Auto-immune Thyroiditis

Its clinical manifestations and associations

by

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"In writing, therefore, a history of diseases, every philosophical hypothesis which hath prepossessed the writer in its favour, ought to be totally laid aside, and then the manifest and natural phenomena of diseases, however minute, must be noted with the utmost accuracy, imitating in this the great exactness of painters, who in their pictures copy the smallest spots or moles in the originals; for it is difficult to give a detail of the numerous errors that spring from hypothesis ....."

Thomas Sydenham ※

(From The Works of Thomas Sydenham, M.D., 1850)

※ Thomas Sydenham 1624 – 1689

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INTRODUCTION.

"The expression "struma lymphomatosa", which I recently invented, I take to mean a proliferation of the lymphatic elements with lymph follicles, as well as a certain alteration of the parenchyma and of the interstitial tissue, which can be seen in the excised struma tissue." (translated from the German). H. Hashimoto. 1912.

The disease defined in these terms nearly half a century ago by the Japanese surgeon, H. Hashimoto, has ever since been attended by interest and controversy. It has been known under various synonyms, including Hashimoto's disease, Hashimoto's thyroiditis, struma lymphomatosa, lymphadenoid goitre, chronic lymphoid thyroiditis, and more recently as auto-immune or auto-immunising thyroiditis, because of the discovery of circulating thyroid auto-antibodied in patients with the condition. This disease forms the study on which this thesis is based.

Chapter I of the thesis is concerned with the background of the present study. The historical aspects, morbid anatomy, and past views regarding aetiology, are reviewed, and an account of the recent immunological developments is also given.

Chapter II of the thesis deals with my observations in 50 patients with the disease and advantage has been taken of modern methods of investigation to study the clinical features. The role of the circulating thyroid auto-antibodies in the pathogenesis of the disease has been investigated in a study of the nature of skin reactions following the intra dermal injection of sterile extracts of human thyroid tissue in patients with auto-immune thyroiditis. The biochemical changes found in this condition also form part of the contents of this chapter and include observations of the serum proteins, serum flocculation tests, and erythrocyte sedimentation rate. The mechanism of these changes is discussed

and/

/and their diagnostic significance evaluated. A detailed investigation of iodine metabolism has been undertaken and the abnormalities in the handling of both stable iodine and radioiodine in this disease is discussed in this Chapter. Finally, the differential diagnosis and treatment of the disease are considered in the light of these investigations.

That auto-immune thyroiditis is related to both the hypothyroid and hyperthyroid state has long been suspected. Chapter III of this thesis is concerned with this problem and evidence is presented that so-called "primary" hypothyroidism is a pathological variant of auto-immune thyroiditis. Thyroid auto-antibodies have been studied in thyrotoxicosis in relation to the clinical features, to the outcome of antithyroid therapy, and to the focal lesions of auto-immune thyroiditis in the thyroid gland after operation.

Chapter IV deals with the wider implications of auto-immune disease resulting from a study of the clinical associations of auto-immune thyroiditis with diseases in which auto-immune mechanisms have been suspected, e.g. the connective tissue disorders, in particular rheumatoid arthritis, the haemolytic anaemias, and cirrhosis of the liver. An experiment designed to measure the antibody-forming potential in patients with auto-immune disease is also reported in this chapter.

Finally, the implications of these studies are discussed in relation to the clonal selection theory of antibody formation and to the concept of acquired immunological tolerance.

CHAPTER I.

The Background to the Present Study.

Introduction.

Introduction

The historical aspects of Hashimoto's thyroiditis are reviewed in Section 1. An account is given of Riedel's struma and of the earlier confusion between this disease and Hashimoto's thyroiditis. The events leading up to the acceptance of Hashimoto's thyroiditis as a separate clinico-pathological entity are outlined and a brief description of subacute thyroiditis (de Quervain) is also given in this section.

A brief account of the morbid anatomy of the disease is given (Section 2).

Past hypotheses to explain the aetiology and pathogenesis of Hashimoto's thyroiditis are reviewed in Section 3.

An outline is given in Section 4 of the events leading up to the discovery of the thyroid auto-antibodies in patients with the disease, and a brief account is given of experimental thyroiditis in animals. The nature of the thyroid antigens and their auto-antibodies is described, together with the methods currently available for the detection of these auto-antibodies. The "leak" hypothesis to explain the aetiology of the disease is critically examined and an account is given of the concept of "auto-immune" thyroiditis in this section.

Section 1.

Historical Aspects.

Section 1. Historical Aspects: review of the original accounts of Riedel's struma and Hashimoto's thyroiditis and the controversy regarding their relationships; description of de Quervain's subacute thyroiditis.

Original accounts of Riedel's struma and Hashimoto's thyroiditis.

Struma fibrosa (Riedel).

In 1896, Bernard Riedel (1), then Professor of Surgery at Jena, described a peculiar and hitherto unrecognised type of chronic inflammation of the thyroid gland, which he had observed in 2 patients, a man 42 years of age and a woman 32 years. The characteristic finding in both these patients was the extreme induration and fixation of the thyroid gland. At operation, Riedel found extensive infiltration of the vessels and nerves of the neck by a diffuse sclerosis which permitted only partial resection of the thyroid isthmus. The histological findings in the first patient were reported: "The biopsy meanwhile showed that there was no evidence of new growth. It was an inflammatory process; infiltration with round cells was demonstrated; carcinoma and sarcoma were excluded; syphilis was also absent from the patients, and so was tuberculosis." (translated from the German). In the second patient microscopic examination revealed: "Interwoven in the normal thyroid tissue there are clusters of round cells, through which more or less the normal thyroid tissue is destroyed." (translated from the German). In neither case report was there mention of fibrosis on histological examination and, indeed, referring to the second case, Riedel remarked, "When one sees the preparation one would not expect how hard the tumour is; one expected dense fibrous tissue to be the constituent of the tumour and not, as has been said, enlarged round cells". (translated from the German).

Scrutiny/

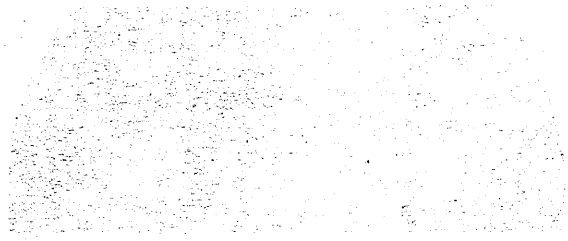


Figure I.

Riedel's Original Histological Illustration of

Struma Fibrosa.

Fig. I.

Fig. 1.

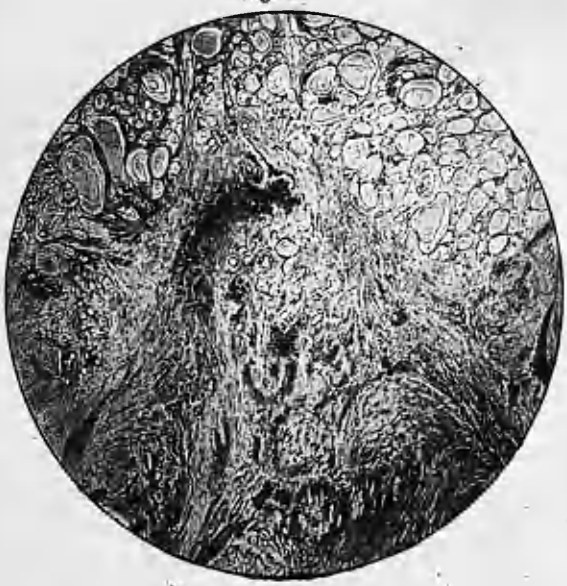
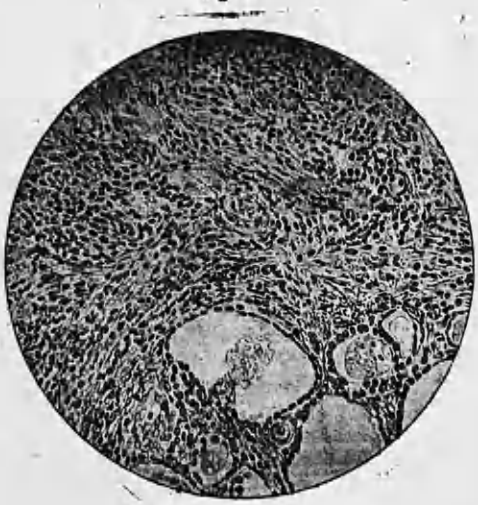


Fig. 2.



/Scrutiny of the original illustrations, of which there are only 2 (Fig. 1.) fully confirms this statement. Indeed, the paucity of pathological detail makes it virtually impossible to define, in retrospect, the disease Riedel described in these 2 patients.

In his second publication in 1897 (2) Riedel presented a third patient in whom the disease occurred in a man of 29. Examination of the thyroid in this patient showed that, "it was made up of spindle and round cells; it remained doubtful whether it was an inflammatory tissue or neoplasia (fibrosarcoma); only the follow-up of the clinical course could decide; it decided in favour of a chronic inflammation". (translated from the German). In 1910, Riedel (3) reported the benign course of this patient's illness and summarised his findings in the previous 2 patients.

Although Riedel's name is now firmly associated by usage with struma fibrosa it is of interest that, in 1885, 11 years before Riedel's first article, Bowlby (4,5) described a lesion of the thyroid which he reported as an "infiltrating fibroma" and which probably corresponds to the disease described by Riedel. Certainly, microscopic examination in Bowlby's case was more in keeping with present-day concepts of struma fibrosa, since the thyroid was found "to be entirely fibrous throughout; there was no disease of the surrounding glands. The rarity of fibroma and the infiltrating manner of the growths were the interesting points". Semple (6) had also previously described a somewhat similar case in 1885, although the presence of cervical lymphadenopathy raises the suspicion that the process was neoplastic.

Following Riedel's original account, Cordua (7) and others (8 - 13) reported similar cases, but dealt primarily with the clinical aspects of the disease./

/disease. Silatschek (14) and Spannaus (15) in 1910 described the pathological changes in more detail and like Delore and Alamartine (13) found a diffuse sclerosis completely obliterating the normal gland elements.

Struma Lymphomatosa (Hashimoto).

In 1912, H. Hashimoto (16), a surgeon from Kyushi in Japan, described 4 patients, clinically similar to these previously described by Riedel, but in whom the histological picture of the thyroid was entirely different. Hashimoto recorded the clinical and pathological findings in these 4 patients in considerable detail and concluded that he was dealing with an entirely different disease from that described earlier by Riedel. He named the disease "struma lymphomatosa" on account of the extensive lymphoid infil-:tration which he found. The clarity of the descriptions can be judged by the excellence of his summary of the clinical and pathological findings:

"If we summarise the clinical observations, until now there are altogether 4 patients who were of the female sex and more than 40 years old. They came from healthy families and they did not live in goitrous areas. The patients previously were never severely sick and first of all they had no serious infectious disease which as a complication of which thyroid disease and especially thyroiditis often happens. Syphilis and tuberculosis were excluded clinically. The thyroid enlargement was found in all cases by chance. There were no significant symptoms on that ground and together with a good general condition and normal body temperature we did not find a rapid enlargement of the thyroid. Both lobes were affected - severe pressure symptoms like dyspnoea or aphonia were never present. The capsule of the tumour was apparently free, but the consistence was so dense that one could/

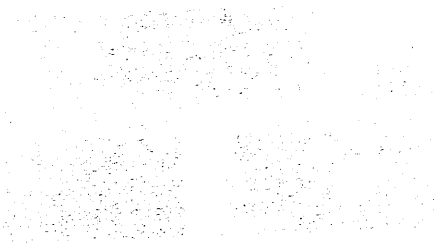
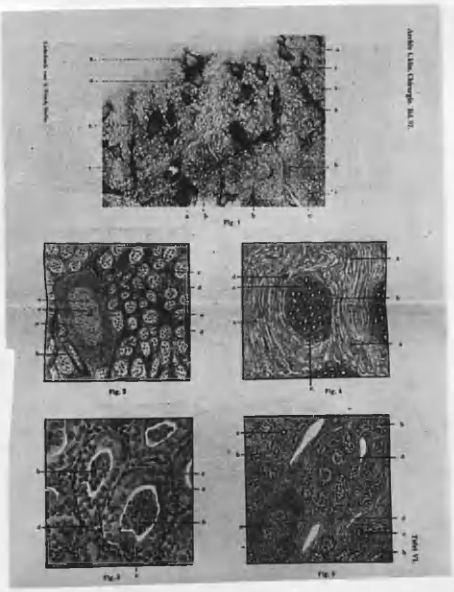


Figure 2(a and b).

Hashimoto's Original Histological Illustration of Struma Lymphomatosa

Fig.2(a).



Erklärung der Abbildungen auf Tafel VI.

Figur 1. Uebersichtsbild der mächtigen Lymphfollikelentwicklung im Parenchym. (Fall 2, Mikroplaner 35 mm. Hauff. Ort. pl. Bulglange 40 cm. Hämatoxylin-Eosinfärbung.) *a* Lymphfollikel mit Keimcentren. *b* Interstitium. *c* Drüsenfollikel.

Hier sieht man sehr kleine Drüsenfollikel, die im Allgemeinen mit wenig Colloid versehen sind. Die Rundzelleninfiltration ist diffus verbreitet. Interstitium ist diffus hypertrophirt.

Figur 2. Fortgeschrittene Veränderung des Interstitiums. (Fall 2, Doppelfärbung mit van Gieson-Hämatoxylin. Vergr. Zeiss Obj. AA, Ocul. 4.) *a* Lymphfollikel mit Blutgefässcapillaren (*c*) und Kerntheilungsfiguren. *b* Blutgefäss. *c* Hypertrophirtes Interstitium, mit Rundzellen stark infiltrirt. *d* Veränderte Follikel (Zellgrenze unklar, im Allgemeinen atrophisch, fast frei von normalem Colloid).

