanced to explain thyrotoxicosis. This disease has been attributed in turn to a nervous, sympathetic, or psychosomatic factor, to a diencephalo-pituitary disorder causing increased secretion of the thyrotropic hormone, to an autonomous thyroid disease, to a genetic factor, or to an infectious process (literature in refs. 22, 55, 88, 127, 136, 221, 236, 271, 296, 319). The discovery of LATS and the demonstration that it is an immunoglobulin have led to the recent hypothesis that thyrotoxicosis of Graves' disease is an autoimmune disorder.[4,17,98,100,215,296]

In view of data reported on the nature of LATS, its origin, and its experimental production, and despite some immunological studies,[64,171,243] LATS may be considered as a thyroid antibody.

Role of the LATS in Graves' Disease

(Literature in refs. 3, 4, 49, 50, 69, 100, 102, 115, 147, 148, 173, 202, 215, 237, 244.)

A number of authors assert that LATS is the causal factor of Graves' disease.[3,215,237] They base their arguments on a series of findings: the detection of the LATS-IgG in 85% of hyperthyroid subjects; the thyrotropic action of LATS in normal man and newborn infants; the absence of any action by thyroid hormones on LATS, accounting for the autonomy of the thyroid gland; and, finally, the correlation observed by a group of researchers between LATS and ^{131}I turnover. On the other hand, a series of facts argue against such a hypothesis: the failure to detect LATS in all cases of Graves' disease, even by using methods which increase the sensitivity of the McKenzie technique;

TABLE. 8.9. PARAMETERS OF THYROID FUNCTION IN THYROTOXICOSIS WITH AND WITHOUT THYROIDITIS

Parameters	No. of cases with thyroiditis	Mean value	No. of cases without thyroiditis	Mean value	Statistical difference
$PB^{127}I$ (μg per 100 ml)	17	11·9	13	12·5	NS
^{131}I uptake (6 hr % dose)	20	71	15	73	NS
^{131}I uptake (24 hr % dose)	21	64	15	71	NS
$PB^{131}I$ (% dose per litre at 24 hr)	18	1·71	13	0·91	< 0·05
Cholesterol (mg per 100 ml)	19	181	14	167	NS

the presence of LATS in euthyroid subjects with Graves' ophthalmopathy (cf. Table 8.7), although in such cases the thyroid is likely to react normally to TSH; the presence of LATS-IgG in near relatives of thyrotoxic patients; the disappearance of LATS under the effect of cortisone without remission of the hyperthyroidism; the persistence of LATS after cure of the disease; the demonstration of a LATS response in both toxic multinodular goitre and toxic adenoma; the presence of a LATS response in a significant percentage of all thyroid diseases and normal subjects; and the absence of appearance of thyroid antibodies indicating lymphocytic thyroiditis in normal subjects after the administration of LATS.

At the present time, certain authors[49,55,56,69,173,176,195] think that there are as many arguments in favour of LATS having a causal role in thyrotoxicosis as of its playing a secondary role, possibly that of maintaining the disease.

Autoimmune Concept of Graves' Disease

Doniach and Roitt[100] have developed arguments expressed by several authors in favour of this view. The direct evidence consists chiefly in the antibody character of LATS and the inhibition of its thyrotropic properties after its absorption by thyroid tissue. Further arguments are furnished by the fact that LATS responses have been observed in one case of monozygotic twins, one of whom was affected with thyrotoxicosis and the other with Hashimoto's disease,[167] and by the presence of LATS or LATS-IgG (in the same titre as other organ-specific antibodies) in the serum of euthyroid subjects closely related to thyrotoxic patients.[307,332]

How far does thyrotoxicosis meet the criteria of Witebsky *et al.*[329] set down in Table 2.2?

(1) There is often a rise in serum gammaglobulins.
(2) The antibody is known: it is a circulating IgG. Its absence in certain cases of thyrotoxicosis (especially those of recent onset) could be explained by its fixation in the thyroid tissue although there is no evidence of this.
(3) The specific antigen is not identified, although its presence is demonstrated in thyroid homogenates.

(4) Pathology has not revealed any inflammatory lesions peculiar to thyrotoxicosis The lesions found in many thyrotoxic patients are no different from those of the general process of autoimmune thyroiditis occurring in all thyroid diseases. Thus the close association with focal or diffuse thyroiditis does not automatically indicate the autoimmune nature of thyrotoxicosis. Indeed, a similar association, although to a lesser degree, exists between lymphocytic thyroiditis, nodular goitre, and thyroid cancer. And obviously neither nodular goitre nor thyroid cancer can be considered as autoimmune diseases merely because of this association.

(5) Thyrotoxicosis has not been reproduced experimentally so far. Certain authors have, however, succeeded in inducing in animals the appearance of a thyrotropic-like factor considered as a gammaglobulin close to LATS. Very recently, Solomon and Beall[294] showed that in rabbits immunized with thyroid extracts the level of free T4 was above normal.

(6) As regards the presence of other autoimmune phenomena in thyrotoxic patients or their families, the question obviously arises as to whether these associations cannot be explained by the presence of superimposed lymphocytic thyroiditis (cf. Chapter 11).

All things considered, the role of LATS in the maintenance of Graves' disease seems probable. The autoimmune origin of the disease is not, however, formally established. The cause of the initial onset remains unknown.

Hypotheses about the aetiological factors involved are given in Fig. 8.11. One idea (Fig. 8.11.(1)) is that the appearance of LATS could be a primary phenomenon, either by its release from forbidden clones or as a reaction to a specific antigen related to an intracellular disturbance. Lymphocytic thyroiditis could be secondary to parenchymatous hyperplasia and hyperactivity of the thyroid. A second concept (Fig. 8.11(2)) is that all the thyroid antigens could appear as a reaction to the intracellular disturbance. This

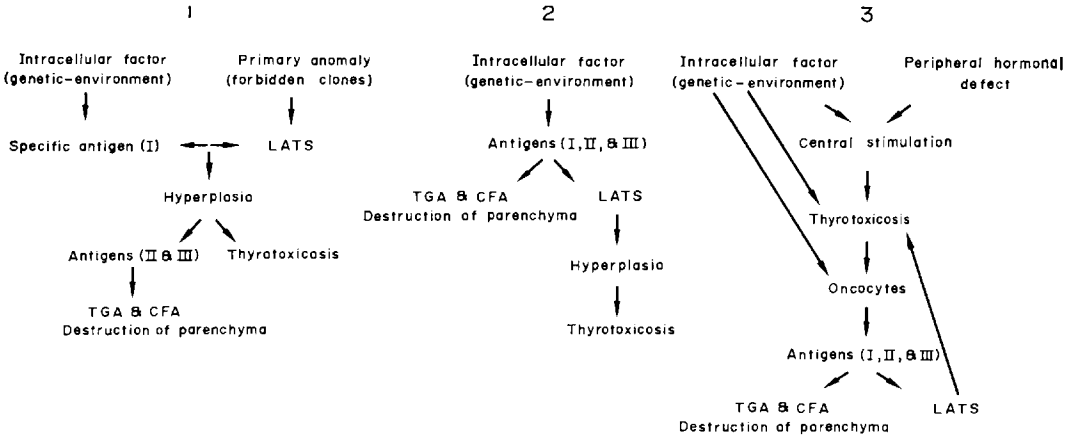

FIG. 8.11. Schematic representation of various hypotheses, accounting for the role of autoimmunity in thyrotoxicosis.

phenomenon could induce the production of TGA and CFA, and LATS possibly outside the thyroid. Finally, a third view (Fig. 8.11(3)) might be that the intracellular disturbance (such as a peripheral defect) could set in motion the phenomenon of thyrotoxicosis. Resulting either from hyperplasia or the intracellular defect, the development of oncocytes could govern the appearance of the usual antibodies and that with LATS properties. The latter, although secondary to the process of thyrotoxicosis and thyroiditis, would nevertheless have the effect of abnormally maintaining thyroid stimulation.

Exophthalmos

The mechanism leading to exophthalmos is still unknown. Various hypotheses have been considered in detail in recent studies.[16,29,71,155,205] Although the intervention of the sympathetic nervous system could account for "sympathicotonic" exophthalmos, neither thyroid hormones nor TSH nor LATS[222] can explain satisfactorily the many aspects in the eye signs of Graves' disease.

Certain authors[93,95,96,97,155] considered that a pituitary factor, different from TSH and possessing exophthalmos-producing properties (exophthalmos-producing substance —EPS), could be responsible for the ocular signs of thyrotoxicosis; this theory is much disputed by the majority of authors.[29,82,145,232,237,328] The frequent association of thyroglobulin antibodies and progressive exophthalmos might suggest the intervention of an autoimmune mechanism; McGill and Asper[205] have looked unsuccessfully for antibodies specifically directed against the retro-orbital tissue. Kriss *et al.*[176] submit the hypothesis that these lesions could be due to a mechanism of delayed hypersensitivity, related to the presence of LATS, as an antibody specifically directed against this tissue. But in many cases of exophthalmos LATS factor is absent and other factors must be invoked.[205]*

Pretibial Myxoedema

The incidence of TGA in pretibial myxoedema is not well known. According to Kriss *et al*[177] it is low and no different from the incidence of TGA in thyrotoxicosis. So for these authors the presence of TGA does not seem to have any particular relation with pretibial myxoedema. On the other hand, on account of the high frequency of LATS in this disease, and of the immunological nature of LATS, these authors suggest it could play a role in the genesis of the lesions, which would be the result of the toxic effects of an antibody–antigen complex forming in the tissues or of a delayed hypersensitivity reaction. However, no experimental work has confirmed such a theory.

9. Diagnosis

It is first necessary to establish the diagnosis of hyperthyroidism by the classic clinical and functional criteria.

The diagnosis of associated thyroiditis rests on indirect and direct signs. There is,

* Recently Winand found an IgG different from LATS in the serum of patients with severe ophthalmopathy (R. WINAND. Contribution à l'étude de l'exophtalmie endocrinienne. Thèse. Presses de Vaillant-Carmanne, Liège, 1970).

generally speaking, no difference in the clinical symptoms of hyperthyroidism within or without thyroiditis. Nevertheless, the existence in a hyperthyroid subject of a large and recently developed goitre, increasing oedematous exophthalmos, multiple lymph nodes, an enlarged spleen,[88] other autoimmune diseases in the subject or his family and antecedents of thyroid disease are all elements for presuming associated thyroiditis. There is no functional sign characteristic of the latter, although increased gammaglobulins, lymphocytosis, and anaemia are more frequent in the presence of thyroiditis. A definite diagnosis is obtained by the detection of circulating thyroglobulin and microsomal antibodies in significant—although often moderate—titres.

In the event of a very intense reaction, with a positive precipitin test, unless the clinical symptoms are those of definite thyrotoxicosis, it is necessary to exclude Hashimoto's disease by a T3 suppression test. Furthermore, in such cases, testing for LATS is of importance, although there have been one or two exceptional reports of positive LATS responses from total serum and from IgG in cases of Hashimoto's goitre. At all events, the isolated presence of LATS in the serum of a thyrotoxic subject cannot serve as a diagnostic criterion for thyroiditis associated with hyperthyroidism: up to the present time, no such case has ever been published without the additional association of thyroglobulin or microsomal antibodies.

10. Treatment

It seems well demonstrated that extensive lesions of thyroiditis associated with hyperthyroidism may entail the spontaneous remission of the latter, or even hypothyroidism, after several years. These lesions are probably themselves the result of prolonged hyperthyroidism. Thyrotoxicosis with associated thyroiditis must be treated according to classic rules, but bearing in mind that, in the opinion of all authors,[18,100,164,165] thyroidectomy is definitely inadvisable if the hyperthyroid subject shows high titres of TGA or CFA, or precipitins, because of the frequent development of hypothyroidism in the years following the operation.[130,327] The contra indications to surgery are even stronger in elderly subjects or when antibody titres are very high.[100] When surgical resection is necessitated for major reasons, the operation must be kept as limited as possible. The presence of antibodies does not influence the results of treatment by antithyroid drugs.[18,100,165] The existence of a high titre of TGA or CFA in a hyperthyroid subject due to be treated with radioiodine justifies the use of a smaller dose than usual.[165]

In conclusion, the existence of thyroid antibodies in a hyperthyroid subject justifies attempted treatment by antithyroid drugs, and always dictates caution in treatment by surgery or radiotherapy.

Effects of Therapy on the LATS Response

The results reported in the literature show that the frequency of LATS in *residual thyrotoxicosis* is higher than that in untreated hyperthyroidism (Table 8.10) whatever

TABLE 8.10. INCIDENCE OF LATS IN DIFFERENT TYPES OF TREATED THYROTOXICOSIS

	No. of cases	No. of LATS response	%
Thyrotoxicosis with hypophysectomy	26	18	69
Residual thyrotoxicosis after thyroidectomy	46	30	65
Residual thyrotoxicosis after ^{131}I therapy	164	92	56
Residual thyrotoxicosis after antithyroid drugs	110	45	40
Inactive thyrotoxicosis (euthyroid)	113	18	16

the nature of the treatment. It is only when hyperthyroidism is cured that the incidence of LATS drops considerably. This probably explains the contradictory observations in the literature regarding the incidence of LATS after treatment. Ten years after cure, the incidence is only 10%.[195] Solomon *et al.*[295] found no LATS response after 10 years. Nevertheless, LATS may be found 35 years after subtotal thyroidectomy,[215] and persists in a high percentage of cases of post-therapy myxoedema.[51,182,201]

After administration of *antithyroid drugs* certain authors observe a reduction in the frequency of LATS;[182,242,252,257] but others find no change[201,210] especially if the hyperthyroidism is not cured.[56,195]

After *subtotal thyroidectomy*, when the hyperthyroidism is not corrected, there may be an increase in the frequency of LATS parallel to the worsening of pre-existent exophthalmos.[31,195,242] It is impossible to know whether it is the presence of LATS which is responsible for the persistence of the disease or vice versa.

In several recent studies[78,79,80] Catz and Perzik report more than 100 cases of hyperthyroidism with progressive exophthalmos treated by *total thyroidectomy* in which they observed diminution of LATS (and disappearance in some cases) and improvement of the ocular signs and pretibial myxoedema in all cases except when a remnant of thyroid tissue persists. Muller *et al.*[234] and Demeester-Mirkine and Bonnyns[89] observed four similar cases, and Boyle *et al.*[58] one case. Other authors find no clinical improvement nor disappearance of LATS after total ablation of the thyroid.[174,248,306,325] If it is assumed that LATS is an antibody against a thyroid antigen, its persistence after total removal of the thyroid could correspond to a phenomenon analogous to the persistence of antibodies in the blood of vaccinated subjects.

The majority of authors, with the exception of Burke,[66] observe an increase in the frequency of LATS responses after administration of a *therapeutic dose of* ^{131}I.[56,176,195,252]

Corticoids are generally given to treat progressive exophthalmos or pretibial myxoedema in adults[30,43,54,61,174,177,195,250,252,292,316,323] and children.[197] It is admitted that LATS may disappear completely after only 8 days of treatment with prednisone doses of 10–100 mg/d. In the majority of cases there is a simultaneous improvement in the ocular signs and pretibial myxoedema. The cessation of treatment may bring a recurrence of the clinical signs and a reappearance of LATS. The resumption of drugs

brings cure in certain cases. Local treatment of pretibial myxoedema produces the same results as general treatment.[177] Although temporary remission of hyperthyroidism has been observed under the effect of heavy doses of cortisone,[323] the latter do not prevent thyrotoxicosis appearing later.[60]

The administration of *immunosuppressors* of the methotrexate, azathioprine or chlorambucil type has been tried by several authors with varying degrees of success in the treatment of severe ophthalmopathy and pretibial myxoedema.[90,92,149,193,203,278,317] Out of a dozen cases treated in this way, two-thirds responded favourably by partial recession of the eye or/and cutaneous signs and by a diminution, or sometimes disappearance, of LATS in the serum. In the other third of the cases there was no response.[26,92,149]

According to Földes *et al.*[119] *triiodothyronine* has no effect on LATS, whereas large doses of D-thyroxine bring down its level. Mahaux *et al.*[198,199] consider that T3 and its derivatives could play a role in the appearance of LATS and the activation of the ocular syndrome. McKenzie[210] and Horster and Klein[155a] observe no action of D-T4 on LATS.

Thymectomy proposed half a century ago as a treatment for hyperthyroidism, was recently brought back into favour by De Groot *et al.*[87] Thymectomy has also been recommended as a treatment for severe myasthenia in young subjects. In a 20-year-old woman from Brussels, myasthenic since the age of 17, the difficulties of classic medical treatment led to re-examination during which thyrotoxicosis was discovered in association with severe thyroiditis. Two months after external irradiation of the thymus and treatment of the hyperthyroidism by methimazole, thyroidectomy was performed and brought improvement of the myasthenia and lasting remission of the hyperthyroidism.

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CHAPTER 9

Thyroiditis and Acquired Hypothyroidism in Adults

P. A. BASTENIE, M. BONNYNS and L. VANHAELST

1. Introduction

Acquired hypothyroidism in adults constitutes a clinical condition with characteristic signs indicating insufficient thyroid hormone secretion. The term myxoedema is used in two different senses. Strictly speaking, it refers to particular changes in the skin tissues, which only occur in certain cases of severe hypothyroidism, although they can develop in non-hypothyroid conditions too. The word is also used as a synonym for severe hypothyroidism, especially in early descriptions of the disease.

Numerous factors may lie at the root of hypothyroidism. The immediate cause is either a deficit of thyrotropic hormone secretion by the pituitary gland or a primary atrophy of the thyroid. Since the report published by the London Clinical Society in 1888, the latter condition is known to be responsible for the vast majority of "spontaneous myxoedema" in adults. For a long time the origin of this atrophy remained a mystery. Histological and clinical observations[61] suggested that it represented the ultimate phase of a form of chronic lymphocytic thyroiditis similar to Hashimoto's lymphocytic thyroiditis;[1] this hypothesis was then confirmed by the discovery of thyroid antibodies in the serum of the majority of hypothyroid subjects.[49] It is now agreed that spontaneous hypothyroidism in adults is the end result of autoimmune lymphocytic thyroiditis.[19,51,63]

True, some patients with primary myxoedema have been or are still carriers of moderate lymphomatous goitres. This is the case particularly in a few younger women.[19] But in the vast majority of cases of spontaneous hypothyroidism a process of atrophic lymphocytic thyroiditis is responsible. The usual absence of goitre, the sex ratio, the associated disorders, and, finally, the treatment, all make it a distinct clinical and histological entity.

2. Illustrative Case Reports

CASE REPORT 9.1: Obs. SP 64,818. *Asymptomatic thyroiditis evolving towards definite clinical hypothyroidism, Haemorrhagic syndrome*

A 77-year-old woman with fifteen past pregnancies was admitted in August 1965 for diabetes. Although there were no signs of thyroid disturbance, thyroid antibodies were detected in the serum (titre 1/625). In March 1966 the patient was readmitted for

TABLE 9.1. LABORATORY FINDINGS IN CASE REPORT 9.1

Blood urea	94 mg per 100 ml
Blood sugar	204 mg per 100 ml
Bilirubin	1·6 mg per 100 ml
Hanger +	Thymol 6·2 U
Cholesterol	214 mg per 100 ml
ERS	130 mm/hr
Hb	9/100 ml
Leucocytes	4500 per mm^3; PTT, 100%; platelets-184,000 per mm^3.
Fibrinogen	465 mg%
Clotting time	6 min 26 sec
Recalcification time	2 min 9 sec
Bleeding time	2 min
Clot-retraction	16% (1 hr) 26% (2 hr)
Torniquet test	+
Total proteins	7 g per 100 ml
Electrophoresis	A 38%; α_1 6·2; α_2 11·7; β 15·7; γ 29

haematemesis. She was found to have anaemia (10 g haemoglobin per 100 ml) and obvious clinical hypothyroidism ($PB^{127}I$, 2·5 μg per 100 ml; ^{131}I uptake, 9% at 24 hr).

In June 1966 the patient was admitted for the third time on account of a fresh bout of anaemia (9 g haemoglobin per 100 ml) and severe haemorrhage, of which she died in a few days (petechiae, ecchymosis, melaena, acute haematuria). The TGA titre was 1/3135; gammaglobulins were 29% or 2 g per 100 ml; TSH was 23 mU per 100 ml. Other laboratory findings are given in Table 9.1.

The clinical diagnosis was: haemorrhagic syndrome, hypothyroidism, possibility of deficient A anti-haemophilic factor. The autopsy showed a fibrous atrophy of the gland with extensive lymphocytic infiltrations surrounding rare islets of eosinophilic epithelial cells, devoid of colloid.

3. Clinical Features

Figure 9.1 shows distribution by age and sex of Hashimoto's goitre and primary myxoedema according to the data of Doniach & Roitt[19] and according to observations made in Brussels. Whereas lymphomatous goitre occurs around the middle years of 40–50, the frequency of spontaneous hypothyroidism increases with age; the sex ratio (9/1 in Hashimoto; 5/1 in myxoedema) is remarkably similar in the two groups studied in London and in Brussels.

The age at which myxoedema is diagnosed depends as much on the alert clinical sense of the physician as on the prominence of the signs.

Because of its slow progress, the disease often goes unsuspected for a long time, particularly in old people.[9,37] It frequently needs a severe complication before the condition is recognized. Early diagnosis would be greatly facilitated by the detection of underlying thyroiditis (Table 9.2).

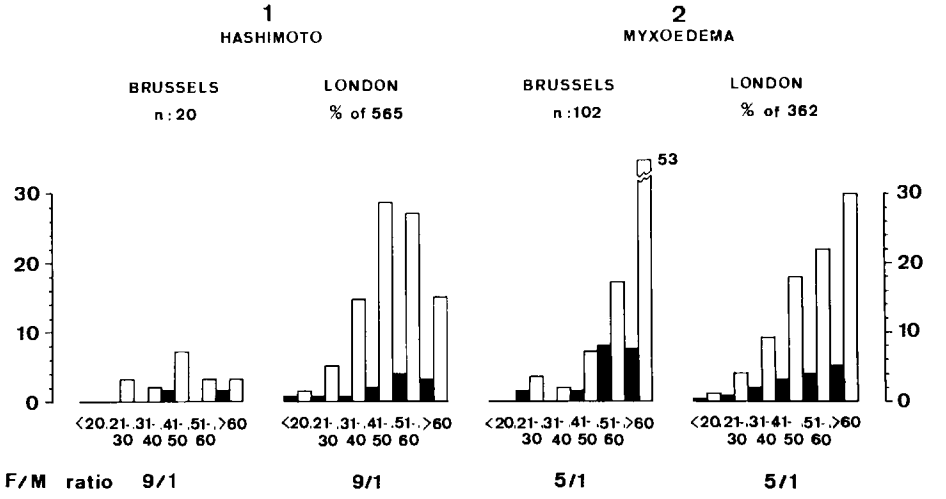

FIG. 9.1. Age and sex incidence in (1) Hashimoto's struma lymphomatosa, and (2) spontaneous hypothyroidism (myxoedema) observed in Brussels and in London. (After Doniach and Roitt[19].)

TABLE 9.2. DURATION OF THE DISEASE BEFORE DIAGNOSIS (ON ADMISSION OR CONSULTATION IN OUT PATIENTS) BASED ON RETROSPECTIVE DIAGNOSIS

	No. of patients	Duration (years)					
		0	1–2	2–5	5–10	10–20	>20
Out-patients clinic	29	0	2	8	8	9	2
Department of Medicine	31	7	9	4	5	3	3

4. Pathology

The histological picture may be built up from data published by various authors[1,2,16,20,47,59,61,73] and from documents relating to the post-mortem investigations of twenty-five cases of severe hypothyroidism in Brussels.[72]

Thyroid

The most striking lesions occur in the thyroid gland. With one exception the glands of the Brussels series were all reduced in size and sometimes so atrophied that they were difficult to locate. However, atrophy is not always so marked. Douglass and Jacobson[20] report 4 of their 9 cases weighing over 20 g, and Sclare[59] found normal-sized glands in 4 of his 22 cases of spontaneous myxoedema, with one gland weighing more than 20 g.

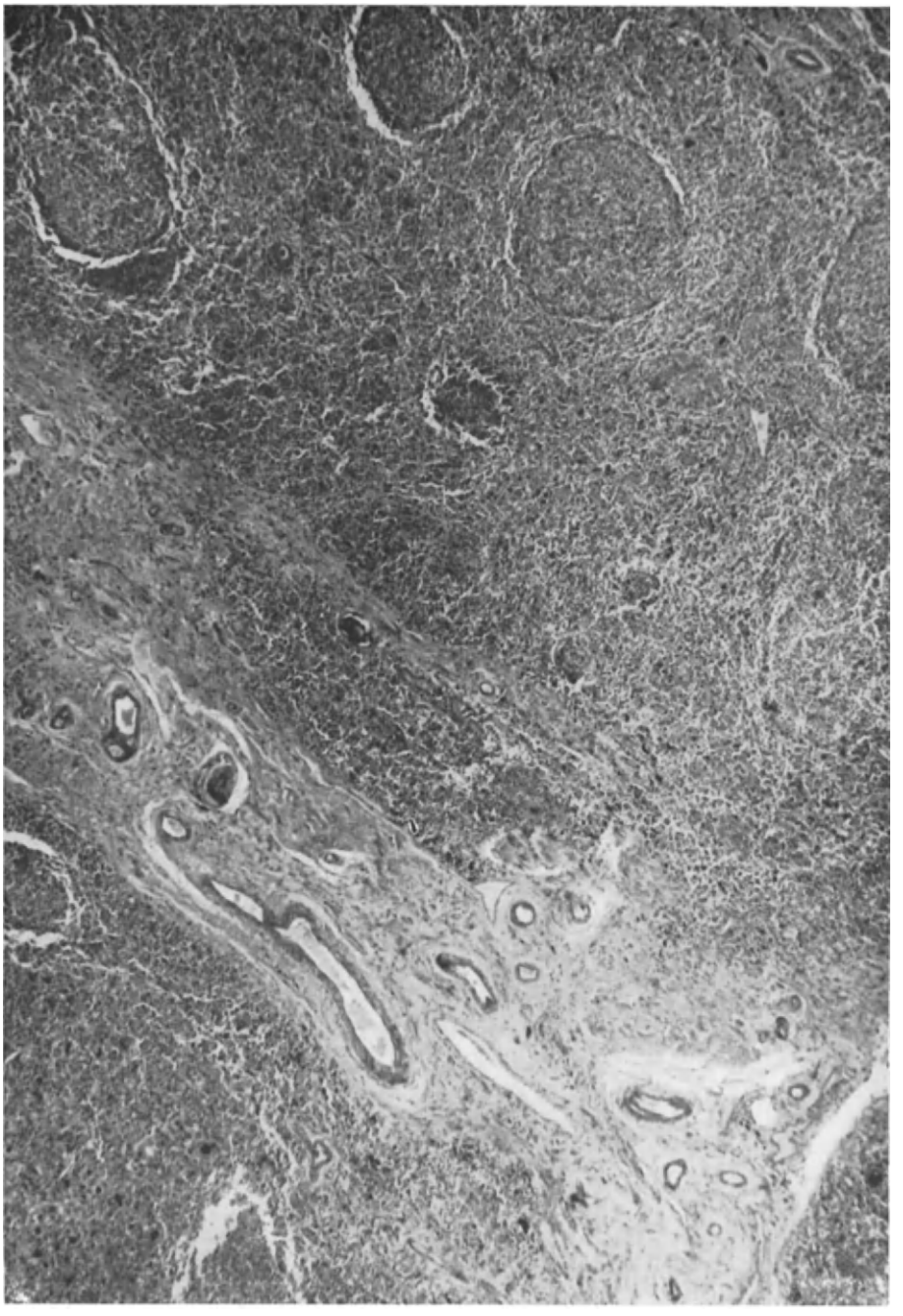

FIG. 9.2 (a). Lymphocytic thyroiditis in myxoedema. (×60).

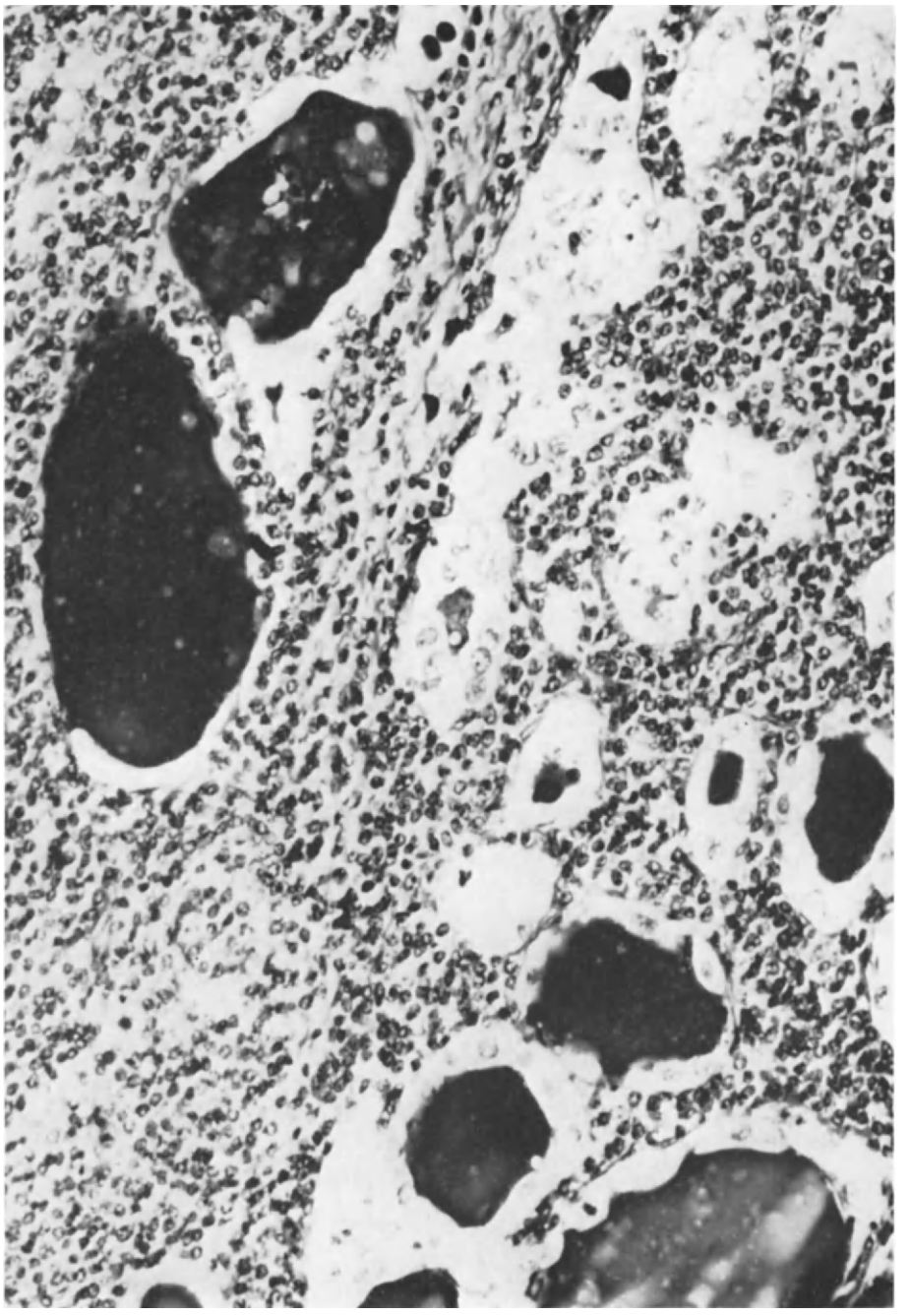

FIG. 9.2 (b). (×320).

Histologically, the picture varies from one of lymphocytic thyroiditis with germinal centres (Fig. 9.2) to one of dense fibrosis with discreet lymphocytic infiltrations (Fig. 9.3). Vestiges of thyroid parenchyma are found inside these inflammatory foci. Sometimes they are fairly large, but may also be reduced to sparse fragments. Most such tissue vestiges show oncocytic changes (Fig. 9.4). Only rarely do they contain any intact vesicles, and, in any case, these are always small and almost completely devoid of colloid (Fig. 9.5). Giant cells may occasionally be observed in isolated patches (Fig. 9.5). Almost all the atrophic glands are marked by the presence of a squamous metaplastic process (Fig. 9.5) sometimes suggestive of neoplastic proliferation (Figs. 9.5 and 9.6). In a general way the fibrosis and atrophy of the parenchyma are proportional to the reduction in the size of the gland. These macro- and microscopic data strongly suggest the natural evolution of non-goitrous diffuse lymphocytic thyroiditis towards atrophic sclerosis with inflammatory residues.[1]

Anterior Pituitary Gland

The pathology of this gland in myxoedema is fully discussed in a special contribution by Prof. M. Herlant and Prof. J. L. Pasteels (cf. Appendix to Chapter 10).

Adrenal Glands

Alterations of the cortex have been observed by Bastenie in 5 out of a series of 10 cases of myxoedema.[2] The peripheral area was found to be atrophied and sclerotic, whilst nodular and even adenomatous formations of swollen fatty cells were found in other parts of the glands. The atrophy of the glomerulosa is probably related to thyroid insufficiency,[75] whereas the fatty adenomatosis, also noted by Ceelen,[16] is perhaps related to the accompanying disorders (diabetes, obesity, hypertension).[57] Lymphocytic infiltrates are frequently observed.

In other organs, the histology of primary myxoedema is characterized by:

(1) Increased volume of the heart.[2,20,70]
(2) Accentuation of vascular sclerosis[2] and coronary sclerosis.[20,67,71]
(3) Atrophy of gastric and colonic mucous membrane[20] with possible development of a megacolon.[3,21]
(4) Infiltrations of complex mucoproteins in the dermis and atrophy of the sweat glands.[12]
(5) Mucin infiltration in the nervous system and muscles.[45,46]

Carbohydrate Metabolism

Although thyroid hormones are known experimentally to be diabetogenic,[25] clinical records show frequent association of myxoedema and diabetes[6,52] (cf. Chapter 11). This association is not observed by authors whose investigations include all cases of hypothyroidism whatever the mechanism of the disease;[29] it is only a possibility in spontaneous hypothyroidism resulting from autoimmune thyroiditis (cf. Chapter 11).

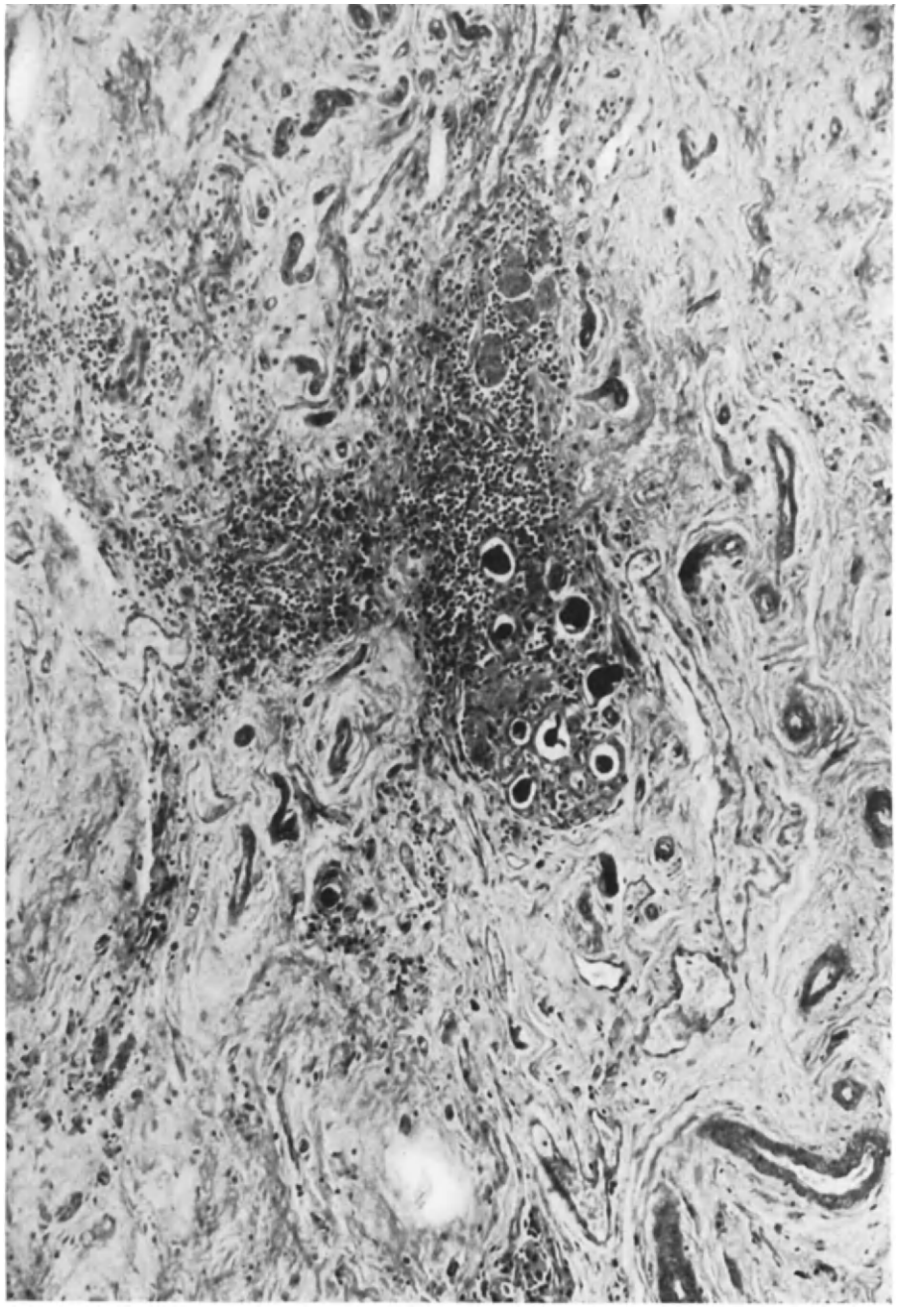

FIG. 9.3. Thyroid fibrosis and atrophy in myxoedema. (×140.)