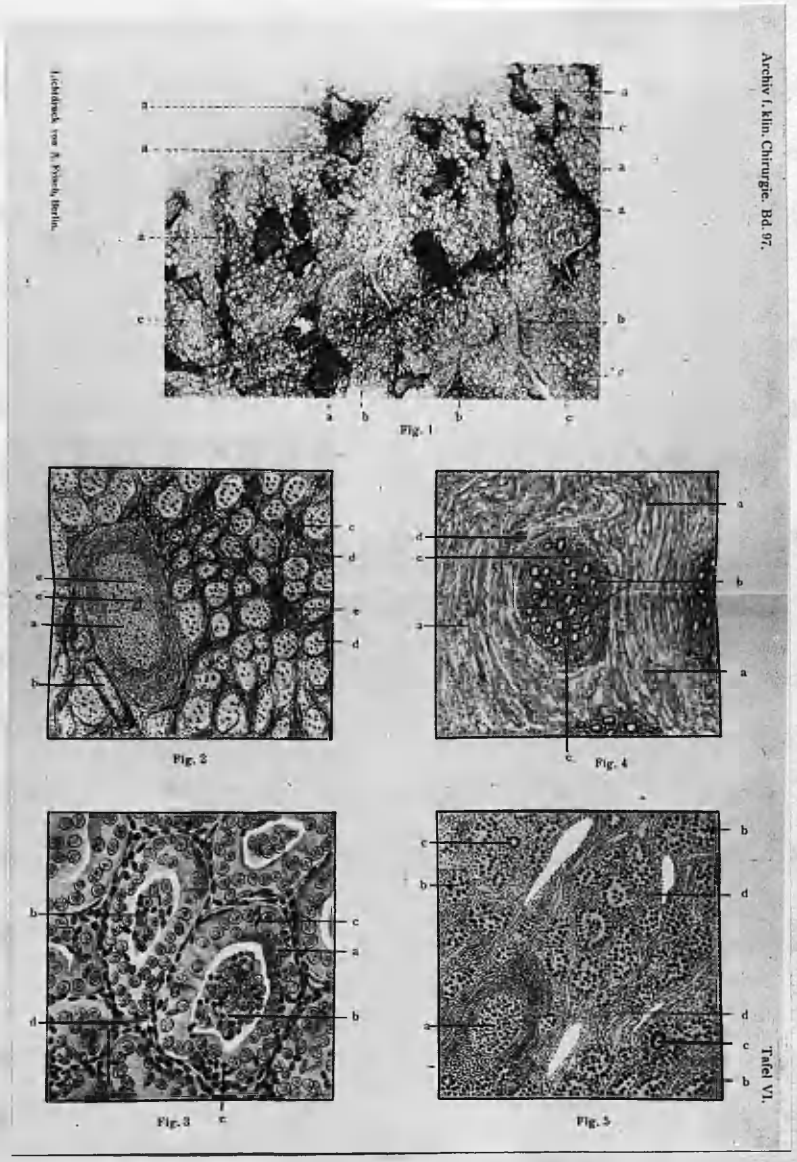
Figur 3. Stark veränderte Drüsenfollikel. (Fall 2, Doppelfärbung mit Hämatoxylin-Eosin. Vergr. Zeiss Obj. DD, Ocul. 4.) *a* Anscheinend geschichtete Follikelepithelien (Zellgrenze undeutlich). *b* Follikelinhalt (veränderte Epithelzellen, Leukocyten und ihre Abkömmlinge). *c* Eingewanderte Leukocyten in der Follikelwand. *d* Interstitium mit Rundzelleninfiltration.

Figur 4. Circumscript stark entwickeltes interstitielles Bindegewebe. (Im Innern atrophirte Follikel einschliessend. Fall 3, Doppelfärbung mit Hämatoxylin-Eosin. Vergr. Zeiss Obj. AA, Ocul. 4.) *a* Stark hypertrophirtes Bindegewebe. *b* Sehr kleine, atrophirte Follikel, fast frei von Colloid. *c* Starke Rundzelleninfiltration. *d* Blutgefässcapillare.

Figur 5. Fortgeschrittene Veränderung. (Fall 4, Doppelfärbung mit Hämatoxylin-Eosin. Vergr. Zeiss Obj. AA, Ocul. 4.) *a* Lymphfollikel mit Keimcentrum. *b* Drüsenfollikel (stark afficirt, frei von normalem Colloid, wenig schollige Masse enthaltend). *c* Riesenzellen (Kerne randständig). *d* Gewuchertes Interstitium mit sehr stark infiltrirten Rundzellen.

Fig.2(b).

(enlarged to show detail).



/could think about malignant tumour or Riedel's thyroiditis. The lymph glands were not palpable either locally or in other parts of the body. We could find nothing abnormal in the internal organs. The operative findings did not show any specially marked growth in the surrounding tissues as in Riedel's thyroiditis, which was emphasised by the author in question. A post-operative huskiness remained more or less in all the cases although it was of a very light degree.

In the subsequent course after the operation, oedema appeared in the entire body, and disappeared with continuous administration of thyroid extract". (translated from the German).

The principle histological findings in all 4 patients consisted of:

"(1) numerous formation of lymph follicles,

(2) changes in the living epithelium of the acini together with their content.

(3) extensive new formation of connective tissue, and

(4) diffuse round cell infiltration."; these are illustrated in Fig. 2.

Subsequent confusion between Hashimoto's thyroiditis and Riedel's struma. 1912 - 1931.

The events which followed the publication of Hashimoto's account have been admirably reviewed by Joll (17). According to this author, little attention appears to have been paid to Hashimoto's publication despite the excellence of the descriptions. However, in 1914, Heineke (18) mentioned struma lymphomatosa and accepted it as a definite entity, although he described no case of his own. Following this, nothing appears to have been published on the subject until 1922, when Ewing (19) in discussing 4 patients with chronic thyroiditis, came to the conclusion that Hashimoto and Riedel had/

/had described, "the early and late stages of the same pathological process". Ewing (20) later described both diseases under the name of "benign granuloma" of the thyroid, which had previously been used for struma fibrosa itself (21). With the sole exception of Reist (22) Ewing's views were widely accepted and during the next decade many cases with the classical features of Hashimoto's thyroiditis were reported either as Riedel's struma (23,24) or as one of its synonyms (25 - 31). Further confusion in the terminology arose with the publications of Williamson and Pearse (32,33), who described a "lymphadenoid" goitre which had all the pathological characteristics of the disease described earlier by Hashimoto.

Clarification of Hashimoto's thyroiditis by Graham and McCullagh 1931.

In 1931, Graham and McCullagh (34,35) clearly defined the 2 diseases, critically compared them, and revived Hashimoto's original contention that they were separate entities. These authors based their argument mainly on the grounds that, "although Riedel's struma is the supposedly later stage of the disease, it nevertheless occurred more commonly in younger persons and also was more frequently a unilateral or localised process."

Subsequent Controversy regarding Relationship between Hashimoto's thyroiditis and Riedel's struma.

Following this important analysis a strong body of evidence grew up in favour of the dualistic concept of the 2 diseases (17,36 - 46); although many cases which were undoubtedly examples of Hashimoto's thyroiditis continued to be reported as Riedel's struma. For example, Renton et al. (47) in a paper in 1937 on Riedel's thyroiditis and its treatment with radium made the surprising assertion, "that Riedel's thyroiditis may be defined as being/

/being characterised by lymphocytic infiltration, with or without germ-centre formation, and increasing fibrosis affecting the gland and often adjacent structures, with alteration and atrophy of thyroid epithelium, each in varying degree". The definition clearly applies to Hashimoto's thyroiditis. Opposing views to those held by Graham and McCullagh were expressed by Eisen (48,49), Boyden et al (50), Vaux (51), Merrington (52), and others (53,54), who continued to believe that Hashimoto had merely described the earlier stage of struma fibrosa. Eisen (48,49) did not believe, however, that one disease necessarily preceded or followed the other, although he claimed to have seen the transition of Hashimoto's thyroiditis to Riedel's struma in one case.

In support of the distinction between the 2 disorders, repeat biopsies in Hashimoto's thyroiditis at intervals ranging from several months (55) to 23 years (56) did not reveal any evidence of progression to Riedel's struma (23,29,43,55 - 66), although an increase in the amount of fibrous tissue in the second biopsy specimen was observed in several instances (23,29,43,44,60). Moreover, as Hazard (67) has pointed out, the disease now recognised as Riedel's struma has many histological dissimilarities with Hashimoto's thyroiditis. These include: (1) the proliferation of fibrous tissue which involves either the whole or localised portion of the gland and which causes loss of the normal lobular structure; (2) the destruction of the capsule and extension of the fibrosing process into the perithyroidal tissue; (3) the presence of neutrophil infiltration; and (4) the absence of any degree of lymphoid infiltration.

It must, however, be appreciated that many of the pathological differences are quantitative rather than qualitative (67); intermediate types/

/types have been recorded (52,57,68), and a few cases have defied precise classification (69).

Since Graham and McCullagh's critical analysis of the two diseases in 1931 (34,35), surprisingly few cases of Riedel's struma have been reported and the number in which strict definition has been adhered to is extremely small (17,57,70,71). Thus, in 1939, Joll (17) reported 5 cases in a series of 5,650 thyroidectomies and Schilling (57) in 1945 described one authentic case from 3,750 hospital admissions for thyroid disease. Lindsay et al. (70) reported 2 cases of Riedel's struma in a total of 6,571 thyroidectomies over a 30-year period. Perhaps the largest well-documented series is that of Woolner et al. (71) in 1957, which described 20 cases observed at the Mayo Clinic in a 36-year period, during which approximately 42,000 thyroidectomies had been performed. Thus, the relative rarity of Riedel's struma makes it difficult to gain an accurate clinical picture of the disease.

Considerations of age and sex incidence have played a large part in the distinction between Hashimoto's and Riedel's disease. It is generally agreed that both are more common in females, and that this seems to be particularly true of Hashimoto's thyroiditis (17,39,49,70 - 73). In contrast to earlier reports (17,35,39) recent studies have shown no apparent difference in the age incidence of the 2 diseases. According to Joll (17) the features of Riedel's struma which differentiated it from Hashimoto's thyroiditis included the complaint of severe pressure symptoms in the presence of a goitre, which although not unduly large was always stony hard and fixed to surrounding cervical structures. Further, the thyroid swelling in Riedel's struma was often unilateral in contrast to the diffusely enlarged goitre in

/struma lymphomatosa, and hypothyroidism was infrequent. However, in the series of 20 patients studied by Woolner et al. (71) obstructive features were uncommon and frank hypothyroidism was observed in 4 of the patients. In all the patients the goitre was "stony-hard" and in half, fixation in the neck was noticed. No clear distinction from Hashimoto's thyroiditis was possible and it may be as Merrington (52) has stated that "there is a single broad clinical picture common to both (diseases), and attempts to draw a line between them have not been con-:vincing."

Present-Day Concepts regarding Relationship between Hashimoto's thyroiditis and Riedel's struma.

Thus, the precise relationship between Hashimoto's thyroiditis and Riedel's struma remains obscure, but it may be as Reist (22) and Womack (74) have suggested that the 2 diseases are varying manifestations of the same pathological process. This holistic concept has recently been supported by Rivière and Martino (75) who stated: "strictly speaking they did not constitute a 'disease' but a histological state susceptible to modification with time, but not necessarily so, and which expresses a unitary response against aggressions and thyroidal perturbations of quite different nature. It seems, so to say, that they can be considered different 'facets' of the same condition." (translated from the French).

Elucidation of Riedel's "rätsel" or riddle as he so aptly described it, must remain unsolved until more facts concerning the disease become available.

Subacute (Granulomatous) thyroiditis.

The third form of chronic thyroiditis which has been confused with both/

/both Hashimoto's thyroiditis and Riedel's struma, is subacute (granulomatous) thyroiditis, which was first described in 1904 by de Quervain (76). The various synonyms used for this form of thyroiditis - granulomatous thyroiditis, pseudo-tuberculous and tuberculous thyroiditis, giant cell thyroiditis, struma granulomatosa, giant cell thyroiditis, pseudo-giant cell thyroiditis of de Quervain, and struma fibrosa - giant cell variant, - call attention to the distinctive histological features: the presence of histiocytes and their frequently focal and pseudo-tuberculous arrangement, giant cells, and phagocytosis (77). Microscopically fibrosis with proliferation of the stroma is also noted and the acini are decreased in size and number, with extravasation of their colloid and associated inflammatory reaction with many polymorpho-nuclear leucocytes. (57,70,78,79).

The granulomatous nature of the disease was taken as evidence of its tuberculous nature by earlier workers (80), but in 1930 Jaffé (81) clearly established it as being of non-bacterial origin and recognised the tubercle-like structures as the result of non-infectious involutionary changes. A virus infection was suggested (56,82) on the basis of a high incidence of upper respiratory tract infection (83), although Lindsay and Dailey (78) were unable to demonstrate inclusion bodies. Recently Eylan et al. (84) demonstrated positive complement-fixation antibodies against mumps virus in 10 of 11 patients with subacute thyroiditis during an outbreak of mumps in Israel, thus providing evidence of a causal association.

Crile (85) and Stalker and Walther (83) consider subacute thyroiditis as the commonest form of thyroiditis in the United States, but it is generally regarded as rare in this country (82,86). Although de Quervain in/

/in 1936, with Giordanengo (87), clearly established subacute thyroiditis as a separate clinico-pathological entity later workers (88) confused it with both Hashimoto's thyroiditis and Riedel's struma. However, consid-:eration of the clinical features serves to differentiate it from the other 2 types of thyroiditis. Thus, the onset is often acute with a sore throat, pain and tenderness of the gland, malaise and fever, and the course is usually subacute or chronic and almost invariably self-limiting with no subsequent derangement of thyroid function. The concept expressed by de Quervain and Giordanengo in their paper in 1936 has been accepted by most workers (70,77 - 80,83,85), although several cases have been reported under other designations (43,90 - 93).

CONCLUSIONS.

In summary, it can be concluded from a study of the literature that there is good evidence for the acceptance of 3 distinct types of chronic thyroiditis: (1) struma lymphomatosa (Hashimoto), (2) struma fibrosa (Riedel), and (3) subacute (granulomatous) thyroiditis (de Quervain).

The relationship between Hashimoto's thyroiditis and Riedel's struma remains obscure, but the comparative rarity of the latter makes the differentiation of little practical moment. Subacute (granulomatous) thyroiditis is probably of viral aetiology, and its clinical and pathological features make it quite distinctive and easily differentiated from the other 2 diseases.

Section 2.

Morbid Anatomy (Review).

Several succinct accounts of the morbid anatomy of Hashimoto's thyroiditis have been given in recent years (1 - 5) and the following review is largely based on the opinions expressed in these papers.

1. Macroscopic Changes.

The goitre in Hashimoto's thyroiditis is usually of moderate size; surgical specimens varying in weight from 24 (6) to 225 (7) g., with means of 45.7 (6), 66.8 (7), 100 (8), and 130 (9) g., in several large series. The goitre is usually uniformly enlarged, although it may be slightly asymmetrical, and the pyramidal lobe is often conspicuous (2). Occasionally the enlargement is unilateral, and when so the right lobe is usually greater than the left (3). The gland is characteristically firm or "rubbery hard" (9), pale in colour, and with a smoothly bosselated or lobulated surface (9). Occasionally the goitre may be nodular (1,7), although generally adenomatous formation is inconspicuous (10). The capsule is generally thick, well preserved, and distinct, and occasionally may be slightly adherent to the trachea and cervical structures (3). The adjacent cervical lymph nodes are frequently enlarged (11). The cut surface has been described as varying in colour from "salmon-pink" (9) to "yellowish white with a brownish tinge" (2). Colloid is absent (3) and the gland is divided up in a lobular manner by dividing fibrous septa (9). The surface is relatively friable, but in the later stages of the disease with increasing fibrosis it may

be/

/be of a "resilient toughness" (2).

2. Microscopic Changes.

These histological changes can best be considered under five headings: (1) Lymphoid elements, (2) Fibrosis, (3) Vesicles, (4) Epithelium, (5) Blood Vessels.

(1) Lymphoid Elements. The characteristic finding in Hashimoto's thyroiditis is diffuse infiltration with lymphocytes and plasma cells (2). Lymph follicles with germinal centres may be evident, and differ in no way from the lymph follicles found elsewhere in the body (9). Parmley and Hellwig (6) have estimated that the lymphocytic infiltration accounts for approximately one third the size of the goitre, and Furr and Crile (12) have stated that it is especially marked in goitres of short duration. Occasionally it may be so dense as to be mistaken for lymphosarcoma (4). Monocytes are present in small numbers (1), but polymorpho-:nuclear leucocytes are rare (5). Foreign body giant cells are seen in 10 per cent. of glands according to Joll (2), but are never as numerous as in subacute thyroiditis (13).

(2) Fibrosis. Fibrous tissue is present in variable amount in Hashimoto's thyroiditis; clasically it is fine in texture and arranged in whorls about the thyroid lobules. In 10 per cent. of glands fibrosis is abundant (3) and may occasionally cause complete replacement of a thyroid lobule (1).

(3) Vesicles. The thyroid vesicles are reduced in size and may be round, oval, or irregular. Hashimoto's original measurements of/

/of the diameter of the thyroid vesicles lay between 30 and 360μ(14). The colloid contained in the acini is reduced in amount and may be absent; it frequently shows considerably variability in its staining properties and is often intensely staining and either granular or homogeneous (13). Occasionally the colloid may show peripheral vacuolation (13) and may contain foreign body giant cells (3,4,13).

(4) Epithelium. Epithelial changes are common in Hashimoto's thyroiditis. They were attributed to degenerative processes by Hashimoto (14) and to hyperplasia secondary to thyroid destruction by later workers (3,15,16). Renton et al. (17) found it difficult to reconcile the hyperplastic appearance of the epithelium with the clinical features of hypothyroidism.

In addition to their hyperplastic appearance some of the acinar cells show a distinctive oxyphilic alteration of the cytoplasm. These cells are often larger than normal, contain abundant cytoplasm, and have hyperchromatic nuclei of variable size and shape. Hellwig (18) considered these cells similar to the changes seen in the epithelium of the breast in chronic mastitis, and Womach (19) thought that they bore a resemblance to the cells previously described by Hürthle (20) in the dog. In 1948, Lennox (21) identified them with the cells described by Askanazy (22) in thyrotoxic glands. Thus, these peculiar epithelial cells have been variously described as Hürthle (20) or Askanazy (22) cells, and from consideration of their appearance have been considered as degenerative (10),/

FIGURES 1 - 8

Histological Appearances in Hashimoto's Thyroiditis

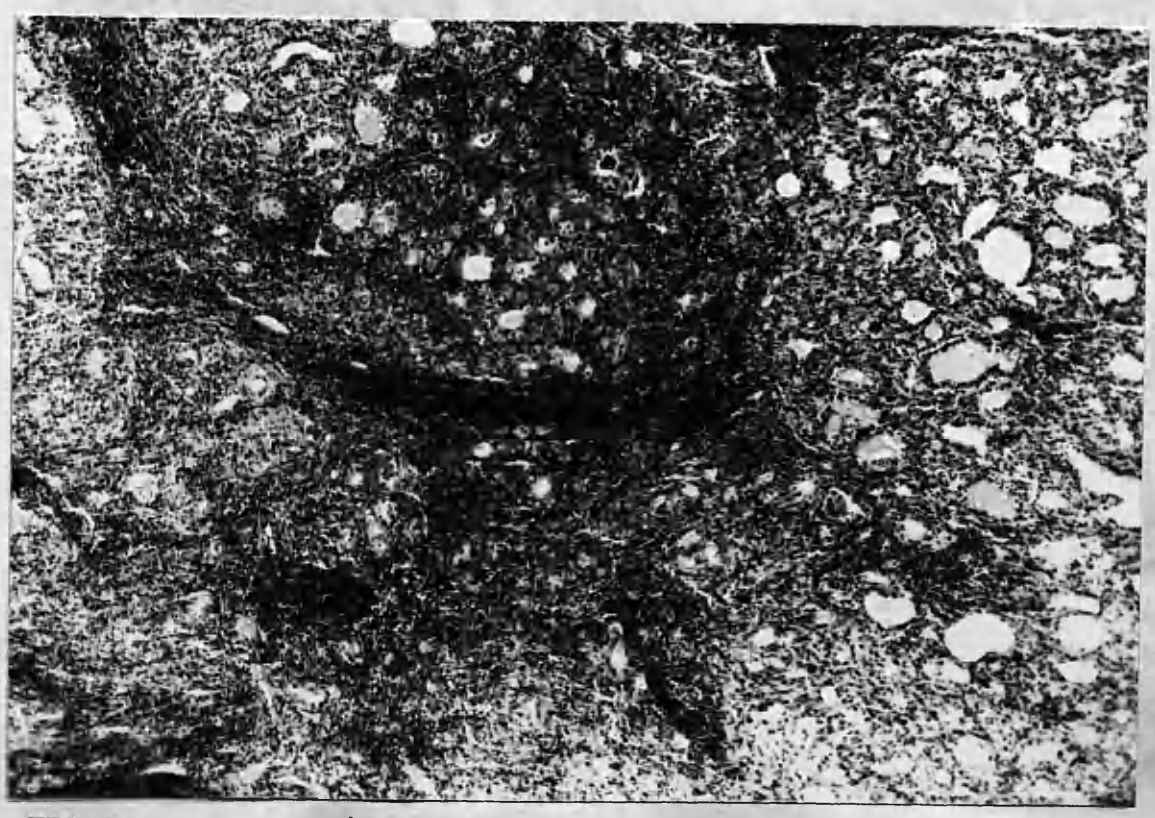


FIG. 1. Hashimoto's Thyroiditis

Showing chronic inflammatory cell infiltration, loss of normal follicular architecture with formation of numerous small follicules. (Haematoxylin and eosin x 60).

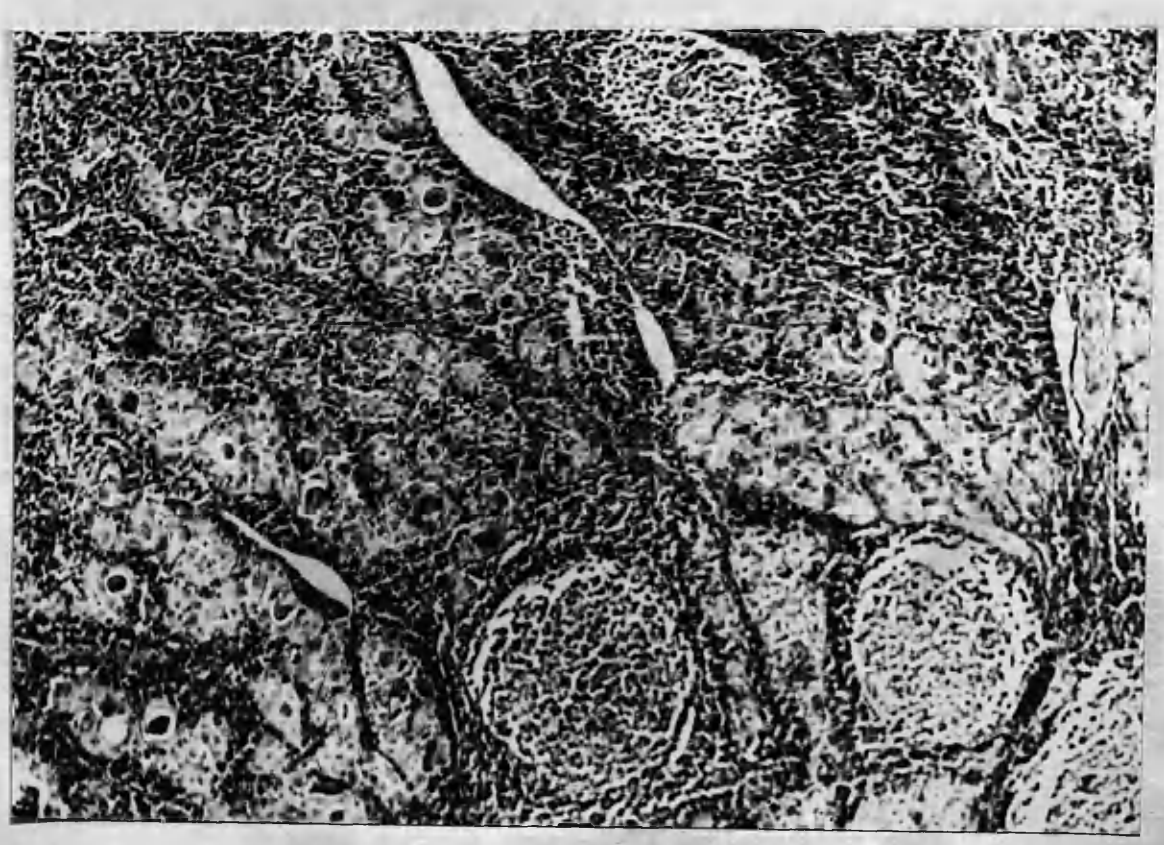


FIG. 2. Hashimoto's Thyroiditis.

Showing lymphoid follicles with germinal centres, and giant cells in thyroid follicles. There is also generalised infiltration with round cells, and the acini are small. (Haematoxylin and eosin x 140).

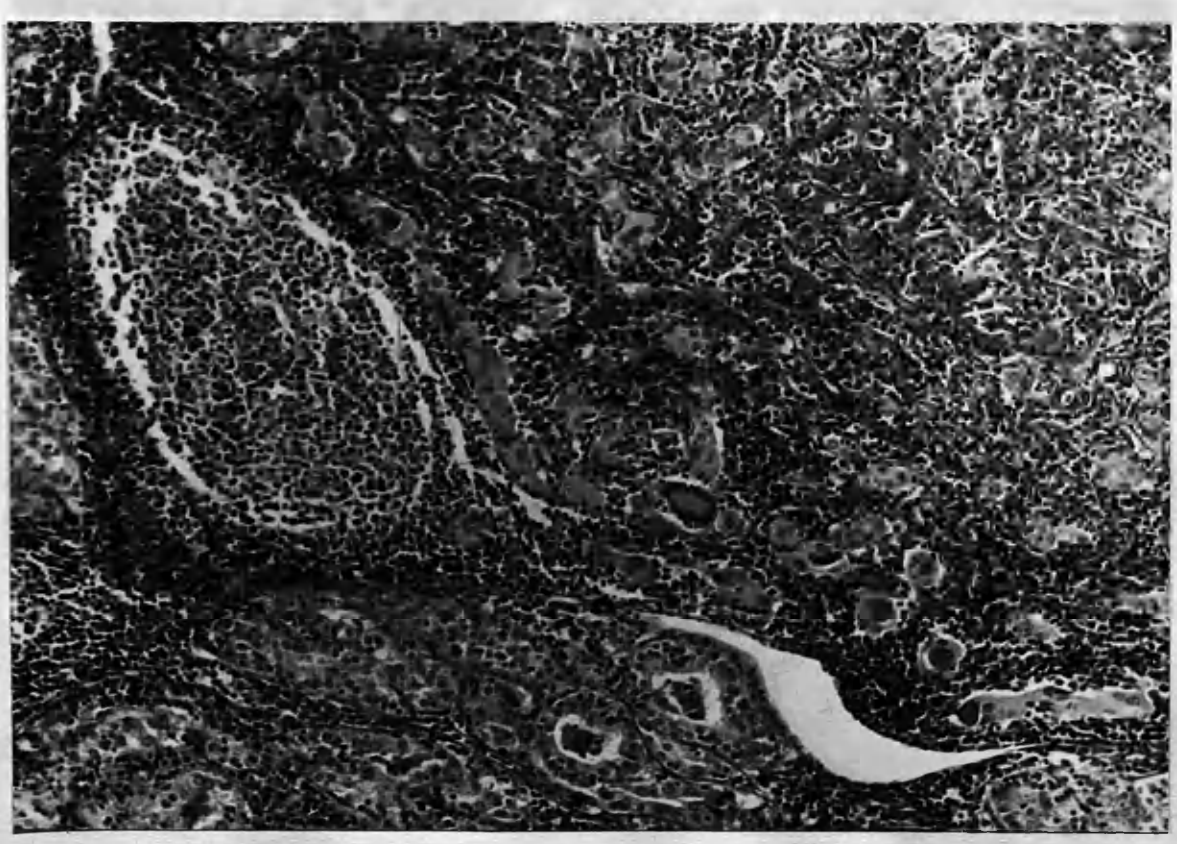


FIG. 3. Hashimoto's Thyroiditis.
Showing diffuse round-cell inflammatory cell infiltration and Askanazy-cell change. A lymph follicle with a large germinal centre can be seen, and there are also multinucleated giant cells and a distended lymphatic present in this section. (Haematoxylin and eosin x 112).