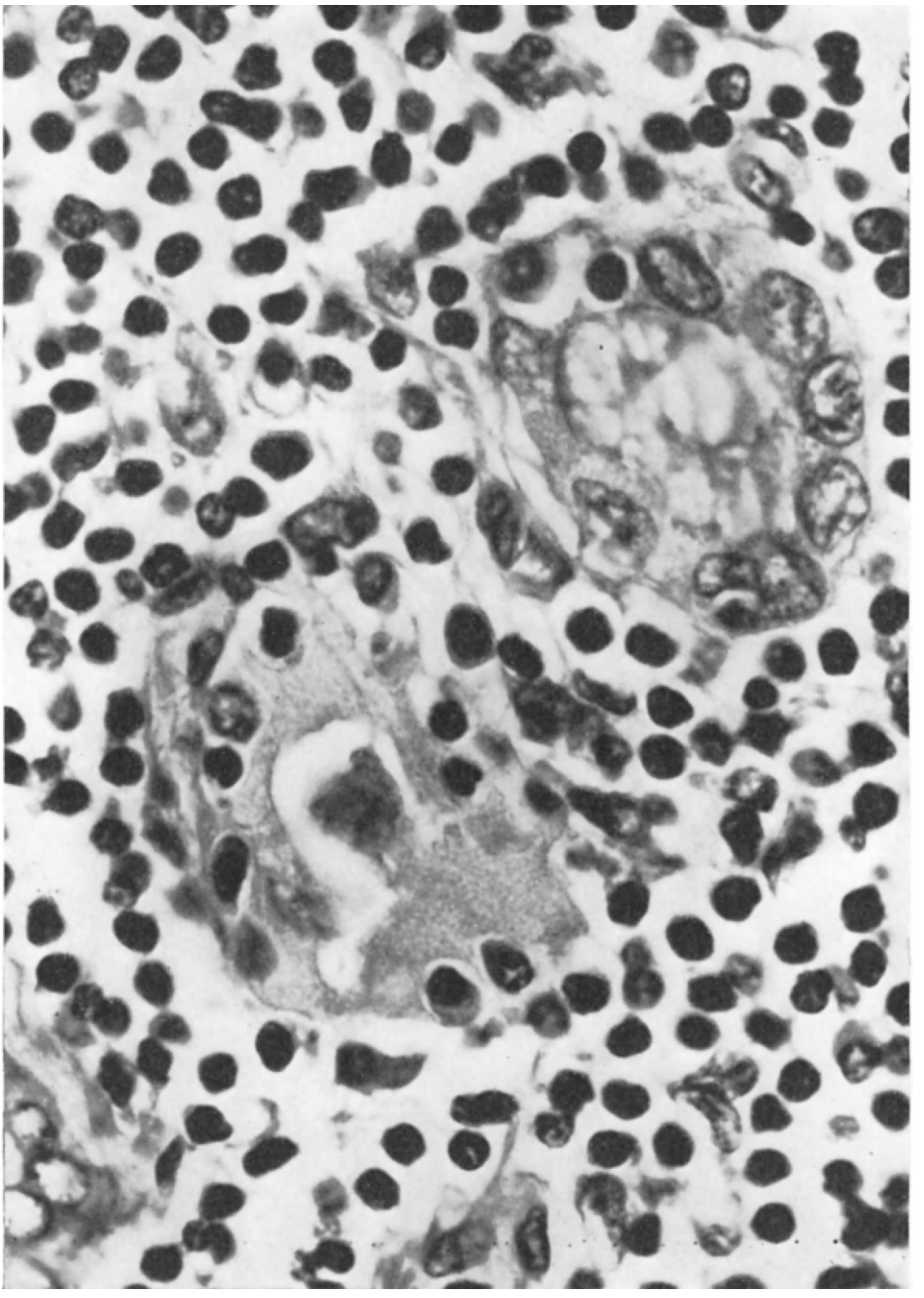

FIG. 9.4. Oncocyte metaplasia and inflammatory infiltration in atrophic thyroiditis of myxoedema. (×1200.)

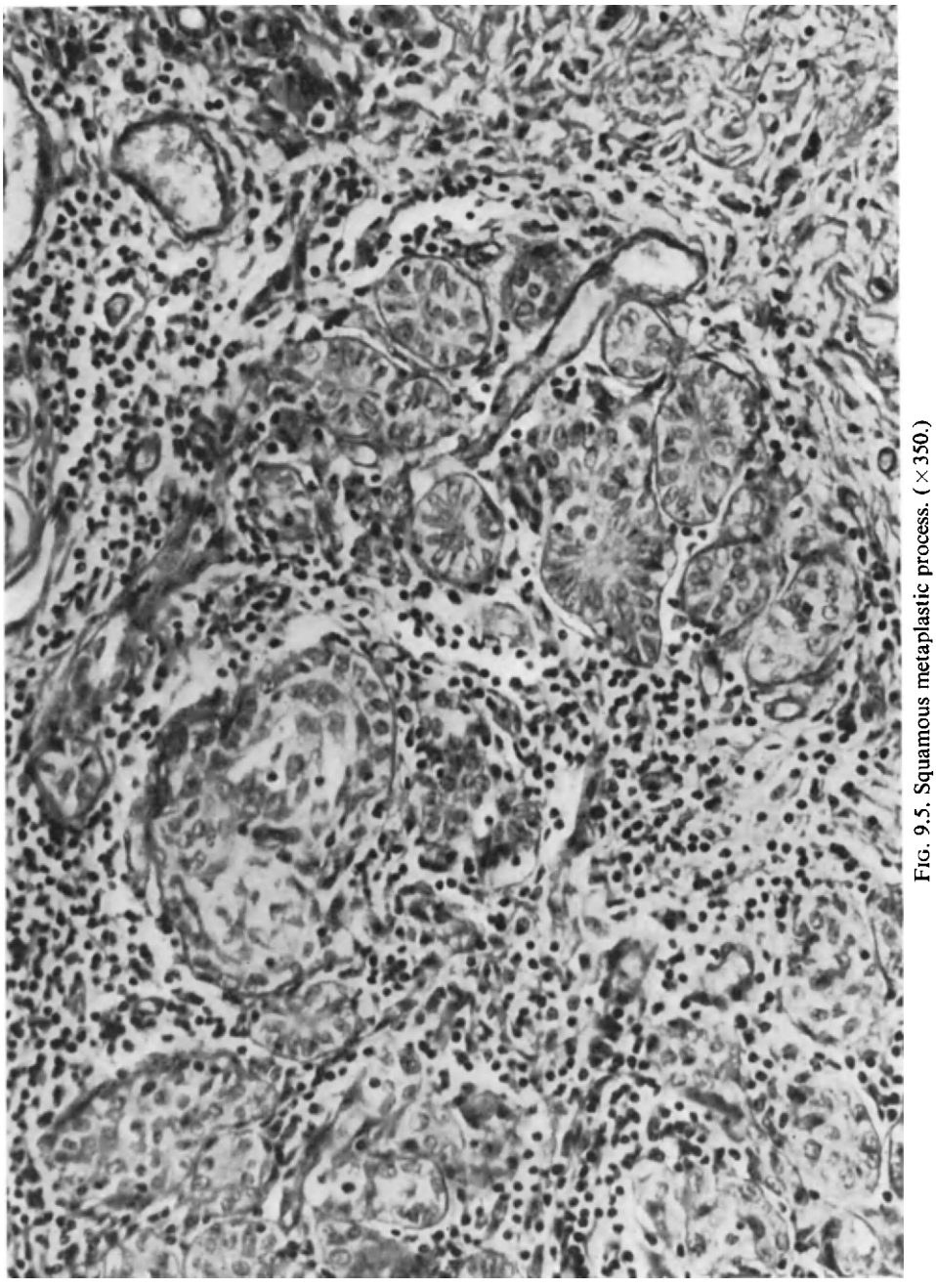

FIG. 9.5. Squamous metaplastic process. (×350.)

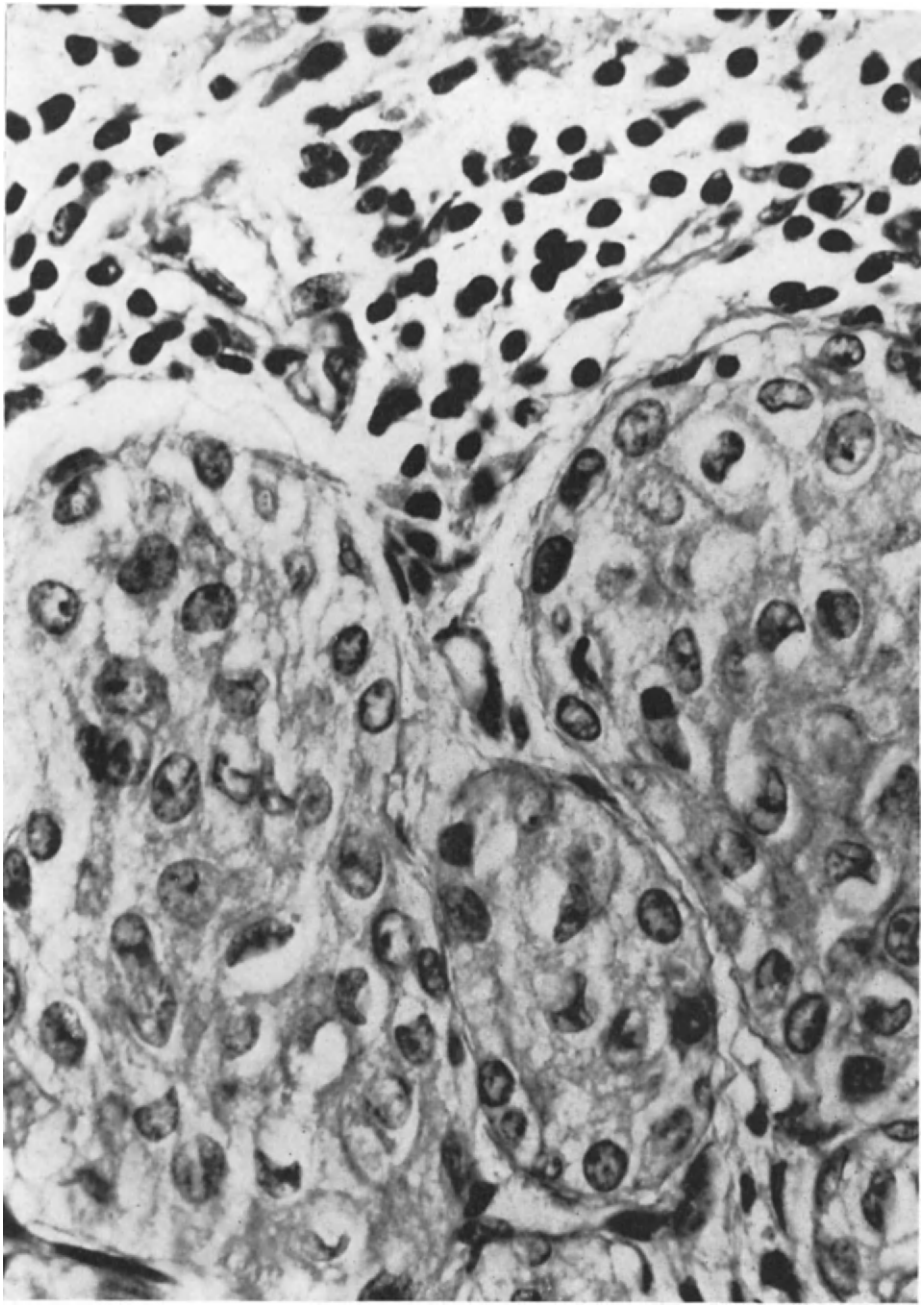

FIG. 9.6. Pseudotumorous aspect. (×600.)

Diabetes usually precedes the development of hypothyroidism. Some cases have been reported in which the diabetes declined in intensity when the subject became hypothyroid, then resumed its initial intensity when thyroid treatment was applied. These seemingly contradictory observations are explained by the idea that diabetes is a condition genetically associated with the causative factors of autoimmune thyroiditis (cf. Chapter 11) and that thyroid hormones are only slightly diabetogenic. Furthermore, because of the general metabolic decline, there is a drop in glucose absorption by the intestine and in the activity of counter-regulatory factors (epinephrine glucocorticoids growth hormone). Under the influence of small doses of insulin or even spontaneously, hypoglycaemia may occur, although less frequently and to a less marked degree than in subjects affected with hypophysial insufficiency. It may, however, be one of the complication of myxoedema coma.[65]

The *metabolism of water and electrolytes* is also likely to alter considerably. Generally speaking, the quantity of water in the body is strikingly increased whilst the plasma volume is reduced.[18,64] In the presence of an excess of water, elimination is reduced and slowed down.[7] Thyroid insufficiency may also be accompanied by marked hyponatraemia[17] and under the influence of excessive hydration a syndrome resembling that of Schwartz-Bartter may occur.[50]

Anaemia is almost always present. It may take the form of associated pernicious anaemia (cf. Chapter 11), or be due to a haemorrhagic syndrome caused by a shortage of anti-haemophilic globulin (cf. case report 9.1) or more often to a thyroid deficit proper. In the latter case the anaemia is usually mild (the number of erythrocytes ranging around 3·5 million per mm^3 and haemoglobulin hovering around 10 g per 100 ml).[69]

The condition is attributed to a drop in erythrocyte formation in response to a decline in tissue demand for oxygen,[43] but it may also be attended by a decreased absorption of vitamin B_{12}.[15,33]

Immunology. The presence of thyroid autoantibodies in spontaneous myxoedema is considered as a classical feature since 1957.[49,57] Their incidence is of the same magnitude as in lymphadenoid goitre, but usually the titres are in a lower range.[62] The usefulness of their detection in differentiating spontaneous from secondary hypothyroidism has recently been stressed.[70]

5. Laboratory Findings and Immunology

Many functional anomalies are observed in confirmed hypothyroid cases; they affect not only iodine metabolism but also the metabolism of proteins, lipids, and carbohydrates, the formation of the blood, and kidney function.

Protein Disorders

The erythrocyte sedimentation rate is very often increased.[36,39] This phenomenon is clearly related to the changes occurring in serum protein levels, namely normal or above-normal total proteins, a drop in albumin,[35,55] and a rise in gammaglobu-

TABLE 9.3. SERUM CHOLESTEROL LIPIDS AND PROTEINS IN PATIENTS OVER 50 YEARS OF AGE, AFFECTED WITH HYPOTHYROIDISM (ATROPHIC THYROIDITIS),[1] ASYMPTOMATIC THYROIDITIS,[2] AND CONTROLS[3]

	Hypothyroidism				Asymptomatic thyroidity				Controls		
	n	$\bar{x}$	*s*	*P* (1)-(2)	*n*	$\bar{x}$	*s*	*P* (2)-(3)	*n*	$\bar{x}$	*s*
Cholesterol	31	403	144	< 0·005	55	290	94	< 0·02	59	247	75
Tot. lip.	29	1050	268	< 0·001	46	780	199		30	767	206
Lipoprot.	17	905	291	< 0·001	25	619	244		18	614	211
Tot. prot. (γ per 100 ml)	19	7·2	0·82		49	7·0	0·64		46	7·1	0·66
Alb. (γ per 100 ml)	19	3·2	0·77		49	3·1	0·51		46	3·2	0·53
α_2 glob.(γ per 100 ml)	19	0·9	0·18		49	0·9	0·31		46	0·97	0·24
γ glob. (γ per 100 ml)	19	1·7	0·52		49	1·6	0·42	< 0·05	46	1·44	0·41

lins[10,55] doubtless related to the development of thyroid antibodies (Table 9.3). The passage of proteins into the cerebrospinal fluid and pleural pericardial abdominal extravasations is facilitated by the increased permeability of the capillaries.[13] This may explain the frequent observations of proteinuria and loss of anti-haemophilic globulins, which can in exceptional cases lead to a haemorrhagic syndrome (case report 9.1).[23,68]

Anomalies in the metabolism of lipids result chiefly in increases of cholesterol and beta-lipoproteins. Figure 9.7 compares cholesterol levels in hypothyroidism of hypophysial origin and in primary hypothyroidism. The high level of cholesterol in hypothyroidism is related to the increase of beta-lipoproteins (low-density lipoproteins) so that the pattern of blood lipids in hypothyroidism closely resembles that of essential hypercholesterolaemia.

6. Iodine Metabolism and Thyroid Function

In spontaneous hypothyroidism resulting from autoimmune thyroiditis in adult subjects, all the stages of iodine metabolism are reduced in proportion to the degree of destruction in the parenchyma (Table 9.4). Radioactive iodine uptake and PB levels are clearly below normal, although occasional normal values may be found. The level of $PB^{131}I$ is usually impossible to calculate owing to low radioiodine trapping. However, some authors report high values, which would reflect the very small exchangeable iodine pool in the islets of tissue still functioning.[8]

Radioactive iodine uptake is barely altered by TSH administration[53,74] (Fig. 9.8). The quantity of hormones secreted per 24 hr is obviously much reduced. Despite diminished peripheral catabolism,[26,27] the blood level varies between 1 and 4, generally being lower than 3·5 μg per 100 ml. Finally, owing to the rise in plasma TBG, *in vitro* uptake of radioactive triiodothyronine by erythrocytes or resins is strikingly low.

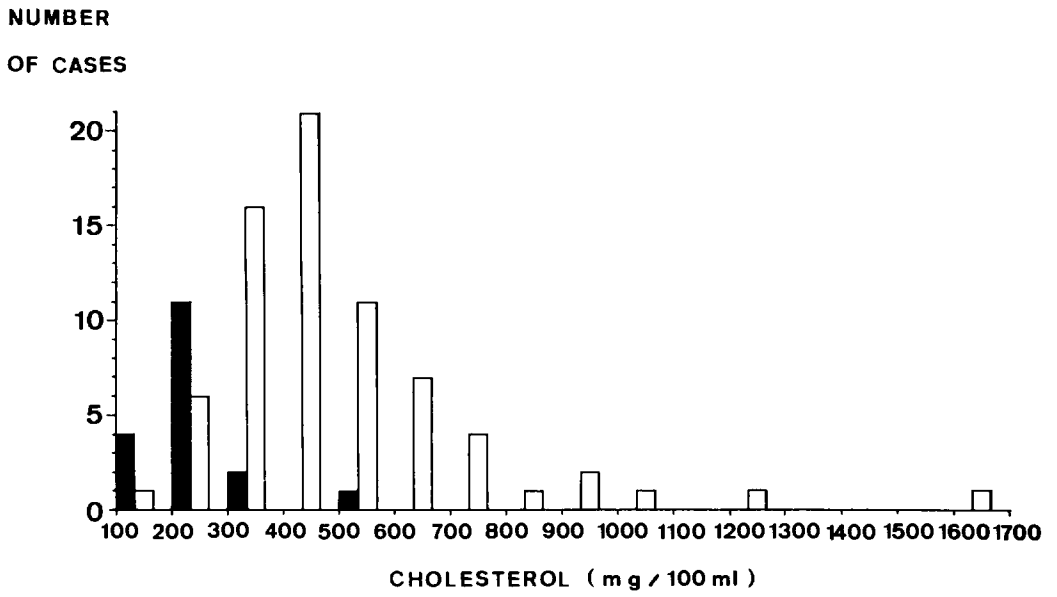

FIG. 9.7. Serum cholesterol values in primary and secondary (pituitary) hypothyroidism. □ Thyroid origin. ■ Pituitary origin.

TABLE 9.4. IODINE METABOLISM AND THYROID FUNCTION INDICES IN HYPOTHYROIDISM

Investigations	No. of patients	Mean values
Basal metabolic rate (%)	45	−18%
Blood-cholesterol (mg per 100 ml)	61	380
^{131}I uptake (% of dose after 24 hr)	38	9·6%
Protein-bound ^{127}I (μg per 100 ml)	28	2·1
Antithyroglobulin antibodies (positive at 1/78125)	40	Positive in 34 patients

7. Pathogenesis

Many authors have likened myxoedema thyroiditis to Hashimoto's disease,[14,38] alleging that (1) the two conditions derive from a fundamentally identical process; (2) many cases of goitre are accompanied by the development of hypothyroidism; and (3) in some cases of spontaneous hypothyroidism the goitre might have escaped notice due to its small size.

However, clinical data show that very few cases are preceded by thyroid swelling.

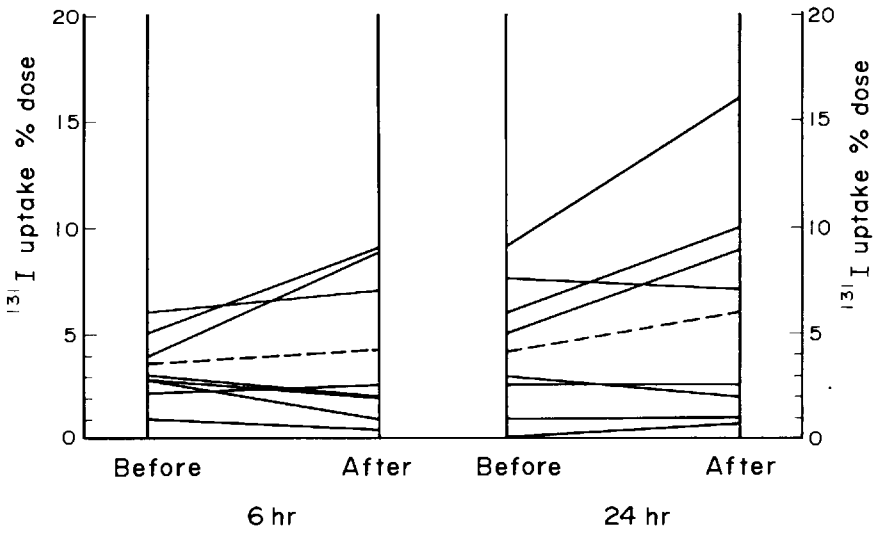

FIG. 9.8. Effect of TSH in radioiodine uptake in eight patients with primary myxoedema.

Furthermore, age and sex distribution curves are clearly different for the two types of thyroiditis (cf. Fig. 9.1). Spontaneous myxoedema in adults is far more frequent than Hashimoto's goitre.[47] The extraordinary number of cases of Hashimoto's disease reported by Doniach and Roitt[19] reflects their selective investigations rather than a hospital's normal contingent of thyroid patients.

Although the basic histological lesions look similar in the two diseases, certain major differences must be stressed. Hashimoto's thyroiditis involves a goitre, whereas spontaneous hypothyroidism concerns an atrophic gland. In the first condition the lesions are more diffuse and contain more inflammatory elements and lymphoid follicles; in the second they contain more sclerotic tissue.

All things considered, it therefore seems clear that spontaneous myxoedema in adults is the result of non-goitrous autoimmune thyroiditis.

8. Diagnosis

It is particularly important to distinguish between myxoedema and thyroid insufficiency of hypophysial origin, which can occur under the disguise of myxoedema especially in older women.[9,37] Clinical evidence rarely offers an adequate basis for a firm differential diagnosis. However, a hypophysial origin may be suggested by other signs of pituitary failure or by the clinical detection of small-sized viscera (heart, liver, and colon); the latter are frequently enlarged in primary myxoedema. Associated diabetes, pernicious anaemia, or atrophy of the gastric mucosa all argue in favour of primary thyroid atrophy.

TABLE 9.5. DIFFERENTIAL DIAGNOSIS IN PRIMARY (1) AND SECONDARY OR PITUITARY (2) HYPOTHYROIDISM

	1	2
Clinical data: Association with obesity, hypertension, diabetes, pernicious anaemia	Frequent	Absent
Splanchnomegalia	Present	Absent
Function tests:		
Cholesterol (mg per 100 ml)	>300	< 250
Eosinophilia (cell per mm^3)	< 250	>250
Serum TSH	High	Nil
Stimulation test	No effect (rarely minimal)	Sometimes minimal
Serology:		
TGA	+55%[a] 80%[b]	0
CFA	+51%	5
Complement fixing antibodies	+34%	0
Gastric mucosa antibodies	+45%	2·5

[a]Valloton *et al.*[70]
[b]Personal data (34 + on 40 studied cases).

Laboratory findings offer a firmer diagnostic base. The presence of thyroid antibodies is an important element in favour of a diagnosis of primary myxoedema[70] (Table 9.5). Nevertheless, intrathyroid lymphocytic infiltrations may be found in cases of insufficiency following on a hypophysial lesion,[60] and thyroid antibodies may be present in the circulation. However, they are generally of a low titre and only exceptionally accompanied by gastric antibodies, whereas the latter are present in almost half the subjects affected with primary myxoedema. The TSH stimulation test (Fig. 9.8) yields a negative response in the majority of primary cases, but may show a slight rise in atrophic thyroids still containing some functional tissue and may occasionally fail to produce stimulation of glands whose secondary atrophy dates back some considerable time. The measurement of serum TSH levels supplies the safest indication by showing an increase in myxoedema due to atrophic thyroiditis.[48]

9. Treatment

The treatment of hypothyroidism associated with atrophic lymphocytic thyroiditis is no different in principle from the substitution treatment prescribed in other forms of hypothyroidism. However, two aspects of this particular condition should dictate greater caution than is necessary in the treatment of thyroid insufficiency occurring in young subjects after medical or surgical intervention. The first of these aspects is the partial atrophy of the adrenal cortex found in some cases, and attaining extreme degrees

in Schmidt's syndrome. The administration of small doses of cortisone acetate is advised during the first stage of thyroid treatment. The second aspect is the vascular sclerosis, especially coronary sclerosis, encountered in a large number of patients. This is undoubtedly related to the long period of latent thyroid insufficiency preceding the time when the condition becomes clinically apparent.[71] In untreated patients, myocardial infarction is no more frequent than in subjects of the same age and affected with the same ancillary disorders (hypertension, diabetes, obesity), but since the treatment steps up cardiac activity and increases heart output flow, the risk of infarction is undoubtedly greater.[28] Treatment should therefore be undertaken very gradually using slow-acting thyroxine equivalents. D-thyroxine seems preferable to L-thyroxine.[24,58,66] The doses should be increased every 3 or 4 weeks, depending on cardiac tolerance. In some cases the development of angina will necessitate reduced treatment, correcting hypothyroidism only partly but avoiding angina and preventing infarction. In cases of thyroid coma or Schwartz-Bartter's syndrome following atrophy due to thyroiditis, the recommended treatment is triiodothyronine, whose action is three to five times more powerful than that of thyroxine and the latency time reduced to 24–48 hr.[22]

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CHAPTER 10

Asymptomatic Atrophic Thyroiditis

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with an Appendix by M. HERLANT and J. L. PASTEELS

1. Introduction

The term "asymptomatic atrophic thyroiditis" is used to designate lymphocytic thyroiditis developing without clinical signs in a gland of normal size, or at least apparently normal on clinical examination.

For a long time it has been known that lymphocytic thyroiditis may be discovered in varying degrees of intensity at autopsy in patients who have died from different diseases and who had shown no signs of goitre or other thyroid disease during their lifetime[2,33] (Table 10.1).

The discovery of thyroid antibodies in the serum of subjects displaying no signs of thyroid disturbance (cf. Tables 10.2 and 10.3) has renewed interest in these studies.[19,37] The collation of histological and serological data has suggested that seemingly normal subjects in whom circulating antibodies are detected are, in fact, affected with lesions of asymptomatic thyroiditis.[4,16,19,26,31]

2. Illustrative Case Reports

CASE REPORT 10.1: SP 57,277. *Asymptomatic thyroiditis developing into definite hypothyroidism in a 74-year-old woman.*

A 74-year-old woman was admitted in March 1963 for hypochromic anaemia and sigmoid diverticulosis.

TABLE 10.1. INCIDENCE OF ATROPHIC THYROIDITIS (AT) IN AUTOPSY MATERIAL FROM GENERAL HOSPITALS

Authors	Patients	No. studied	No. with AT[a]	Incidence (%)	
Bastenie, 1937[2]	M	192	27	14	25
	F	198	64	34	
Williams and Doniach, 1962[37]	M	724		6	
	F			22	
Malaisse-Lagae, 1965[3]	M + F	311	55	25	
Chailly, 1967[4]	M + F	390	91	26	

[a] In about 10% of cases the thyroiditis is of marked degree (i.e. = 2·5% of total autopsy material).

TABLE 10.2. THYROID AUTOANTIBODIES IN THE SERUM OF SUBJECTS WITHOUT THYROID DISEASES

Authors	Methods	Patients	No.	TA (%)
Roitt and Doniach, 1958[30]	TCR	M & F	146	5·5
Owen and Smart, 1958[28]	TRC	M & F	52	6
Goudie *et al.*, 1959[19]	CF	M & F	485	7
Blizzard *et al.*, 1959[7]	TRC		219	
Hackett *et al.*, 1960[21]	TRC	M & F[a]	337	18
Hackett *et al.*, 1960[20]	CF	M & F[a]	945	11
Hill, 1961[23]	TRC	M[b]	706	8 } 6
		F[b]	591	3 }
Nève *et al.*, 1966[26]	TRC	F[a]	430	16
Bastenie *et al.*, 1967[4]	TRC	M & F[a]	785	12

[a] The sera originated from in-patients admitted for miscellaneous non-thyroid diseases.
[b] The sera studied in this investigation were sent to the laboratory for blood grouping in view of surgical treatment or for Wasserman test.

TABLE 10.3. THYROID ANTIBODIES IN THE SERUM OF PATIENTS ADMITTED FOR VARIOUS (NON-THYROID) DISEASES AND IN HEALTHY BLOOD DONORS

	Female subjects			Male subjects		
	Total number studied	TGA (≥1/125)	Incidence (%)	Total number studied	TGA (≥1/125)	Incidence (%)
Patients						
I. 1963	397	63	16			
II. 1963–4	590	87	15	205	9	4·5
III. 1964–5	687	111	16	421	23	5·5
Total	1674	261	15·5	626	32	5
Blood donors						
III. 1964–5				134	3	2·2

The routine examinations revealed a positive Hanger response, an increase of serum gammaglobulins (26% = 1·9 g per 100 ml), and the presence of thyroglobulin antibodies (1/78125). Radioactive iodine uptake was normal and the serum cholesterol level was low. A year later the patient was admitted with definite signs of myxoedema.

The Kahn reaction was positive, PBI was 1·3 g per 100 ml and radioactive iodine uptake was down to zero (cf. patient 4 of Table 10.4).

CASE REPORT 10.2:SP 27287. *Lymphocytic thyroiditis discovered by serum tests and biopsy in a woman affected with pernicious anaemia.*

In this case an obese 74-year-old woman admitted with the diagnosis of pernicious

TABLE 10.4. DEVELOPMENT OF CLINICAL HYPOTHYROIDISM IN PATIENTS WITH ASYMPTOMATIC ATROPHIC THYROIDITIS

Name	Sex Dates of investigation	Age	Clinical data	TGA[a]	Cholest. (mg per 100 ml)	Serum $PB^{127}I$ (μg per 100 ml)	BMR (± %)	^{131}I Uptake (% dose per 24 hr)
1. Nsch. F.	F	76	Diabetes					
64818	1965		Posthepat. cirrhosis	78125	278		− 5	
	1966		Hypothyroidism	3125	316	2·5		16[a]
2. Bar. L.	F	43	Addison's disease		308		− 9	59
57207	1962							
	1963		Addison treated	3125			−12	
	1965		Addison treated Mild hypothyroidism	78125	311	3·3	−23	35
	1966		Hypothyroidism	78125	350	2·4		41
3. Vand. M.	F	78						
48282	1960		Diabetes. Obesity					
	1962		Gout. Diabetes	125				
	1964		Hypothyroidism	78125	635	2·4		6
4. Cru. C.	F	75						
57277	1963		Latent diabetes Anaemia	78125	177			41
	1964		Hypothyroidism	78125	240	1·3		9

anaemia: erythrocytes, 1,850,000 per mm^3; Hb, 5 g per 100 ml; leucocytes, 2,400 per mm^3 of which 35% lymphocytes and 4% metamyeolocytes; sternal puncture, 24·5% of megaloblasts; total bilirubin, 2·2 mg per 100 ml of which 2 mg indirect; Histamine fast achlorhydria.

The thyroid was not enlarged and there were no signs of hypothyroidism. Thyroglobulin antibodies were present in the titre of 1/78125. $PB^{127}I$, 4·3 μg per 100 ml; ^{131}I uptake, 7·8% at 24 hr; $PB^{131}I$, 0·18% of the dose per litre at 24 hr.

A thyroid biopsy showed extensive lesions of chronic thyroiditis, with lymphocytic infiltrations around small vesicles and fairly pronounced fibrosis.

3. Clinical Features

Although by definition asymptomatic, latent lymphocytic thyroiditis offers considerable clinical interest due to the complications it may carry, namely definite hypothyroidism (cf. Table 10.4) or atherosclerosis particularly in the coronary arteries (cf. Chapter 11).

The frequency of asymptomatic lymphocytic thyroiditis varies little, at least according to the histological criteria used by different authors (cf. Table 10.1). In Brussels the rate has kept very steady for 30 years (25% of autopsy material). Virtually 10% of these cases have shown large focal or diffuse infiltrations. Williams and Doniach[37] and Masi *et al.*[25] have observed similar figures. Doniach and Roitt[17] class the latter types of lesions under the heading of severe atrophic thyroiditis. But no clear serological or morphological limit can be established between the stages of different intensity.

Table 10.3 gives the frequency of thyroglobulin antibodies[9] discovered in subjects admitted to this hospital for a variety of non-thyroid diseases. The figures were collected during investigation periods of 3–4 months, when all the patients admitted were tested systematically. Table 10.5 shows the results of a fresh series of investigations in 1967–8, when tests were made for cytoplasmic antibodies as well as thyroglobulin antibodies. The TGA overall frequency of 15% in women and 5% in men increases with age, particularly in the over 50 group (Table 10.6).

In a number of cases, comparisons of post-mortem data showed good correspondence between serum anomalies and morphological changes (Table 10.7). The odd exceptions may be explained by the limits of routine pathological examinations or by a defective serological technique.

TABLE 10.5. INCIDENCE OF CIRCULATING THYROID ANTIBODIES (THYROGLOBULIN AND CYTOPLASMIC) IN MALE AND FEMALE PATIENTS ADMITTED FOR NON-THYROID DISEASES

Male patients	TGA + CFA		Female patients	TGA + CFA	
	Present	%		Present	%
400	40	10	406	79	20

TABLE 10.6. INCIDENCE OF THYROGLOBULIN ANTIBODIES IN HOSPITALIZED PATIENTS IN RELATION TO AGE

	Age group						Total	% mean
	15–39	40–49	50–59	60–69	70–79	80–89		
Male cases studied	68	58	96	101	65	33	421	
TGA +	2	3	6	5	7	0	23	
Incidence (%)	3	5	6	5	9			5·5
Female cases studied	261	154	175	239	273	175	1277	
TGA +	24	17	23	33	64	37	198	
Incidence %	9	11	13	14	23	21		15·5

TABLE 10.7. CORRESPONDENCE OF CIRCULATING (TGA) AND LESIONS OF THYROIDITIS IN 246 ROUTINE AUTOPSY CASES

Titre of serum TGA	Thyroiditis			Total	Incidence (%)
	0[a]	I[b]	II[c]		
0–1/25	172	21	3	24/196	12
1/125–1/1625	5	9	76	15/20	75
1/78125	1	14	15	29/30	96

[a] No lesions except subcapsular infiltrates in four cases.
[b] Focal lesions of moderate intensity (cf. Fig. 10.1).
[c] Focal or diffuse lesions of marked intensity (cf. Fig. 10.3A).
Statistical analysis: χ^2, $p < 0{\cdot}001$.