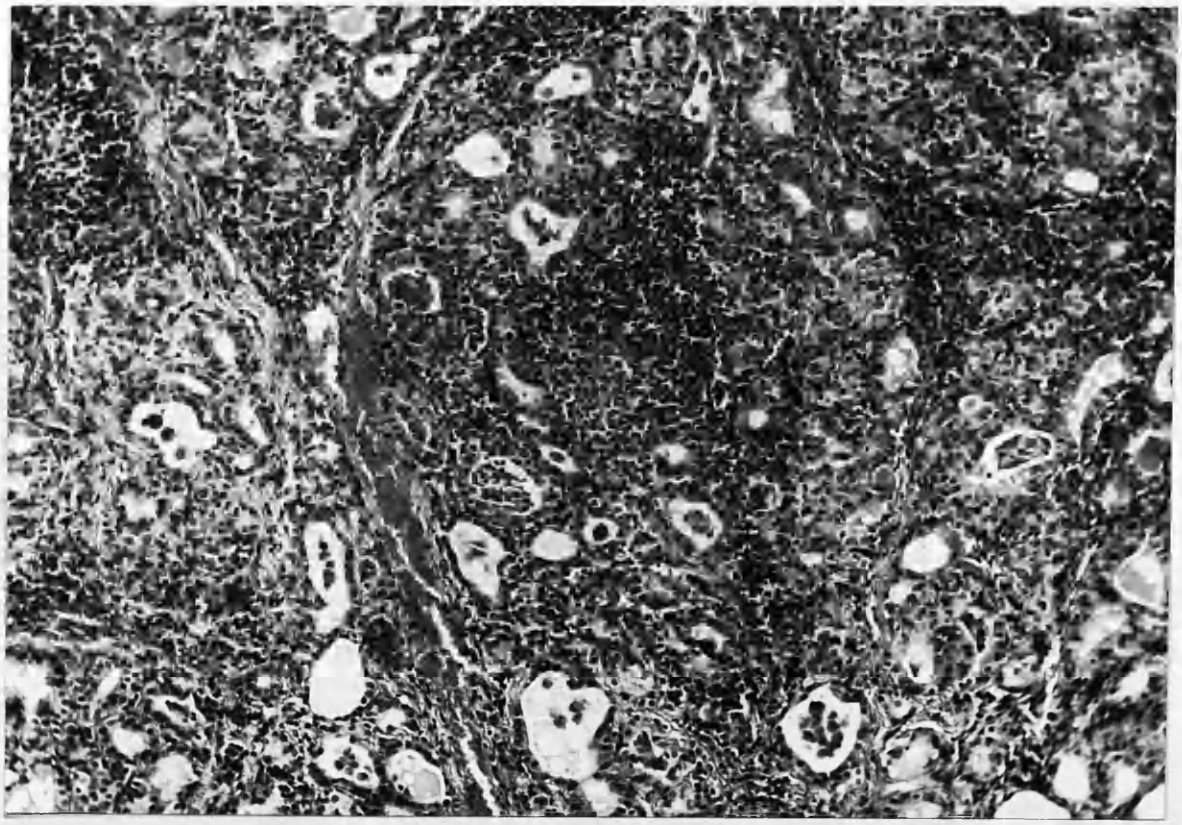


FIG. 4. Hashimoto's Thyroiditis

Showing diffuse chronic inflammatory cell infiltration with foci of more dense aggregation. The acini are small and there is virtually no colloid storage. Colloidophagy is evident in the lumen of the acini. There are also dense strands of fibrous tissue (left of centre) and a general increase in connective tissue between individual acini. (Haematoxylin and eosin x 150).

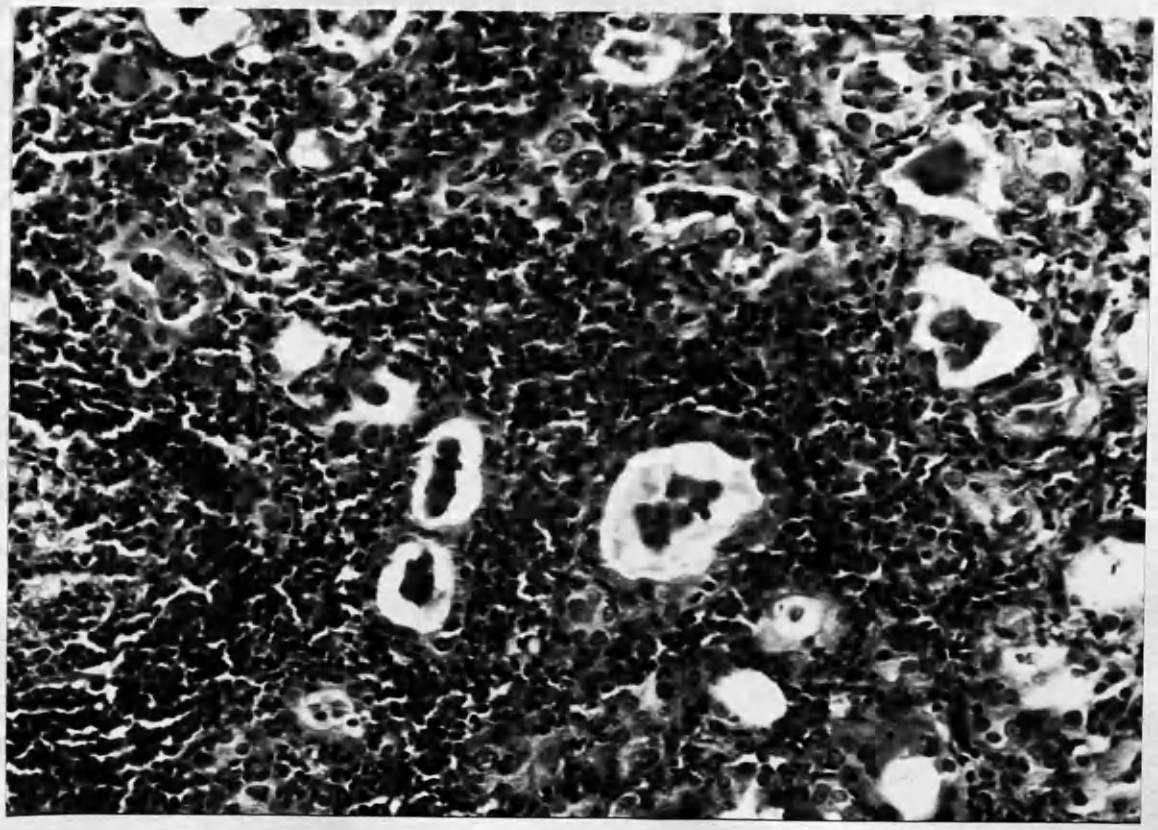


FIG. 5. Hashimoto's Thyroiditis.

Showing diffuse chronic round-cell infiltration, small acini, and colloidophagy. Epithelium is in the form of Askanazy cells. (Haematoxylin and eosin x 430).

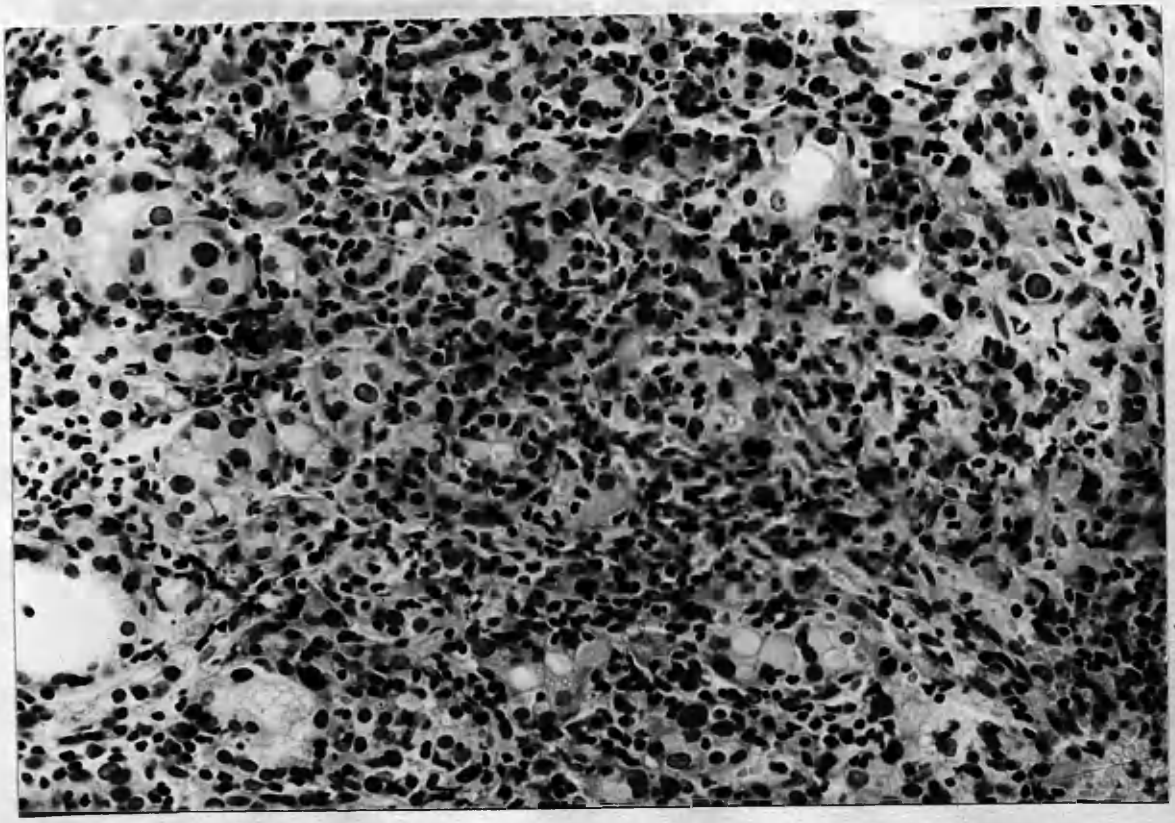


FIG. 6. Hashimoto's Thyroiditis.

Showing diffuse infiltration with plasma cells and lymphocytes. All epithelium is in the form of small acini and solid clumps, and shows Askanazy-cell change. There is virtually no colloid in any of the acini. (Haematoxylin and eosin x 500).

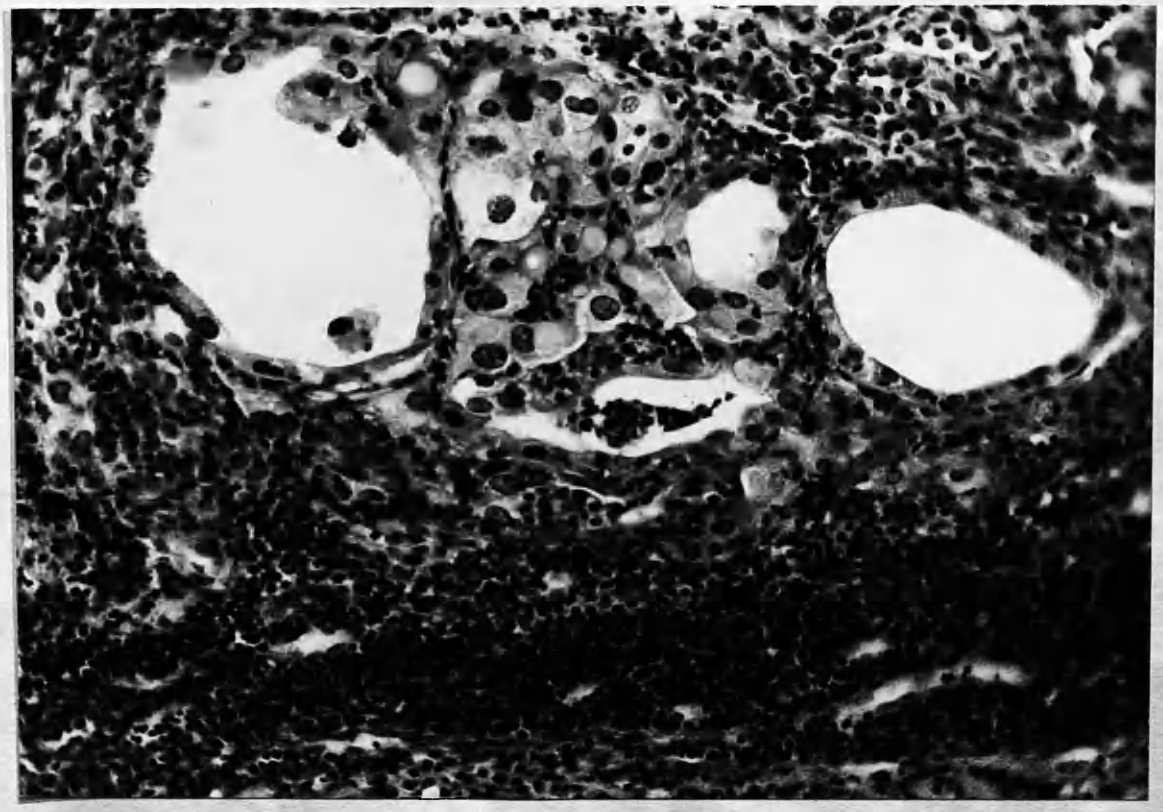


FIG. 7. Hashimoto's Thyroiditis.

Showing very dense chronic inflammatory cell infiltration and a group of acini showing tendency of epithelium to form solid clumps. The epithelial cells are enlarged irregularly and have the typical appearances of Askanazy-cells. Colloidophagy is seen in one of the small acini. (Haematoxylin and eosin x 500).

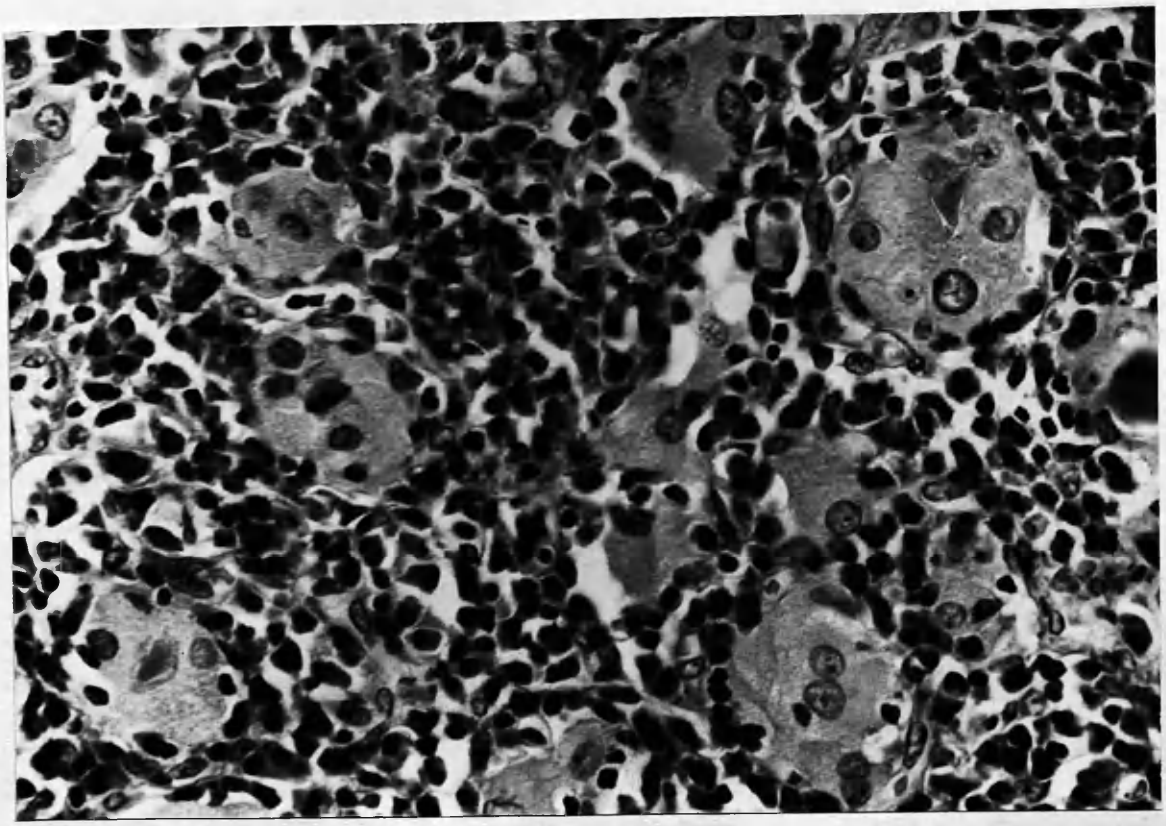


FIG. 8. Hashimoto's Thyroiditis

Showing diffuse round-cell infiltration and Askanazy-cell change in the thyroid epithelium. The majority of the round-cells are plasma cells.
(Haematoxylin and eosin x 425).

/degenerative (10), involutional (23), or exhausted (3) forms of thyroid epithelium.

(5) Vessels. Apart from atherosclerotic changes no specific abnormalities have been recorded in the blood vessels in Hashimoto's thyroiditis (1 - 3, 13).

In summary, the histological findings in Hashimoto's thyroiditis are characterised by: diffuse lymphocytic and plasma cell infiltration, lymph-follicle formation, small acini devoid of colloid, hyperplastic epithelium showing Askanazy-cell change, and fibrosis, present in variable degree. Some of these features are illustrated in Figs. 1 - 8.

Histological Criteria of Hashimoto's thyroiditis.

Considerable confusion has existed in the past regarding the histological criteria of Hashimoto's thyroiditis. Thus, some workers (2,7,24) have restricted the term to those glands showing diffuse changes of characteristic type, whereas others (3,23,25) have extended the description to include a focal lesion of the same type. Furthermore, some pathologists do not accept glands with diffuse changes which lack one of the essential characteristics of the disease, such as Askanazy-cell change or plasma cell infiltration,as examples of Hashimoto's thyroiditis. Thus, Crile (26) and others (2,4,8,9), have emphasised the importance of the epithelial changes, and Crile and Hazard (27) and Gribetz et al. (28) have referred to goitres occurring in adolescents and young girls which showed diffuse lymphocytic infiltration with little or no Askanazy-cell change as "lymphocytic" or "lymphoid" thyroiditis. Paine et al. (29) contend that/

/that Hashimoto's thyroiditis should only be made in the absence of plasma-cell infiltration and use the term "chronic non-specific" thyroiditis when these cells are present. There is, however, no historical justification for this view, since Hashimoto (14) stated that the round-cells present "included a number of plasma cells" (translated from the German). In recent years there has been a tendency to include such variants under the general designation of Hashimoto's thyroiditis (11).

The histological criteria adopted in the present thesis are those of Joll (2). In this author's opinion, the characteristic microscopic feature is the uniformity of the changes and the diffuse nature of the lymphocytic infiltration, although, as he observed, this did not "preclude considerable differences in detail according to the stage reached by the disease". Later in Chapter III of the thesis, evidence will be brought forward to suggest that the focal lymphoid lesions of chronic thyroiditis can be accepted as an early stage of the diffuse disease process.

Section 3.

Aetiology and Pathogenesis (Review).

It is perhaps not surprising that earlier writers should have considered an infective basis for the aetiology of Hashimoto's thyroiditis, since histologically the disease has many characteristics of an inflammatory condition. Both Brünger (1) and Eason (2) regarded the presence of lymph follicles as evidence of an inflammat-:ory reaction, although Hashimoto (3) originally compared struma lymphomatosa with Mikulicz's disease. Since it was known that thyroiditis was never primary, foci of infection were sought in the teeth (4), tonsils (5), and upper respiratory passages (6,7). Bohan (4) for instance isolated organisms in dental infection which when injected into rabbits produced Hashimoto-like changes in the thyroid. Meeker (5) described a patient with a persistent posterior branchial body and suggested that infection might have reached the thyroid in this way. Although unable to demonstrate the presence of tubercle bacilli Wegelin (8) did not dismiss the possibility that tuberculosis might be an aetiological factor. Likewise, syphilis was incriminated by Williamson and Pearse (9) in 1929, although Ewing (10) had previously considered Hashimoto's thyroiditis to be a "benign granulomatous" infection. That the thyroid gland was resistant to bacterial infection was demonstrated by Womack (11) who injected pure cultures of streptococci and staphylococci directly into the superior thyroid artery in dogs and showed that abscess formation rarely followed. The possibility of a viral infection was not so readily dismissed, and indeed a few cases have been reported in which/

/which the concurrence of a virus infection with a tender goitre has occurred and progressed over several years to classical Hashimoto's thyroiditis (12,13,19). It was generally agreed, however, that tuberculosis, syphilis, and infection with pyogenic organisms could be excluded.

Graham (14) thought that Hashimoto's thyroiditis was a "local expression of a constitutional disorder" and Crile (15) emphasised the evidence for this view. Vaux (16) considered that the changes in the thyroid were comparable to the changes seen in other organs. Levitt (17) also believed it was a constitutional disorder since corresponding changes were occasionally found in the adrenals (18,19) adenohypophysis (20) and ovaries (21). In one of the fatal cases reported by Lindsay et al. (22), there was an extremely large hyperplastic thymus gland and abundant lymphoid tissue in all portions of the body. Skillern et al. (23), however,believed it to be due to "primary thyroid failure".

There was considerable speculation as to the cause of the lymphoid infiltration in Hashimoto's thyroiditis. The production of a "lymphogenic" substance by the thyroid (9), and a deficiency of the "effective lymphoid-moderating hormones" (24), were both postulated. Goldberg and Dawson (25) adduced evidence to suggest that it might be an expression of relative ischaemia. Davison and Letton (26) regarded it as an exaggeration of that normally occurring in thyrotoxic glands. Ferguson (27) believed that the lymphoid infiltration was the result of irritation by hydrolyzed lipid materials from colloid. More recently, Hellwig and his co-workers/

/co-workers (28 - 32) suggested that it might be explained on the basis of colloidophagy. By the use of supra-vital stains Chesky et al. (32) were able to show that macrophages, which had ingested colloid in the vesicles, on re-entering the stroma, disintegrated and liberated colloid which acted as an irritant focus for lympho-:cytic infiltration. This was attributed by these authors to excessive thyroid stimulating hormone (TSH) production - a view also later supported by Furr and Crile (24). This hypothesis was supported by the experimental work of Hellwig (28 - 31), who produced lymphocytic infiltration by TSH stimulation, and by the work of Rawson et al. (33) who showed that normally TSH was neutralised only by thyroid tissue or lymphocytes. Cheney and Mezey (18) and Parmley and Hellwig (21) suggested that excess TSH production might be mediated through reduction in ovarian function at the time of the menopause. The role of TSH in the aetiology of Hashimoto's disease is still uncertain. No direct measurements have as yet been made (34). The suggestion that there is normally an increase in TSH production after the menopause has, however, not been confirmed (35).

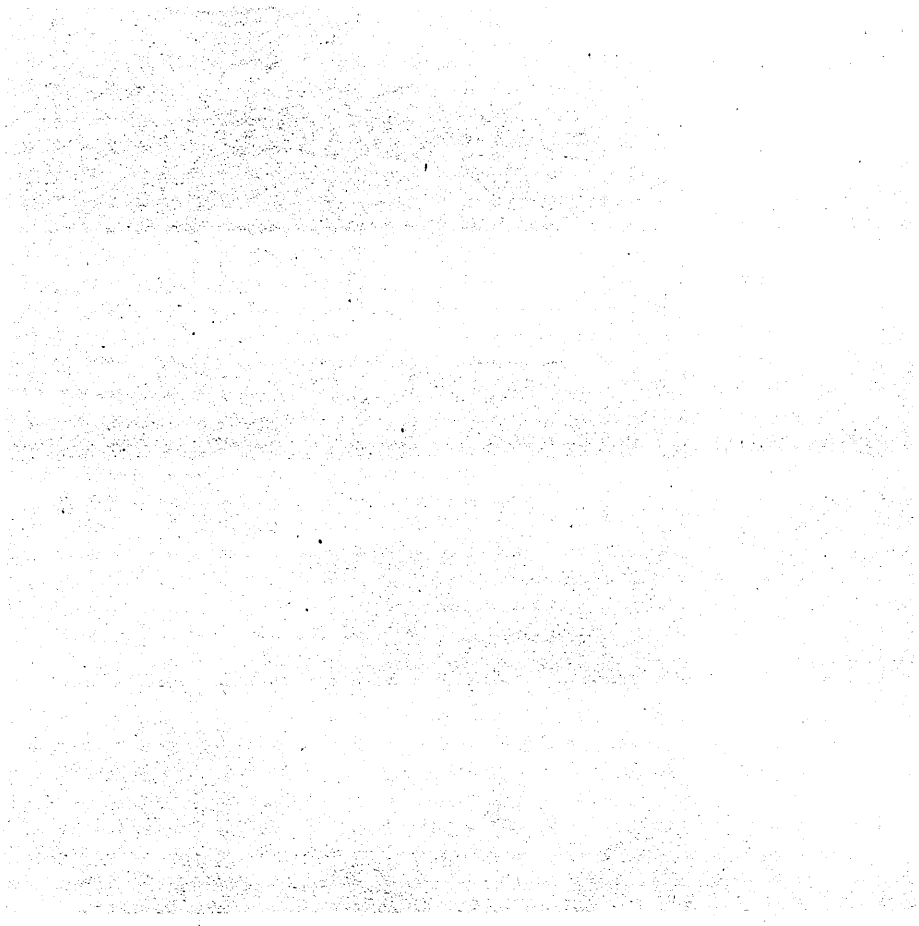
Boyden et al. (37), after considering the views of Warthin (38) on the histological effect of administration of iodine in exophthalmic goitre, concluded that "the pathological changes peculiar to the disease are largely the result of an over-response on the part of the thyroid to prolonged iodide administration" - a view which was also held by Dunhill (39). Follis (40) produced lymphocytic infiltration/

/infiltration in the thyroid of hampsters by excessive iodide administration. Statland et al.(41), however, pointed out that most patients with Hashimoto's thyroiditis have not received previous iodide therapy; and Lennox (42) found no relation between the oxyphilia of thyroid epithelium and previous iodine medication. Furthermore, the histological appearance of iodide-induced goitre in man is entirely different from that in Hashimoto's thyroiditis. Iodide goitres show parenchymatous hypertrophy with variable amounts of colloid storage, but no lymphocytic infiltration (43).

A vitamin deficiency was suggested by the work of McCarrison (44 - 46). He reported lymphocytic infiltration, fibrosis and atrophy in the thyroids of rats fed on a diet deficient in vitamins and manganese for periods ranging from $2\frac{1}{2}$ to 6 months. This work was corroborated by Bastenie (47). On the other hand, Rinehart (48) found no lesions like those of Hashimoto's thyroiditis in animals on diets deficient in many vitamins. Lederer et al. (49) reported a patient with Hashimoto's thyroiditis who had long-standing vitamin B deficiency. Lupulescou (50) observed that in human pellagra, "one finds at autopsy alterations (in the thyroid), like chronic thyroid atrophy" (translated from the French). However, no definite clinical relationship to vitamin deficiency has been found in the English literature on Hashimoto's thyroiditis (22,41).

It is of interest that out of the mass of information and speculation regarding the aetiology and pathogenesis of the disease only/

/only Ferguson (27) and Hellwig et al. (28-32) pointed out the possible significance of leakage of colloid as an aetiological factor and were thus anticipating the immunological aspects of the condition.



Section 4.

Thyroid Auto-immunity (Review).

Recent interest in thyroid auto-immunity springs largely from the discovery of Roitt et al. (1) in 1956 that a high proportion of patients with Hashimoto's thyroiditis have circulating thyroid auto-antibodies in their blood serum. These observations have since been confirmed by these (2 - 4) and other (5 - 16) workers and have been the subject of several recent reviews (17 - 20). Before outlining these discoveries short accounts will first be given of the earlier work on thyroid immunology and on the more recent studies on experimental thyroiditis in animals.