This statistical material bears out the idea that a thyroglobulin antibody titre of 1/125 or over, in the serum of any patient, indicates the existence of lesions of lymphocytic thyroiditis.[4,26] The presence of cytoplasmic antibodies, demonstrated by the complement fixation test[19] or by immunofluorescence (personal observations), also constitutes a faithful serological indication of thyroiditis lesions.

In normal subjects, circulating antibodies are found almost as frequently as in hospital patients.[15,32] According to several authors,[30,31] patches of lymphocytic thyroiditis detected in normal subjects or in patients affected with non-thyroid disorders merely represent non-progressive lesions with no clinical significance. This is true only in certain cases. In others the lesions are sufficiently advanced to produce a condition of latent hypothyroidism, liable to develop into definite myxoedema (cf. Table 10.4).

4. Pathology

Whereas Hashimoto's thyroiditis is characterized by visible enlargement of the thyroid gland, most cases of atrophic thyroiditis show no macroscopic changes. Half the

TABLE 10.8. WEIGHT OF THE THYROID GLAND IN FORTY-NINE AUTOPSY CASES WITH CIRCULATING TGA

Weight (g)	< 15	15–30	> 30
Number of cases studied	19	22	8[a]

[a] These eight cases represent colloid goitre with superimposed thyroiditis which escaped clinical examination. None of the glands had the characteristics of Hashimoto's thyroiditis.

glands maintain a normal weight, and quite a number decrease in weight and size (Table 10.8).

Microscopical lesions consist of tissue alterations with oncocytic metaplasia, lymphoid infiltrations, and varying degrees of fibrosis (Figs. 10.1 and 10.2). The latter phenomenon is absent if the lesions are small and focal. Parenchymatous lesions, although sometimes discrete, are observed regularly in serial sections. In the affected parts, the thyroid follicles are reduced in size and contain little colloid (Fig. 10.1), whilst the areas unaffected by thyroiditis show a normal structure. Under high-power, the essential lesions of focal thyroiditis are indistinguishable from those of Hashimoto's thyroiditis.[2,25]

Electron microscopy in the two conditions reveals the same alterations.[27] Figures 10.4 and 10.5 illustrate these points.

Specific morphological changes occur in the pituitary gland of subjects affected with chronic asymptomatic thyroiditis (cf. Appendix, pp. 251-260).

5. Laboratory Findings and Immunology

Laboratory findings are confused in these cases by the influence of the diseases for which the patients were admitted to hospital. Nevertheless, by classing the patients into two groups, one with and the other without antibodies, but otherwise well matched for age and sex, and as far as possible for associated disorders too (diabetes, obesity, hypertension, malignancy, etc.), it can be seen that the subjects affected with thyroiditis show a significant increase in gammaglobulins and serum cholesterol (Figs. 10.6 and 10.7).

Occasionally, in subjects unaffected by any acute disease, a hitherto unexplained high sedimentation rate or positive Bordet–Wasserman reaction may be due to a process of thyroiditis (cf. Chapter 5, case report 10.1).

It is generally admitted that serological responses are of low intensity in atrophic thyroiditis.[17,18,31] Table 10.9 shows that the titre was only 1/78125 in half the cases observed in Brussels.

In twenty-five cases of this last group, subsequent dilutions were performed. Nine cases showed positive reactions for dilutions ranging from 1/390,625 to 1/1,220,703,125.

The data reported in the present study underline the high incidence of thyroid autoimmune reactions observed in subjects without thyroid disease and the often marked intensity of these reactions. Thus, in contrast with current opinions, the significance of this asymptomatic thryoiditis is not to be dismissed.

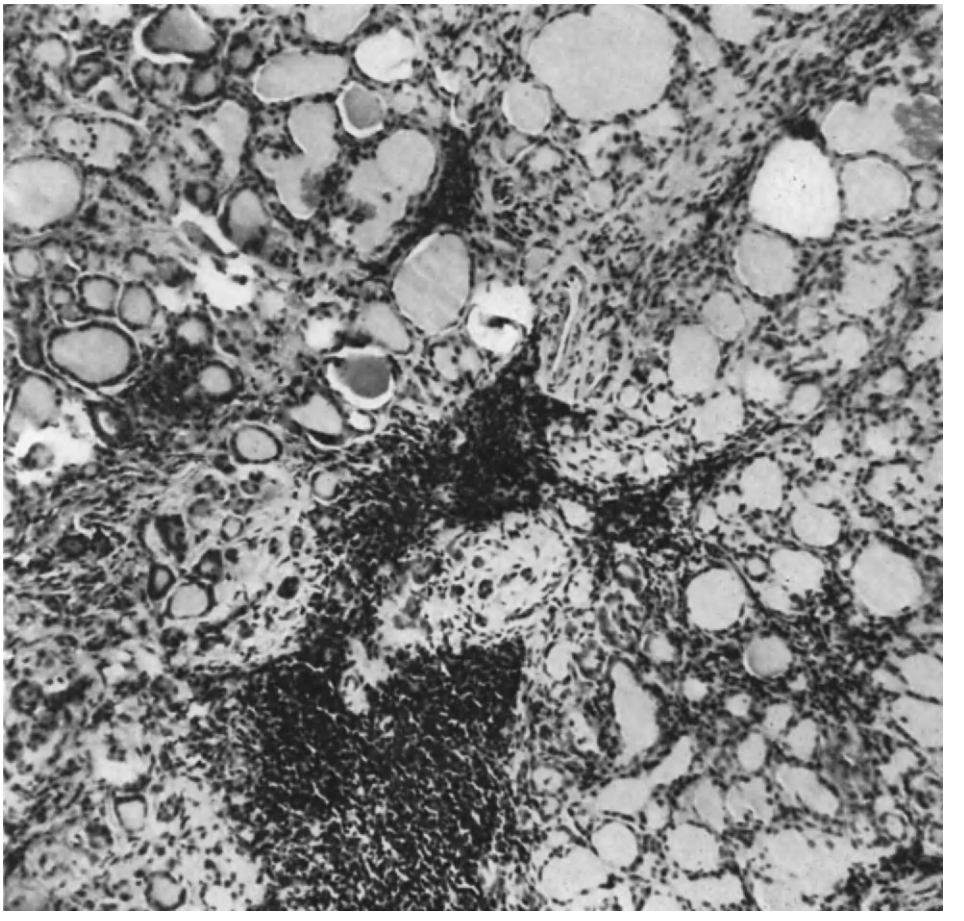

FIG. 10.1. Asymptomatic atrophic thyroiditis in a 75-year-old female. TGA, 1/78125. Moderate fibrosis, infiltrates, and Askanazy cells in the centre. Cell hyperplasia in vesicles near the infiltrates. (×120.)

6. Iodine Metabolism and Thyroid Function

Iodine metabolism in asymptomatic thyroiditis has so far been studied only by Buchanan *et al.*[11] and by Camus *et al.*[13,14] On the whole, the two research teams agree that metabolic disorders resemble those described in Hashimoto's goitre, although generally less marked.

Buchanan *et al.*[11] find the average level of plasma $PB^{127}I$ slightly below normal. In the Brussels material, the value is 5·6 μg per 100 ml $\pm$ 1·7 in seventy-nine affected subjects and 5·9 μg per 100 ml $\pm$ 1·4 in fifty-four matched reference subjects. Although the mean values are similar in both groups, a greater number of affected subjects have values below 4 g (Table 10.10). Furthermore, a certain amount of the $PB^{127}I$ results from the

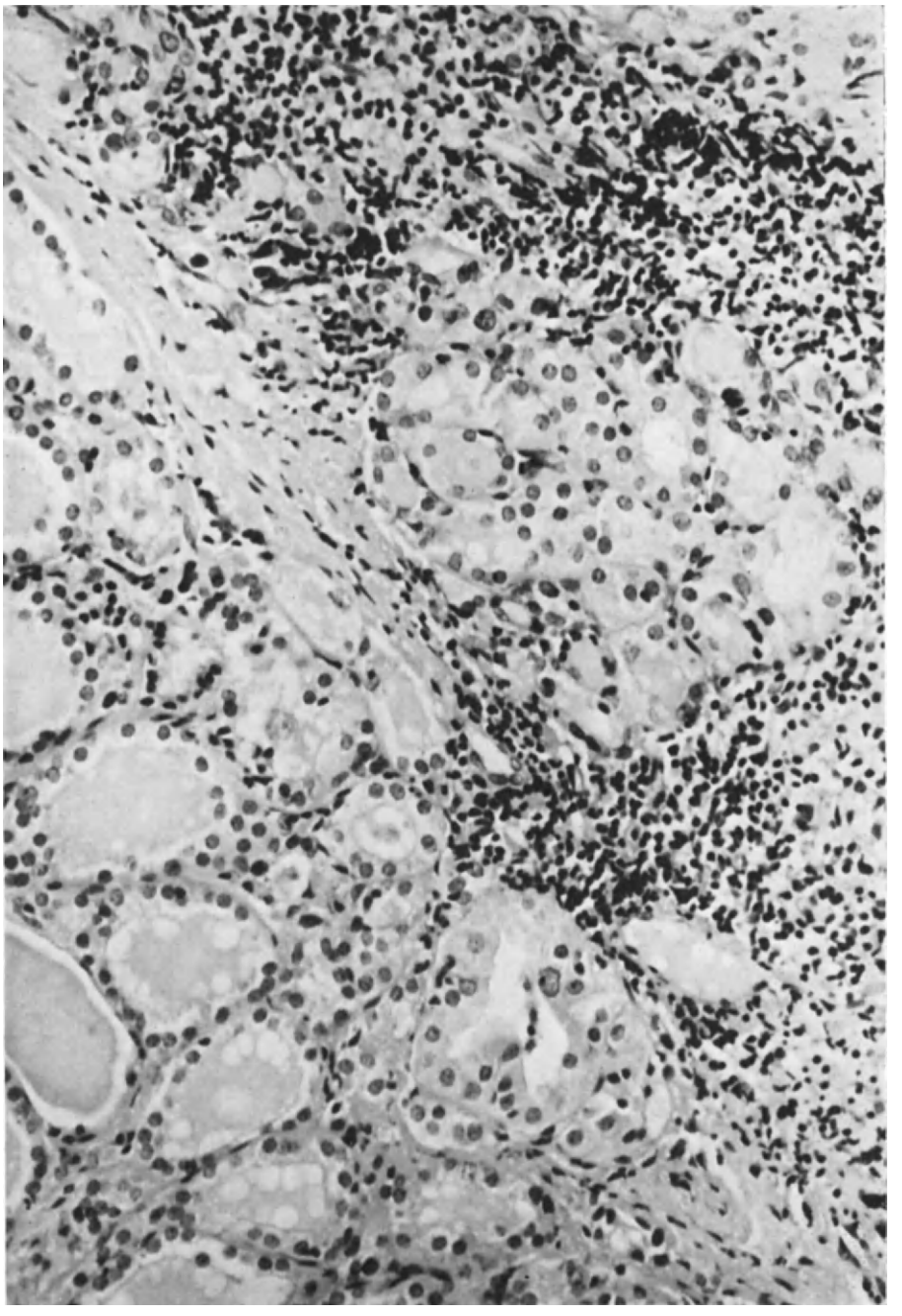

FIG. 10.2. Same case as Fig. 10.1. Oncocytic metaplasia and inflammatory infiltration. (×340.)

TABLE 10.9. TITRE OF THYROGLOBULIN ANTIBODIES IN 420 CASES OF ATROPHIC ASYMPTOMATIC THYROIDITIS

1/Titre:	25	125	625	3125	15625	⩾78125	25–78125
No. of cases:							
(1966–7)	17	39	29	14	4	84	170
(1967–8)	39	51	43	36	4	77	250
Total	56	90	72	50	8	161	420

TABLE 10.10. PLASMA $PB^{127}I$ IN NINETY-TWO PATIENTS WITHOUT (TGA −) AND IN SEVENTY-TWO PATIENTS WITH CIRCULATING THYROGLOBULIN ANTIBODIES (TGA +)

	Plasma PBI (μg per 100 ml):			Total
	< 4	4–8	8–10	
No. of patients TGA −	6 (6·5%)	80 (87%)	6 (6·5%)	92
No. of patients TGA +	13 (18%)	49 (68%)	10 (14%)	72

Statistical analysis: $\chi^2 = 6{\cdot}86$; $p < 0{\cdot}05$.

presence of non-butanol-extractable iodinated proteins (Table 10.11). Figure 10.8 shows the quantity of this material in relation to the total level of $PB^{127}I$.

Iodine kinetics have been studied in detail in a number of subjects affected with asymptomatic thyroiditis (Table 10.12). The ^{131}I uptake rate shows the same average value in the groups of affected subjects as in the reference group, although abnormally high rates are observed in a few antibody carriers (Table 10.13). These high uptakes are easily brought down by the administration of T3[36] or potassium iodide[11] (Table 10.14). In some cases perchlorate administration[29] induces abnormal iodine release; furthermore, after administration of TSH, radioiodine uptake rises only slightly at 24 hr. In certain subjects thyroid radioactivity at 24 hr is even lower after TSH than before (Fig. 10.9). This particular phenomenon is explained by the fact that radioactive material is found to be discharged very rapidly, as shown by further investigations.

Indeed, 24 hr after ^{125}I administration, the plasma radioactive PBI (expressed in per cent of the dose per litre) is statistically higher than in normal subjects. After TSH stimulation the $PB^{125}I$ rises sharply, whereas the $PB^{127}I$ increase is only moderate. Thus thyroid glands of thyroiditis patients release organic iodine with greatly increased specific activity (Fig. 10.10).

In patients with asymptomatic thyroiditis the half-life of thyroidal radioiodine is reduced to half of its normal value. The exchangeable thyroidal organic iodine pool[6] is reduced to 3·3 mg in the patients with circulating thyroglobulin antibodies; in the normal group it is of 8.1 mg (Table 10.12).

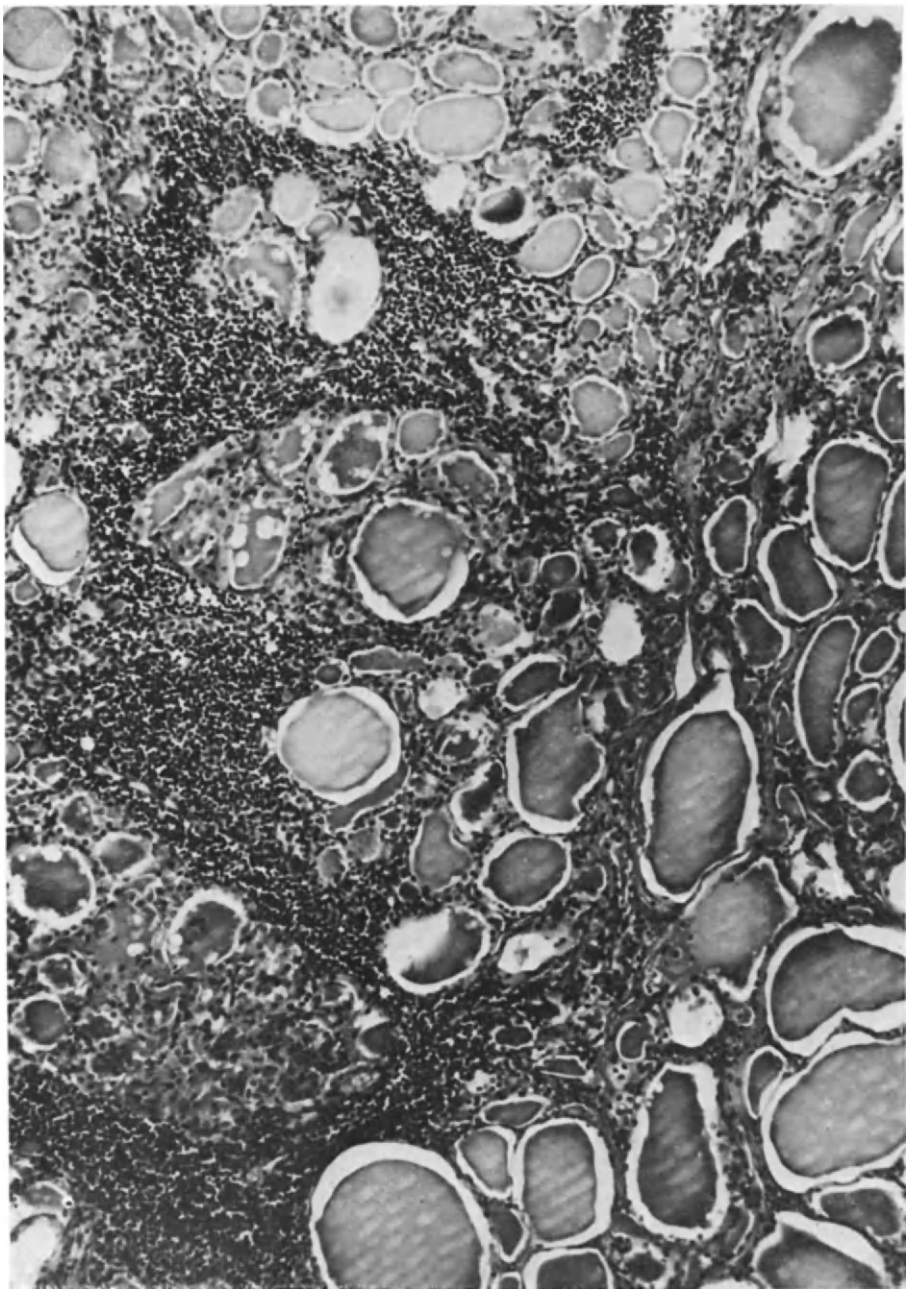

FIG. 10.3A. Autopsy—A 62192. Asymptomatic atrophic thyroiditis in a 76-year-old female. TGA: 1/78125. Lymphocytic thyroiditis with extensive oncocytic metaplasia without fibrosis. (×120.)

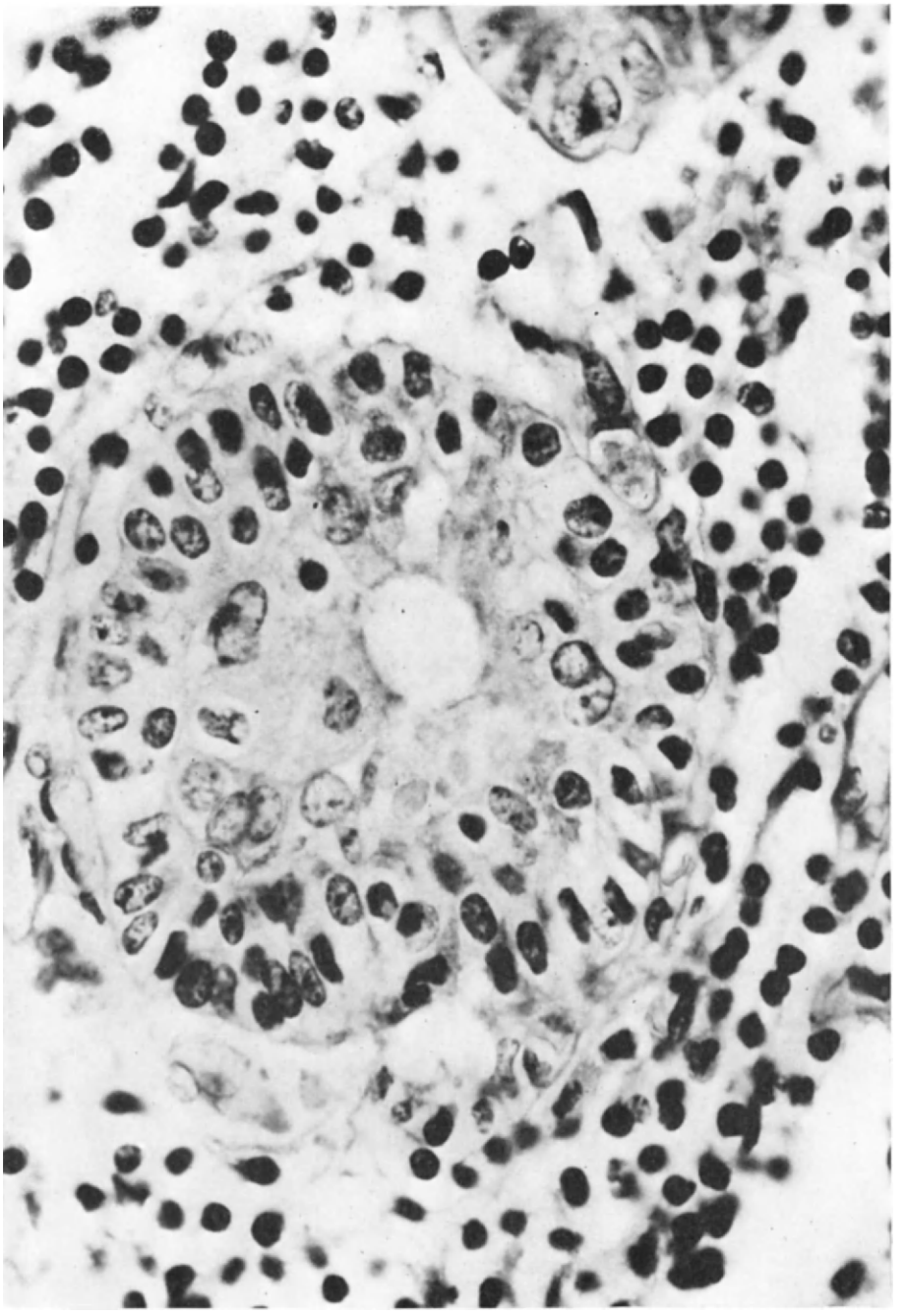

FIG. 10.3B. Autopsy 62572. Asymptomatic thyroiditis. Atypical follicle with pluristratification. Similar structures have been observed in Hashimoto's thyroiditis and in myxoedema thyroiditis. (×900.)

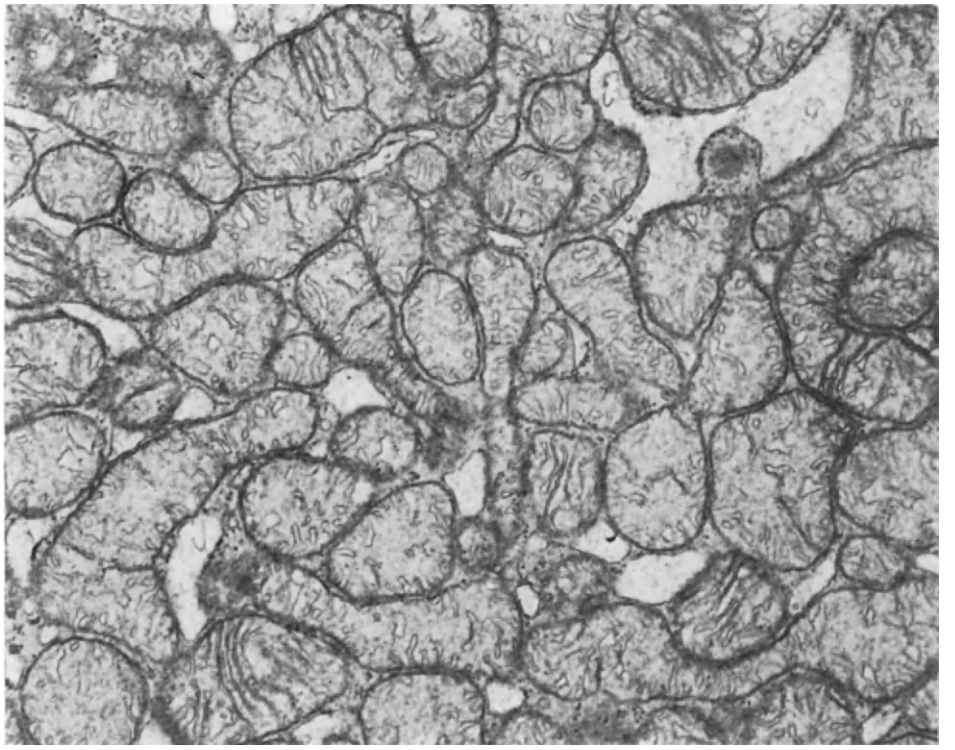

FIG. 10.4. Oncocyte cell in a case of chronic asymptomatic thyroiditis. (×18,500.)

In a number of affected patients, a significant rise in serum TSH values was noted[8] (Fig. 10.11). These data correspond well with morphological findings[3,22] and suggest that in several subjects affected with thyroiditis, relative euthyroidism is maintained only as a result of pituitary overactivity.

There are no laboratory signs of totally deficient thyroid function, although some functional defects are indicated in a number of patients by the drop in BEI, the increase in cholesterol, and the high level of thyrotropic hormone in the serum.

In these three respects, the subjects affected with asymptomatic thyroiditis are situated between normal subjects and those suffering from definite hypothyroidism, although individually certain asymptomatic thyroiditis patients show normal values for all three indicators.

TABLE 10.11. SERUM PBI AND BEI IN ASYMPTOMATIC THYROIDITIS

	No. studied	PBI	BEI	BEI (%)
Asymptomatic thyroiditis	17	7 ± 2·3	5·1 ± 1·8	73 ± 15
Control subjects	18	6·3 ± 1·4	5·6 ± 1·5	93 ± 6

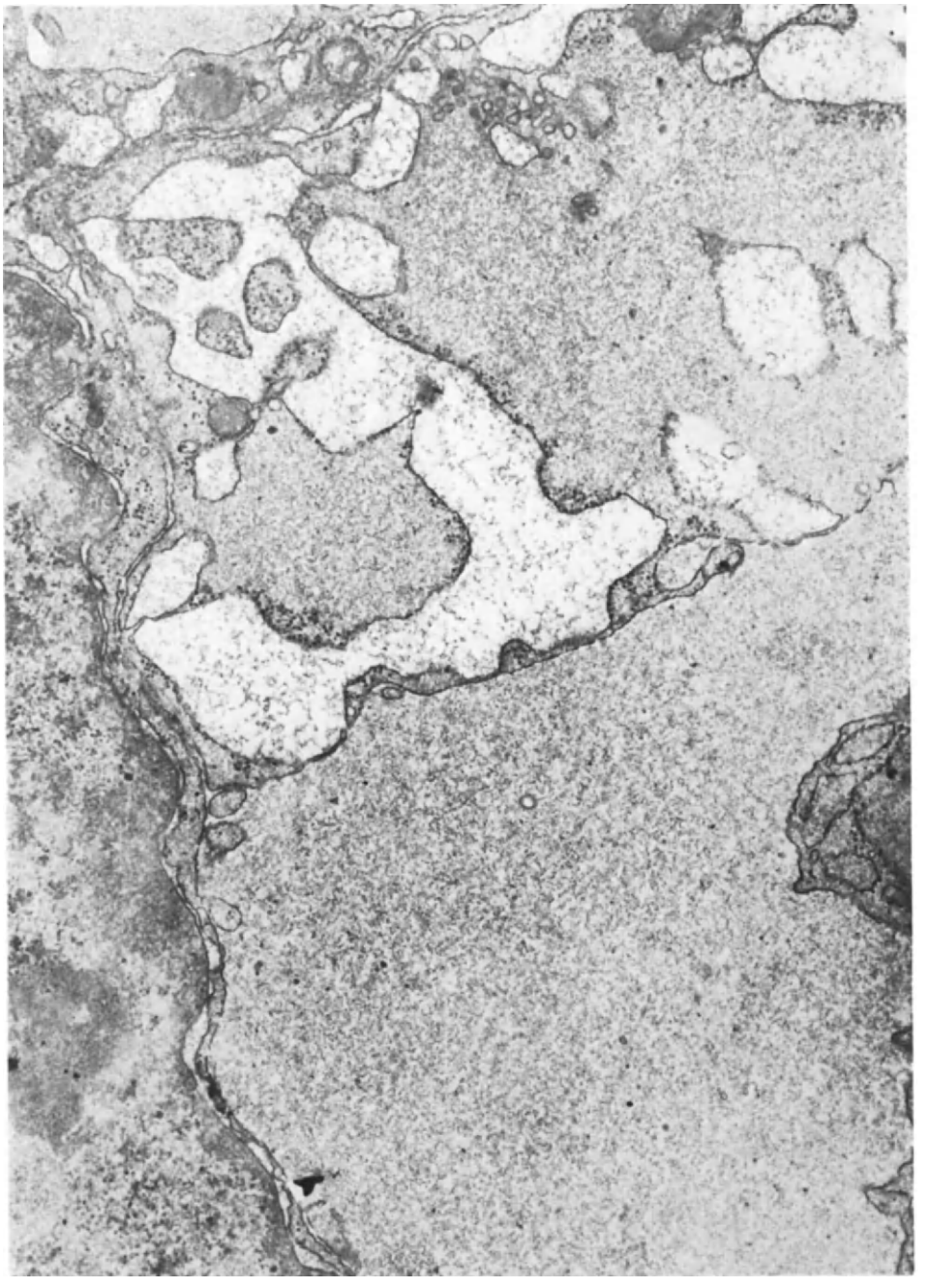

FIG. 10.5. Chronic asymptomatic thyroiditis cells with large homogeneous hyaloplasmic areas: colloid cells. (×20,700.)

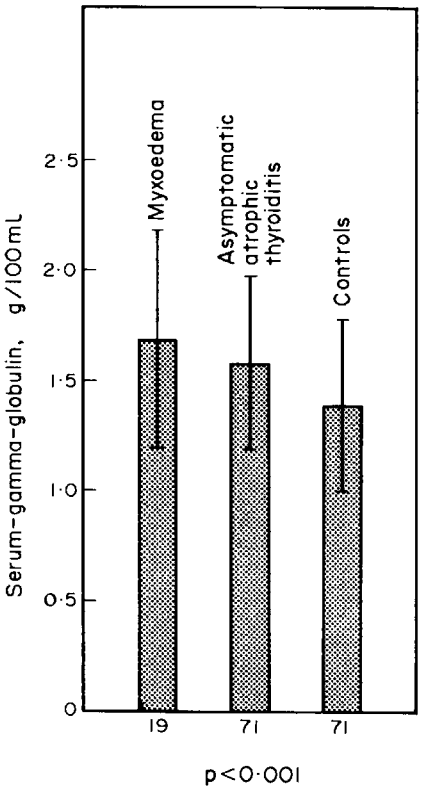

FIG. 10.6. Serum gammaglobulins in patients with myxoedema or asymptomatic thyroiditis, and in matched controls.

To estimate the degree to which the gland is affected, several means may be employed: measurement of serum TSH (hitherto not available for routine diagnosis), measurement of cholesterol (depends on accompanying disorders), estimation of the antibody titre (liable to vary considerably), and, finally, measurement of the capacity of the gland's response to TSH administration. Doniach and Roitt[18] recommend the latter test to assess the reserve of a gland affected with thyroiditis. The absence of response to thyrotropin injections observed in a number of asymptomatic atrophic thyroiditis cases is taken to indicate "low thyroid reserve".[24]

However, morphological studies of glands affected with asymptomatic thyroiditis show that generally only 50% of the parenchyma is involved and that the intact tissue shows no signs of stimulation (cf. Figs. 10.1 and 10.3). Stimulation seems to be limited to the tissues surrounding lymphocytic infiltrations. Autoradiography in two deceased cases 3–6 weeks after administration of ^{125}I confirms the hypothesis that the metabolic

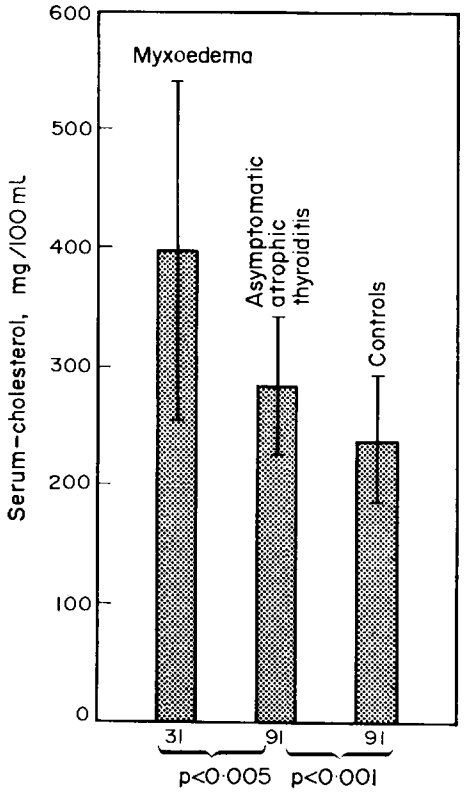

FIG. 10.7. Serum cholesterol levels in patients aged over 50, with myxoedema or chronic asymptomatic thyroiditis, and in healthy controls matched for age, sex, and associated diseases.

activity is confined to very limited areas (Fig. 10.12). In oncocytes no uptake of radioiodine has been observed.

The reasons why thyrotropic action might be concentrated on such localized regions are unknown. Consequently, an abnormal response to TSH stimulation—albeit compatible with the existence of asymptomatic thyroiditis lesions—offers no indication of the extent of the lesions.

To sum up; in many cases of asymptomatic atrophic thyroiditis, major anomalies of iodine metabolism are observed, although these anomalies may not always be apparent in the classical routine tests. The exchangeable iodine pool is very reduced. A series of other anomalies (discharge induced by iodide and perchlorate: secretion of NBEI material) could be due to a primary defect of iodine organification. However, these anomalies could as well be a consequence of the reduced exchangeable iodine pool working under intense TSH stimulation.[14,34]

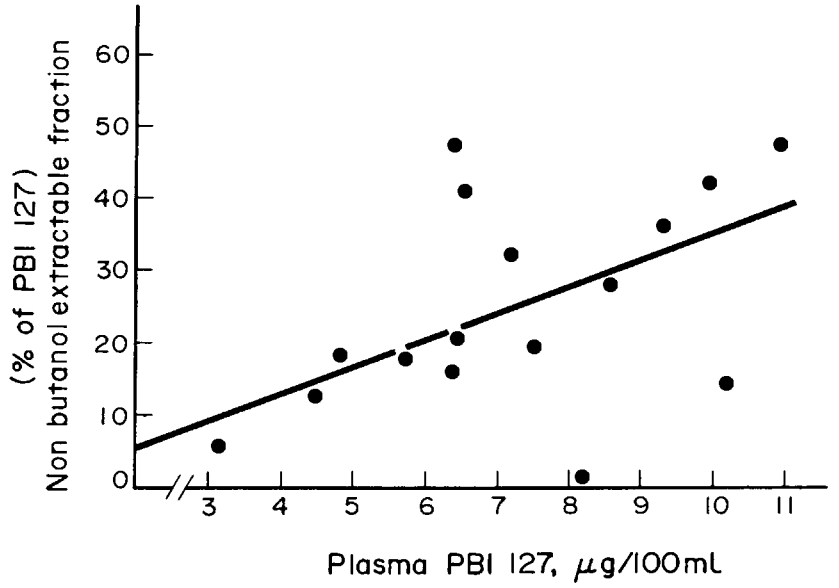

FIG. 10.8. Relationship between NBEI and PBI in plasma of fifteen patients with chronic asymptomatic thyroiditis.

TABLE 10.12.