Earlier Literature.

During the first decade of this century several workers (21 - 25) demonstrated that thyroid-specific agglutinins could be produced by injection of crude thyroid extracts, although Schulhof (26) and Rosen and Marine (27) were later unable to repeat these observations. In 1942 Lerman (28) made the fascinating observation that prolonged immunisation with isologous (human) thyroglobulin in the rabbit ultimately led to hypothyroidism. In a series of brilliant experiments Professor Hektoen and his co-workers (29 - 31) in Chicago demonstrated that thyroid-specific antibodies could readily be produced byimmunisation with thyroglobulin. These workers (31) showed that the antibodies produced had a variable degree of cross-reaction with mammalian thyroglobulins from other species, although in general the antibodies were species-specific. These observations were later confirmed by several other workers (32 - 36).

Experimental Thyroiditis

Professor Witebsky and his collaborators in Buffalo chose thyroglobulin as a readily available protein for their studies of organ-specific auto-antibodies (8,37-39). They (8) first demonstrated that thyroid-specific auto-antibodies could be produced in rabbits, dogs, or guinea-pigs, by injection of a combination of crude homologous thyroid extracts with Freund adjuvants (40) containing mineral oil, Arlacel and killed mycobacteria; later they showed that homologous antibodies to thyroid could be produced by using refined (90% pure) thyroid extracts (8). Witebsky et al. (8) proved that these antibodies were true auto-antibodies by showing that they could be produced by immunisation with the animal's own thyroid. It was also found that mycobacteria could be omitted from the adjuvants and still allow antibody formation (8).

Some years elapsed before these workers noted that after 2 to 3 months some of the immunised animals showed histological evidence of thyroid damage (8,41). This consisted of infiltration with lymphoid cells, and eosinophils surrounding thyroid vesicles, which in extreme cases contained little or no colloid (8). The overall picture resembled that seen in Hashimoto's thyroiditis; an observation which first appears to have been made by Dr. Riggs working in Professor Witebsky's laboratory (42). However, nothing comparable to Askanazy-cell change was reported and goitres were not produced. Thyroiditis was also observed in animals immunised with cross-reacting heterologous thyroid antigens (43). These findings/

/findings have since been confirmed by Milcu et al. (44) in the rabbit, and Lilien (45) and Jones and Roitt (46) in the rat.

Terplan et al. (47) concluded that the thyroid auto-antibodies resulting from immunisation with crude or refined thyroid extracts reacted with components of the thyroid tissue in situ and resulted in subsequent damage to the thyroid. However, these workers could find no strict correlation between the titre of humoral antibody and the presence and extent of the thyroid lesion. Furthermore, Jones and Roitt (46) noted that in the rat regression of the lesions occurred if the immunisation procedure was discontinued.

Outline of the Events leading up to the Hypothesis that Hashimoto's thyroiditis is a disease of Auto-immunisation.

Various workers (48 - 51) had demonstrated abnormal serum flocculation tests and raised gamma-globulin levels in Hashimoto's thyroiditis. The known association of raised gamma-globulins with circulating antibodies (52) and the infiltration of the diseased thyroid with lymphocytes and plasma cells, which are known to produce antibodies, suggested to Dr. Doniach and her colleagues (1,2) that Hashimoto's thyroiditis might be explained on the basis of auto-immunisation. In support of this hypothesis these workers were able to obtain easily demonstrable precipitates by making an extract of human thyroid gland and adding it to the serum of patients with Hashimoto's thyroiditis. They further demonstrated that the precipitin reaction occurred with either crude or refined extracts of human/

/human thyroid gland (2), suggesting immunisation against thyro-:globulin. They also showed that the antibody was also organ-specific and did not react with extracts of thyroid gland from any of 6 mammalian species including the rabbit, rat, sheep, pig, cow, and horse. White (53) labelled the precipitating antibody of a patient with Hashimoto's thyroiditis with fluorescin and was subsequently able to demonstrate staining of the colloid in the thyroid, thus providing convincing evidence of the auto-immune nature of the reaction.

The "Leak" Hypothesis

It has been mentioned in the previous section of this Chapter that colloid may act as an "irritant", and the demonstration that the thyroglobulin component of the colloid is antigenic could be adduced as evidence to support the concept of Doniach and Roitt (2) that Hashimoto's thyroiditis might be the consequence of auto-antibodies acting on the thyroid gland, These workers argued that a reaction of this type once initiated might be expected to become self-perpetuating, since damage to the thyroid would cause release of more antigen and hence enhance the level of circulating antibody which in turn would result in further thyroid damage. The confinement of thyroglobulin in the thyroid acini during foetal life was considered by Roitt et al. (54) to possibly lead to a failure of establishment of immunological tolerance so that escape of thyroglobulin in adult life would set in motion a self-destructive auto-immune reaction.

Certain facts were against the view that structural and hence immunological alteration of the thyroglobulin present in the diseased gland/

/gland was responsible for the initiation of the auto-immune process. Firstly, Doniach and Roitt (2) demonstrated that the antibody reacted just as strongly with thyroglobulin obtained from normal glands as it did from goitres with Hashimoto's thyroiditis; secondly, Rose and Witebsky (41) demonstrated in their rabbits that antibodies produced by autologous immunisation reacted with extracts made from the animal's own thyroid.

Problems associated with the Acceptance of the "Leak" Hypothesis.

Implicit in the acceptance of the "leak" hypothesis to explain the pathogenesis of Hashimoto's thyroiditis is that there is an initial release of thyroid antigen or antigens. Stuart and Allan (55) working in Edinburgh studied the basement membrane changes by a silver-staining method. These workers concluded that failure of the integrity of the basement membrane was particularly widespread and severe in Hashimoto's thyroiditis and that a direct relationship existed between the irregularities observed and the level of thyroglobulin auto-antibodies and the degree of round-cell infiltrat-:ion. Although these observations may serve as an anatomical basis for thyroid auto-antibody formation, it is equally possible that the changes described are the consequence rather than the cause of the disease.

Leakage of antigen could conceivably be brought about by simple mechanical rupture of follicles, due to increase in size of the goitre, although, as will be discussed later, thyroid auto-antibodies are/

/are also found in association with the shrunken glands in primary hypothyroidism (4,11,9,12,14). Excessive TSH stimulation by its hyperplastic effect might help to maintain release of antigen, but, as has been previously discussed, it is difficult to conceive how this by itself could initiate the process. Because of the adjuvant effect attributed to viruses in the causation of auto-allergic diseases (57) Doniach et al. (58) considered the possibility of a viral infection initiating the auto-immune process. So far, no satisfactory evidence has been produced in favour of this view.

The subsequent experience of Roitt and Doniach (4) suggested that the thyroid antibodies may not in themselves be the direct cytotoxic agent, but may merely reflect the underlying pathological process. Passive transmission of the disease by infusion of Hashimoto-sera containing high antibody titres has not so far been successful (4), and Irvine (59) and Pulvertaft et al. (60) have been unable to demonstrate any effect of thyroid auto-antibodies on either the growth or morphology of trypsinised thyroid cells in tissue culture. A cytotoxic factor has, however, been demonstrated by these workers in a high proportion of sera from patients with Hashimoto's disease (59,61-63) but its significance relevant to the pathogenesis of the disease has not been so far fully assessed.

That the auto-immune process, once initiated, is not necessarily self-perpetuating is clear from studies in subacute thyroiditis (4,6,12,14,64). In this disease the appearance of auto-antibodies is temporary and presumably associated with the viral infection and subsequent/

/subsequent thyroid damage does not occur, although from the history Hashimoto's thyroiditis may have supervened on subacute thyroiditis in the patient reported by Décourt et al. (65). It is therefore clear that at the moment the "leak" hypothesis is insufficient to explain the pathogenesis of Hashimoto's thyroiditis, although auto-immunisation can clearly be demonstrated.

Multiplicity of Antigen Antibody Reactions.

Further work in the immunology of auto-immune thyroiditis has led to the knowledge that the antigens involved are multiple (4,5,7,11,12). Early experience with the complement-fixation (CF) technique led Trotter et al. (7) to suggest that a different reaction might be involved in this reaction as compared with the precipitin test. This suggestion was confirmed by Goudie et al. (5) who demonstrated CF antibodies in all of 16 untreated patients and in 15 of 16 treated patients with auto-immune thyroiditis, whereas the precipitin test was positive in only 20 of the 32 patients. The antigen used by Goudie et al. (5) in the CF reaction was an extract of thyrotoxic gland as Trotter et al. (7) had been unable to detect CF antibodies using extracts made from a normal gland. The implications of these earlier studies was that the antigens involved in the precipitin and CF reactions were quite distinct and also that the CF antigen might be specific for thyrotoxicosis. However, both White (53) and Anderson et al.(9) were subsequently able to detect the antigen responsible for the CF test in normal glands and simple/

Table I.

Methods for Detection of Thyroid Auto-antibodies.

Table I.

Methods for Detection of Thyroid Auto-antibodies

Antigen	Methods of Detection of Auto-Antibodies
Thyroglobulin in Colloid	Precipitation. Tanned Red-cell haemagglutination. Radioactive Co-precipitation. Coon's fluorescent Antibody Technique on Fixed Sections. Passive Cutaneous Anaphylaxis in Guinea Pigs. Skin Tests.
"Microsomal" Antigen in Acinar Cells	Complement-Fixation. Coon's Fluorescent Antibody technique in Unfixed Sections.

/simple goitres, and in the glands of goitrous cretins.

Nature of the Thyroid Antigens.

Subsequent studies have confirmed that there are at least 2 separate antigen-antibody systems involved in thyroid auto-immunity (4,20,). In the first of these the antigen is presumed to be thyroglobulin which is stored in the colloid, and the second has been shown by ultra-centrifugation of thyroid tissue extracts to be located in the "microsomes" of the acinar cells (4,11). Rarely precipitating sera may deviate complement when reacting with thyroglobulin (11,67).

Methods available for the Detection of Thyroid Auto-antibodies.

Several methods are now available for the detection of these auto-antibodies and these have been summarised according to Roitt and Doniach (20) in Table 1. In practice the precipitin and tanned red-cell haemagglutination (TRC) tests are most commonly used for detection of thyroglobulin auto-antibodies and CF test for microsomal auto-antibodies; the principles of these techniques will now briefly be described.

1. Precipitin Test for Thyroglobulin Auto-antibodies.

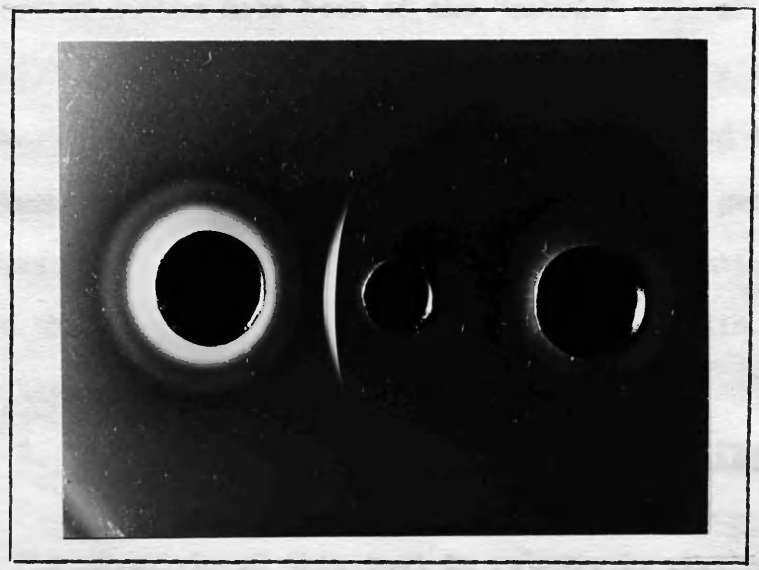
It has been known for a long number of years that certain antibodies react with their specific antigen to form large precipit-:ating protein aggregates. Thus, precipitating antibodies may be demonstrated by either mixing the serum directly with the antigen or by employing the agar-diffusion methods of Oudin (68) or Ouchterlony (69). Precipitating auto-antibodies are most conveniently tested for/

FIGURE I.

Illustration of a Positive Precipitin test by the Agar-diffusion Method of Ouchterlony.

FIGURE I.

Left



Right

Ouchterlony Plate. Antigen has been placed in the central well and a positive precipitating serum in the well on the left, and a control serum on the right. Both the antigen and the two sera have diffused into the agar, and on the left a white line of precipitate has formed at the line of interface, indicating a positive test. The agar has remained clear on the right.

/for by the Ouchterlony technique and an example of a positive test is illustrated in Fig. 1. The amount of antibody detected by the precipitin test is of the order of 5 mg. per ml. of serum, but quantities exceeding 15 mg. per ml. of serum have been recorded (20). The precipitating antibodies to thyroglobulin are of either the 7S or 18S type (70,71) or a mixture of both (72), and quantitative precipitin curves have been of the "rabbit" (53) or "horse-flocculation" type (73). Occasionally a clear line develops in the agar in place of an opaque line; Goudie et al. (74) interpreted this as indicating non-aggregating antigen-antibody complexes. In general precipitating auto-antibodies to thyroglobulin are true auto-antibodies in the sense that they react with autologous thyroglobulin, but exceptions have been recorded (75).

2. Tanned Red-Cell Haemagglutination Test (TRC) for Thyroglobulin Auto-antibodies.

The principle of this test is relatively simple. Red-cells are first treated with tannic acid so that they become adhesive and are then coated with thyroglobulin; when serum containing thyroglobulin auto-antibodies is added agglutination of the red-cells occurs. The test is more sensitive than the precipitin test and occasionally detects titres of antibodies exceeding several million dilution in auto-immune thyroiditis (76). In general there is good agreement between the precipitin and TRC test, although some overlap does occur (76).