Parameters	Units	Patients (n: 14) with negative TGA test	Patients (n: 12) with positive TGA test	Significance of difference
^{131}I thyroid uptake (24 hr)	% dose	45 ± 11	44 ± 16	$p > 0{\cdot}50$
Plasma PB^{127}I	μg per 100 ml	6·1 ± 1·6	5·4 ± 1·9	$p > 0{\cdot}20$
Urinary ^{127}I excretion	μg per 24 hr	54 ± 25	45 ± 17	$p > 0{\cdot}40$
Plasma PB^{125}I (24 hr)	% dose per l.	0·02 ± 0·10	0·10 ± 0·10	$p < 0{\cdot}025$
Plasma PB ^{125}I (4 days)		0·10 ± 0·04	0·27 ± 0·23	$p < 0{\cdot}05$
Plasma PB ^{125}I (7 days)		0·14 ± 0·03	0·38 ± 0·24	$p < 0{\cdot}05$
^{125}I Urinary excretion from 4th to 7th days	% dose per 24 hr	0·170 ± 0·070	0·460 ± 0·270	$p < 0{\cdot}10$[a]
"Apparent" release rate of thyroid ^{131}I	%/24 hr	0·46 ± 0·25	1·12 ± 0·93	$p < 0{\cdot}025$[a]
Half-life of thyroid radioiodine	days	209 ± 131	106 ± 66	$p < 0{\cdot}025$
Exchangeable thyroidal organic iodine	mg	8·1 ± 4·6	3·3 ± 3·5	$p < 0{\cdot}050$
S.A. of discharged PBI 24 hr after TSH	$\cdot 10^{-3}$ % dose per μg	6·5 ± 4·5	26·6 ± 21·4	$p < 0{\cdot}025$

[a] Estimations only obtained for six patients of each group.

TABLE 10.13. THYROID UPTAKE (24 HR) IN PATIENTS WITH AND WITHOUT CIRCULATING THYROGLOBULIN ANTIGLOBULIN TGA

Uptake % dose (24 hr):	10–30	30–60	> 60
Patients with TGA 83 { 69 ≤ 50 years 14 > 50 years Sex ratio 3F/1M	15 (18%)	52 (63%)	16 (19%)
Patients without TGA 50 { 41 ≤ 50 years 9 > 50 years Sex ratio 1F/1M	8 (16%)	36 (72%)	6 (12%)

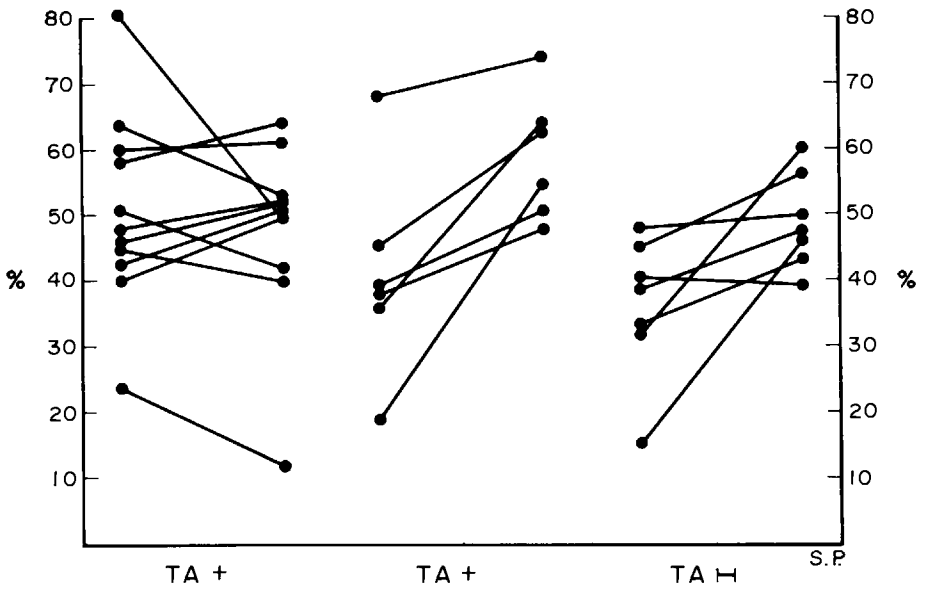

FIG. 10.9. Of seventeen subjects with circulating thyroglobulin antibodies (TA +), only six presented with a normal reaction to TSH administration. In four of the others a reduction of radioiodine content of the thyroid was observed.

TABLE 10.14. THYROID ^{131}I UPTAKE: INHIBITION OR STIMULATION TESTS EXPRESSED AS PER CENT OF CONTROL 24-HR VALUE

	Patients with negative TGA test	Patients with positive TGA test
Triiodothyronine (75 μg for 6 days)	−50[a]	−70 ± 22 (8)[b]
IK (2 mg, single oral dose)	−32 ± 8 (5)	−64 ± 20 (6)
TSH (15 USP units, IM)	+53 ± 64 (7)	+28 ± 48 (17)

[a] Werner.[36]
[b] Number of cases.

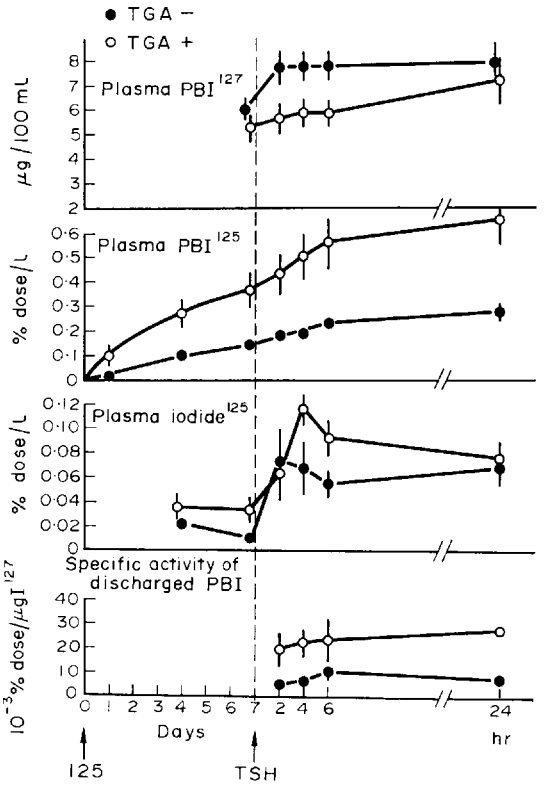

FIG. 10.10. Changes in plasma $PB^{127}I$, $PB^{125}I$, ^{125}Iodide, and specific activity of discharged PBI, induced by a single injection of TSH, 7 days after ^{125}I administration in patients with and without circulating thyroglobulin antibodies (TGA). Vertical bars indicate standard deviation of means.

TABLE 10.15. DECREASE IN THYROID ANTIBODIES IN A PATIENT WITH MYASTHENIA AND ASYMPTOMATIC THYROIDITIS TREATED WITH AZATHIOPRINE (100 mg/d)

Date	TGA	Reaction CFA
20.2.1968	1/78125	++
8.3.1968	1/625	+
20.3.1968	1/625	+
16.5.1968	1/25	neg.

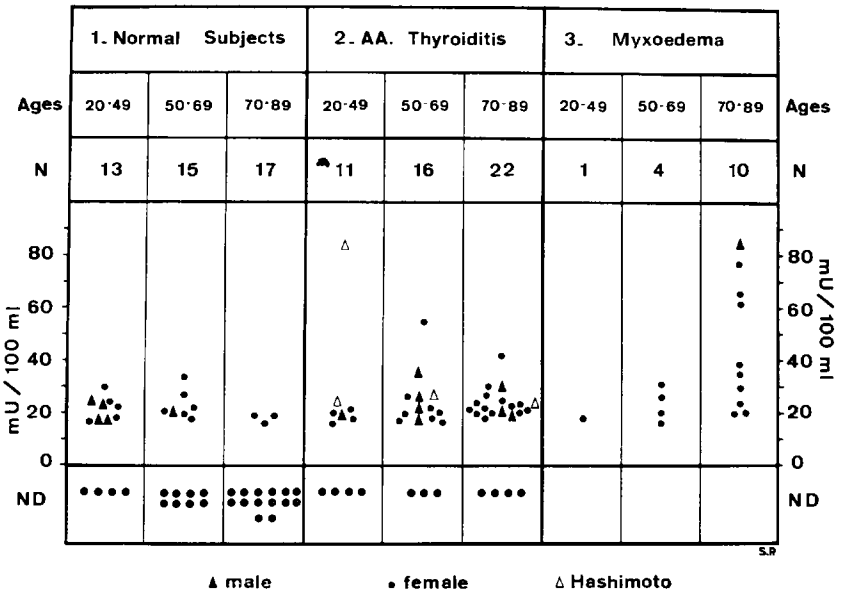

FIG. 10.11. Serum TSH levels in normal subjects, in atrophic thyroiditis and in myxoedema. In normal subjects the level does not increase with age. The contrary is observed in myxoedema thyroiditis patients.

7. Diagnosis

The definition of atrophic asymptomatic thyroiditis obviously prevents any confusion with autoimmune thyroiditis associated with a goitre, whether toxic or malignant.

The condition will be looked for in various clinical circumstances such as hypercholesterolaemia, a family history of thyroid diseases, pernicious anaemia*, myasthenia*, and, above all, if there is any clinical suspicion of latent hypothyroidism. The diagnosis

* Diseases frequently associated with thyroiditis (cf. chap. 11).

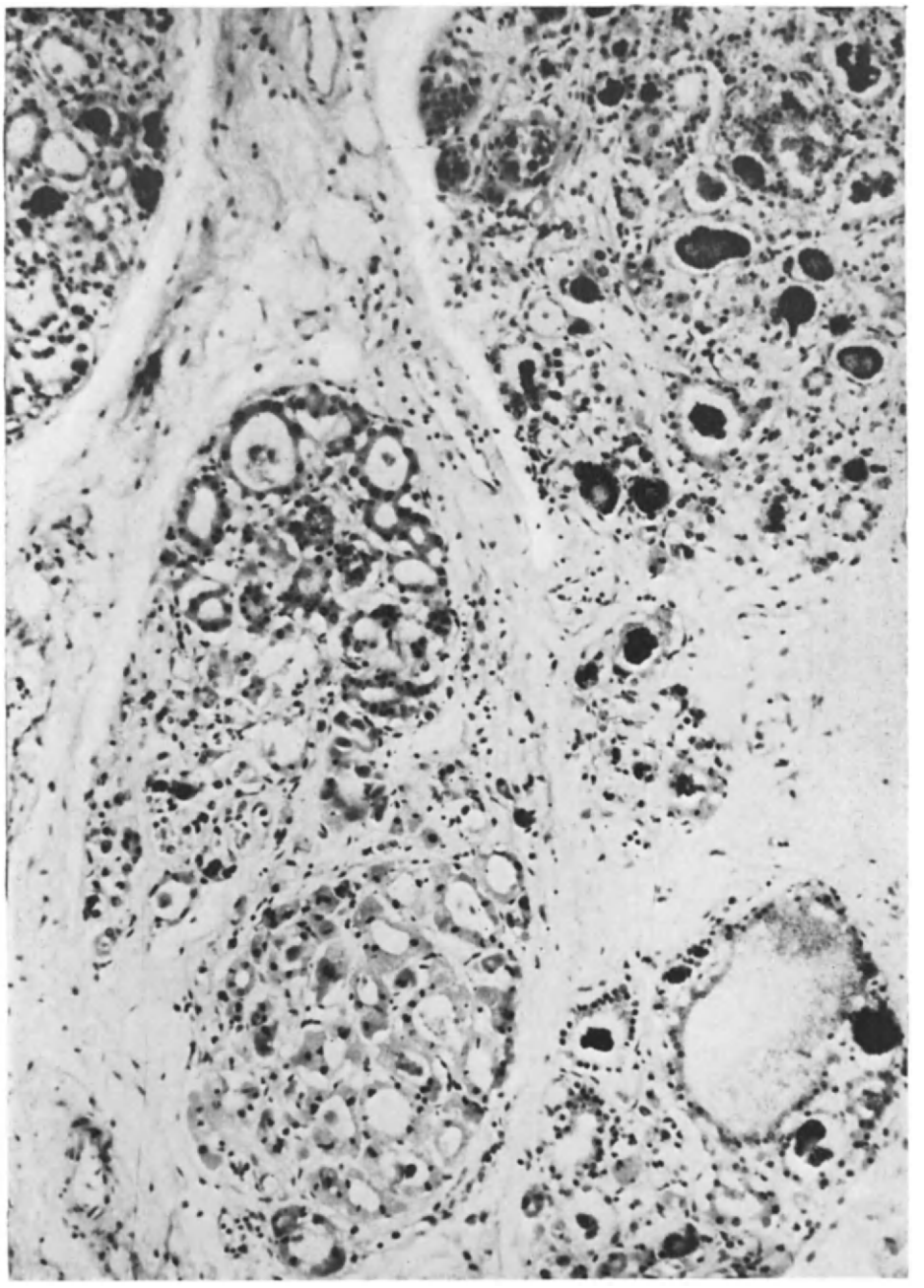

FIG. 10.12. Case report SP. 85432. Autopsy 70/178. Autoradiography of asymptomatic thyroiditis; 27 days after administration of ^{125}I. Irregular uptake of radioiodine in some vesicles usually of small or medium size. No uptake in the oncocytic tissue (upper central and left part of the picture). This 68-year-old woman was admitted in October 1969 for A-V block with Adams-Stokes syndrome and treated by implantation of a pace-maker. In February 1970 she was readmitted for thrombophlebitis, multiple pulmonary infarcts, urinary infection. She developed hemiplegia and a syndrome of inadequate ADH secretion. The presence of asymptomatic thyroiditis was indicated by high titres of TGA (1/3125) and CFA. (×140.)

will be based on the existence of a significant level of thyroid antibodies and anomalies of iodine metabolism, particularly an abnormal response to TSH injection.

Conversely, if thyroid antibodies are discovered in a patient's blood in the absence of any clinical signs of thyroid disease, thyroid function should be explored with a view to an early diagnosis of mild hypothyroidism.

8. Treatment

At first sight it may seem surprising to want to treat an asymptomatic condition. However, this particular condition is liable to progress imperceptibly into definite hypothyroidism. Furthermore, it is attended by a serious risk of atherosclerosis, especially coronary atherosclerosis (cf. Chapter 12). Treatment with small doses of thyroid hormones therefore seems justified, particularly as this is an inoffensive, relatively cheap, and easily supervised form of treatment. In any case, it is an effective way of bringing down the excessive levels of serum cholesterol usually present in a patient affected with asymptomatic thyroiditis.

Over a period of 3 years, a series of such patients were treated systematically with low doses of thyroid hormones, either in the form of thyroid powder (25–50 mg/d), triiodothyronine (25 g/d), or D-thyroxine (2–4 mg/d). Out of 24 subjects whose titres were checked on several occasions, 11 patients showed no change in their serum antibody titres and in 11 others the TGA titre fell from an average value of 1/3125 to 1/5 and the immunofluorescent antibody reaction from an intensity of ++ to +++ down to reaction of 0 to +, the reduction being observed within a space of 3–24 months.

A group of eleven subjects affected with asymptomatic thyroiditis and showing high cholesterol levels was observed regularly over 6 months. Particular precautions were taken to ensure accurate measurements of blood cholesterol. After a period of placebo administration in order to eliminate psychological and dietary factors, the patients received D-thyroxine, first of all for one month in a dose of 2 mg/d, then for a further month in a dose of 4 mg/d. After this treatment the values of cholesterol declined more sharply in the subjects affected with thyroiditis than in the control subjects.[12]

Immunosuppressive treatment is obviously only justified in exceptional cases by the necessity for treating a severe accompanying disease. This was the case of a patient affected with severe myasthenia who failed to respond to classic treatments.

Table 10.15 shows a rapid drop in thyroid antibodies which was paralleled by a spectacular improvement in the myasthenia.

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Appendix

M. HERLANT and J. L. PASTEELS

Pituitary Changes in Myxoedema and Chronic Thyroiditis

From a very early date, pathologists have observed the presence of large clear cells in the anterior pituitary lobe of hypothyroid subjects. These changes have been noted in both congenital thyroid aplasia and acquired myxoedema, and are, in fact, associated so frequently with all states of severe thyroid deficiency that since Kraus[33]—one of the earliest authors—described them in 1914 they have been customarily known by the term of "thyreoprive" cells.

However, it was not until all the cell forms in the anterior pituitary were identified that the genesis and true nature of these cells—hitherto considered as hypertrophied chromophobe elements—were properly understood.

Experimental research opened the way to our understanding of these cells. In the rat, especially, it was observed that thyroidectomy caused extensive hyperplasia and vacuolization of the basiphil cells very reminiscent of the effects produced by castration.[23,48] But since it was not known at that time that there could be several forms of basiphil cells, it was assumed that a single cell type could react in a similar way to either thyroid or gonadal deprivation. However, on comparing the cells of thyroidectomized and castrated rats, Smelser[47] had already in 1939 arrived at the conclusion that these elements were of separate origin.

This thesis was confirmed by the subsequent use of more selective histological techniques—such as the PAS and fuchsine aldehyde staining—in the study of the anterior pituitary lobe. By these techniques it was proved that the pituitary carries a distinct type of basiphil cell which—unlike the gonadotropic elements—only reacts to thyroidectomy or the administration of anti-thyroid drugs. Halmi[25] was the first to demonstrate that

in the rat these basiphil cells, which react to thyroidectomy, are the only ones stained by fuchsine aldehyde. Purves and Griesbach,[38] for their part, arrived at the same conclusion using PAS. Although all basophil cells are shown up by the PAS method on account of the mucoprotein nature of their granules, the cells reacting to thyroidectomy differ from the ones vacuolized by castration in that they are smaller in size, more irregular in shape, and have a more central location. The reaction of this type of basophil cell either to thyroidectomy or to antithyroid drugs has been observed in the most diverse animal species and especially in mammals. Amongst the first authors to note the phenomenon were Goldberg and Chaikoff (in the dog),[19] Bimes *et al.*,[5] D'Angelo (guinea-pig),[12] Halmi and Gude (mouse),[26] Serber (hamster),[44] and Racadot (cat).[41]

In the different species observed, the basophil cells react to the absence of thyroid activity by undergoing a series of constant modifications: they multiply often on a large scale, they become hypertrophied, and the hypertrophy is often accompanied by vacuolization and, above all, degranulation, making their appearance very similar to that of thyreoprive cells in man. The appearance of vacuoles and the degranulation following thyroidectomy have been confirmed by electron microscopy in the rat.[17] It has also been confirmed by electron microscopy that the cells resulting from thyroidectomy are, indeed, hyperactive elements. This conclusion was already indicated by Halmi's discovery[26] that thyroxine cancels out the pituitary changes created by hypothyroidism. But the findings of D'Angelo[12,13,14] are even more conclusive. This author compared the state of the pituitary in experimental hypothyroidism and TSH measurements in the pituitary itself or in the serum. The results are not identical in the rat and guinea-pig, but in the respective cases there is close agreement between the pituitary appearances and the TSH content of the gland. In the rat, thyroidectomy or the administration of antithyroid drugs brings about a sharp rise in the TSH content in the pituitary and a rise in the serum. This phenomenon tallies with the appearance of thyroidectomy cells and their degranulation. In the guinea-pig a rise in the plasma TSH level is also observed, but in the pituitary, after an initial fall, the TSH content becomes gradually much higher than in controls. In guinea-pigs treated with antithyroid drugs, thyroidectomy cells do indeed appear, but as they increase in size they become congested with granules.

It is now well established that the action of hypothyroidism is not direct: it works through the hypothalamus. The thyrotropic activity of the pituitary is controlled by a specific hypothalamic intermediary—TRF—which has been identified in many laboratories.[22,43,45] It further seems that, by a so far unknown mechanism, thyroid deficiency steps up the release and probably the synthesis of this intermediary. Indeed, it has been observed that the TRF content in the hypothalamus is considerably increased after thyroidectomy in the rat.[46] This explains how hypothalamic lesions can completely cancel out the thyroid hypertrophy induced by antithyroid drugs,[7,21] Normally, this hypertrophy is merely an indication of excess TSH secretion by the pituitary due to the cessation of thyroxine synthesis. This also explains how propylthiouracil treatment can have very different effects on pituitary grafts, depending on whether the latter are located in the anterior chamber of the eye or in the hypothalamus itself; it is only in this last case that the appearance of numerous thyreoprive cells has been observed.[18,24]

The experimental results just reviewed throw light on the genesis and significance of the thyreoprive cells characteristic of myxoedema in man.

They proved that these elements result from the hypertrophy of a specific form of basophil cell which may reasonably be assumed to be responsible for the secretion of thyrotropin. The hypertrophy is in fact the morphological outcome of a negative feedback process. The cells are activated by the fall in circulating thyroxine, since a thyroxine

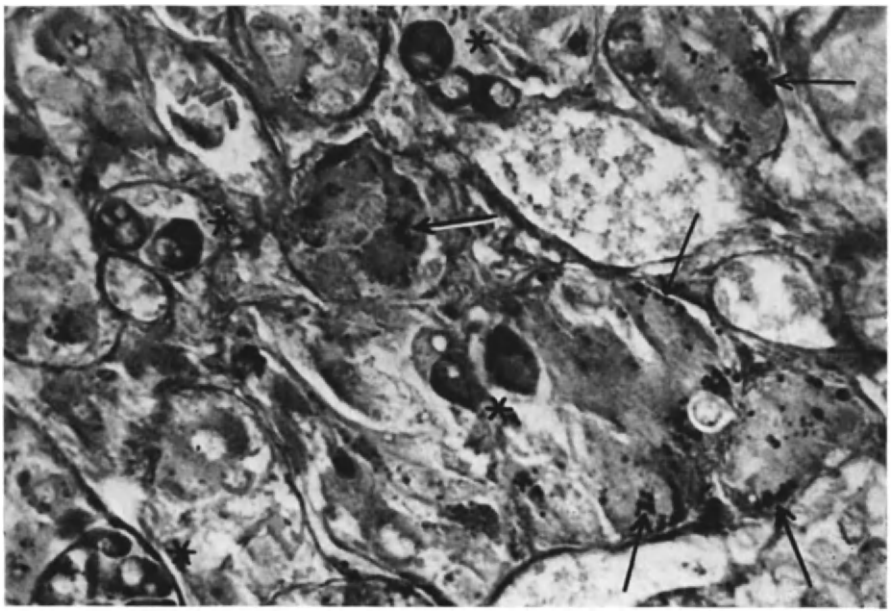

FIG. 10.A.1. Severe untreated myxoedema in a 74-year-old woman. Aldehyde thionin–PAS–Orange G staining. The clusters of large, pale cells are formed by numerous hypertrophied and degranulated thyrotrophs, containing some dark inclusions (lysosomes: arrows). The smaller and darker cells (*) belong to the β-category, and secrete MSH: they are not hypertrophied.

deficiency causes them to secrete more TSH. However, the thyroxine deficiency actually exerts its influence in the hypothalamus by provoking excess release of the intermediary which controls the secretory activity of the thyrotropic cells. So, in fact, the appearance of the thyreoprive cells is directly attributable to this excess of TRF.

Morphology of Thyroidectomy Cells in Myxoedema in Man

In cases of acquired myxoedema which have been evolving for many years, there is no difficulty in identifying thyroidectomy cells even after staining of the pituitary by an ordinary trichromic technique. The basophil effect is only slight, but sufficient to show that the anterior lobe is congested with large, clear cells often arranged in thick strands (Fig. 10.A.1, 10.A.5). The number of these cells is often so high that the gland is visibly

enlarged. This hypertrophy of the pituitary in myxoedema has been known since the last century,[10,36] and may cause enlargement of the sella turcica on radiographic examination.[42]

The reaction of these thyroidectomy cells is equally discreet when using the PAS technique.[11,27,28,39] They acquire a faintly pink colour, although the staining is much more intense in the granules of varying size which the cytoplasm of these cells often contains. It is now known that these rounded elements are lysosomes (Fig. 10.2).

Furthermore, even in cases of long-standing myxoedema, there generally persist a few more chromophil cells which seem to have kept some of their granulations. However, the PAS is not an ideal technique for showing up thyrotropic cells, even when associated with the orange G technique as we ourselves used it, and in particular when the cells are still not very plentiful and only in the process of formation. Of course, this technique enables an easy distinction between thyrotropic cells and classic cells which remain unchanged in myxoedema.[27] But other mucoid cells can react to the PAS in the same way as the thyrotrophs, particularly the FSH cells. So this method of staining does not allow a correct interpretation of the pituitary changes in partial thyroid insufficiency.

For a more accurate identification of thyrotrophs it is necessary to use histological techniques capable of showing up normal cells in a specific manner. Various such techniques have been proposed. The ones that have proved the most favourable consist in associating the PAS with acid polysaccharide colour indicators such as alcian blue[29,30,40] or thionine-aldehyde.[16,37] The elective affinity of thyrotropic cells for these stains derives from the fact that their granulations are richer in acid radicals than those of the other glycoprotein containing cells.

These two techniques produced excellent results in our investigations of a large number of pituitaries in myxoedema subjects. In particular, they show up the granulations much more precisely than the PAS used alone, and they reveal that even in long-standing cases of myxoedema there may be some thyroidectomy cells still containing a fine scattering of granulations. Furthermore, the lysosomes are more apparent than with the PAS technique, and a better idea is obtained of how abundant and widely dispersed they may be in some of the cells.

Genesis and Evolution of Thyroidectomy Cells

These changes in the thyrotropic cells are observed chiefly in patients whose myxoedema has been evolving for some years, and in such circumstances the thyrotropic cells have undergone profound transformations which make it difficult to follow the sequence of changes from the start.

In the pituitaries of subjects with no history of thyroid disease, staining with PAS–alcian blue or PAS–thionine aldehyde reveals a very different picture. The thyrotrophs are strongly chromophil and stand out sharply on account of their dark blue colour against the other mucoid cells whose colours range from violet to purple (Fig. 10.A.3). The cytoplasm appears finely granular, but in fact the granulations are invisible, which is easily explained because electron microscopy has shown that the granulations of thyro-

tropic cells are very fine and below the limit of optic resolution; the only dark granules distinguishable in these cells are lysosomes. Thyrotropic cells are further identified by their often angular and irregular shape, and they frequently appear to be bristling with elongated protuberances. Morevover, as Purves has pointed out,[40] the thyrotropic cells are mainly located in the anterior peripheral zones of the gland and are usually very scattered, rarely occurring in clusters of more than three or four cells.

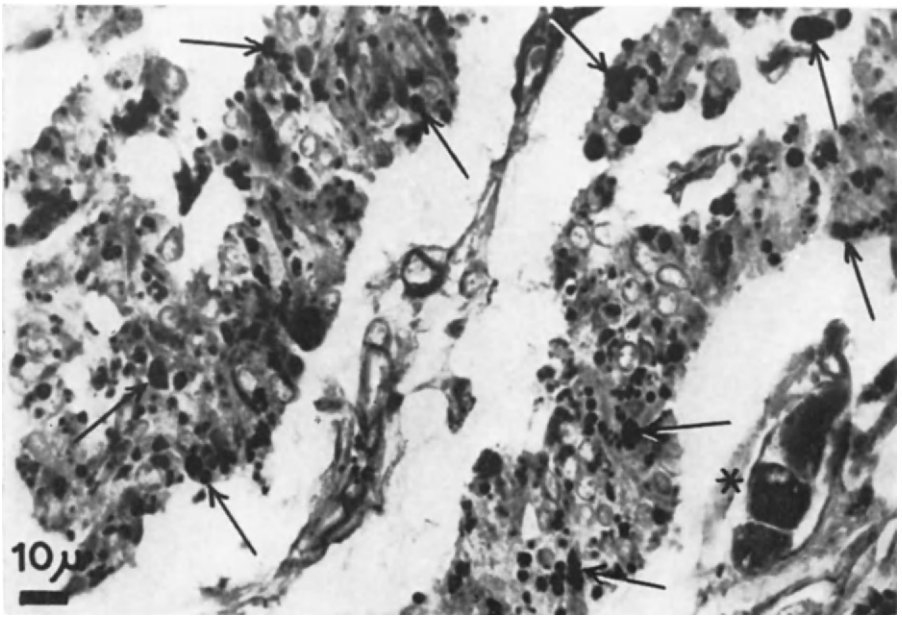

FIG. 10.A.2. Part of a thyrotrophic adenoma in a 79-year-old man, suffering severe myxoedema but treated with D-thyroxine. Despite some cadaveric alterations, the very numerous thyrotrophs, now filled with lysosomes (dark inclusions: arrows) can be easily recognized. Two features are characteristic as a result of thyroxine treatment: however numerous, the thyrotrophs are reduced in size; their small cytoplasm is filled with lysosomal material (compare with Fig. 10.A.1). Once again, MSH cells (*) are unchanged.

At first sight there hardly seem to be any common features between these cells and the ones characteristic of long-standing myxoedema. However, the opportunity arose in Brussels of examining the pituitary of an 82-year-old man in the early stages of myxoedema with a partially atrophied thyroid gland. It was possible to observe all the stages of transition between still virtually normal and granular thyrotropic cells and hypertrophied thyroidectomy cells almost free of granulations. Furthermore, even the granular thyrotropic cells were far more numerous than in the pituitary of a subject of the same age with no thyroid disorders.

This example led us on to envisage the changes that might be observed in the thyrotropic cells of patients with asymptomatic thyroiditis,[3,4] diagnosed chiefly by the detection of thyroglobulin antibodies in the blood. Unfortunately, out of the 45 cases

detected clinically in this way, and which had died of other diseases, there were only 6 whose pituitary had been preserved in satisfactory condition.

At the autopsy of these patients the thyroid showed only focal lesions with lymphocytic infiltrations and oncocytic degeneration in a few vesicles. The comparison of their pituitaries with those of subjects who may be considered as controls revealed a marked increase in the number of thyrotropic cells (Fig. 10.A.4), still occupying the anterior region of the gland, but already arranging themselves into homogeneous cords. Most of these cells were strongly chromophil but some showed incipient degranulation, the

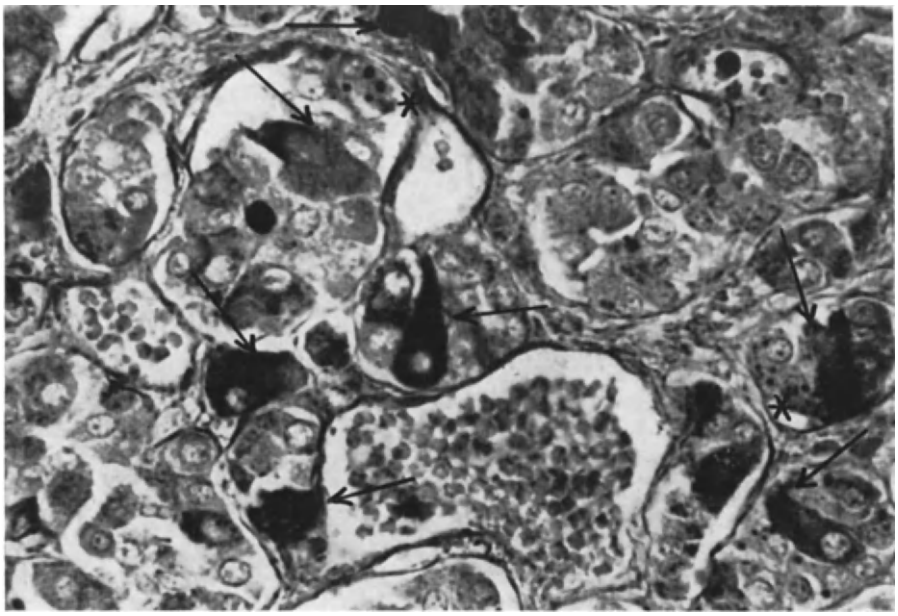

FIG. 10.A.3. Normal thyrotrophs in a 59-year-old woman. Aldehyde thionin-PAS-Orange G. In normal conditions, thyrotrophs are elongated dark cells (arrows), disseminated among the numerous other pituitary cells. They contain numerous secretory granules, intensely stained with aldehyde thionin (black) but far thinner than lysosomes. For comparison, some lyso somes can be recognized in other cells (gonadotrophs*).

presence of a large nucleolus in the nucleus, and the frequent existence of a dilated Golgi area suggesting hyperactivity.

These changes were consistent with the TSH levels measured in the serum[8] and in the pituitary,[9] all of which were above normal and very much so in the actual gland. In these patients, therefore, the histological investigations confirmed the hyperactivity of the thyrotropic cells. Not only do they accumulate hormonal material, as shown by their granular content, their hypertrophy, and the high level of TSH in the gland, but they are also in a state of hypersecretion, this being indicated by their partially degranulated hypertrophy, their nucleolus, and the size of the Golgi apparatus. This was confirmed by measurements of serum TSH.

It may therefore be concluded that in asymptomatic thyroiditis the thyrotropic cells are in the initial phase of an evolutive process whose final stage is represented by the thyroidectomy cells of myxoedema.

But the process may follow its course for years, and is hardly comparable to the effects of thyroidectomy in animals, which already appear after a very short lapse of time. In other words, there could be grounds for wondering whether the thyroidectomy cells of myxoedema in man represent hyperactive elements or exhausted cells on the way to atrophy.

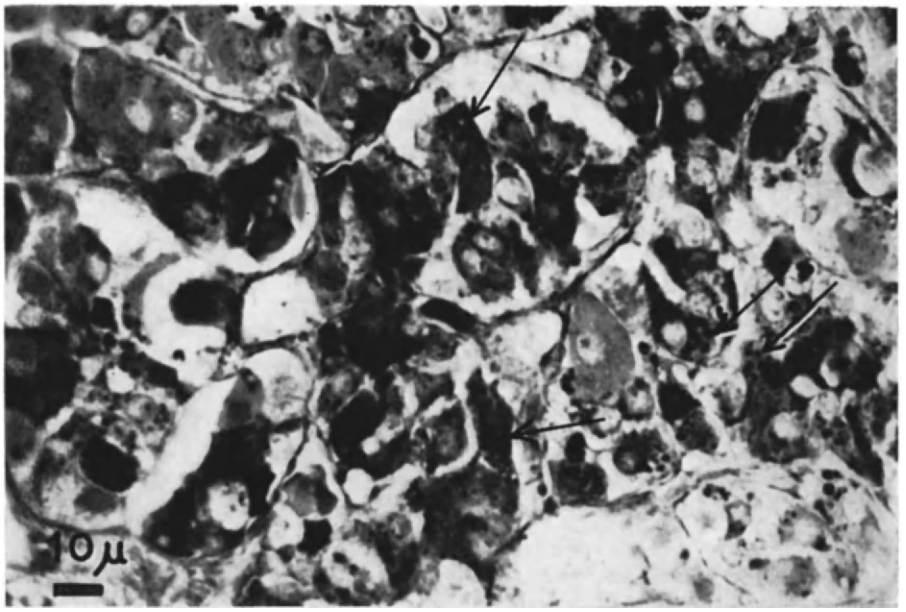

FIG. 10.A.4. Typical case of thyroiditis in a 77-year-old woman (compare with Fig. 3 and Fig. A). In this condition, thyrotrophs are obviously increased in number and in size. They are still containing abundant secretory material, and, for this reason, stained in black with aldehyde thionin. Some are already containing lysosomes (arrows). Such features are thus a transition between the normal condition and the hypertrophy of thyroid-deficiency cells.

It is classically admitted that in myxoedema there is a rise in plasma TSH which would fit in with the hypothesis of thyroidectomy cells being hyperactive. However, treatment with thyroxine or triiodothyronine inhibits hypersecretion of TSH and brings it down to an undetectable level in the serum. In this connection, we compared the pituitary of a 75-year-old myxoedema patient who had received large doses of D-thyroxine with those of untreated myxoedema patients of the same age. The pituitary of the treated case showed marked atrophy of the thyroidectomy cells; they were much reduced in size and congested with lysosomes, although none showed granular repletion.[30] It may thus be concluded that in the absence of treatment, the thyroidectomy cells of myxoedema closely resemble activated thyrotropic cells.

Thyroidectomy cells in myxoedema are not necessarily elements at the end of their evolution. As in animals, tumours of thyrotropic cells, secreting vast quantities of TSH into the blood, may appear as a result of radiothyroidectomy,[20] surgical thyroidectomy,[15] antithyroid drugs,[35] or even an iodine-deficient diet;[2] the proliferation of thyrotropic cells in myxoedema in man can lead to the formation of a real adenoma. Usually these are very small and detected only at autopsy.[42] A microadenoma of this type with cells showing the same atrophic involution as the neighbouring thyroidectomy cells, was found in the pituitary of the myxoedema patients treated with D-thyroxine mentioned in the previous paragraph (Fig. 10.A.5). Such a finding suggests that these adenoma are functional. They are most often observed in patients with untreated myxoedema of many years' standing. Their formation apparently needs a long period of time, and there has been no evidence so far of a case of acquired myxoedema entailing the appearance of a pituitary tumour large enough to justify surgery. The same is not true of congenital myxoedema. Autopsy discoveries of large allegedly chromophobic adenomas have been reported on several occasions in cases of congenital myxoedema.[1,11,32] However, in three similar cases the pituitary adenoma was diagnosed *in vivo* and removed by surgery.[6,31,34] In two of these, the histological examination showed that the tumour was composed of hypertrophied and partially degranulated thyrotropic cells.

Conclusions

It may be concluded from this appendix that the invasion of the human pituitary by thyroidectomy cells in myxoedema is conditioned by the same mechanism as that which causes the multiplication and hypertrophy of thyrotropic cells in animals subjected to thyroidectomy or antithyroid drugs. Furthermore, in both man and animals, the thyroidectomy cells are by no means elements in the course of involution but hyperactive cells capable of releasing excess TSH into the blood.

So it must be assumed that, in humans, too, the appearance of thyroidectomy cells reflects stimulation of the hypothalamic centres controlling the thyrotropic activity of the pituitary and that these centres react to thyroxine deficiency by releasing excess TRF. This conclusion confirms the humoral nature of the control exercised by the hypothalamus over the thyrotropic activity of the pituitary. It must be admitted that in myxoedema the excess release of the intermediary factor may continue for years. Furthermore, the fact that in an old man with acquired myxoedema the thyrotropic cells show the same changes as in a young subject with congenital myxoedema reveals that the response of the hypothalamic centres to thyroid deficiency remains just as strong even in old age.

The example of asymptomatic thyroiditis further suggests that the mechanism is probably exceedingly sensitive. The number of well-preserved pituitaries at our disposal has so far been insufficient to be categorical in our conclusions. But there is no doubt that in these cases the thyrotropic cells are stimulated. True the degree of stimulation cannot be compared to that observed in myxoedema, but it results in the hypertrophy of the thyrotropic cells and their enrichment in granular material, and also in signs of functional hyperactivity, appearances in perfect accord with the results of TSH measurements both

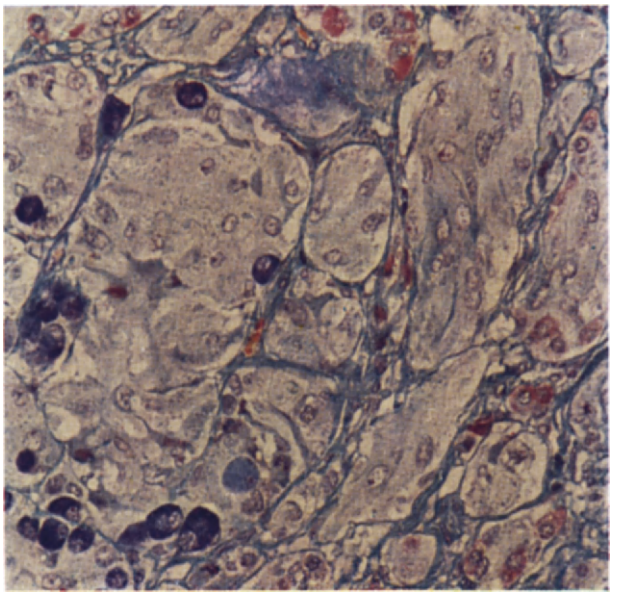

FIG. 10.A.5. Colour plate of FIG. 10.A.1.

in the blood[8] and in the pituitary itself.[9] And yet in these cases the thyroid deficiency was only incipient, solely detectable by the presence of thyroglobulin antibodies in the blood and by an inconstant drop in the PBI. Such observations apparently imply that in man the hypothalamic centres controlling the thyrotropic activity of the pituitary can react to a very partial diminution of thyroid hormone secretion.

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CHAPTER 11

Diseases Associated with Autoimmune Thyroiditis

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1. Introduction

There are several diseases whose association with one or another form of autoimmune thyroiditis seems to attain too great a frequency to be the result of chance.

However, most of the studies dealing with such associations fail to define the thyroid condition with sufficient precision. The term "Hashimoto's thyroiditis" is too often used to mean lymphocytic thyroiditis, even in the absence of goitre. The associated diseases themselves fall into several groups:

(1) Organ-specific autoimmune diseases such as adreno-cortical deficiency, gastritis.
(2) Non-organ-specific autoimmune diseases such as systemic lupus erythematosus (SLE), or certain other collagen diseases.
(3) Metabolic diseases such as diabetes and obesity.
(4) Diseases characterized by a chromosomal anomaly in the offspring of subjects affected with thyroiditis or in certain patients themselves. These diseases form a very particular section of pathology studied in Chapter 13.

Hypertension and atherosclerosis (especially coronary heart disease) have only been reported in association with atrophic forms of thyroiditis (cf. Chapter 12).

Generally speaking, associations between thyroiditis and other autoimmune diseases have been reported first of all as isolated cases, then in statistics based on hospital material. Masi *et al.*[60] are strongly critical of the value of either type of observation. Sporadic reports showing the combination of several diseases attract considerable interest amongst clinicians and tend to give a false idea of the real significance of the associations. Thus Mulhern *et al.*,[64] in contrast to other authors, find no particular diseases associated with Hashimoto's goitre in subjects observed regularly at thyroid disease clinics. As for hospital surveys, Mulhern *et al.* criticize the fact that they generally do not comprise exactly matched controls, that they ignore the economic and psychological factors which influence consultation by the patient, and that they ignore the bias introduced in the statistics by the very fact that university hospitals will attract the more exceptional cases. The severe criticisms which must be laid against these authors in their turn, in view of their confusion of the different variants of lymphocytic thyroiditis, and the variety of sources from which they derive their material—clinical, surgical, and post-mortem—have already been set forth in Chapter 5. Nevertheless, many of the observations of Masi

et al.[60] are pertinent, and statistical studies seeking significant associations must be viewed with exceeding caution.

2. Illustrative Case Reports

CASE REPORT 11.1: SP 63,120. *Thymome, asymptomatic thyroiditis, and Sjögren syndrome in a patient with myasthenia gravis.*[32]

A 44-year-old patient was admitted to hospital for the first time in 1964. At the age of 30 she had been treated medically for hyperthyroidism. In 1964 myasthenia gravis was diagnosed on the basis of severe clinical symptoms, a positive Tensilon test, a typical electrodiagnosis, and characteristic changes in the muscle biopsy. Thymoma (discovered by radiology) and asymptomatic thyroiditis (Table 11.1) were also diagnosed.

TABLE 11.1. ASYMPTOMATIC THYROIDITIS IN A PATIENT WITH MYASTHENIA GRAVIS (TGA + ⩾1/78·125; serum $PB^{127}I$, 4·8 μg per 100 ml)

	^{131}I uptake (% per dose)		$PB^{131}I$ (% dose per l. per 24 hr)	Conversion rate (% per 24 hr)
	6 hr	24 hr		
17.12.1964	46	60	0·11	29
22.12.1964 (TSH)	53	61	0·68	80
5.1.1965 (T3)	11	23		

Treatment with high doses of pyridostigmine bromide (Mestinon ®) and Prostigmine gave satisfactory results until March 1966 when the patient was readmitted for pneumonia. At this time, the Sjögren syndrome was also present. The patient died of respiratory failure. The autopsy showed the existence of a thymome (40 g) with pleural and pulmonary infiltrations, an atrophic thyroiditis (9·5 g) with fibrosis and diffuse lymphoid infiltration, but with no germinal centres.

CASE REPORT 11.2: SP 80,087. *Thyroiditis and Addison's disease (Schmidt syndrome) in a 23-year-old diabetic patient.*[24]

A 23-year-old man was admitted in January 1968 for Addisonian crisis and diabetes. Adrenocortical insufficiency had been diagnosed 2 years previously and treated with cortisone acetate (37·5 mg/d). In October 1967 the patient developed diabetic coma; afterwards, the diabetic condition required 40 *u* of insulin daily. Thyroid (TGA, CFA) and adrenal cortex (ACA) antibodies were present (Table 11.2).

3. Clinical Features

I. Association with Organ-specific Autoimmune Diseases

Pernicious anaemia

In an earlier study,[6] out of 100 cases of asymptomatic lymphocytic thyroiditis

TABLE 11.2. IMMUNOLOGICAL REACTIONS IN A PATIENT AFFECTED WITH COINCIDENT ADDISON'S DISEASE AND DIABETES MELLITUS AND IN HIS RELATIVES

	Patient	Brother	Sister	Mother
$PB^{127}I$ (μg per 100 ml)	6·4	4·6	6·6	
TGA	1/78125	1/125	neg.	neg.
CFA	+++	neg.	neg.	neg.
ACA	++	neg.	+	neg.

detected in a series of 500 autopsies from a medical department, four showed associated hyperchromic anaemia of the pernicious type. Indeed, although considered as coincidental by Danowski,[26] this type of anaemia is not rare in myxoedema.[55,61,85] Tudhope and Wilson[86] attribute the pernicious anaemia of myxoedema to autoimmune gastritis. In 1962 Irvine *et al.*,[47] Taylor *et al.*,[84] and Markson and Moore,[58] using the complement fixation test, detected in certain subjects circulating antibodies likely to react with antigenic constituents of the gastric mucosa. Serafini *et al.*[77] have defined this condition as asymptomatic chronic atrophic gastritis. It is known that primary hypothyroidism as well as thyrotoxicosis[81] is often accompanied by gastric achylia.[7] Taken as a whole, almost 30% of subjects with autoimmune thyroiditis have gastric antibodies.[47,84] Feltkamp[36] and Serafini *et al.*[77] reported similar findings in large series of patients with thyroid diseases compared to series of controls.

Conversely, thyroid antibodies have been detected with abnormal frequency in subjects with pernicious anaemia.[31,50,59] Feltkamp,[36] studying ninety-four such patients, found anti-thyroid reactions in 80% of them, whereas only 13% of a group of ninety-four controls showed similar reactions.

In a series of twenty-four well-documented cases of pernicious anaemia studied in this hospital during the last 5 years, antithyroglobulin and/or anticytoplasmatic serological reactions were observed in ten cases (TGA titre varying from 1/625 to 1/78125). In two of these cases, a histological examination revealed asymptomatic thyroiditis. However, none of the cases of myxoedema studied in the last 15 years showed pernicious anaemia.

Adreno-cortical insufficiency

Primary atrophy of the adrenal cortex is now observed more frequently than destruction by tuberculosis. The disease comprises lymphoid infiltrations, destruction of the parenchyma, and progressive fibrosis of the organ, accompanied by the presence of adreno-cortical antibodies in the circulation.[2,13,20,36,51]

Lymphocytic thyroiditis is often observed in subjects with severe adreno-cortical lesions[14,16,33,36] to the extent that the simultaneous development of thyroiditis and adreno-cortical insufficiency has been known since 1926 as the "Schmidt syndrome".[74] The latter author described extensive infiltration of the thyroid in two Addisonian patients and referred to the condition as "eine biglanduläre Erkrankung (Nebennieren und Schilddrüse)." He presumed that the patients would have developed hypo-

thyroidism if they had survived their Addison's disease. This pattern of development has in fact been observed in a patient with the Schmidt syndrome and is reported in Table 10.4 (p. 231). In 1937, one of our team,[6] studying 12 autopsied cases of Addison's disease, observed typical thyroiditis in 2 of the 5 cases of adreno-cortical tuberculosis and in 5 of the 7 cases with simple atrophy. Alongside the thyroiditis lesions, sometimes with the formation of germinal centres, the thyroid parenchyma often showed considerable hyperplasia, sometimes reminiscent of the appearance in thyrotoxicosis. Similar observations have been reported by Wells[89] and Sloper[82] (Table 11.3).

TABLE 11.3. FOCAL THYROIDITIS IN ADRENO-CORTICAL INSUFFICIENCY OF TUBERCULOUS OR ATROPHIC ORIGIN

Authors	Tuberculous lesions		"Simple atrophy"	
	No. of cases studied	No. with lymphocytic thyroiditis	No. of cases studied	No. with lymphocytic thyroiditis
Wells[89]	10	2	8	7
Bastenie[6]	5	2	7	5
Sloper[82]	12	1	11	8
Total	27	5	26	20

Carpenter *et al.*[20] reported 15 new cases of Schmidt syndrome of which 10 showed coincident diabetes. According to these authors, the thyro-adrenal syndrome was accompanied by primary atrophy of the adrenal in 82% of the cases. Isolated reports (cf. case report 11.2) have increased the number of reports of the Schmidt syndrome accompanied by diabetes.[23,24,30,41,69] So there was nothing unexpected in the Blizzard and Kyle discovery of thyroid antibodies in a large proportion of patients affected with idiopathic Addison's disease.[13] Several authors have since confirmed these observations (summarized in Table 11.4).

TABLE 11.4. INCIDENCE OF TAB (CFA AND/OR TGA) IN PATIENTS WITH IDIOPATHIC ADDISON'S DISEASE

Authors	No. of cases studied	No. of cases with TAB
Blizzard and Kyle, 1963[13]	69	22
Feltkamp, 1966[36]	21	6
Nerup *et al.*, 1966[65]	48	27
Irvine *et al.*, 1967[51]	35	17
Total	173	72 (41%)

Out of 741 patients admitted to this hospital for non-endocrine diseases and examined systematically for thyroid and adrenal antibodies, 5 subjects showed adrenal antibodies; 4 of these also had thyroid antibodies.

Finally, out of 10 Addisonian patients studied during the last few years, 4 had both thyroid and adrenal (ACA) antibodies in their serum.

By contrast with these findings, no lymphocytic infiltrations were found in the adrenal cortex of Hashimoto patients.[20,60] In seventy-six patients with autoimmune thyroiditis, Feltkamp[36] observed no significant rise in ACA antibodies.

Myasthenia

This disease has only recently been classed amongst autoimmune disorders;[83] its relationship with thyroid diseases has long been known.[27,40] Between 3% and 8·8% of myasthenic cases suffer from hyperthyroidism.[66] Sahey *et al.*[72] found 5 cases of hypothyroidism in 260 subjects with myasthenia. Osserman *et al.*[66] reported 6% hypothyroid subjects amongst their 801 myasthenic cases.

Lesions of lymphocytic thyroiditis have been frequently observed at autopsy or after thyroid biopsy in myasthenic patients,[12,37,80] almost all of the non-goitrous asymptomatic thyroiditis type. Circulating thyroid antibodies were detected in nearly a third of the 200 patients described in the publications of Van der Geld,[87] Simpson,[80] and Adner *et al.*[1] The findings of Osserman *et al.*,[66] summarized in Table 11.5, indicate that myasthenia is associated with thyroiditis more particularly in cases of clinically evident thyroid disease, although the tendency to this association is also definitely established for cases without thyroid symptoms.

TABLE 11.5. INCIDENCE OF THYROID ANTIBODIES IN MYASTHENIC PATIENTS (Osserman *et al.*, 1967)[66]

	No.	CFA+	%	TGA+	%
Control subjects without myasthenic or thyroid disease	52	2	4	1	2
Clinical thyroid disease (without myasthenia)	63	33	52	32	51
Myasthenia gravis with thyroid disease	39	16	41	18	46
Myasthenia gravis without thyroid disease	114	19	17	28	25

It is striking that out of all the cases reviewed by Osserman *et al.*,[66] only one was a conclusive case of Hashimoto's thyroiditis. All the others consisted of asymptomatic lymphocytic thyroiditis, sometimes grafted on to nodular goitre or thyrotoxicosis, or severe atrophic thyroiditis with hypothyroidism. Other authentic cases of Hashimoto goitre associated with myasthenia gravis have been reported only rarely.[25,34]

Idiopathic hypoparathyroidism

According to Blizzard *et al.*,[15] parathyroid antibodies are found with twice their

normal frequency in subjects affected with Hashimoto's thyroiditis. Similarly, these authors have reported an abnormally high incidence of thyroid antibodies amongst patients with idiopathic hypoparathyroidism. Isolated instances of associated hypoparathyroidism, thyroiditis, and adrenal insufficiency have been reported.[21,52]

II. Association with Non-organ Specific Autoimmune Diseases

Patients with *systemic lupus erythematosus* (SLE) rarely seem to develop thyroid diseases and, conversely, thyroid patients are not predisposed to SLE. Nevertheless, low titres of TGA have been found,[3,44] and isolated cases of SLE in association with Hashimoto's thyroiditis and with thyrotoxicosis have been recorded.[39,56,63,67,88]

Rheumatoid arthritis has been observed more frequently among Hashimoto patients than in control subjects.[11,18] Buchanan *et al.*[18] found thyroid antibodies with abnormal frequency in women treated for rheumatoid arthritis at a Glasgow hospital. But in a study excluding cases with both rheumatism and clinical signs of thyroid disease, Hymans *et al.*[44] were unable to confirm this association. Elling *et al.* also report no association.[35]

Table 11.6 summarizes the observations made in Brussels during systematic tests for circulating antibodies. The investigations revealed thyroglobulin antibodies in 15% of all the female hospitalized patients and in 6 of the 19 patients affected with "collagen diseases".

TABLE 11.6. INCIDENCE OF TAB IN SO-CALLED AUTOIMMUNE DISEASES

	No. studied	Positive ATA reaction
Adrenal cortical insufficiency	10	4
Pernicious anaemia	24	10
Myasthenia gravis	5	2
Rheumatoid arthritis	13	4
Systemic lupus erythematosus	4	2
Periarteritis nod.	2	0
	58	22

III. Association with Metabolic Diseases

Diabetes

The diabetogenic action of thyroid hormones, albeit weaker than that of hypophysial or glucocorticoid hormones, has been established by experimentation.[19,38,45,57] So the frequent association of thyrotoxicosis and diabetes[53] causes little surprise (Table 11.7). However, an analysis of twenty-six patients with diabetes and thyrotoxicosis in this hospital has shown that the diabetes is often present before the development of thyrotoxicosis (Table 11.8). Furthermore, the association of diabetes and myxoedema, first

TABLE 11.7. FREQUENCY OF DIABETES, THYROTOXICOSIS, AND OF ASSOCIATED DIABETES AND THYROTOXICOSIS

Clinic	Patients	No. observation	Condition	No. observation	Frequency (‰)
Non-university policlinic	General consultants	2000	Diabetes	6	3
Non-university policlinic	General consultants	2000	Thyrotoxicosis	1	0·5
Non-university policlinic	Diabetics	1587	Thyrotoxicosis	10	6
University policlinic	Diabetics	2819	Thyrotoxicosis	26	9

TABLE 11.8. CHARACTERISTICS OF TWENTY-SIX CASES OF COEXISTENT THYROTOXICOSIS (T) AND DIABETES (D)

	Sex F	Heredity of diabetes	Obesity	Age (years) at onset		Severity of thyrotoxicosis	Nodular goitre	Exopht.
				T	D			
I. Thyrotoxicosis precedes diabetes (8 cases)	7/8	1/8	6/8	50	56·8	3/8	3/8	4/8
II. Simultaneous onset (10 cases)	7/10	3/10	6/10		56·7	3/10	1/10	0/10
III. Diabetes precedes thyrotoxicosis (8 cases)	6/8	4/8	5/8	57·7	48·4	5/8	1/8	0/8
Total (26 cases)	20	8	17		54·2	11	5	4
%	76	30	65			42	20	15

considered as rare, has now been found with a frequency that cannot be fortuitous.[46,71,75] Baron[4] found between 3% and 4% of diabetics in his series of hypothyroid patients. In this hospital, out of 80 well-documented cases of hypothyroidism, 16 (20%) had diabetes.[9] This considerable frequency is no doubt due in part to the interest shown by this university department for the study of thyroid deficiency. However, Pirart's analysis [70] of patients attending a non-university clinic showed that the association of the two diseases leaves no room for doubt. Hecht and Gershberg[43] recently reported 9 hypothyroid subjects amongst 530 diabetics (a prevalence of 1·7%).

TABLE 11.9. INCIDENCE OF THYROID ANTIBODIES (TAB) IN DIABETIC PATIENTS

Authors	No. diabetics studied	% of cases with TAB	No. controls studied	% of cases with TAB
Pettit *et al.*, 1961[68]	58 (children)	22	178	1·1
Landing *et al.*, 1963[54]	109 (adolescents)	17·3		
	99 (adults)	21·2		
Moore *et al.*, 1963[62]	65	9	65	8
Simkins, 1968[78]	317	10	424	4
Bastenie *et al.*, 1967 [8]	91 (women)	28	687	16
Recent survey	200 (men and women)	32	806	9

TABLE 11.10. INCIDENCE OF DIABETES IN HOSPITALIZED PATIENTS WITH OR WITHOUT CIRCULATING TGA AND/OR CFA

Patients	Male[a]				Female[b]			
	Mean age	No. studied	No. diabetics	%	Mean age	No. studied	No. diabetics	%
With thyroiditis	66	40	22	55	68	79	43	54
Without thyroiditis	58	360	57	16	62	327	78	24
Total		400	79			406	121	

[a] $\chi^2 = 34{\cdot}84$; $p < 0{\cdot}001$. [b] $\chi^2 = 28{\cdot}44$; $p < 0{\cdot}001$.

The significance of this association has been interpreted in many ways. It seems impossible that hypothyroidism could have a diabetogenic effect. Sendrail *et al.*,[73] analysing 195 instances of coexistent diabetes and hypothyroidism in the earlier literature, noted that in at least two-thirds of the cases the diabetes preceded the development of thyroid insufficiency. Furthermore, Cassano *et al.*[22] have found family histories of diabetes in almost half their cases of associated diabetes and hypothyroidism. These data are confirmed by two recent notions: namely that the majority of adult cases of hypothyroidism result from the evolution of asymptomatic autoimmune thyroiditis (Chapter 9); and, secondly, that there is an undoubted relationship between diabetes and asymptomatic autoimmune thyroiditis.[8]

The presence of thyroid antibodies in the serum of diabetic subjects, noted for the first time in 1961,[68] has been confirmed by several studies (Table 11.9). Figure 11.1 gives the results of a systematic survey for thyroid antibodies in all the subjects admitted to this department of medicine for various non-thyroid diseases. The association thus demonstrated is confirmed by more recent investigations (Table 11.10).

The Brussels statistics seem to escape epidemiological criticisms; all the patients admitted to the hospital were examined systematically. No thyroid patients were included.

The research was carried out in ignorance of the diagnoses made: the final analysis of the data was entrusted to a statistician unaware of the nature of the study, and only having access to coded cards. Moreover, as shown in Table 10.3 (p. 230), the unchanged incidence of TGA in the systematic surveys performed during four successive years indicates that the population of the hospital apparently remained stable.

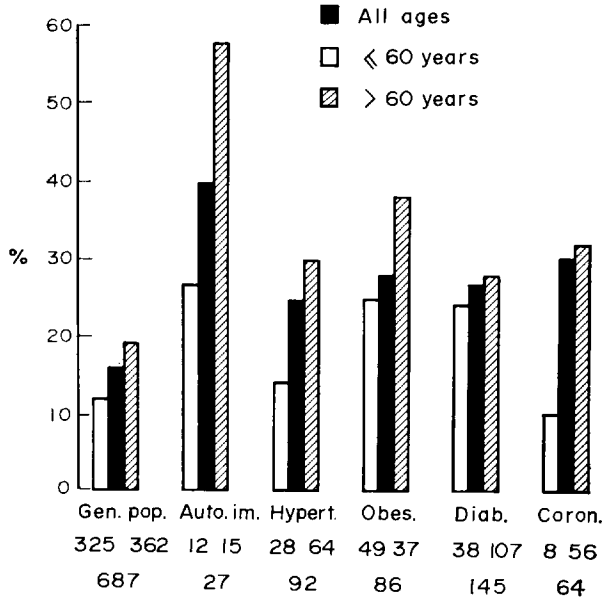

FIG. 11.1. Incidence of thyroglobulin antibodies (TGA) in a general population (GEN. POP.) and in different diseases: autoimmune diseases (AUTO. IM.), hypertension (HYPERT.), obesity (OBES.), diabetes (DIAB.), and coronary artery disease (CORON.).

Obesity

In the systemic surveys described previously a relationship was also found between thyroiditis and obesity in women (Table 11.11 and Fig. 11.1). This finding confirms the conclusions of earlier pathological studies.[6,79]

4. Pathogenic Considerations

The associations between different pathological conditions and the various forms of autoimmune lymphocytic thyroiditis are not all apparent to the same extent. The most firmly established relationships are those associating asymptomatic thyroiditis and hypothyroid thyroiditis with progressive atrophy of the adrenal cortex and atrophy of the gastric mucosa in pernicious anaemia, myasthenia, and also with diabetes (in women only) and obesity.

TABLE 11.11. INCIDENCE OF OBESITY IN HOSPITALIZED PATIENTS WITH OR WITHOUT ASYMPTOMATIC THYROIDITIS
(detected by TGA and/or CFA)

Patients	Male[a]				Female[b]			
	Mean age	No. studied	No. obese	%	Mean age	No. studied	No. obese	%
With thyroiditis	66	40	5	12	68	79	25	32
Without thyroiditis	58	360	25	7	62	327	36	11
Total		400	30			406	61	

[a] $\chi^2 = 1{\cdot}6$; n.s. [b] $\chi^2 = 21{\cdot}22$; $p < 0{\cdot}01$.

The relationship between lymphocytic thyroiditis and certain diseases characterized by non-organ-specific autoimmunity (such as systemic lupus erythematosus and rheumatoid arthritis) remains a subject of controversy.

Finally, there seems to be little association between the diffuse lymphocytic thyroiditis of Hashimoto's goitre in the strict definition of this entity and the afore mentioned pathology.

Generally speaking, the associations have been interpreted in two ways: either on the basis of common antigens or of an anomaly in the immune system. The existence of common antigens has been suggested for pernicious anaemia and thyroiditis in view of the common embryological origin of the gastric mucosa and the thyroid, and in view of a common physiological property of these tissues, namely the selective trapping of iodine. However, there are no immunological cross-reactions between these two organs.[10,48] Furthermore, the association of thyroid autoimmunity with pathological conditions entailing the production of muscle antibodies (myasthenia) or adrenal antibodies (Addison's disease) does not fit in with this interpretation.

It was therefore suggested that these associations might reflect primary anomalies of the immune apparatus[28,49] or even an innate predisposition.[42,76] It is, however, surprising that the thyroid disease comprising the most marked autoimmune processes, namely Hashimoto's thyroiditis, has few associated diseases. Similarly, diffuse lupus erythematosus, whose immunological reactions are the most varied, and which is characterized by a particularly sharp increase in gammaglobulins, is classed at the bottom of the list of conditions associated with thyroiditis. If they are unexplainable by the existence of common antigens or by primary anomaly of the immune system, these pathological associations must owe their origin to more complex mechanisms. Lymphocytic thyroiditis, and especially certain diseases most frequently associated with it (diabetes, pernicious anaemia, obesity) are caused by genetic and constitutional factors. They comprise various metabolic disorders affecting practically the whole body. Thyroiditis could be the consequence of a thyroid metabolic disorder secondary to one of these diseases. In support of this hypothesis one might quote the relationship between adreno-

cortical deficiency and thyroiditis. Lymphocytic thyroiditis develops very frequently during idiopathic atrophy of the adrenal, but it is not rare in tuberculosis of these organs. In both cases the thyroid shows striking histological signs of stimulation.[6] A similar histological picture is obtained in adrenalectomized animals.[5] By contrast, no lesions of the adrenal cortex are observed in Hashimoto's thyroiditis. The association between adrenal deficiency and atrophic thyroiditis is thus apparently established by a one-way metabolic interaction.

One last aspect of the problem deserves consideration. In Chapter 2 the frequency is recalled of cellular autoimmune processes of low intensity in various tissues, especially the stomach, thyroid, and adrenal cortex. Several authors see these processes as a quasi-physiological function of "cell waste evacuation". This cleansing process could be transformed into a destructive process with the appearance of antibodies either by an acceleration of the catabolism of cell components or by a general increase of antibody production. An example of the latter phenomenon is furnished by the development of thyroid antibodies during diseases such as leprosy.[17]

In short, the appearance of several autoimmune processes in a single individual may be caused by several genetic metabolic mechanisms. The frequent coexistence of such processes—in a subclinical form—in "normal" subjects, probably constitutes a simple explanation to the pathological associations.

5. Therapeutic Considerations

Increased therapy may be required when thyroiditis is detected in association with certain pathological conditions and, vice versa, when other diseases are found in association with clinically apparent thyroid disorders. Such supplementary treatment may be useful in preventing the development of thyroid deficiency as, for instance, in the case of latent hypothyroidism in pernicious anaemia. In other cases it may be life-saving, such as the treatment of latent adrenal insufficiency in thyrotoxicosis.

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CHAPTER 12

Atrophic Thyroiditis, Hypertension and Coronary Heart Disease

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1. Introduction

The classic idea that hypothyroidism has an atherogenic effect is based upon sound clinical, pathological, and experimental arguments. Nevertheless, in recent years some doubts have been expressed as to the validity of this view.[1,33,34] The reasons invoked are as follows:

(1) Pathological studies of untreated myxoedema subjects are rare and most deal with subjects over 60 years of age when "spontaneous atherosclerosis is almost universally present".[25]

(2) Therapeutic induction of hypothyroidism in euthyroid subjects to combat otherwise irreducible cardiac insufficiency or persistent angina pectoris does not seem to be followed by atherosclerotic changes.[7]

(3) Arterial hypertension is frequent in subjects affected with severe hypothyroidism,[2,24,44] and could be responsible for any atherosclerosis that might develop.[27,42] As shown in Chapters 9 and 10, spontaneous myxoedema in adults is due to the destruction of parenchyma by generally asymptomatic autoimmune thyroiditis. So it is logical to study the relationship between atrophic thyroiditis, hypertension, and atherosclerosis both in patients affected with clinical hypothyroidism and in subjects with asymptomatic thyroiditis.

Whereas atherosclerosis is difficult to study clinically, coronary sclerosis is easy to detect from its clinical symptoms and by electrocardiography. Therefore, in the present study, coronary heart disease (CHD) was taken as a yardstick of general atherosclerosis.

Admittedly, the diagnosis of coronary disease is based on indirect evidence, when no angiographs are used to show the arterial lesions directly. It is also admitted that atherosclerosis is not the only factor playing a role in the development of coronary artery disease. But there is a definite relation between the two disorders,[20,30] although the extent of atherosclerosis is not strictly parallel to the frequency of coronary complications,[46] and, on the whole, the clinical diagnostic signs constitute a reliable index.

2. Illustrative Case Reports

CASE REPORT 12.1: SP 55,246. *Parallel development of atrophic asymptomatic thyroiditis and coronary disease leading to myocardial infarction in an obese subject with high blood pressure.*

In 1961, S.A., a man aged 66, having suffered from high blood pressure and angina for several years, was admitted to this hospital for the first time for myocardial infarction. In 1965, when readmitted for anginal pains on effort, this obese subject still had a blood pressure of 200/100 mm hg and suffered from arteritis in the lower limbs. Glucoregulation was normal, but serum cholesterol was up to 311 mg per 100 ml, and testing for TGA revealed a titre of 1/78125. In 1968 the patient died of acute pulmonary oedema due to a second myocardial infarct. The autopsy showed an atrophied fibrotic thyroid (8·8 g) with lymphocytic infiltrations, and confirmed the diagnosis of infarction by coronary atherosclerosis.

CASE REPORT 12.2: SP 86,729. *In a female patient suffering from hypertension and angina, treatment with an iodine containing drug was followed by the appearance of severe hypothyroidism. Intense substitutive treatment triggered off persistent angina. The discovery of thyroid antibodies allowed a retrospective diagnosis of autoimmune thyroiditis with hypothyroidism due to iodine therapy.*

During 1969 this 62-year-old patient, with a history of 17 years of hypertension, hypercholesterolaemia, and incipient signs of coronary disorders (revealed by ECG changes), was treated with a coronary dilating drug containing small quantities of iodine (cordarone ®). In a few months the complete picture of hypothyroidism had set in. The condition was diagnosed in December 1969. Treatment with 150 μg of T4 and 37·5 μg of T3 rapidly improved the hypothyroidism but sparked off very severe angina, necessitating admission to hospital in February 1970. The patient showed signs of thyroid hormone overdosage. Testing for thyroid antibodies gave positive results (CFA+++). Twenty days after the cessation of thyroid treatment, the anginal attacks became less frequent; trinitrine tablets, first taken at a rate of 9 per day, were gradually reduced then stopped altogether.

3. Clinical Features

Hypothyroidism and Hypertension

The frequency of hypertension in myxoedema subjects was already underlined in earlier studies.[24,44] More recently, Attarian[2] also observed as many as 24 cases of hypertension among 92 hypothyroid patients. In contrast, Watanakunakorn *et al.*,[48] studying 400 cases of hypothyroidism, considered that hypertension was not abnormally frequent (18%) since most of the patients were over 40. These conflicting views are explained by the fact that many statistical studies pay no attention as to whether the

TABLE 12.1. BLOOD PRESSURE IN HOSPITALIZED PATIENTS: TWENTY-SEVEN SEVERELY HYPOTHYROID PATIENTS AND TWENTY-SEVEN CONTROLS MATCHED FOR AGE AND SEX[16]

Patients	No. studied	Mean age	Blood pressure (mm Hg)	
			Systolic	Diastolic
Hypothyroid	27	61·4	138 ± 26	81 ± 10
Control	27	60·8	145 ± 27	81 ± 12

hypothyroidism is of a primary or secondary nature, whether the subject is bedridden or ambulant, and whether the arterial pressure has been measured in the strictest conditions or not. The importance of the latter point was underlined by Rose,[37] by Goossens and Messin,[21] and by Demanet *et al.*[16]

Of the hypothyroid cases studied in Brussels, 25% showed or had in the past a blood pressure of more than 160/100 mm Hg. Amongst 25 patients with severe myxoedema, 10 had shown definite arterial hypertension (over 160/100 mm Hg whilst in a resting position) at one point in their clinical history. However, when comparing the blood pressure of bedridden hypothyroid subjects (generally bedridden because of the hypothyroidism itself) with that of normal subjects matched for age and sex, no difference was found[16] (Table 12.1). But the maximum blood pressure values of these patients were raised significantly by thyroid treatment. Finally, very low blood-pressure values were observed in four comatose myxoedema patients.[18]

These findings indicate that myxoedema tends to lower blood pressure even before the stage of coma is reached. This fact is not incompatible with the idea that hypertension may be found in the past history of hypothyroid subjects, or even that hypertension may be observed in non-bedridden hypothyroid subjects. The mechanisms by which thyroid hormones act on blood pressure are still fairly ill-defined, although the role of the catecholamines is well understood.[15,16]

Asymptomatic Thyroiditis and Hypertension

At all events, the idea that hypertension generally precedes rather than accompanies hypothyroidism is well demonstrated by the association of asymptomatic thyroiditis and hypertension[3] (cf. Fig. 11.1 (p. 269)).

The results of a recent systematic investigation confirm this association (Table 12.2).

Almost all the observations concern cases of essential hypertension. These statistics comprise two possible weak points: the blood pressure, albeit measured on several occasions, was not always measured by the same investigator; secondly, a few cases of symptomatic hypertension may have been included. Nevertheless, as the immunological survey was carried out blindly these limitations apply equally to the whole populations whether antibody positive or not.

TABLE 12.2. HYPERTENSION IN SUBJECTS WITH AND WITHOUT ASYMPTOMATIC THYROIDITIS (TGA + or/and CFA +)

	Male patients[a]				Female patients[b]			
	Age	No.	Hypertension	%	Age	No.	Hypertension	%
Thyroiditis	66	40	9	22	68	79	29	37
Without thyroiditis	58	360	25	7	62	327	45	14
Total		400	34			406	74	

[a] $\chi^2 = 11{\cdot}2$; $p < 0{\cdot}001$. [b] $\chi^2 = 22{\cdot}48$; $p < 0{\cdot}001$.

Hypothyroidism and Atherosclerosis

The ECG of patients with severe hypothyroidism is classically characterized by bradycardia, low voltage, and abnormal auriculo-ventricular conduction. In a study of fifty-six cases, signs of ischaemia were observed rather frequently. But the number of infarcts was equal to that observed in controls matched for age and sex (Table 12.3). The incidence of arterial changes in the coronary and peripheral vessels in hypothyroid patients and the association with hypercholesterolaemia and diabetes is further indicated in Fig. 12.1. In a series of 25 autopsied cases, the heart was found to be very enlarged (> 300 g in 22 cases), mainly because of the interstitial oedema observed in almost half the subjects[47] (Table 12.4). Coronary atherosclerosis studied anatomically in twenty-five hypothyroid cases was of a much greater intensity than in control material (Table 12.5). Comparable findings have been reported recently by Steinberg.[42] But this author thinks that myxoedema only induces atherosclerosis when accompanied by high blood pressure.