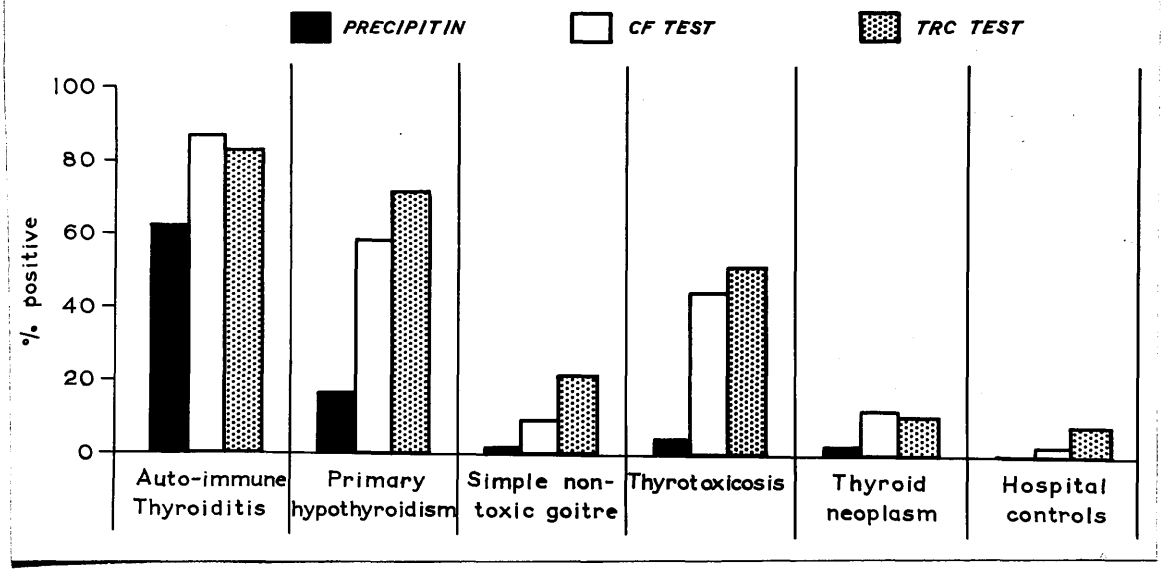
The standard technique of Boyden (77) has recently been modified by/

FIGURE 2

Prevalence of Various Thyroid Auto-antibody Tests in Thyroid Disease as Compiled from the Literature

FIG. 2

PREVALENCE OF VARIOUS THYROID AUTO-ANTIBODY TESTS IN THYROID DISEASE AS COMPILED FROM LITERATURE



It is to be noted that the levels of auto-antibody titres indicating a positive C.F. or T.R.C. test varies with different authors. The prevalence of these two auto-antibody tests in the various diseases is therefore only approximate.

/by the introduction of a stable preparation of formalised sheep cells (78).

3. Complement-Fixation (CF) Test for Detection of "Microsomal" Auto-antibodies.

The detection of "microsomal" auto-antibodies is based on the standard complement-fixation test, such as used in the Wasserman reaction. The antigen-antibody complexes combine with complement and this fixation can be detected by the addition of an indicator system of sensitized sheep red-cells which are lysed in the presence of complement. The absence of lysis indicates the presence of complement. Like the TRC test the CF reaction is quantitative and titres exceeding 1/20 dilution are common in auto-immune thyroiditis (4).

The other methods available for detection of thyroid auto-antibodies include Coon's fluorescent technique (53,74), radioactive co-precipitation (73), and passive cutaneous anaphylaxis (80,81), but these are of research rather than practical interest, and will not be considered further.

Prevalence of Thyroid Auto-antibodies in Various Thyroid Diseases.

The results of serological studies obtained by a number of workers (4,6,9,11,12,14,16,82-90) in the principal thyroid diseases have been summarised in Fig. 2. It can be seen that the 3 types of thyroid auto-antibody tests are more frequently positive in Hashimoto's thyroiditis than in any other form of thyroid disease. Furthermore it can be seen that the precipitin test is less frequently/

/frequently positive than either the TRC or CF test and that it is seldom positive in simple non-toxic goitre or thyroid neoplasm, conditions which are most likely to be confused with Hashimoto's thyroiditis. Indeed, in goitrous thyroid disease, excluding thyrotoxicosis, the finding of a positive precipitin test is, in the words of one American reviewer (91), "enough to serve as a confirmatory test in the diagnosis of lymphadenoid goiter".

In this hospital, thyroid biopsy in 25 consecutive patients with goitre and a positive precipitin test showed the typical appearances of Hashimoto's thyroiditis in all but one patient who had Sjögren's syndrome. The thyroid in this patient revealed diffuse Askanazy-cell change, but virtually no round-cell infiltrat-:ion. The diagnostic value of the precipitin test has likewise been confirmed by Doniach (92).

Concept of Auto-immune thyroiditis.

Because the diagnosis of Hashimoto's thyroiditis is now made in the vast majority of cases on the basis of serological tests, the terms "auto-immunising" (16) thyroiditis and "auto-immune" (4) thyroiditis have been introduced to describe the condition. The term "auto-immunising" thyroiditis does not appear entirely satis-:factory as it is somewhat ambiguous and might be taken to imply that auto-immunisation is the sole factor responsible in the pathogenesis of the disease. On the other hand, it appears both justifiable and convenient to adopt the term "auto-immune" thyroiditis and this has been done in the present thesis.

CHAPTER II.

Auto-immune Thyroiditis:

Clinical and Experimental Studies.

Section 1.

Discussion of the Clinical Features of Auto-immune Thyroiditis based on a Study of 50 Patients.

Until the finding of raised gamma-globulins (1-6) and thyroid auto-antibodies (7-9) auto-immune thyroiditis was thought to be a relatively rare disease and was of interest mainly to surgeons and pathologists. For, although the disease might sometimes have been suspected on clinical grounds, the diagnosis could only be confirmed by histological examination and surgical intervention was not always justified. Consequently, previous clinical studies (10-14) have been based on arbitrarily selected series drawn from surgical or pathological material, in which the diagnosis was often retrospective.

The introduction of tests for thyroid auto-antibodies, in particular the precipitin test, has enabled the diagnosis to be made in many patients at an early stage of the disease, thus making possible a more adequate study of the clinical features and progress of the disease without unnecessary surgical intervention. However, only 2 studies dealing with the clinical aspects of auto-immune thyroiditis have been reported since the introduction of the thyroid auto-antibody tests: firstly, Hubble (15) who, in his Honeyman-Gillespie Lecture in 1958, discussed the clinical features in 18 patients; and secondly, Doniach et al. (6) who, in 1960, summarised their clinical experience based on a study of 106 patients.

The purpose of the present section of the thesis is to provide a detailed account of the clinical features of auto-immune thyroiditis as revealed by modern diagnostic methods. The results of this study have/

/have been presented for convenience in the form of a discussion. The findings in the individual patients of the study are summarised in the Appendices.

Patients Studied

The study comprises 50 patients with auto-immune thyroiditis. All the patients were seen and personally examined by me at the Endocrine Clinic in the University Department of Medicine, Western Infirmary, where they had been referred to, either by their own doctor (41 patients), or by a physician or surgeon in the hospital (9 patients).

Diagnostic Criteria

The diagnosis of auto-immune thyroiditis was based on the presence of a goitre, either diffuse or nodular, in a euthyroid or hypothyroid patient; and confirmed in every patient by a positive precipitin test (38 patients), by histological examination of the thyroid (16 patients),or both (4 patients). The histological criteria were those of Joll (17). Further supportive evidence of auto-immune thyroiditis was provided by: a positive CF test (45 patients), high gamma-globulin levels (23 patients), abnormal serum flocculation tests (31 patients), abnormal routine radioiodine tests (37 patients), and by follow-up studies. Special care was taken to exclude subacute thyroiditis, which may occasionally be associated with temporary positive thyroid auto-antibody tests (16), both clinically and by radioiodine tests. Patients with thyrotoxicosis or with hypothyroidism without a goitre (i.e. primary hypothyroidism) were excluded from the study.

Methods

The clinical history in each patient included the results of an enquiry regarding age, presenting symptoms, and the onset and duration of the goitre. In addition, a history of mumps or contact with mumps, or febrile illness at the onset of the goitre was sought. Enquiry was also made concerning a family history of thyroid disease and of the type, if known. Local symptoms, such as pain or dysphagia associated with the goitre was noted and enquiry was also made regarding systemic symptoms.

The clinical features of the goitre were recorded; size (slightly enlarged - approximately 50 g., moderately enlarged - approximately 75 g., and considerably enlarged - 100 g. or more), type (diffuse or nodular), consistency ("soft", "firm", or "hard"), fixation, tenderness, bruit, and associated lymphadenopathy.

The clinical status of the patient was assessed by the methods described by Wayne (18). By these methods a score is allotted to the relevant symptoms and signs and the sum of the scores is described as the "diagnostic index". Thus, in the assessment of hypothyroidism, scores less than 5 indicate the euthyroid range, scores between 5 and 15 the equivocal range, and scores exceeding 15 the definitely hypothyroid range.

Evidence of systemic disease was also sought in every patient who had a careful physical examination. In the female patients the age of the menarche, menstrual irregularities, number of pregnancies including miscarriages, and the age of the menopause was noted, and compared with those found in a control series of 70 hospital patients matched/

* I am grateful to Dr. R.R. Macdonald of the University Department of Obstetrics for carrying out the cervical mucus tests.

** I am grateful to Dr. J.R. Anderson, Dr. R.B. Goudie, and Miss Kathleen C. Gray, B.Sc. for the results of the thyroid auto-antibody tests.

/matched for age. Evidence of hyperoestrogenism was sought in 12 post-menopausal female patients with auto-immune thyroiditis by the "ferning" test of the cervical mucus (19). *

The precipitin test** was performed by the Ouchterlony technique of double diffusion in agar, as described by Anderson et al. (20). After filling the serum and antigen wells, the plates were kept at room temperature and examined 14 days later. The thyroid antigen was prepared from saline extracts of thyroid tissue obtained at operation from patients with thyrotoxicosis and simple colloid goitre or from normal thyroids obtained shortly after death. The results of the precipitin test were recorded as either negative (-) or positive (+).

The CF test was performed as a 3-tube test as described by Anderson et al. (20). Anticomplementary (AC) activity was tested for in the first tube, and in the second and third tube respectively the sera was tested undiluted and in a 1 in 4 dilution. The complement in these tests consisted of guinea-pig serum and the antigen was prepared from thyrotoxic gland extracts.

The tubes were incubated at 37 degrees C. for one hour and then 0.5 ml. of a 3% suspension of sheep red cells sensitised with four minimal haemolytic doses of immune horse-serum, was added to each tube to determine the presence of residual complement. The results of the test were then recorded as follows: inhibition of lysis in Tube 1 indicated AC activity; inhibition of lysis in Tube 2 a positive (+) test; and inhibition of lysis in Tube 3 as a strongly positive (++) reaction. The specificity of the CF reaction for thyroid/

TABLE I.

Prevalence of Auto-immune Thyroiditis relative to Number of Thyroid Operations.

Table I.

Prevalence of Auto-immune Thyroditis Relative to Number of Thyroid Operations.

Author	Year	Ref. No.	Total No. of Thyroid operations	No. with Auto-immune Thyroditis	Prevalence (%)
Great Britain					
Renton et al.	1938	27	418	7	1.7
Joll	1939	17	5,650	51	0.9
Keynes et al.	1939	28	1,600	25	1.5
Levitt	1951	29	2,114	30	1.4
Heptinstall and Eastcott	1954	30	600	16	2.7
United States					
McSwain and Moore	1943	31	1,999	15	0.75
Ficarra	1946	32	1,938	9	0.4
Marshall et al.	1948	25	25,000	78	0.3
Lasser and Greyzel	1949	33	1,595	9	0.5
Chesky et al.	1951	26	2,031	14	0.7
Statland et al.	1951	11	3,676	51	1.4
Lindsay et al.	1952	12	6,571	170	2.6
Werner	1955	34	4,750	47	1.0
Walt et al.	1957	35	13,600	160	1.2
Woolner et al.	1959	14	42,000	145	0.4

/thyroid tissue extract was confirmed by testing against other tissue extracts (i.e. liver, kidney and adrenal) and was carried out in all patients who had diseases likely to give rise to CF isoantibodies (21).

The precipitin and CF tests were performed on each patient at the time of his or her first appearance at the clinic and were subsequently repeated at varying intervals during the period of follow-up. All sera were examined within one week of collection.

Basal metabolic rate (BMR) determinations were performed by the method described by Crooks et al. (22) using the standards of Robertson and Reid (23).

The serum cholesterol was estimated by the method of Sackett (24) and electrocardiograms (ECGs) included 13 leads (standard, unipolar, and precordial).

Prevalence

Assessment of the prevalence of auto-immune thyroiditis is beset with the difficulty of changing opinions among pathologists regarding the classification of thyroiditis and of the preselected nature of hospital material. The prevalence among thyroid operations has in general been low, varying between 0.3 (25) and 7.1 (30) per cent. (Table 1). Experience in the present study suggests that the disease is not as rare as most of these figures from surgical series would imply, and the disease accounted for approximately 4.5 per cent. of all thyroid disorders. However, this figure might well be misleading as it undoubtedly reflects a personal interest in the disease and the range of investigations that were undertaken. Clearly there is a need for a field survey of random samples of the population.