TABLE 12.3. ECG IN FIFTY-SIX CASES OF MYXOEDEMA AND IN FIFTY-SIX MATCHED CONTROLS

	Myxoedematous patients	Controls
Normal	3	16
Non-specific myocardial alterations	24	27
Low voltage	18	4
Bradycardia	11	0
Disturbances of atrioventricular conduction	10	1
Disturbances of intraventricular conduction	5	4
Ischemia	6	0
Myocardial infarct (old and recent)	9	8
Left ventricular strain	9	6

TABLE 12.4. PATHOLOGY OF THE HEART IN TWENTY-FIVE AUTOPSIED CASES OF SEVERE HYPOTHYROIDISM
(Mean age: 70·4)

Mean weight	421 g
Left ventricle hypertrophy (thickness of the wall > 14 mm)	19 cases
Left ventricle dilatation	7 ,,
Pericardial effusion (> 50 ml)	8 ,,
Myocardial oedema	12 ,,
Coronary atherosclerosis	24 ,,
Myocardial infarction	6 ,,

As regards the 6 cases of myocardial infarct observed in 25 hypothyroid subjects compared to only 3 cases found in 50 controls, it must be mentioned that in 4 of the hypothyroid cases recent thyroid treatment could have been responsible for the heart attack. Keating *et al.*[29] have stressed the relative rarity of myocardial infarct in untreated hypothyroid patients, in contrast with the frequency of coronary disorders after treatment (cf. case report 12.2). In prolonged hypothyroidism, atherosclerosis is therefore undeniably more marked than in euthyroid subjects of the same age, living in the same social, economic and dietary conditions. Atherosclerosis is also one of the features observed in the rare cases of prolonged juvenile hypothyroidism.[26]

These observations contrast with the data of Blumgart *et al.*[7] on the absence of atherosclerosis due to iatrogenic hypothyroidism. It must not be forgotten that spontaneous myxoedema is the final result of a long process of thyroiditis accompanied, if not by clinical signs, at least by functional abnormalities (cf. Chapter 10). The premyxoedema state, involving thyroiditis, could well be of cardinal importance in the genesis of atherosclerosis.[4,19]

Asymptomatic Thyroiditis and Atherosclerosis

One of the results of the systematic serological investigations described in Chapter 10 was the demonstration of a statistical relationship between thyroiditis and coronary disease in women over 50[4] (cf. Fig. 11.1 (p. 269)).

This association has been confirmed by a recent survey[5] (Table 12.6). As before, a slight non-significant difference was found between the frequency of infarcts in male subjects with thyroiditis and in male subjects without thyroiditis. But in women the difference was very significant. In the general population of hospital patients* the pre-

* Although the hospital population in a department of medicine cannot be taken as a representative sample of the general population, it is striking to find that within the hospital population the "relative risk" by sex (18/11 = 1·7) is similar to that (9·1/4·5 = 2) of the general population of the United States. This finding is important for judging the validity of the present observations; an intensive-care unit has increased the frequency of myocardial infarction cases in this department apparently without changing the general sex ratio of this disease.

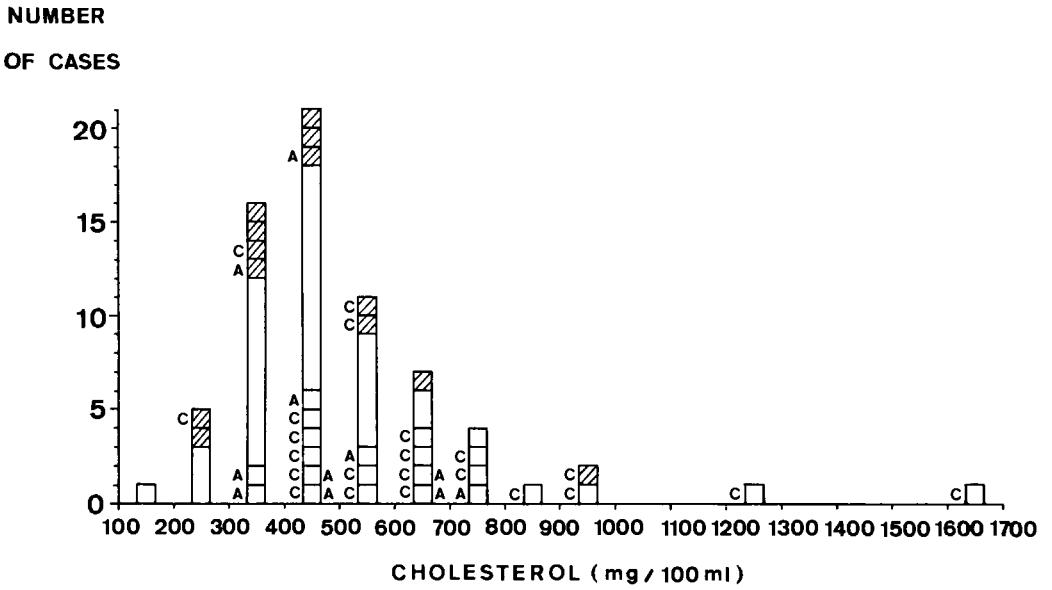

FIG. 12.1. Serum cholesterol in primary hypothyroidism; related incidence of vascular disease. Distribution of cases with regard to the level of serum cholesterol. The hatched squares represent patients with coincident diabetes. C indicates coronary artery disease; A indicates peripheral arteritis.

TABLE 12.5. CORONARY ATHEROSCLEROSIS AND MYOCARDIAL INFARCTION IN NECROPSIES OF MYXOEDEMA SUBJECTS AND CONTROLS

	Myxoedema patients (20 females; 5 males)				Matched controls (40 females; 10 males)			
	Coronary atherosclerosis			Myocardial infarction	Coronary atherosclerosis			Myocardial infarction
Degree	0	I	II		0	I	II	
No. of subjects	1	3	21	6	20	7	23	3
Incidence (%)	4	12	84	24	40	14	46	6

valence of infarcts in men was almost twice that in women. In a population affected with thyroiditis, the incidence was the same in the two sexes. In other words, it is the presence of thyroiditis and not the menopause itself which cancels out the privilege enjoyed by the female sex with regard to myocardial infarction.

4. Pathogenic Features

The mechanism by which asymptomatic thyroiditis favours the development of atherosclerosis is obscure.

TABLE 12.6. PREVALENCE OF MYOCARDIAL INFARCTION IN PATIENTS WITH AND WITHOUT ASYMPTOMATIC ATROPHIC THYROIDITIS

Patients	Male				Female			
	Median age	No. studied	No. infarct	%	Median age	No. studied	No. infarct	%
With thyroiditis	66	40	9	22	68	79	16	20
Without thyroiditis	58	360	62	17	62	327	28	8·5
Total		400	71	18		406	44	11

TABLE 12.7. SERUM CHOLESTEROL (mg per 100 ml) ± STANDARD ERROR IN PATIENTS WITH AND WITHOUT SEROLOGICAL SIGNS OF ASYMPTOMATIC ATROPHIC THYROIDITIS (NOT PAIRED FOR AGE AND ASSOCIATED PATHOLOGY)

Patients	Male		Female	
	No.	Cholesterol	No.	Cholesterol
With thyroiditis	37	214·35 ± 10·6	72	241·79 ± 7·1
Without thyroiditis	325	212·87 ± 3·6	295	225·43 ± 3·9
	n.s.		$t = 2{\cdot}03$; $p < 0{\cdot}05$	
Total	362		367	

In studying the causes of atherosclerosis, one of the major difficulties lies in diagnosing vascular lesions in living subjects and in evaluating the intensity of the process. In the present study, coronary atherosclerosis was taken as an indication of atherosclerosis because it is in the coronary artery that the disease is the most marked and also the most easy to diagnose.

Even if the diagnosis is made only by indirect means, and CHD should be distinguished from coronary lesions of atherosclerosis, in the large majority of cases the clinical and electrocardiographic signs of CHD are, in fact, due to lesions of coronary atherosclerosis.

Several factors could play a pathogenic role in coronary atherosclerosis associated with asymptomatic thyroiditis: hypercholesterolaemia; certain associated diseases such as obesity, hypertension, or diabetes; and some constitutional factor.

The major anomalies of iodine metabolism detected in this condition[10,12] are accompanied by a rise in blood cholesterol.[3] This may be demonstrated in both men and women when subjects affected with thyroiditis are compared with controls of the same sex, same age, and similar associated pathology (Fig. 10.7 (p. 243); Table 12.7). An abnormal rise of serum cholesterol is generally recognized as a risk factor for CHD.[27,28,45]

In hypothyroidism the frequent increase in serum cholesterol could be responsible for the additional development of atherosclerosis, even in young subjects.[26]

The atherogenic effect of asymptomatic thyroiditis could therefore be due, at least in part, to the high levels of serum cholesterol resulting from latent thyroid insufficiency.[3,14,19]

But it is obvious that the atherogenic role of asymptomatic lymphocytic thyroiditis cannot be entirely explained by the functional deficiency of the affected gland. Indeed, the relationship between infarction and lymphocytic infiltration, demonstrated by pathological studies (Table 12.8), is not limited to diffuse infiltrations but includes moderate focal infiltrations which leave the parenchyma almost intact. So the fundamental cause of the association between thyroiditis and atherosclerosis is not yet apparent.

Perhaps one should no longer consider a cause-and-effect relationship but rather the

TABLE 12.8. RELATIONSHIP BETWEEN MYOCARDIAL INFARCT AND THYROID INFILTRATES IN POST-MORTEM MATERIAL

	No. studied	No. infiltrates	Incidence of infiltrates (%)
Male cases			
With myocardial infarct	154	30	20
Without myocardial infarct	154	12	8
Female cases			
With myocardial infarct	91	40	44
Without myocardial infarct	91	10	11

dependence of both conditions on a single non-thyroid pathogenic factor. There is no direct indication as to the nature of this factor; at the most one may interpret the effects that it produces (Fig. 12.2).

The association demonstrated earlier between thyroiditis and diabetes, obesity and hypertension, suggests that it is through the intermediary of these pathological conditions, which are also factors in atherosclerosis, that thyroiditis may be related to the development of CHD.

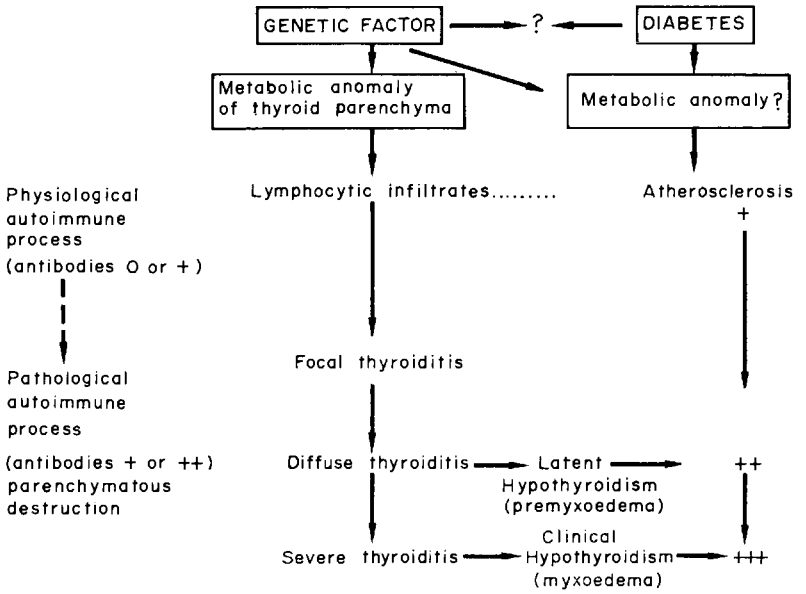

FIG. 12.2. Diagram of the possible relationship between atrophic asymptomatic thyroiditis and atherosclerosis.

TABLE 12.9. RELATIONSHIP OF LYMPHOCYTIC INFILTRATIONS WITH MYOCARDIAL INFARCTION (IN THE ABSENCE OF DIABETES, OBESITY, AND HYPERTENSION) IN POST-MORTEM STUDIES

	Infarct detected at necropsy			No infarct detected at necropsy		
	Number studied	Thyroiditis (lymphocytic infiltrates)	Incidence of thyroiditis (%)	Number studied	Thyroiditis (lymphocytic infiltrates)	Incidence of thyroiditis (%)
Male subjects	64	13	20	64	6	9
Female subjects	25	12	48	25	3	12
Total	89	25	27	89	9	10

To explore this possibility, two lines of investigation were pursued: analysis of pathological records and statistical study of the interrelationships detected during the most recent survey.[5] The first set of results is summarized in Tables 12.8 and 12.9. It is a general practice for the pathologists of this hospital to take samples of thyroid tissue from each autopsied case in the medical department and to record the existence of lymphocytic infiltrations of any magnitude. Because of this practice it was possible to make a retrospective study of the pathological data of 1964–6 and to examine the records in the cases of coronary thrombosis for evidence of thyroiditis as noted by the pathologists. The latter at that time were unaware of this correlation. As indicated in Table 12.9, lymphocytic infiltrations are observed with roughly the same frequency as in London[49] and in the United States,[32] i.e. about 25% of the cases which consist of one-tenth extensive thyroiditis lesions, whilst in the other nine-tenths the integrity of the thyroid is barely affected. The 154 male cases of infarcts and 91 female cases autopsied during the 3 years were compared with a consecutive series of 154 men and 91 women matched for age and as far as possible for other pathological conditions (malignancy, diabetes, hypertension, etc.).

Compared to subjects with no record of infarct, the male and female cases with old or new infarctions had respectively 2·5 and 4 times more lymphocytic infiltrations in their thyroid glands.

Out of the total of 245 subjects whose autopsy had shown the presence of a myocardial infarct, 89 (64 women and 25 men) had had no obesity, hypertension or diabetes in their clinical history. Compared to eighty-nine controls also free from such diseases, the subjects with infarcts again showed (depending on sex) 2 to 4 times more lymphocytic infiltrations in the thyroid. So the diseases associated with thyroiditis—diabetes, obesity, and hypertension—do not seem to play a direct role in the association of lymphocytic thyroiditis and atherosclerosis.

A similar conclusion seems to emerge from the computer study of associations between asymptomatic thyroiditis, obesity, hypertension, diabetes, and CHD (Table 12.10).

In women over 50 with asymptomatic thyroiditis the prevalence of CHD increases

TABLE 12.10. INCIDENCE OF CHD IN FEMALE PATIENTS WITH AND WITHOUT ASYMPTOMATIC THYROIDITIS WITH AND WITHOUT OBESITY (O), HYPERTENSION (H), AND/OR DIABETES (D)

Patients	No. studied	No. with CHD	Incidence (%)
Thyroiditis with O, H, D	54	11	20
No thyroiditis with O, H, D	113	17	15
Thyroiditis without O, H, D	25	5	20
No thyroiditis without O, H, D	214	11	5

n.s.

n.s.

$\chi^2 = 7{\cdot}91$
$p < 0{\cdot}01$

beyond its incidence in normal men (Table 12.6). This association between thyroiditis and CHD is particularly marked in women with no obesity, hypertension, or diabetes. It is much less apparent among women with these diseases in whom the incidence of CHD rises only slightly when thyroiditis is present.

In women not affected with thyroiditis, the presence of obesity, hypertension, and diabetes triples the incidence of CHD. But the existence of these associated diseases (taken as a whole) does not seem to affect the incidence of myocardial infarction in women with thyroiditis. However, a more detailed investigation suggests that diabetes—but not hypertension or obesity—increases the incidence of CHD in women with thyroiditis (Table 12.11).

This latter finding perhaps enables us to complete a diagram linking up the various conditions (Fig. 12.2): the hypothetical nature of this diagram cannot be stressed enough.

Asymptomatic atrophic thyroiditis may follow on a process which normally allows the gland to get rid of its cell debris and metabolic waste. Already in these stages of cleansing infiltrations, one witnesses the development of severe vascular changes probably due to metabolic factors associated with heredity. As the thyroid parenchyma is affected by the spread of thyroiditis, gradual functional deficiency gives rise to an increase in serum cholesterol and TSH and a decrease in thyroid hormones. In their turn these anomalies probably play a pathogenic role in the arterial changes.

5. Therapy

If, indeed, asymptomatic thyroiditis constitutes a definite pathogenic factor in coronary atherosclerosis in women and a possible factor in men, treatment of this condition would have the definite advantage of reducing an abnormality considered as a coronary risk factor. It may be assumed that the abnormal rise in serum cholesterol, conclusively demonstrated in many subjects with AAT, plays a harmful role in vascular diseases and that reduction or prevention of hypercholesterolemia may be beneficial. However, it cannot be deduced that the treatment would place women with asymptomatic thyroiditis

TABLE 12.11. INCIDENCE OF CHD IN FEMALE PATIENTS WITH ATROPHIC THYROIDITIS, WITH AND WITHOUT COEXISTENT DIABETES

Patients with thyroiditis	No. studied	No. with CHD	Incidence (%)
With diabetes	43	11	25·6
Without diabetes	36	5	13·9
Total	79	16	20·2

safely out of danger of myocardial infarct. Proof of the latter point would demand a long-term prospective study. Such a study, if positive, would lend support to the arguments of several authors who have proposed such treatments.[6,9,22,40]

On the other hand, it is certain that arterial—and particularly coronary changes—may already be present when serological tests reveal the existence of the first thyroiditis lesions. Two questions therefore arise: Does thyroid hormone treatment have an inhibiting effect on the vascular process? Can it not be dangerous, since the treatment of hypothyroidism is a frequent cause of infarction?

To the first question one can only reply by showing the regression of experimentally induced lesions of atherosclerosis and the rarity of arterial lesions found in subjects who die of thyrotoxicosis.

The second question has occasioned much research, notably in order to find thyroxine substitutes which have a definite effect on the metabolism of lipids without affecting the heart or general metabolism to any significant degree.[6,8,40] It seems, indeed, that in small doses all the analogues of thyroxine possess this property of dissociating their cardiotropic and metabolic effects.[6,31]

From this point of view, the fast-acting derivatives, like Triac and Triiodothyronine, seem more difficult to handle than L-thyroxine and especially D-thyroxine (DT4). The administration of the latter in doses of 2–4 mg may be used as substitution treatment for severe hypothyroidism.[23,38,41] In doses of 4–6 mg it has been used as a hypocholesterolaemic agent with satisfactory results in half the cases,[13,17,22,39,43] generally without causing cardiac intolerance.[22,36] Accidents have been reported with doses of 4 and even 2 mg/d in subjects with angina.[35]

In this department about forty subjects with asymptomatic thyroiditis were subjected to treatment with desiccated thyroid, D-thyroxine or triiodothyronine. In a few of them strictly controlled investigations revealed a more marked decline in total lipids and cholesterol than in controls who had no circulating thyroid antibodies.[11]

In conclusion, data here reported suggest that administration of small amounts of desiccated thyroid or slow-acting thyroxine analogues may be of therapeutic value in lowering the cholesterolaemia in patients with AAT. This innocuous therapy certainly will prevent the development of clinical hypothyroidism. Future work will show whether it may also constitute a preventive treatment for CHD in women affected with thyroiditis.

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CHAPTER 13

Thyroiditis and Chromosomal Anomalies

L. VANHAELST, M. BONNYNS and P. A. BASTENIE

1. Introduction

Benda was the first[10] to draw attention to the abnormally high frequency of thyroid disorders in mongolian children; Myers[70] and Benda[11] also demonstrated this phenomenon in the mother of such children. These early findings have attracted interest more recently since numerous reports have shown close association between autoimmune thyroiditis and Down's and Turner's syndromes.

The various observations reported have thrown new light on the pathogenesis of these chromosome abnormalities.

2. Illustrative Case Report

CASE REPORT 13.1: E 2673. *Turner's syndrome with asymptomatic thyroiditis in the patient and her mother.*

Miss V. J., 26 years old, complained of primary amenorrhoea and short stature. Vaginal smears revealed a definite atrophy. The urinary FSH level was up to 700 U per 24 hr. Exploratory laparotomy failed to yield any trace of ovarian tissue, even on microscopical examination of the samples removed. Testing for sex chromatin proved negative. The caryotype showed a pattern of 46 XX/45 XO.

Both the patient and her mother had thyroid antibodies in their serum. The patient had obviously developed thyroiditis with latent hypothyroidism. Under administration of oestrogens and desiccated thyroid a more satisfactory mental and physical condition was achieved. Abnormal thyroid stimulation was depressed and the level of NBEI was brought back to normal (Table 13.1).

3. Observations in Down's Syndrome

There are only a few reports on clinical thyroid disorders in Mongols. Goitre frequency has been calculated at 0·6%[12,73,78] out of 988 cases, whereas thyroid swelling was absent in 327 controls.[78]

Hypothyroidism has been observed in ten cases of mongolism,[23,51,52,62,64,74] sometimes associated with diabetes.[23] Hyperthyroidism has been reported in nineteen cases.[1,52,78]

TABLE 13.1. PARAMETERS OF THYROID FUNCTION OF A PATIENT WITH TURNER'S SYNDROME BEFORE AND DURING TREATMENT WITH DESICCATED THYROID (CASE REPORT 13.1)

	Date	Thyroglobulin antibodies (TGA)	Microsomal antibodies (CFA)	$PB^{127}I$ (μg per 100 ml)	$BE^{127}I$ (μg per 100 ml)	$NBE^{127}I$ (μg per 100 ml)	^{131}I uptake		Cholesterol (mg per 100 ml)	Blood lipids (mg per 100 ml)
							6 hr	24 hr		
Without treatment	8.6.66	++		8·8			57	71	350	
	27.6.66	++		8·3					360	1050
Desiccated (50 mg/d)	23.12.66	neg.		5·3			14	20	248	
	20.10.67	neg.		6·5	3·1	3·4			237	635
	4.3.68	+	+++							
	7.11.68	+	+++							
	14.2.69	neg.	+++	5·9	4·7	1·2				
	18.8.69	neg.	+++						268	

Morphological studies of thyroid glands in mongolian subjects are also fairly rare. Benda[12] found only one normal gland in forty-eight cases investigated; in the other forty-seven cases he reports colloid goitres (with depressed activity or with areas of hyperactivity), foetal-type glands, and fibrotic atrophy. Only two pathological reports of lymphocytic thyroiditis have been recorded so far[5,12] (Fig. 13.1). Various authors have studied thyroid function in mongolian children. Although ^{131}I uptake, $PB^{127}I$, and serum cholesterol are usually normal,[9,19,58,75] the half-life and turnover of ^{131}I in the thyroid are accelerated[58] and the trapping of radioactive triiodothyronine by the erythrocytes or resins is increased.[36,55,58,79] Kurland *et al.* considered that their observations of ^{131}I turnover in the thyroid were compatible with the hypothesis that only part of the gland was functional and was working at a faster pace.[58] This situation may be compared to the one existing in asymptomatic lymphocytic thyroiditis[15] (cf. Chapter 10). One study[69] reports the presence of LATS in four mongolian children without signs of hyperthyroidism.

In the mothers of mongolian children, several authors have laid emphasis on the high prevalence of thyroid disorders,[6,11,18,39,70] associated with a marked frequency of thyroid antecedents in the family.[84] Diabetes is also encountered with greater frequency, not only in the mothers but also in the maternal grandparents.[6]

Mellon *et al.*[64] were first to report unusually frequent thyroid antibodies in mongolian children and their parents.

Numerous studies have confirmed and amplified these early results both for mothers[6,14,20,38,41] and for fathers,[84] the mongolian children themselves, and their brothers and sisters.[14,84] For all these subjects, in comparison with controls, there is a definite increase in the incidence of positive serological reactions. Only one study[87] has reported negative results. In the mothers of mongolian children the frequency of positive cases is remarkably stable in the different age groups (Table 13.2). This contrasts with the increase related to age in a control population of hospital patients[4] or healthy subjects.[27,41] Although $PB^{127}I$ is usually normal in mongolian children, the butanol extractable fraction is almost always reduced.[28] This pattern of distribution of iodinated proteins in the serum is found not only in the mongolian children, but also in their mothers, fathers, brothers and sisters. The findings of Vanhaelst *et al.*[84] illustrate this point: in 83 mothers, 38 fathers, 58 brothers and sisters, and 21 affected children, the $PB^{127}I$ level was comparable with that of 106 normal controls, but $BE^{127}I$ was lowered and there was a clear increase in the non-butanol-extractable fraction (Table 13.3). In contrast to the results obtained by Dodge *et al.*,[28] the BEI levels still remained within normal limits, but the high level of NBEI differentiated the mongolian population decisively from the controls (Fig. 13.2). It was not possible statistically to break down the families of mongolian children into various sub-categories; for this particular biochemical abnormality they formed a homogeneous group. Correlation studies revealed hereditary transmission of the high NBEI levels (cf. Chapter 14).

The value of 1·5 μg per 100 ml was arbitrarily considered as the upper normal limit of NBEI in the serum, since 85% of the normal subjects showed values equal to or below this figure. A significant statistical relationship between the increased level of NBEI and

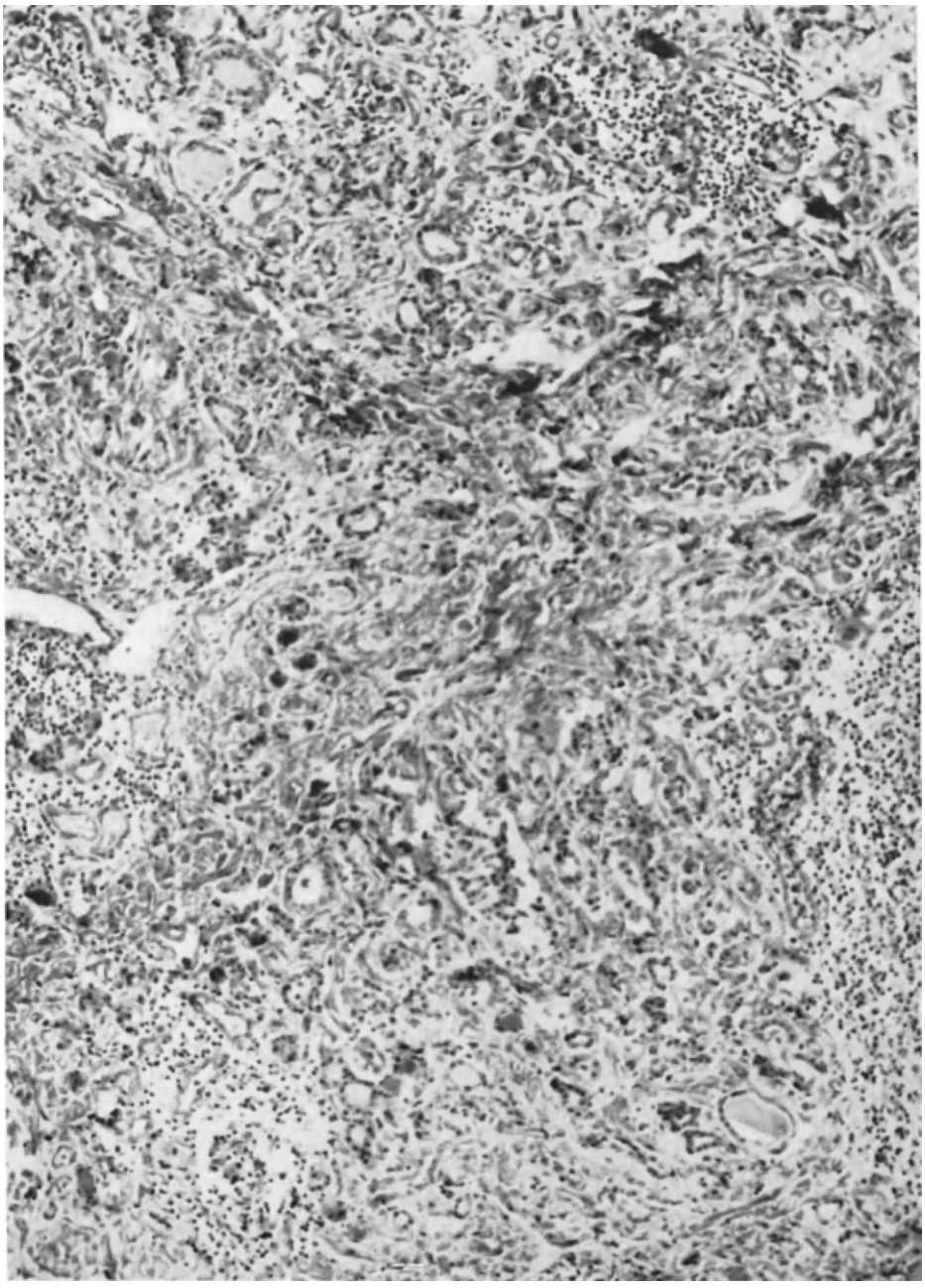

FIG. 13.1. Thyroiditis in a mongolian subject. (×140.)

TABLE 13.2. INCIDENCE OF THYROID ANTIBODIES IN MOTHERS OF A MONGOLIAN CHILD AND IN CONTROL SUBJECTS

Mothers of mongolian subjects	Study of Fialkow[41]			Present study[84]		
	n	+	%	*n*	+	%
Aged 18–32	66	18	27	17	5	29
33–45	97	27	28	35	10	29
over 45	79	24	30	31	8	26
Total number	242	69	28	83	23	28
Control (females)						
Aged 18–32	52	2	4	67[a]	1	2
33–45	58	8	14	47[b]	6	13
over 45	38	11	29	153[b]	29	19
Total number	148	21	14	267	36	13

[a]Normal women aged 18–32 having delivered normal children.
[b]Forty-seven and 153 female subjects hospitalized in the Department of Medicine for miscellaneous non-thyroid diseases.

TABLE 13.3. SERUM IODINATED PROTEINS
(μg per 100 ml $\pm$ standard error)

	Control subjects	Mongolian subjects and relatives		
	n = 106	Parents *n* = 74	Children *n* = 63	Total *n* = 137
PBI	6·39 ± 0·13	6·32 ± 0·12	6·41 ± 0·10	6·36 ± 0·11
BEI	5·61 ± 0·13[a]	4·64 ± 0·11	4·81 ± 0·12	4·72 ± 0·11[a]
NBEI	0·79 ± 0·07[a]	1·68 ± 0·11	1·60 ± 0·11	1·64 ± 0·11[a]

[a] $p < 0{\cdot}001$.

the frequency of thyroid antibodies was established with reference to this limit of 1·5 μg per 100 ml (Table 13.4). The same relationship was noted for asymptomatic thyroiditis (cf. Chapter 10).

4. Observations in Turner's Syndrome

Observations on the incidence of thyroid diseases in subjects affected with Turner's syndrome are rare.

Clinical hypothyroidism has been recorded in 9 cases[26,33,46,47,50,53,68,86] and

hyperthyroidism in 4 cases.[47,48] Non-systematic morphological studies report thyroid cancer in 2 subjects[48,80] with associated lymphocytic thyroiditis in one of them,[80] Hashimoto's thyroiditis in 7 subjects,[17,47,63,80,86] and atrophic thyroiditis in 2 subjects.[2,86] Pathological investigations were possible in a single series of 11 Turner patients,[86] they revealed a normal-looking gland in 3 cases, lymphocytic thyroiditis in 6 cases, fibrosis in 1 case, and a colloid goitre in another.

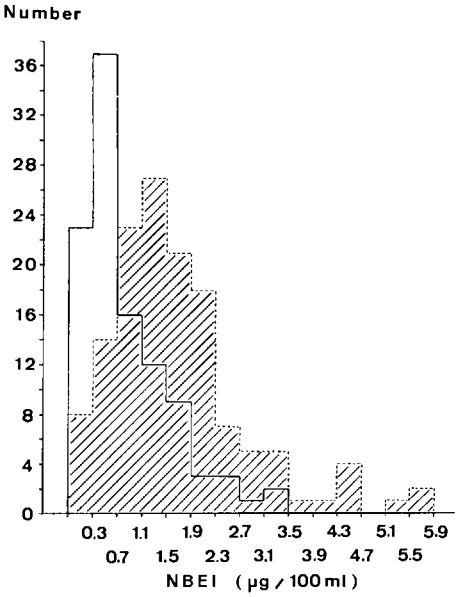

FIG. 13.2. Distribution of NBEI values in the members of families of mongolian children (hatched area) and in normal control subjects (white area).

Thyroid function has also received little attention. In general $PB^{127}I$ is normal.[77] A number of cases with abnormally high thyroid uptakes have been reported in otherwise euthyroid patients.[48,56,60] After noting no increase of uptake under TSH, Lewitus[60] has suggested that the thyroid glands of these patients are working under maximum thyrotropic stimulation, as in Hashimoto's thyroiditis.

In 27 mothers and 24 fathers of subjects with Turner's syndrome, Price and Irvine failed to find more thyroid diseases than in the general population.[77] Only diabetes is mentioned with particular frequency, both in the parents of affected subjects and in the patients themselves.[47,61,65,72] Engel and Forbes[30] were first to report thyroid antibodies in a patient with gonadal dysgenesis. Later, more cases were reported, revealing increased frequency of positive serological reactions not only in the affected subjects[5,29,32,43,47,48,82,86] but also in the mothers[43] or relatives generally.[82] Alongside high frequency of thyroid antibodies, Vallotton and Forbes[82] have also found frequent positive serological responses to gastric parietal cells or to the cytoplasm of rabbit ova.

TABLE 13.4. RELATIONSHIP OF THYROID ANTIBODIES TO SERUM NBEI LEVEL

NBEI (μg per 100 ml)	$< 1{\cdot}5$	$\geqslant 1{\cdot}5$
Members of families with a mongolian child	$n = 70$	67
Thyroid antibodies present	7	19
%	10	28

$\chi^2 = 6{\cdot}35$; d.f. $= 1$; $0{\cdot}01 < p < 0{\cdot}02$.

In a recent study, Price and Irvine[77] were unable to demonstrate an abnormal frequency of antibodies against thyroid, or against gastric parietal cells either in subjects affected with ovarian dysgenesis or in their parents. Their negative findings are difficult to understand in view of the data given in the rest of the literature. The same is true for the study of Doniach *et al.*[29] who found no significant difference between the incidence of thyroid antibodies in 103 parents of patients and that of a control population.

For some authors the incidence of positive serological reactions is independent of the caryotype of the affected patients,[32,48,82,86] but others stress a much greater incidence in subjects with an irregular caryotype (mosaic patterns, presence of an X-isochromosome).[29,43,77,80]

5. Observations in Klinefelter's Syndrome

According to Fraser,[45] patients affected with Klinefelter's syndrome have more goitres than the normal population. Their thyroid function is often modified: low thyroid uptake,[24,88] not rising after TSH injection[3,16] and low $PB^{127}I$.[88] Although no family incidence of thyroid diseases is reported, diabetes is frequent both in affected subjects[8,88] and in the members of their families.[66,71,85]

In general, thyroid antibodies are not encountered with any greater frequency in the patients[25,29,35,82] or their parents.[35] Only the investigations of Engelberth[34] yielded positive results.

6. Discussion

Engel and Forbes[31] were first to suggest that the non-disjunction of chromosomes could be encountered more frequently in families with a genetic predisposition to autoimmunity.

In 1964 Fialkow[37] discussed various interpretations of the link between thyroid autoimmunity and chromosome anomalies. He considered four possibilities:

(1) The influence of aneuploidism on the development of thyroid disorders in a single individual.

(2) The influence of aneuploidism in a child on the appearance of autoimmune disorders in its mother.
(3) The influence of maternal autoimmunity on the birth of aneuploid children.
(4) The action of a third factor (viral or metabolic) responsible for both maternal autoimmune disorders and chromosome anomalies in the children.

Vallotton[83] made a similar analysis. One argument in favour of the first possibility is that positive serological responses in patients with gonadal dysgenesis vary with their caryotype. Burch and Rowell[13] have suggested that certain genes involved in the genesis of autoimmunity are situated on the chromosome X. But the absence of increased frequency of thyroid antibodies in patients with Klinefelter's syndrome with an XXY pattern, contrasting with the high frequencies observed in patients with Turner's syndrome (XO or X-iso X), argues against this simple hypothesis. Two further points also throw doubt on it:

(1) The frequent existence of thyroiditis in mongolian children in whom the chromosome anomaly affects the chromosome 21 and not the X;
(2) The high prevalence of autoimmune phenomena, noted by most authors, in the families of Turner patients and of mongolian subjects.

The hypothesis that a child's aneuploidism might cause the development of autoimmunity in the mother is contradicted by the abnormally high frequency of thyroid antibodies in children born before the aneuploid subject as well as in the father.

The third explanation suggests that the mother's autoimmunity induces chromosome aberrations in her descendants. Fialkow, who supports this approach,[37] has stressed the high frequency of thyroid antibodies in young mothers of mongolian children (under 35 years of age), in relation to a control population, whereas older mothers show no higher frequency of circulating antibodies than reference subjects of the same age.[41] This increased frequency in young mothers goes hand in hand with a large number of non-classic caryotypes in the mongolian children born to them (mosaics, translocations). For Penrose[76] the birth of a mongolian child to a young mother may be due to a factor other than the age factor usually cited. These observations are similar to those made in mothers of Turner children in whom the frequency of thyroid disorders is much greater when their children have an irregular chromosome pattern (mosaics, isochromosome X).[43] Fialkow suggests that the role of maternal autoimmunity is particularly important in the birth of aneuploid children with non-classic caryotypes.

However, *in vitro* experiments made to check this third hypothesis have produced contradictory results. Studies of the effect of lymphocyte extracts on allogenic fibroblasts under culture have shown a significant increase of hyperploidism and chromosome breaks when the extracts come from lymphocytes of patients affected with autoimmune diseases.[40,42] However, Israsena *et al.*[54] observed no significant increase of aneuploidism in cultures of blood cells from patients with such diseases. The direct influence of autoimmunity on the genesis of anomalous caryotypes thus seems far from being established.

The role of a common factor, perhaps responsible for both the appearance of thyroid autoimmunity and aneuploidism in the descendants, has recently been proposed.[22,84]

The studies of Dallaire *et al.*[22] are based on the idea of increased frequency of births of mongolian children 9 months after an epidemy of viral hepatitis[81] and on the very frequent presence of thyroid antibodies in patients with hepatitis.[21,22] They suggest that the viral attack may be responsible for the birth of aneuploid children, either by direct effect on the gonads or by indirect action linked with the induced autoimmunity.

However, the interference of viral hepatitis in the genesis of Down's syndrome is currently the subject of much controversy.[57,59] Furthermore, no abnormally high frequency of thyroid antibodies has been found in patients with hepatitis hospitalized in Brussels.[4]

Vanhaelst *et al.*[84] have suggested that the thyroid abnormalities frequently discovered in the members of families of mongolian children are related to the development of autoimmunity in these families, and constitute a risk of chromosome anomalies occurring in later generations.

High levels of NBEI seem to reflect a metabolic thyroid disorder, occurring independently of any stimulation of the gland. Dodge's idea[28] that low BEI levels are explained by a defect in the thyroid hormone binding proteins has been invalidated.[36] High levels of NBEI are characteristic of autoimmune thyroiditis and are frequently found in the near relatives of patients affected with this disease.[7,49] They are associated significantly with a greater frequency of positive serological responses in clinically unaffected subjects, both in the families of subjects with thyroiditis and in the families of mongolian subjects. These facts constitute further arguments in favour of the existence of a thyroid metabolic disorder in the families of mongolian children.

The greater frequency of miscarriages observed in the mothers of mongolian children[84] may be related to the existence of caryotype anomalies in the foetus, which has been observed in certain spontaneous abortions.[67]

The link between diabetes and Turner's syndrome or mongolism seems more difficult to establish. Diabetes itself could have an action on the gametes and therefore be a risk factor. Bastenie *et al.*[4] have shown that diabetes is associated significantly with asymptomatic atrophic thyroiditis, probably on account of constitutional factors (cf. Chapter 10). These factors may perhaps explain the greater frequency of diabetes in families of aneuploid children.

7. Conclusions

The various studies devoted to the association between autoimmune thyroiditis and chromosome disorders have revealed the existence of a "thyroid" risk factor for the birth of aneuploid children.

This risk may be reflected by the presence of thyroid antibodies in the serum of the relatives of affected children, indicating, at least in families with Down's syndrome, a more widespread metabolic disorder and characterized by an abnormally high level of non-butanol extractable iodinated proteins in the serum.

The exact link between chromosome disorders and thyroid metabolic abnormalities remains to be determined.

The following hypothesis could explain the findings reported so far:

(1) A metabolic defect could induce the development of thyroid antigens to set off and maintain the process of thyroiditis.
(2) The high level of NBEI in the serum would reflect this phenomenon.
(3) The defect would be transmitted hereditarily.
(4) The high NBEI would correspond directly or indirectly to a risk of chromosome anomalies developing in the children.

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CHAPTER 14

Heredity of Autoimmune Thyroiditis

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1. Introduction

The hereditary transmission of thyroid autoimmunity comprises two fields of research: that of the appearance of autoimmunity in families, and that of the family distribution of thyroid disorders. In other words, research for the hereditary factor of autoimmune thyroiditis may be concerned with the detection of an anomaly in the immune system or of a metabolic defect presumed to underlie the autoimmunity. Such studies based on subjects selected from hospital patients or those attending medical consultations have been very strongly criticized by epidemiologists. Masi *et al.*[44] support the view, already advanced in 1959 by Haenszel,[29] that the population samples used in these studies are over-representative of families with more than one affected member. Clinicians more readily publish such cases because they are struck by the coincidence.

Furthermore, when one member of a family is affected with a particular disease, the close relatives are more likely to observe similar phenomena and go to the hospital for examination. According to Masi *et al.*,[44] it is impossible to talk about family aggregation of Hashimoto's thyroiditis until more reliable data are available on the frequency of the disease in the general population and in the families of properly selected index subjects. To overcome these pitfalls, two methods have been used. Roitt and Doniach[48] have reviewed their statistical material keeping back families with only one member having thyroiditis and discarding from the other families all the subjects with a clinically apparent thyroid syndrome. Bastenie *et al.*[4] studied families with no obvious thyroid diseases such as families of subjects with Down's syndrome; they also investigated the frequency of asymptomatic thyroiditis in families of subjects admitted to hospital for various reasons and in whom asymptomatic thyroiditis was detected incidentally. By these means it seems possible to determine the hereditary nature of thyroiditis by surveys free from the criticism mentioned earlier.

2. Heredity of Thyroid Diseases

Sporadic Goitrous Cretinism

It has long been known that sporadic goitrous cretinism tends to run in families (Osler[47] quoted by McGirr and Greig[46]). As indicated in Chapter 1, several bio-

chemical defects may be responsible for this condition. Family surveys have revealed that at least two of the biochemical anomalies are transmitted as recessive autosomal characteristics, namely the deshalogenase deficit and defective organification due to a peroxidase deficit. Furthermore, a number of subjects with the latter defect, whilst remaining euthyroid, develop goitre with congenital deafness, called Pendred's syndrome. The hereditary transmission of this disease seems certain.[10,24,26,40,51]

Euthyroid Simple or Nodular Goitre

The genesis of nodular goitre comprises a phase of benign hyperplasia of the thyroid tissue, usually associated with a relative shortage of iodine. The basic mechanism is no different in kind from that which produces endemic goitre.[17] Ermans *et al.*[18,19] have shown that sporadic goitrous hyperplasia depends on the iodine concentration per gram of thyroid tissue, and more specifically on the degree of iodination of the thyroglobulin. However, except in endemic regions, the incidence of goitre is very uneven. Nodular goitre seems to be more frequent in certain families whose diet is not obviously different from that of the rest of the population. The relative shortage of iodine seems to reveal a hereditary disorder of iodine utilization. In studying 71 subjects affected with sporadic goitre, Bonhold[5] found a family history of goitre in 25 of them: of the 514 people belonging to these families, 102 were goitrous subjects, sometimes spread over several generations. Furthermore, nodular goitre has been encountered with greater frequency in the families of hyperthyroid subjects. This observation suggests the existence of a common metabolic anomaly in these two thyroid diseases. Slight anomalies of iodine utilization were already suggested by Horst[36] and Clayton *et al.*[7] in the physiopathology of nodular goitre.

Investigations of the families of 31 male subjects thyroidectomized for nodular goitre revealed a metabolic defect in 6 of them, transmitted either as a recessive genetic error or as a dominant defect.[25] From a comparative study of monozygotic and bizygotic twins, one of whom had nodular goitre, it was concluded that the development of a goitre in the other twin depended on genetic factors "but not to a striking degree", and that environmental factors could also play a role.[27,28,46] It must be admitted that the metabolic disorders involved are difficult to demonstrate, for one thing because the anomaly is necessarily of a minor degree and for another because the parenchyma is stimulated by secondary secretion of TSH. This adaptation mechanism is capable, in its turn, of causing metabolic disorders. Nevertheless, Floyd *et al.*[22] and De Luca *et al.*[9] have noted abnormal iodine organification, and Van Wyck *et al.*,[55] Wynn *et al.*,[58] Dowling *et al.*[15] have observed the presence of abnormal iodinated proteins in the blood in cases of familial nodular goitre. Kitchin and Howell-Evans[41] conclude from their review of earlier literature that if a hereditary mechanism plays some part in the development of nodular goitre, it is probably of a very complex nature, dependent on more than one gene, and with a sex-limited character since it is much more apparent in women than in men.

TABLE 14.1. INCIDENCE OF THYROTOXICOSIS AND SIMPLE GOITRE (PERCENTAGE) IN RELATIVES OF THYROTOXIC PATIENTS
(After Bartels[3])

	Graves' disease	Simple goitre	Total
Mothers	3·5	5·2	8·7
Sisters	8·2	9·7	17·9
Aunts	2·7	3·3	5·9
Daughters	9	17·1	26·1

Toxic Goitre

As early as 1937, Lehmann[42] made a group study of the members of 29 families comprising thyrotoxic subjects. Out of the 468 subjects examined, apart from the 29 thyrotoxic subjects, 79 showed some degree of hyperthyroidism. Amongst the brothers and sisters of the patients the frequency of hyperthyroidism was 33·8%, amongst the uncles and aunts 17·1%, and amongst cousins 16%. Bartels[3] (Table 14.1) has studied 204 propositi affected with Graves' disease, 21 subjects with toxic adenoma, and 498 normal subjects considered as representative of the Danish population. Sixty per cent of the subjects with Graves' disease had a family history of hyperthyroidism and increased frequency of nodular goitre and myxoedema. Martin and Fisher[43] confirmed the family incidence of thyroid diseases in a series of ninety cases of thyrotoxicosis, suggesting that a genetic anomaly favours the development of the disease. Means *et al.*[46a] after citing several reports of cases in the same families, describe a remarkable family in which goitres, thyrotoxicosis, and severe exophthalmos were observed in three successive generations. Finally, mention must be made of the work of Ingbar *et al.*[37] who observed high thyroxine turnover rates not only in the hyperthyroid subjects of a family but also in several of their close relatives.

Spontaneous Myxoedema

Spontaneous hypothyroidism in adults, albeit a relatively rare disease, has also been observed several times in a single family, and it has been reported in homozygotic twins.[23,34] Its family association with other thyroid diseases, including thyrotoxicosis, is illustrated in Table 14.2.

3. Heredity of Autoimmunity in Families of Patients with Thyroid Diseases

In the opinion of a number of authors[14] the aggregation of Hashimoto's goitre, primary myxoedema, and thyrotoxicosis in certain families is best understood if it is assumed that these diseases develop by an autoimmune process. Such an assumption

TABLE 14.2. INCIDENCE OF VARIOUS THYROID DISEASES IN FAMILIES OF PATIENTS AFFECTED WITH THYROTOXICOSIS, HASHIMOTO'S THYROIDITIS, AND SIMPLE GOITRE

	No. prop.	Relatives studied	With Hashimoto No.	With thyrotoxicosis		With goitre		With myxoedema No.	Total	
				No.	%	No.	%		No.	%
Thyrotoxicosis										
Bartels, 1941[3]	93	Mothers			3·5		5·2			
		Sisters			8·2		9·7			
		Maternal aunts			2·7		3·3			
		Daughters			9·0		17·1			
Lehmann, 1937[42]	29	(468)								
		Siblings			33·8					
		Uncles			17·0					
		Cousins			16·0					
Martin and Fisher, 1945[43]	90			20		16				
Hashimoto's goitre										
Hall *et al.*, 1962[31] Doniach and Roitt, 1963[11] Volpé *et al.*, 1963 [55a]	105	322	26	17		27		6	76	24
Simple goitre										
Doniach *et al.*, 1965[12]	37	—	2	11		39				
Bonhold, 1945[5]	71	514 (in 25 families)				102	20			

TABLE 14.3. INCIDENCE OF THYROID ANTIBODIES IN HEALTHY RELATIVES OF 145 ADULT HASHIMOTO'S PROBANDS AND OF 35 PATIENTS WITH THYROTOXICOSIS
(After Roitt and Doniach, 1967[48] and Doniach and Roitt, 1969[14])

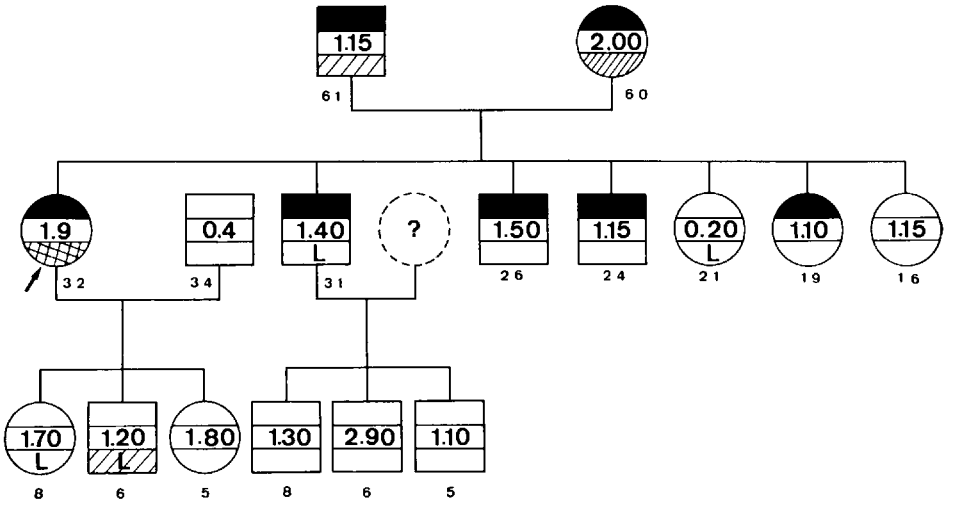
	No. tested	% with TGA	
I. HASHIMOTO (proband sole member with clinical disease)			
Males	60	32	
Matched controls	60	12	$p < 0{\cdot}02$
Females	76	45	
Matched controls	76	12	$p < 0{\cdot}001$
II. THYROTOXICOSIS			
Males	10	33	
Matched controls	10	10	n.s.
Females	25	60	
Matched controls	25	12	$p < 0{\cdot}001$

TABLE 14.4. THYROGLOBULIN ANTIBODIES AND ABNORMAL IODINATED PROTEINS IN THE SERUM OF SIBLINGS OF PATIENTS WITH AUTOIMMUNE THYROIDITIS

Population	No. of cases studied	Age (mean and range)	TGA +	TGA %	NBEI $\geq$ 1·5 μg per 100 ml incidence	
Down syndrome with TGA	30	12·7 (3–29)	9	30	16/29	55%
Thyroid patients	38	27·7 (15–68)	17	45	12/32	38%
Controls (normal subjects)	50	35·6 (15–60)	3	6	10/50	20%

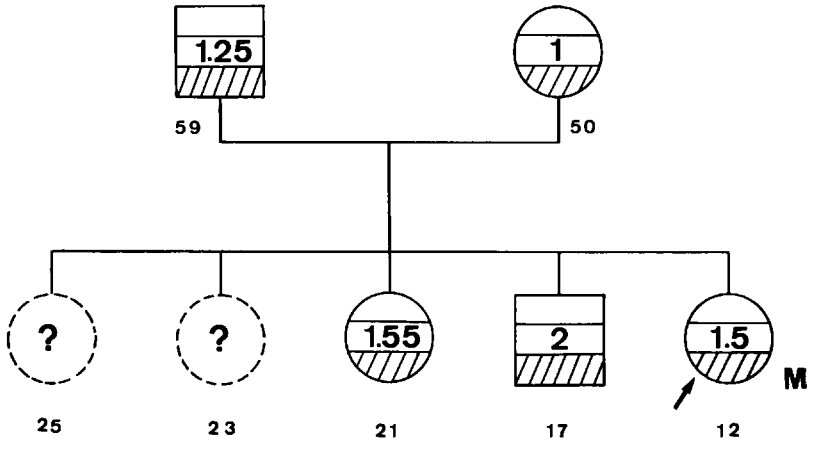
takes no account of the fact that nodular goitre, which has definitely no autoimmune origin, has also been observed with high frequency in these families (cf. Tables 14.1 and 14.2) Hall *et al.*[30] were the first to study the distribution of antibodies in families of eleven subjects affected with autoimmune thyroiditis (either Hashimoto's, myxoedematous atrophy, or thyrotoxicosis with autoimmunity). These authors found that 56% of the near relatives of these patients had significant levels of thyroid antibodies in their serum, whereas only 25% of the aunts, uncles, and cousins showed high antibody titres. Several other studies have arrived at the same results[11,12,14,20,33,48,50] (Table 14.3).

FAM. «DEG.»



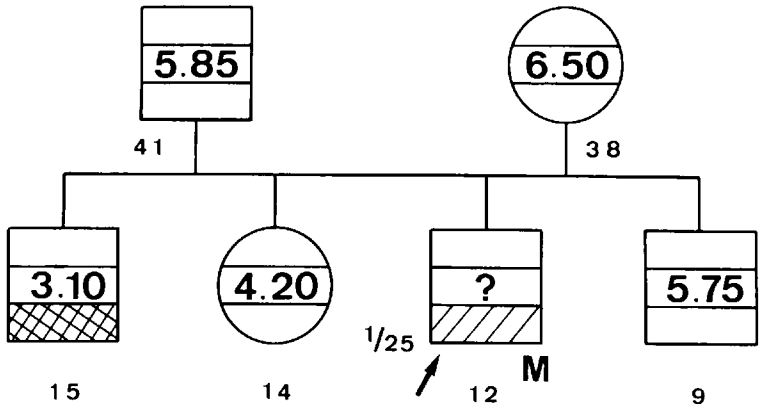
(a)

FAM. «SPET.»



(b)

FAM. «MAR.»



(c)

FIG. 14.1.a. b, c, Familial pedigrees.

A Thyroid disease, Presence: black. Absence: white.
B NBEI in absolute value (μg per 100 ml).
C Antithyroid antibodies. Conventional: presence with a titre of 1/125 or more. (slightly hatched ▨, hatched ▨, or cross-hatched ▩ in relation with increasing titre); presence with a titre of 1/25: written; absence: white. LATS: presence: L.

The age of the subjects is written under the symbols, the propositi are indicated by arrows and the mongolian subjects by M.

These ideas are supported by the results of pedigree studies[8,16,31,32,35,45,49,50,52] and twin studies.[34,38,59] De Groot *et al.*[8] have also found an abnormal iodinated protein in the serum of these goitrous subjects. Similar observations were made in Brussels[54] in the brothers and sisters of subjects with asymptomatic thyroiditis or clinical thyroiditis (Hashimoto's or thyrotoxicosis) (Table 14.4 and Fig. 14.1a).

Furthermore, LATS has been observed in the serum of homozygotic twins[39] and euthyroid relatives of thyrotoxic patients[56,60] (cf. Chapter 8, Table 8.7, and Fig. 14.1).

In conclusion, even when the statistics, to avoid criticism, cover families in which only one member shows a clinical disease, an abnormally high frequency of family cases is apparent. However, this family frequency attains the figure of 42% only in the female members of the families studied, the overall percentage being only 38%.[48] As shown by Anderson *et al.*[2] and in Table 14.1, the family aggregation of thyroid diseases includes nodular goitre as well as thyrotoxicosis. Furthermore, abnormal incidence of circulating thyroid antibodies is just as high in the families of subjects with nodular goitre as in those of thyrotoxic subjects.

Thus genetic transmission of thyroid autoimmunity seems indisputable, but does not present with the characteristics of a dominant gene. Furthermore the observations on monozygotic twins may be explained as well by transmission of a metabolic defect as by that of a primary anomaly of the immune system.

4. Heredity of Clinical and Metabolic Thyroid Disorders in Families of Subjects Affected with Asymptomatic Thyroiditis Studied Outside the Hospital Environment

In a study[53,54] of a large population of families each with one child affected by Down's syndrome, it was possible to conduct a valid investigation of iodine metabolism and autoimmunity in the families of subjects with asymptomatic autoimmune thyroiditis. The parents, brothers, and sisters of propositi were normal subjects; the children were living in their families and did not require special medical attention apart from pedagogical and psychological care. The inquiry was launched with the object of establishing the frequency of antibodies in the near relatives of subjects affected with this syndrome. The description of the population studied is given in Chapter 13.

As described, the incidence of antibodies is very high in this population, attaining 26% of the subjects with Down's syndrome, 20% of their brothers and sisters, and 28% of their mothers. Moreover, in this population with its high incidence of asymptomatic lymphocytic thyroiditis, very frequent antecedents of thyroid disease were noted (Table 14.5) and also signs of thyroid dysfunction in the form of high levels of NBEI in the serum (cf. Chapter 13). The two factors—thyroid antibodies and abnormal iodinated proteins—are definitely related both in the hospital population and in the families of mongolian subjects. The two factors seem to be transmitted hereditarily.

TABLE 14.5. FAMILIAL AND PERSONAL HISTORY OF THYROID DISEASES AND DIABETES

	1[a]		2[b]	
	No.	%	No.	%
Diabetes				
Familial history	15	13	4	6
Personal history	3	4		
Thyroid diseases				
Familial history	20	24	3	4
Personal history	22	27	7	10

[a]In 83 mothers of a mongolian child.
[b]In 67 mothers of normal children.

TABLE 14.6. THYROID ANTIBODIES AND NBEI VALUES IN THE SERUM OF THE MEMBERS OF NINE FAMILIES WITH AT LEAST ONE PARENT AFFECTED WITH ASYMPTOMATIC THYROIDITIS
(After Bastenie *et al.*, 1969[4])

Family	Antibodies				NBEI ⩾ 1·5 μg per 100 ml			
	Father	Mother	Children		Father	Mother	Children	
			No.	+			No.	+
Deg.	+	+	7	1	−	+	7	2
Dut.	−	+	3	1	−	+	3	2
Zim.	−	+	4	2	−	−	3	2
Boi.	+	−	7	2	−	+	7	4
Spe.	+	+	3	3	−	−	3	3
Dev.	−	+	3	0	−	+	3	1
Bou.	+	−	3	0	−	−	3	1
Dew.	−	+	3	0	+	+	3	1
Ver.	−	+	2	0	−	·	2	1
Total	4	7	35	9	1	5	34	17

In this study, the transmission of thyroid autoimmunity does not have the dominant gene characteristics reported in hospital studies. Out of thirty brothers and sisters of mongolian subjects, belonging to five different families each including at least one member with asymptomatic thyroiditis, the number of antibody carriers was only 9, i.e. 30% instead of the expected 50% (cf. Table 14.4). Out of 35 subjects belonging to 9 families investigated in another study,[4] each with at least one asymptomatic thyroiditis patient, 9 were antibody carriers, or 26% instead of the expected 50% (Table 14.6). On the other hand, in the two family groups, half the subjects showed abnormally high NBEI levels; 16 of the 29 brothers and sisters (cf. Table 14.4) and 17 of the 34 children (cf. Table 14.6).

The pedigrees given in Fig. 14.1b and c show (respectively) the "apparently Mendelian dominant" transmission of immune thyroiditis in the descendants of two affected subjects, and the absence of thyroiditis in the parents of two affected children, but with the "apparently Mendelian dominant" distribution of serum NBEI.

5. Conclusions

A series of studies offering no reason for criticism on epidemiological grounds have demonstrated the family aggregation of thyroid autoimmunity. The genetic nature of this family aggregation also seems established beyond all reasonable doubt, particularly by the pedigrees furnished by various studies. But the question of the genetic mechanism involved is still unanswered. The idea that autoimmunity is transmitted by a sex-related gene,[6] based on the early observations of hereditary autoimmunity in subjects with Turner's syndrome (XO, or X iso X), has generally been abandoned. Not only have similar

observations been made in connection with Down's syndrome, which involves anomalies of chromosome 21, but it has been demonstrated that chromosome disorders are frequently dissociated from familial thyroid autoimmunity* (cf. Chapter 13). However there does seem to be a sex-limiting factor since all the studies report a much higher frequency of thyroiditis in women than in men. Contrary to the opinions of the early investigators, it now seems that the idea of genetic transmission by a dominant gene must be discarded.

The studies seem to yield a series of arguments in favour of the genetic transmission of a thyroid metabolic disorder, with the autoimmunity appearing as a secondary manifestation linked to the disorder. The first of these arguments is the considerable frequency of other thyroid diseases in the families of subjects with thyroid autoimmunity, including nodular goitre[1] (cf. Table 14.2). Correlatively, in the families of adolescents with nodular goitre present, the same incidence of thyroid antibodies as the close relatives of subjects with Hashimoto's thyroiditis is found.[12] Since nodular goitre is definitely not an autoimmune disease, this latter finding led Doniach and Roitt to envisage "a more peripheral abnormality which determines the organ orientation of the immunologic attack". It seems more logical to interpret these findings as an indication of the existence of a primary thyroid abnormality in the family which predisposes its members both to nodular goitres and to the development of thyroiditis (Chapter 6). A primary metabolic disorder is also suggested by the frequent history of thyroid disease found in families of mongolian subjects (cf. Table 14.5).

A major argument is the demonstration of an abnormal NBEI level in families with a high incidence of asymptomatic thyroiditis. For Hall and Stanbury[33] the presence of abnormal iodinated proteins in the serum constitutes one of the biochemical characteristics of thyroid autoimmunity.

Observations of subjects affected with asymptomatic thyroiditis studied in the hospital population (Chapter 11) and in families of mongols (Chapter 13) have confirmed this relationship. In Chapters 1, 5, 7 and 8, the significance of these abnormal proteins has been discussed. In the near relatives of mongolian subjects, such an anomaly seems to reflect a congenital thyroid defect which is genetically transmitted[33] (cf. Table 14.6).

Finally, one last feature which indicates the constitutional nature of the defect governing the development of thyroid autoimmunity is the significant association of thyroid disorders with diabetes. This association is observed in the study of myxoedema (Chapter 9), of thyrotoxicosis (Chapter 8), and of asymptomatic thyroiditis (Chapter 11). It is also observed to a striking degree in the family history of subjects with Turner's syndrome[57] and Down's syndrome (cf. Table 14.5). These observations do not mean that diabetes is a feature of autoimmune process but may be more reasonably interpreted as an indication that diabetes—a metabolic disease of probable congenital origin—is associated with the complex genetic anomalies which are responsible for thyroid autoimmunity.

As Anderson *et al.*[2] have said, progress in the study of the hereditary transmission of autoimmunity will be achieved by the establishment of more numerous and more

* In Klinefelter's syndrome (XXY) the absence of circulating thyroid antibodies is conspicuous.[13,21]

extensive pedigrees. The question also arises whether progress could not be accelerated by subjecting the near relatives of affected individuals to a "pharmacogenetic" test involving the measurement of radioiodine uptake before and after the ingestion of 2 mg of KI. This test, which is almost always positive in cases of lymphocytic thyroiditis, might detect a metabolic anomaly before the appearance of biochemical or serological disorders.

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CHAPTER 15

The Significance of Lymphocytic Thyroiditis

P. A. BASTENIE

1. Introduction

The subject of thyroiditis is now so well documented that any classification demands, before all else, a return to precise definitions and clarity of language—"the lost tool of learning in medicine and science".[20] In this chapter of conclusions and discussion, emphasis will be laid on the need to distinguish clearly between the various pathological states and their morphological and clinical characteristics. A classification of the different conditions will serve as a starting point.

The discussion of the pathogenic significance of each type of autoimmune thyroiditis cannot avoid certain hypothetical considerations, but the point of view will be as pragmatic as possible. The detection of thyroid autoimmune phenomena is of considerable practical interest both for diagnosis and for treatment; so this aspect will be reviewed in detail.

Finally, the problems raised by non-immune thyroiditis will be examined, for their importance must not be underestimated.

2. Classification of Thyroiditis Variants

Research into thyroiditis has revealed our ignorance of the fundamental aetiological processes which govern the various morphological and clinical forms.

These processes doubtless involve several factors, one of which is obviously sex, since all varieties of the disease are encountered more frequently in women than in men. Even in this narrow field, the data are confusing: women are more frequently affected with autoimmune thyroiditis than men, but paradoxically more so after the menopause, and subjects with ovarian dysgenesis are conspicuous for a high incidence of circulating antibodies, whereas subjects with Klinefelter's XXY karyotype show almost complete absence of these autoimmune reactions. A disorder of immunological tolerance[19] by itself can hardly be the decisive factor: the concept of its dominant genetic transmission is no longer tenable;[27] Doniach and Roitt, the pioneers in this field,[9] suggest that a more peripheral abnormality "determines the organ orientation of the immunological attack". So it is not surprising that all attempts at classification on an aetiological basis have failed up to now.

Since the morphological and clinical variants may comprise successive phases of

TABLE 15.1. CLASSIFICATION OF SUBACUTE AND CHRONIC THYROIDITIS

Pathological variants of thyroiditis	Thyroid function	Etio-pathogenic hypothesis
1. Granulomatous with giant cells (de Quervain)		
(a) Subacute	Euthyroid (except for hypermetabolic phase)	Viral infection (probable)
(b) Chronic	Euthyroid (sometimes hypothyroid after surgery)	
2. Fibrous invasive (Riedel)	Euthyroid: occasionally hypothyroid after surgery	Vascular disease (possible)
3. Lymphomatous (Hashimoto)	Euthyroid in two-thirds; hypothyroid in one-third of untreated cases; often hypothyroid after surgery	Sex-limited Metabolic factors (?)
4. Focal—in goitre or carcinoma	Euthyroid	Iodine therapy (?) Sex-limited
5. Focal or diffuse—in thyrotoxic goitre	Hyperthyroid; sometimes hypothyroid after surgery or radiation therapy	Autoimmunity Involution process due to increased cell turnover or/and ageing;
6. Asymptomatic focal or diffuse	Euthyroid; in many cases latent hypothyroid	(oncocytic metaplasia)
7. Severe atrophic	Hypothyroid	

hyper-, eu-, and hypothyroidism, a general classification of thyroiditis according to thyroid function can obviously not be made.

We must humbly revert to a morphological and clinical classification with marginal notes on the functional condition of the gland and the aetiological hypothesis currently held to be the most probable.

The proposed classification (Table 15.1) is only valid if the definitions given are respected and if no attempts are made, by misuse of language, to apply a precise term like "Hashimoto's thyroiditis" to ill-defined forms of lymphocytic thyroiditis.

3. Non-autoimmune Thyroiditis

Despite the considerable interest of autoimmune processes, the non-autoimmune types of thyroiditis cannot be ignored.

Although *Riedel's* hard, pseudo-tumorous goitre is very rare, its possible presence must be borne in mind. A definite diagnosis may be made by surgery, which must be kept to the very minimum. Other organs (orbit, liver, retroperitoneal tissue) must be examined for proliferation of dense, fibrous tissue (Chapter 4).

In sharp contrast with Riedel's goitre, *de Quervain's thyroiditis* is a fairly common disease, although often unrecognized. It is easy to diagnose, on the basis of clear-cut clinical and laboratory signs, and treatment by triiodothyronine and corticosteroids (or sometimes salicylates) is usually effective and rapid.

After an attack of subacute thyroiditis, certain subjects are found to have circulating antibodies in their serum (Chapter 3). The increase is often temporary and slight, showing that the leakage of antigenic thyroid products is not sufficient to trigger off autoimmune thyroiditis. Undoubtedly, for autoimmunity to develop, some prior abnormality must be present. This is how granulomatous thyroiditis of viral origin may evolve into autoimmune lymphocytic thyroiditis in isolated cases no doubt predisposed to the disease.

In other cases, granulomatous thyroiditis gives rise to the development of non-immune chronic thyroiditis. Sometimes histological evidence shows persistent granulomas amidst the dense tissue and moderate lymphocytic infiltrations. Certain fibrotic forms of thyroiditis, with no serological immune phenomena, are perhaps caused by a viral infection and may develop in similar fashion into a fibrotic process with scattered chronic inflammatory nodules, still with no immune phenomena. These rare cases may make diagnosis extremely difficult (Chapter 3). It would seem that the often misused term "non-specific chronic thyroiditis" should be reserved for this condition, since, in contrast to all other forms of thyroiditis, there seems to be no characteristic factor in its genesis, pathology, or evolution.

4. Significance of the Process of Autoimmune Lymphocytic Thyroiditis

The forms of thyroiditis involving an autoimmune process have attracted particular interest during the last 10 years. But the significance of the process is still a subject of discussion.

Lymphocytic thyroiditis constitutes a general process with a number of morphological characteristics which do not vary with the clinical setting in which they occur.[4]

These characteristics are:

(1) Vasodilatation of the capillaries.
(2) Diapedesis and accumulation of white blood cells in the stroma, chiefly lymphocytes and plasma cells.
(3) Alterations of the parenchyma reflecting relative hyperplasia and oncocytic metaplasia of certain epithelial elements, usually located in small vesicles with little or no colloid.

In serial histological sections of glands invaded by lymphocytic thyroiditis, these epithelial lesions appear as primary cell phenomena. They are not necessarily accompanied by lymphocytic infiltrations, although on contact with any infiltration, however slight, some oncocytic elements are always to be found (Fig. 15.1). These cells are absent in de Quervain's and Riedel's thyroiditis and, when present in the thyroid, may be considered as specific for human autoimmune thyroiditis.

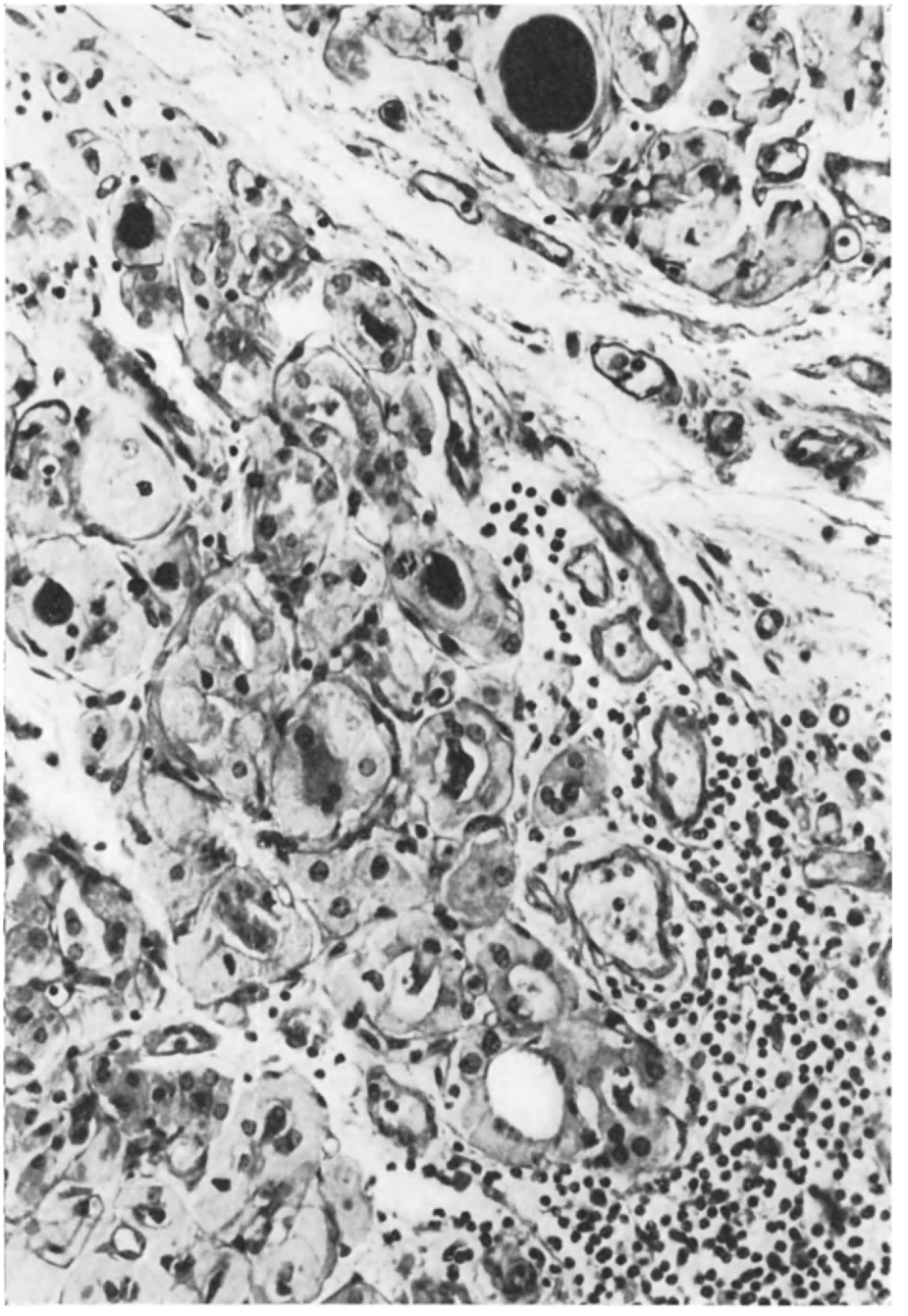

FIG. 15.1. Case report SP 85,432: autopsy 70/187. Oncocytic metaplasia in small thyroid vesicles almost entirely devoid of colloid. In contact: dilated capillaries and localized lymphocyte infiltration. Autoradiograph (4weeks after a dose of ^{125}I) showed absence of radioiodine uptake in these cells. The patient was a 68-year-old woman admitted for vascular sclerosis. A-V block with Adams-Stokes syndrome. She had suffered from rheumatoid arthritis, and serum TGA (titre 1/3125) and CFA were the only markers of asymptomatic thyroiditis. (×330.)

The hypothesis has long been advanced that these elements indicate parenchymatous metabolic disorders and that the inflammatory infiltrations develop in response to the release of cytolytic products.[4,14,25] For this reason, some authors have even refused the term "inflammation" to describe a process which is primarily degenerative. The term of thyroidosis has been proposed to underline the morphological similarity of this disease with that of certain degenerative processes occurring in the liver, and the term of cirrhosis was suggested by Simmonds[24] as early as 1923 to describe the process of atrophy in myxoedema. Nevertheless, the anatomical process is inflammatory, even if its orgin lies in a metabolic anomaly of the epithelium.[11] The metabolic nature of the epithelial alterations is confirmed by two kinds of observations. First of all, histochemical and electron microscopical investigations have detected the existence of severe cytological anomalies in the oncocytes (cf. Chapter 5) entailing changes in mitochondrial respiration and the production of energy, and also signs suggestive of the disorganization of protein synthesis. Secondly, the oncocytes no longer trap radioactive iodine (cf. Fig. 10.12 (p. 248)) and comparisons of histological and clinical data show that thyroids containing nothing but these oncocytic elements are functionally crippled.

Apart from these morphological features, the process of lymphocytic thyroiditis is characterized by the appearance of thyroid antibodies. Thyroglobulin and cytoplasmic antibodies are constituted by the same immunoglobulin classes, whatever the clinical syndrome involved. Although there may be a few exceptions, the development of morphological lesions and serological anomalies is roughly parallel. The pathological conditions comprising the most extensive degenerative cell lesions and the most dense lymphocytic infiltrations are also characterized by the highest antibody levels in the serum.

There are many reasons for considering this close correlation as an indication of the autoimmune nature of the process: in fact lymphocytic thyroiditis satisfies all the criteria of an autoimmune disease set forth in Table 2.2 (p. 41).

It is commonly known that two major theories vie with each other to explain autoimmunity: one suggests the existence of a normal autoimmune apparatus reacting to the presence of an abnormal antigenic stimulation, whereas the other claims that an abnormal autoimmune apparatus is the cause of the phenomenon (cf. Chapter 2). Those who uphold the latter hypothesis assert that no abnormal antigenic protein has so far been identified.[7] The partisans of the first theory reply that no demonstration has yet been made of an anomaly of the immune apparatus in thyroiditis carriers. Without taking sides in this doctrinal dispute, we must stress that the majority of the authors who accept a primary alteration of the immune apparatus nevertheless seek the causes of the initial mechanism in a peripheral anomaly.[9] The present study has furnished a number of arguments in favour of the existence of such an anomaly of iodine mechanism in nodular goitre, cancer, and atrophic thyroiditis, although the actual nature of the anomaly has admittedly not been identified.

Furthermore, two arguments cited in support of the hypothesis of a primary anomaly of the immune apparatus are very much open to doubt.

First of all, the idea of autoimmunity being handed down by a predominant autosomal genetic factor[16] is thrown into question by the observations reported in Chapter

14, which seem to relate the appearance of antibodies to some metabolic phenomenon hereditarily transmitted. On the other hand, the appearance in a single individual of antibodies against various tissues and the family aggregation of autoimmune diseases have been considered to be unexplainable outside the theory of forbidden clones. In fact, these concepts would presume the simultaneous appearance of an extraordinary number of mutations capable of producing new clones, each manufacturing one of the several antibodies present.

Clearly, in certain subjects—and notably women over 60—focal intrathyroid infiltrations are encountered so frequently that it is difficult to see them as a serious anomaly; however, these alterations are accompanied at a certain point in their development by the appearance of low titres of circulating antibodies; they occur in the same diseases in which more extensive lesions are found: hypertension, atherosclerosis, diabetes, etc. (cf. Chapter 11).

If, like Assem,[2] Boyden,[6] Haurowitz,[18] Weir,[30] and Grabar,[15] one interprets the process as one which basically performs a physiological function of cleansing tissue waste (cf. Chapter 2), the preceding observations are explained very satisfactorily.

In this idea the development of more progressive lesions with the passage of greater quantities of antibodies into the serum would reflect the transformation of the "physiological" process into one of pathological auto-aggressivity. Furthermore, as similar phenomena have been reported in other tissues, especially the gastric mucosa and the corticoadrenals, this theory would offer a simple and logical explanation of the simultaneous appearance of various antibodies in the same subject. However, there is no doubt that the reaction of the patient's immune system must play an important part in the process. This is indicated by the high incidence of thyroid antibodies in patients whose immune reactions have been stimulated by other processes such as leprosy (cf. Chapter 2), viral attacks (Chapter 3), or perhaps by some other autoimmune disease like myasthenia (Chapter 11).

To sum up, the processes of thyroid autoimmunity depend on a twofold phenomenon, namely on increased activity of immune responses (from a normal or abnormal system) and on the occurrence of thyroid anomalies. Although perhaps of a minor character, the latter seem to be of genetic origin and capable of inducing the denaturation of certain constituents of the thyroid cell or its secreted products. This concept fits in with recent experimental studies (Chapter 2) and would account satisfactorily for the wide variety of thyroiditis lesions, ranging from intense inflammatory reactions in Hashimoto's goitre to slight lymphocytic infiltrations encountered in otherwise normal thyroid glands.

5. Iodine Metabolism in Autoimmune Thyroiditis

The fundamental disturbances of iodine metabolism are remarkably similar in all the varieties of lymphocytic thyroiditis. The similarity is most striking between true Hashimoto's thyroiditis and asymptomatic thyroiditis.

Amongst the principal metabolic phases described in detail in Chapters 1, 5, and 10,

three are particularly liable to be disturbed: in the first place, the intrathyroid exchangeable iodine pool is much reduced. This reduction is perfectly understandable in Hashimoto's thyroiditis or in atrophic thyroiditis with hypothyroidism, when the still active parts of the parenchyma are severely diminished in volume. It is much less understandable in asymptomatic thyroiditis which very often involves only a small part of the gland, leaving a large part of the parenchyma apparently intact (cf. Fig. 10.3A (p. 238).

The second pathological feature is the abnormal response to TSH: since the latter no longer increases the apparent uptake of radioactive iodine, it is said that the gland affected with thyroiditis has no functional reserve. This interpretation is undoubtedly true for Hashimoto's thyroiditis and for thyroiditis in myxoedema. The response of the gland invaded by asymptomatic thyroiditis proceeds in an identical way (cf. Fig. 10.9 (p. 245)). However, histological examination shows the persistence of large areas of intact parenchyma (cf. Figs. 10.1 and 10.3A) suggesting that defective mobilization or abnormal tissue reactivity is at fault. This idea should be explored by further research, which might well reveal one of the fundamental parenchymatous abnormalities responsible for the development of thyroiditis.

A third feature considered by some authors as the most characteristic of the metabolic deviations peculiar to thyroiditis is the presence of large quantities of NBEI in the serum.[17] This anomaly has been studied at length in Chapters 1, 5, 8, 10, 13, and 14. The presence of abnormal iodinated proteins not soluble in butanol can obviously reflect several possibilities. In a series of cases, this particular feature seems to result from physiological stimulation (i.e. in pregnancy) or experimental stimulation of the parenchyma or pathological disruption of the follicles (cf. Chapter 3). In other cases it may result from a metabolic anomaly, for instance in malignancy.

The high NBEI of thyroiditis has been attributed to the stimulation of the parenchyma which accompanies all advanced states of thyroiditis. In asymptomatic thyroiditis, the explanation by abnormal stimulation is even more plausible in view of the reduction of the exchangeable pool and the limitation of the active zones demonstrated in that condition. However, observations in a population of families with Down's syndrome (cf. Chapter 13) make this interpretation improbable and suggest rather that NBEI, sometimes present in young children, without signs of thyroiditis, reflects a primary thyroid anomaly transmitted genetically.

Purely as a hypothesis, it might be considered that this fundamental anomaly could entail the denaturation of certain endogenous constituents and their transformation into antigens. Autoimmunity and NBEI could thus result from a single parenchymatous defect.

6. Significance of the Individual Clinical Processes

It is only since the discovery of thyroid antibodies that the majority of authors have recognised the common basis of all variants of lymphocytic thyroiditis.

At the present time some authors have adopted an extreme view in wanting to include all conditions of autoimmune lymphocytic thyroiditis under a single heading. The work of Masi *et al.*[20] is typical in this respect. Having demonstrated very clearly that with

high magnification histological preparations of Hashimoto's goitre removed by surgery and of certain types of non-goitrous diffuse thyroiditis collected from autopsy material cannot be distinguished from each other by qualified observers, these authors have concluded, rightly, that the basic process involved is always the same. But they have gone on to consider that there is only one disease for which they have, with no justification, traced an "hypothetical" biological gradient. Denying the existence of different variants of immune thyroiditis, they claim that there must be common aetiological factors and identical distributions by age and sex for all the variants of thyroiditis. As Chapters 5–10 have shown, these diseases in fact constitute separate nosological entities with their own symptoms and treatments, their own sex ratio and age distribution and certainly also their own aetiological factors.

In *Hashimoto's goitre*, the immune reactions are at their height, reflected not only by the persistently high levels of circulating antibodies but also by the extensive growth of lymphocytic centres in the parenchyma. The rapid swelling of the thyroid gland is largely due to the proliferation of lymphoid and plasma cells, and the parenchyma is the seat of diffuse metaplasia and hyperplasia sometimes to the point of simulating malignancy.

The goitre declines rapidly under the influence of thyroid hormone treatment, but the antibodies remain in the serum a very long time.

In nodular goitre and malignancy, the immunological phenomena in the cells and serum are undoubtedly due to the metabolic changes directly related to the goitre or neoplasm. These immunological reactions are generally of moderate intensity and the aetiological conditions are those of the goitre or tumour. Finally, treatment by thyroid hormone has little effect.

Non-goitrous thyroiditis, whether asymptomatic or revealed by signs of thyroid insufficiency, is by far the most common form of autoimmune thyroiditis. Unknown or at least misunderstood for a long time, it now appears to play a significant role in various pathological conditions.

There is a definite statistical association between this condition and obesity, essential hypertension, and diabetes. In women, the disease undoubtedly predisposes to coronary atherosclerosis (cf. Chapter 12).

Asymptomatic thyroiditis is by far the most frequent precursor of spontaneous atrophy of the thyroid, leading to acquired hypothyroidism in adults. It is true that in a series of cases of genuine Hashimoto's goitre, spontaneous progression towards hypothyroidism is observed (cf. Chapter 5). But in the large majority of cases of spontaneous myxoedema in adults, no thyroid swelling is noted. The oft-repeated suggestion that thyroid atrophy in myxoedema is generally the outcome of lymphocytic thyroiditis, in which the goitre was small enough to go undetected, is in contradiction with three findings: (1) post-mortem studies show the common occurrence of diffuse asymptomatic thyroiditis in an atrophic form; (2) clinical studies show the development of the latter into clinical myxoedema (cf. Chapter 9); (3) distribution by age and sex is very similar for asymptomatic thyroiditis and hypothyroidism but not for Hashimoto's thyroiditis and hypothyroidism (cf. Fig. 9.1 (p. 213)).

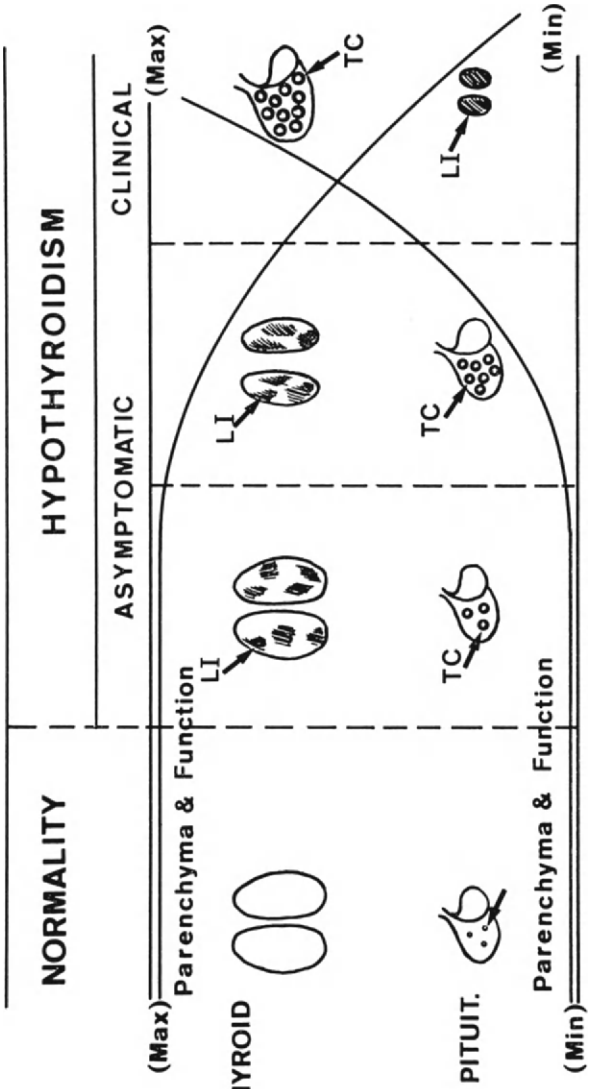

FIG. 15.2. Schematic representation of changes in thyroid and pituitary morphology and physiology under the influence of auto-immune thyroiditis. LI lymphocytic infiltration of the thyroid. TC thyrotropic cells in the pituitary.

The reasons why, in some cases, asymptomatic thyroiditis progresses towards severe destruction and hypothyroidism, are still unknown. For some time it was believed that low titres of antibodies in the presence of focal thyroiditis were of doubtful clinical importance. More recently it was thought by some authors that the presence of thyroid antibodies in apparently normal individuals "remains one of the chief deterrents to attributing pathogenic significance to these antibodies".[1] It is true that in this condition one does not observe positive precipitation tests which would indicate very high levels of TGA (cf. Chapter 2). However, as indicated in Table 10.8 (p. 234), in more than one-third of the cases the TAB titre is equal or superior to 78125. The bimodal distribution of TGA titres in the asymptomatic thyroiditis population may reveal the presence of two sorts of processes: a group with limited development and a group with progressive lesions. Increased immune reactivity or increased cell turnover with antigen formation might account for this difference. Once the thyroiditis has progressed beyond a certain point, the process is probably self-maintained. The course of development from normality to clinical hypothyroidism might be as indicated schematically in Fig. 15.2.

Progressive destruction of the thyroid tissue is accompanied by progressive hyperplasia of pituitary thyrotroph cells and increased secretion of TSH (cf. Appendix to Chapter 10). There is indirect evidence but no definite proof that the TSH activity may accelerate the inflammatory process.

7. Significance of Lymphocytic Thyroiditis in Thyrotoxicosis

Lymphocytic thyroiditis in cases of thyrotoxicosis merits particular discussion. In this disease, the thyroiditis shows no morphological signs distinguishing it from other forms of thyroiditis, and the circulating antibodies are identical except for LATS. The presence of the latter antibody in the blood has induced some authors to class thyrotoxicosis as an autoimmune disease and even to include the process of lymphocytic thyroiditis often encountered in thyrotoxicosis within the blanket term "thyrotoxicosis autoimmune disease".

As explained in Chapter 8, the lymphocytic thyroiditis found in thyrotoxicosis most probably has the same significance as that occurring in nodular goitre or thyroid cancer. It does not in itself seem a likely cause of thyrotoxicosis, but rather constitutes an induced process possibly leading to the destruction of the parenchyma and the spontaneous disappearance of hyperthyroidism: this sequence of events definitely explains the frequent development of thyroid insufficiency after surgery or radiotherapy.

The initial phases of thyrotoxicosis, even if acute, only rarely exhibit lymphocytic infiltrations (cf. Figs. 8.3 (p. 175) and 1.2A (p. 7)). On the other hand, oncocytes and infiltration increase in frequency and intensity as the thyrotoxicosis pursues its course. At this point, lesions, antibodies, and LATS are significantly correlated.[5]

These considerations do not contradict the still disputed view that thyrotoxicosis is the result of an autoimmune phenomenon involving the production of a thyroid-stimulating antibody. The observations reported in the present study throw doubt on the theory that the conventional autoimmune process is the prime cause of thyrotoxicosis.

But they furnish no proof in favour or against the idea that an anomaly of thyroid metabolism sparks off thyrotoxicosis. Until now, the study of LATS, although of considerable interest, has had no influence on the treatment of thyrotoxicosis.

8. Thyroiditis and Chromosome Disorders

The frequent association between thyroiditis and the karyotype anomalies of Turner's and Down's syndromes, discovered originally by Engel[12] and widely confirmed (cf. Chapter 13), has given rise to numerous hypotheses. There seems to be no possibility that the chromosome aberrations, affecting either the X-chromosomes of chromosome 21 could cause the autoimmune disease. Nor is there any confirmation of the theory that subjects with Hashimoto's goitre might more than occasionally carry karyotype anomalies.

Most of the authors have observed thyroiditis in apparently normal parents and siblings, with none of the phenotype signs displayed by the subjects affected with the genotype disorder. Mention must be made of the work of Doniach *et al.*[8] who found no increase in the frequency of thyroid diseases in the parents of subjects with Turner's syndrome. On the other hand, in both Turner's and Down's syndromes, several authors (cf. the personal studies reported in Chapter 13) report not only the high frequency of antibodies but also family history of thyroid diseases and diabetes.

The association between diabetes and thyroid diseases is once again strikingly evident. It probably indicates a constitutional disorder (Chapter 12).

The variety of chromosome anomalies and the absence of signs of thyroid insufficiency in the parents of subjects affected with these disorders obviously exclude the hypothesis that a thyroid hormone insufficiency is the direct cause of these malformations. A plausible theory may be based on the presence of a metabolic abnormality, of which thyroid disease, thyroid autoimmunity, and chromosome anomalies would be the consequences.

All in all, the presence of thyroiditis in parents might constitute a risk of malformations in their offspring, but only to a slight degree, impossible to assess precisely at the moment.

9. Lymphocytic Thyroiditis and Atherosclerosis

The demonstration that lymphocytic thyroiditis is frequently associated with myocardial infarction, especially in women, suggests that there is a case to be made for the involvement of thyroid anomalies in the genesis of arterial atherosclerosis generally and coronary artery disease in particular.

The atherogenic role of thyroid insufficiency is well established by early studies and confirmed in the present work (Chapter 12). Myocardial infarction and cerebral vascular lesions are frequent causes of death in myxoedema patients.

This association is usually explained by the rise in blood lipids, especially the cholesterol of the β-lipoproteins. For a long time the role of the thyroid in the control of serum lipids has been better established than that of the other endocrine glands.[21] Even authors

such as Schrade and Böhle[23] and Van Buchem,[28] who refuse to accept a causal relationship between hyperlipidaemia or hypercholesterolaemia and atherosclerosis, admit that "hyperlipidaemia is a sign and to some extent a measure of metabolic defects which promote the development of atherosclerosis".

Total blood lipids are already well above normal levels in the premyxoedematous stages (cf. Chapter 10). Fowler and Swale[13] report similar observations. However, the close association between CHD or coronary atherosclerosis and thyroiditis, established either on clinical and serological evidence or by pathological studies, cannot entirely be explained by latent thyroid insufficiency. Indeed, in many cases of fatal myocardial infarction, post-mortem examination detected only focal thyroiditis, leaving large parts of the thyroid parenchyma unaffected.

The association of two pathological conditions (in this case thyroiditis and atherosclerosis) does not necessarily imply a direct link between them, and even less so a cause-and-effect relationship: it may be due to the action of a third factor.

Admittedly the nature of this factor remains a mystery. Pathologists have noted that the greatest rise in coronary disease occurs in men around the age of 50, while in women the rise occurs some 10 years later. This age and sex difference points to a possible protective effect of hormonal factors in premenopausal women. The presence of thyroiditis in women constitutes a considerable risk of CHD, the incidence of which then rises to the level observed in men. Whether thyroiditis is contributory in male subjects is much more difficult to demonstrate; it is definitely less marked, but certainly not absent (cf. Table 12.6 (p. 281)).

10. Practical Clinical Significance of the Detection of Thyroid Antibodies in the Serum

The discovery of thyroid antibodies in a patient's serum is usually of practical interest, although this varies according to the clinical context in which they are found. Generally speaking, and whatever the context, the presence of thyroglobulin and cytoplasmic antibodies corresponds to the presence of *lesions of lymphocytic inflammation* in the thyroid* (cf. Chapters 5, 8, and 10).

The detection of very high titres in a euthyroid woman of middle age with a firm, fast-growing, symmetrical goitre, strongly suggests *Hashimoto's goitre;* biopsy will often be unnecessary.

Average levels do not allow this diagnosis because focal lymphocytic thyroiditis often occurs in *simple nodular goitres.*

The presence of such average or high levels in no way excludes *malignant neoplasia.* Indeed, lymphocytic thyroiditis is often superimposed on relatively well differentiated thyroid neoplasms, such as papilliferar carcinoma or certain follicular carcinoma. If the diagnosis of thyroid tumour is certain, the coexistence of thyroiditis, proved by histology or serology, constitutes a fairly favourable prognostic element.

* The term "markers of an autoimmune process" was recently used by Doniach and Walker[10] to describe serum antibodies in autoimmune hepatitis.

In contrast, the fast development of a thyroid tumour without circulating antibodies suggests either a relatively undifferentiated neoplasm or, more rarely, *Riedel's thyroiditis* or a "non-specific chronic inflammation" (cf. Chapter 3).

In cases of *thyrotoxicosis*, the presence of moderate to high antibody titres betrays the existence of thyroiditis lesions superimposed on the thyrotoxicosis. This finding must therefore dictate caution in surgical treatment or radiotherapy since such patients show a marked tendency to develop post-therapy hypothyroidism.

In the presence of *exophthalmos*, whether bilateral or unilateral, in a euthyroid subject, the discovery of thyroid antibodies constitutes a very important argument in favour of the thyroidal origin of the exophthalmos. The diagnosis may be "Graves' disease without thyrotoxicosis" or "ophthalmic Graves' disease".

In subjects showing no thyroid swelling or any recent history of thyroid disease, the discovery of thyroid antibodies indicates *asymptomatic thyroiditis*. The latter may be demonstrated by specific radioactive iodine uptake tests with TSH stimulation and inhibition by potassium iodide. The antibody titre will give only an approximate reflection of the intensity of the process. Any repeatedly positive reaction must induce a search for clinical and biological signs of *thyroid deficiency*. This is particularly true for subjects affected with Addison's disease, pernicious anaemia, and diabetes. Particular mention must be made of subjects with persistent high levels of serum cholesterol. In these subjects the presence of thyroid antibodies indicates that the hypercholesterolaemia is probably due to *latent hypothyroidism* and may regress rapidly under the influence of small doses of thyroid drugs.

Finally, in subjects suffering from clinically evident hypothyroidism, high levels of antibodies indicate the thyroid origin of the hormone insufficiency. When the latter owes its origin to defective secretion, serum antibodies are usually at low titre or absent.[29]

11. Conclusions

The concept of chronic thyroiditis seems to have become much clearer in recent years. True, the ambition of classifying the different forms on an aetiological basis is still beyond the possibilities of our present knowledge. But the general significance of the processes involved seems to be emerging plainly, and the delimitation of the various clinical conditions is sufficiently precise to allow for certain diagnosis and effective treatment in most cases.

From a more general point of view, there is room for hope that the study of thyroiditis will yield new ideas on the aetiology of the majority of thyroid syndromes. The mystery which used to surround the origin of severe myxoedema has already been greatly dissipated, and the natural history of this once enigmatic disease can now be written.

In various domains of pathology, other prospects have been opened up by these studies, especially by the demonstration of the frequency and extension of asymptomatic autoimmune thyroiditis.

Until recently, the most popular forms of thyroiditis with physicians were Riedel's

disease, Hashimoto's goitre, and de Quervain's thyroiditis—in that order. The discovery of thyroid autoimmunity has given first place to Hashimoto's thyroiditis. The accidental discovery of antibodies in apparently normal subjects revealed that the latter could be carriers of asymptomatic thyroiditis. This condition was first considered to be of little clinical interest, but its frequency and, more recently, its importance, were recognized. Its implications are, indeed, numerous: disturbances of iodine metabolism and thyroid function; association with various diseases, especially diabetes and other autoimmune diseases; relationship with atherosclerosis; relation with chromosome anomalies, and—most important—its role as a precursor of clinical myxoedema.

Finally, two general ideas seem to emerge from the study of this process.

The first is that a genetic anomaly seems responsible for a very frequent hereditary enzymatic defect in the thyroid. This causes minor metabolic disorders in its turn which may be unmasked by simple procedures like the screening of NBEI and the test of iodine uptake depression by potassium iodide. Some of the studies reported in this monograph suggest that such metabolic defects may play a role in the development of thyroid antigens, especially in stimulated glands with high cell turnover.

The second is that autoimmune thyroiditis is only the accentuation of a process which starts off as the physiological cleaning of tissue waste.

These two ideas, if they were to be confirmed, would be of cardinal importance for the general understanding of the processes of autoimmunity.

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APPENDIX

Patients and Methods

1. Patients Studied

The vast majority of the patients studied are Belgians and most are living in or around Brussels. The middle part of Belgium, although located at about 100 km from the seaside, has a rather limited iodine supply. Calculations by Ermans estimate the mean iodine output at about 80 μg/day. Thyroid diseases are not infrequent, although goitre is far from being endemic.

The larger part of the patients studied were observed at the outpatients department of endocrine diseases or in the wards of the University Hospital St. Pierre, Brussels. This hospital is mostly patronized by economically lower class and low-middle class patients.

The recent creation of a model intensive care unit has increased the number of myocardial infarctions admitted to the hospital without otherwise changing the recruitment of the hospital population. A special study in families of mongolian subjects has been carried out, outside the hospital, on subjects enjoying normal health and asking no medical advice. Control studies have been performed on physicians, technicians, and nurses who considered themselves as being in good health.

2. Morphological Methods

Light Microscopy

Classical techniques were used.

Fixatives:	Bouin.
	Zenker Formol.
Embedding:	Paraffin.
Staining:	Haematoxylin—Eosin.
	Periodic acid—Schiff.

Electron Microscopy

Fragments of thyroids were removed in surgical room, transferred within 1 minute after excision to a drop of fixative (glutaraldehyde 4·2% in Millonig's buffer solution[21] 0·1M at pH 7·4). The pieces were divided with a razor blade into small fragments (about 1 mm^3), which were placed in fresh chilled fixative for 4 hr at 20°C.

They were rinsed overnight with 0·1 M buffer solution to which 0·54 g glucose per

100 ml of solution had been added. Postfixation occurred for 30 min in osmium tetroxide 2%, in glucose Millonig's buffer, pH 7·4.

Dehydration took place in rising concentrations of ethanol. The specimens were embedded in Epon.[17] Thin sections were made with a diamond knife on a LKB ultramicrotome. The staining of the sections was carried out with both uranyl acetate and lead citrate[24] or with Karnovsky's method.[15]

A Siemens Elmiskop I electron microscope was used.

Semi-thin sections stained with toluidine blue served as controls.

3. Biochemical Methods

Protein Electrophoresis

Electrophoresis of serum proteins was performed with acetate cellulose strips; the different fractions were coloured with Ponceau S.

The normal values for this method are:

	g per 100 ml of serum	% of total proteins
Albumin	3·64–5·27	56·1–64·5
α_1 globulin	0·11–0·31	1·7– 3·9
α_2 globulin	0·40–0·83	6·2–10·1
β globulin	0·58–1·17	8·7–14·5
γ globulin	0·78–1·53	11·4–19·9

Total proteins (g per 100 ml): 5·5–8·2

$PB^{127}I$, $BE^{127}I$, $NB^{127}I$

PBI was measured by an automated technique.[25] The butanol extraction has previously been described.[7] BEI was also measured automatically. NBEI was calculated by difference. The results were expressed in micrograms of iodine per 100 ml of serum.

LATS-IgG Separation

DEAE-Sephadex A-50 was used for the separation of IgG from human serum[4] prior to the LATS assay. Four millilitres of serum were added to the "prepared" gel in a first tube, the mixture was shaken for 5 min and immediately centrifuged. The manipulations were repeated three times, supernate and serum being transferred each time into another tube containing DEAE-Sephadex. LATS activity of the final supernate was compared to the response obtained with the unconcentrated serum in the same lot of mice.

The separation of LATS-IgG is used to characterize the non-specific LATS responses[1,29] from the specific ones.

4. Methods of Isotopic Studies

Thyroid uptakes[8] were performed with a 2 in. scintillation crystal according to the recommendations of the International Atomic Energy Agency, 6 and 24 hr after an oral dose of 3 or 50 μc of ^{131}I iodide. For euthyroid patients the mean and SD are as follows: 32 $\pm$ 9% at 6 hr and 44 $\pm$ 9% at 24 hr.

PB^{131}I was measured on serum drawn 24 hr after an oral dose of 50 μc of ^{131}I iodide. Protein bound and inorganic radioactivity were separated by passage on ion exchange resins (Iobeads T15-0150, AutoAnalyzer®, Technicon Corporation). Normal values are below 0·1% of the dose per l. of serum.

Thyroid scanning was performed 24 hr after an oral dose of 50 μc of ^{131}I or after an intravenous dose of 1 mc of Technetium^{99m} as pertechnetate. These examinations were performed with a scanner Pho-Dot Nuclear Chicago or with the Philips colour scanner.

Triiodothyronine uptake tests[22] were performed using the standard Triosorb® (Abbott Laboratories). The results are expressed in percent of a normal pool serum.

Inhibition and stimulation tests. Inhibition of thyroid uptake was achieved by using the Werner method of daily administration of 75 μg of T3 for 6 days.[28] Inhibition was also obtained by giving 2 mg of potassium iodide as indicated by Boyle *et al.*[6] Both tests were performed 2 weeks after a conventional radioiodine uptake test. For the TSH stimulation test, a single intramuscular injection of 10 units (USP) of TSH (Ambinon) was given 24 hr before the administration of a second radioiodine tracer.

The perchlorate discharge test was performed according to the method of Stewart and Murray.[27] The thyroid radioiodine content at 60, 90, and 120 min after the intravenous injection of 10–15 μc of ^{131}I was derived from the measured neck radioactivity; potassium perchlorate (400 mg) was administered orally at 63 min. The test was considered positive when the iodine content was lower at 130 than at 60 min.

The Achilles reflex was performed using the Lawson Kinemometer. The duration of contraction (from the point of stimulus to the end of the contraction) was measured.[16]

5. Immunological Methods

Thyroglobulin Antibodies (TGA)

Thyroglobulin antibodies were detected by an haemagglutination technique after Boyden.[5] Sheep red blood cells were formolized, tanned, and finally coated with thyroglobulin.

Each week one new batch of red cells was tanned and coated. Thyroglobulin was purified by salting-out[9] from human thyroids taken at necropsy, and kept in a lyophilized form.

The serum to be tested (100 μl) was added, in a test tube, to 400 μl of saline containing 1% of normal rabbit serum; fivefold dilutions were successively made until a final dilution of 1/78125; in each tube per 100 μl of a 5% solution of sensitized cells was added. After one hour, the aspect of an heterogeneous deposit of the coated cells indicated the presence

of TGA in the serum; a more regular pattern, with dense edges, was characteristic of a negative reaction.

Two types of control reactions for specificity were performed for each serum:

(1) An haemagglutination inhibition reaction, with a solution of thyroglobulin.
(2) A search for heterophile antibodies against sheep red blood cells, with only the addition of formolized cells to the reaction medium.

Reactions were considered as positive above a 1/25 dilution. Sera with known positive titres were utilized as sensitivity controls.

Some batches of thyroglobulin may occasionally give a significant decrease of the sensitivity. Controls with commercial preparations have consistently given less frequent and less intense positive results.

Antisera against human albumin react with the thyroglobulin coated red cells; after purification of the thyroglobulin by gel filtrations, this positive reaction disappears.

The immunofluorescent technique[2] with methanol fixed human thyroid sections may also be helpful for TGA detection. An irregular pattern of the colloid fluorescence is characteristic of a positive reaction (Fig. 2.4 (p. 49)).

Microsomal Antibodies (CFA)

CFA were detected by an *immunofluorescent technique*, with unfixed thyroid sections providing the antigen.[13] Thyrotoxic goitres were preferentially used. A cytoplasmic fluorescence, sparing the nucleus, indicated the presence of CFA in the serum (Fig. 2.3 (p. 48)).

A quantitative detection of CFA may be performed with the *complement fixation test.*

Complement Fixation Test for Thyroid Antibodies[14]

The serum to be tested was added in successive dilutions in a mixture containing microsomal thyroid antigen, sheep red cells sensitized with rabbit anti-sheep red cells haemolysins, complement (at the minimal dosage capable of completely haemolysing the sensitized sheep red cells).

If the serum tested contains CFA, there will be a reaction between CFA, thyroid microsomal antigen, and complement. The complement is thus no more available to haemolyse the sensitized sheep red cells. The reaction is positive when there is no haemolysis. The highest dilution for which it is positive indicates the titre of CFA.

CA_2

Antibodies against the second colloid antigen (CA_2) were detected by immunofluorescence on methanol fixed human thyroid sections.[2] The colloid fluorescence is homogeneous and contrasts with the TGA pattern. The serum to be tested was pre-incubated with highly purified thyroglobulin to avoid a TGA fluorescent reaction.

Thyrotropin (HTSH)

Radioimmunossay of HTSH was performed with the double antibody technique.[23] A careful purification of the labelled antigen has enhanced the sensitivity of the method, allowing to measure as little as 0·5 μU of HTSH.[11] According to this method results in Belgian controls were 15·3 $\pm$ 0·8 μU/ml (mean $\pm$ SEM). Results were expressed in terms of the Reference Preparation A, kindly given by the National Institute for Medical Research (London). Purified HTSH and specific antiserum were kindly supplied by the National Pituitary Agency, Endocrinology Study Section, and the National Institute of Arthritis and Metabolic Diseases (U.S.A.).

6. Biological Methods

Serum TSH and LATS Bioassay

TSH and LATS assays were carried out on unconcentrated serum and LATS-IgG, using the McKenzie[19] method slightly modified.[3]

A standard TSH line was established for each assay. The 90% fiducial space of the standard line was calculated. When the data of any assay did not satisfy the statistical criteria of the standard line, this assay was rejected.

Serum TSH levels of unknown sera were calculated from the standard line by interpolation.

The sensitivity of 0·05 mU made it possible to detect a TSH level of 17 mU per 100 ml. TSH levels below 17 mU per 100 ml were considered to be undetectable. Serum LATS activity was expressed as the ratio R of the blood radioactivities of mice at 20 and 2 hr after injection of the unknown serum. The LATS response was considered to be positive when R was equal to or greater than 1·5.[3] A serum rich in LATS activity was used in any bioassay as a qualitative test of the sensitivity of the mice.

Some authors proposed modifications of the McKenzie method to improve its sensitivity and its accuracy in the assay of TSH[12] and LATS.[10,18,20,26]

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