FIGURE 1

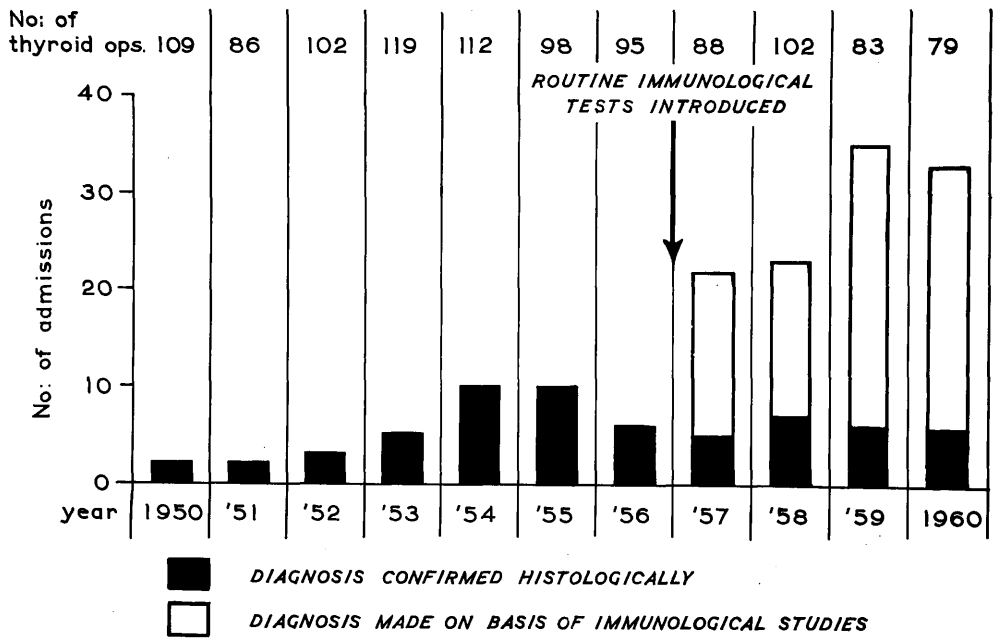
Hospital Admissions for Auto-immune Thyroiditis

Western Infirmary, Glasgow. 1950 - 1960.

Fig. I.

HOSPITAL ADMISSIONS FOR AUTO-IMMUNE THYROIDITIS

Western Infirmary, Glasgow 1950-1960



Hetz et al.(36) have suggested that there has been a true increase in the prevalence of auto-immune thyroiditis in recent years. However, Lindsay et al. (12) found no significant alteration in the incidence during each of 3 decades from 1920 to 1950 in a series of 6,571 thyroidectomies. In the author's opinion the apparent rise in the prevalence of auto-immune thyroiditis can be adequately explained on the basis of improved diagnosis. Thus, in Fig. 1 it can be seen that the increased number of hospital admissions to the Western Infirmary coincided with the availability of the routine serological tests.

Geographical Prevalence

Most reports on auto-immune thyroiditis have come from the United Kingdom and North America, but the disease has been reported from most countries with adequate medical services. However, Joll (17) considered that the disease was rare in mountainous regions, where goitre was common and thyrotoxicosis rare. This had previously been noted by de Quervain in Berne (37) and by Hass (38) in Munich. Lehman (39) reported that 21 of his 23 patients lived in non-endemic areas; and of Joll's 51 patients (17), only 5 came from districts where goitre was regarded as endemic. Both Emerson (40) and Lindsay et al. (12) found a history of residence in an endemic area with essentially the same frequency as in the general out-patient popul-
:ation. Only two/ patients of the present series gave a past history of residence in an endemic region.

No conclusions can be drawn regarding the prevalence of auto-immune/

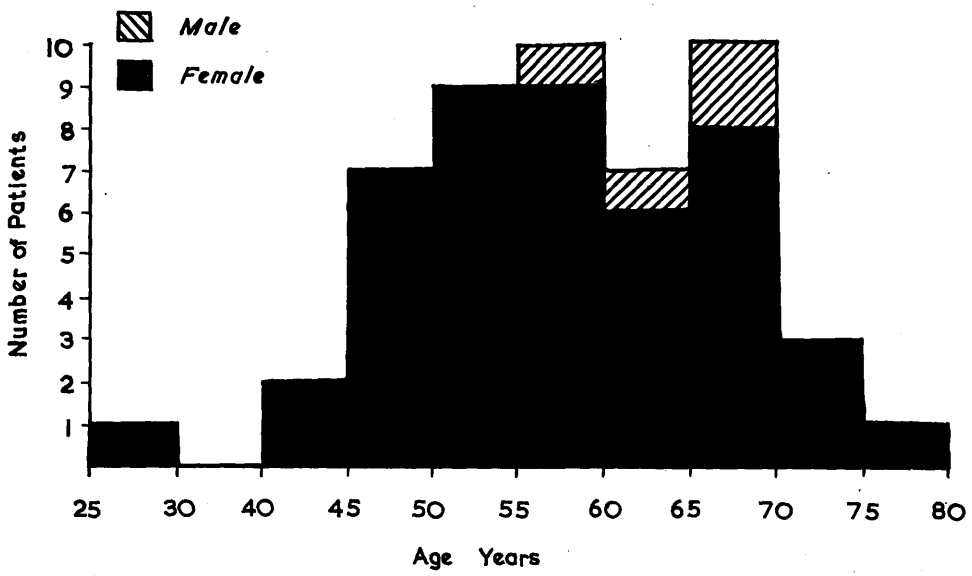
FIGURE 2

Auto-immune Thyroiditis : Age and Sex Distribution

Fig.2.

AUTO - IMMUNE THYROIDITIS

AGE AND SEX DISTRIBUTION



/auto-immune thyroiditis in relation to the endemicity of goitre, but it would be of considerable theoretical interest to know whether such a reciprocal relationship as suggested by Joll (17) actually exists or not.

Racial Prevalence

Auto-immune thyroiditis has been generally regarded as uncommon in the negro races in the United States (41) and Stein (42) formed the impression that it occurred less frequently in Jewish patients. No definite conclusions can be drawn from the present study regarding the racial prevalence of the disease, since all the patients were either of Scots or Irish descent with the exception of one who was Jewish.

Social Prevalence

There was nothing in the present study to confirm McCarrison's suggestion (43) that a poor dietary intake associated with a low social status may be an aetiological factor. This is in agreement with Joll (17) who found the disease equally distributed among all classes.

Age and Sex Distribution

The age distribution in the present series (Fig. 2) conforms to that reported in the literature. The age range was from 28 to 70 years, with a mean age of 52.5 years. The mean age of published series lies between 30 (44) and 53 years (42), and the age range from $7\frac{1}{2}$ (33) to 78 years (45). Joll (17) considered the disease a rarity in childhood, but several instances of its occurrence in children and young/

FIGURE 3

Sex Distribution in Thyroid Disease

FIGURE 4

Age of Onset of Goitre in 46 Female Patients with Auto-immune Thyroiditis

Fig.3.

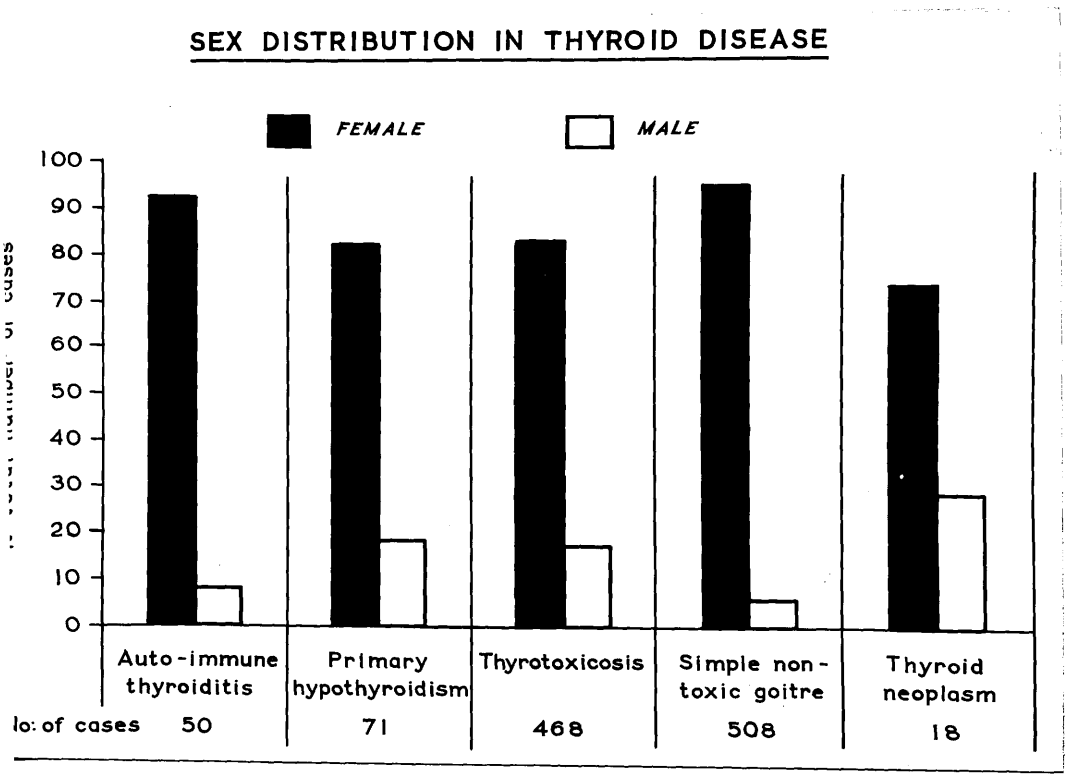
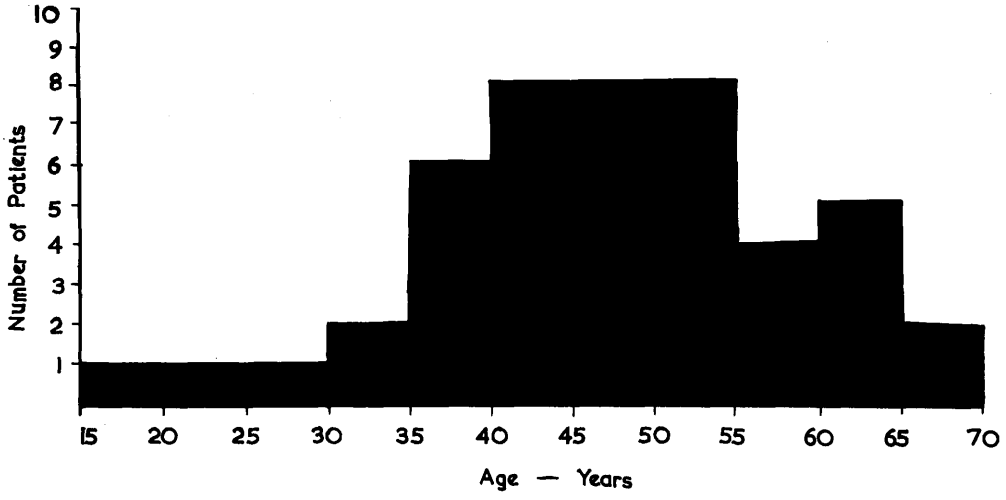

SEX DISTRIBUTION IN THYROID DISEASE
FEMALE
MALE
100
90
80
70
60
50
40
30
20
10
0
Auto-immune thyroiditis
Primary hypothyroidism
Thyrotoxicosis
Simple non-toxic goitre
Thyroid neoplasm
No. of cases
50
71
468
508
18

Fig.4.


Number of Patients
10
9
8
7
6
5
4
3
2
1
15
20
25
30
35
40
45
50
55
60
65
70
Age — Years

/young adults have been reported (3,11,14,42,46-51). No such case has been seen in the present study.

The striking preponderance of auto-immune thyroiditis in females is confirmed; 46 of the 50 patients were females (92%). Apart from simple non-toxic goitre no other type of thyroid disease demon-:strated as marked a predisposition for affecting the female as auto-immune thyroiditis (Fig. 3).

A relationship between the disease and the ovarian hormones has been suggested on the basis of the high prevalence of females with the disease. Parmley and Hellwig (52) were impressed with the high incidence of menstrual irregularities among their patients and Lindsay et al. (12) and Hendrick (53) observed that the onset of the illness originated most frequently during the child-bearing years. The only precipitating factor elicited by Skillern et al. (3) was the stress of pregnancy although nothing to support this was found by Furr and Crile (13) in their patients.

The wide distribution of the age at the onset of the goitre in the present series (Fig. 4) would appear to preclude any direct relationship with the ovarian hormones; and only one patient had noticed the onset of her goitre during a pregnancy. However, the possibility remains that the excessive demands on the thyroid during the sexual life of the female may predispose the thyroid to destruction by chronic thyroiditis. For this reason, the age of the menarche, menstrual irregularities, number of pregnancies including miscarriages, and the age of the menopause, in the patients with auto-immune thyroiditis were compared with a control hospital group matched for/

TABLE II.

Reproductive History in Female Patients with Auto-immune Thyroiditis.

Table II.

Reproductive History in Female Patients With Auto-immune Thyroiditis.

		Auto-immune Thyroiditis	Female Hospital Controls
	Total Number	46	70
Age (Yrs.)	Mean	51.9	56.1
	Range	28-70	31-74
Menstrual History	Mean age at menarche (yrs.)	13.8	14.0
	History of Menorrhagia	4	6
	History of Oligomenorrhoea	3	0
	Mean age at menopause (yrs.)	45.9	46.1
Reproductive History	No. married	40 (87%)	52 (65%)
	No. of births/person	2.7	2.5
	No. of abortions/person	0.5	0.4
	Infertile	7 (17.5%)	8 (15.4%)

/for age (see Appendices for further details). It can be seen from Table II that no significant differences were found; this is in agreement with the observations of Statland et al. (11) and Woolner et al. (14). Furthermore, no evidence of excessive oestrogen secretion secretion was found in 12 post-menopausal patients of the present study as judged by "ferning" of the cervical mucus (54). Moreover, thyroid lesions resembling auto-immune thyroiditis have not so far been produced experimentally by either excess or deficiency of oestrogen hormones (55).

From these studies it is clear that the ovarian hormones cannot be incriminated directly in the pathogenesis of auto-immune thyroiditis; it is possible that female proneness to the disease may be genetically determined.

Clinical Picture

Presenting Symptoms

The presence of a goitre, either alone (15 patients), or associated with recent increase in size (11 patients), mild pressure effects (4 patients), or with symptoms of hypothyroidism (7 patients), was the most common cause of the patient seeking medical advice. This is in agreement with the experience of Joll (17) and other workers (11,12). One patient had a "painful" goitre and 5 presented with thyrotoxic manifestations. Seven patients complained of symptoms of hypothyroidism and were unaware of the presence of a goitre, which was found incidentally on physical examination.

Clinical findings relevant to the goitre

(1) Onset and duration. The onset of the goitre in auto-immune thyroiditis/

FIGURE 5

Duration of Goitre in Auto-immune Thyroiditis

FIGURE 6

Clinical Assessment of Goitre Size in Auto-immune Thyroiditis.

Fig.5.

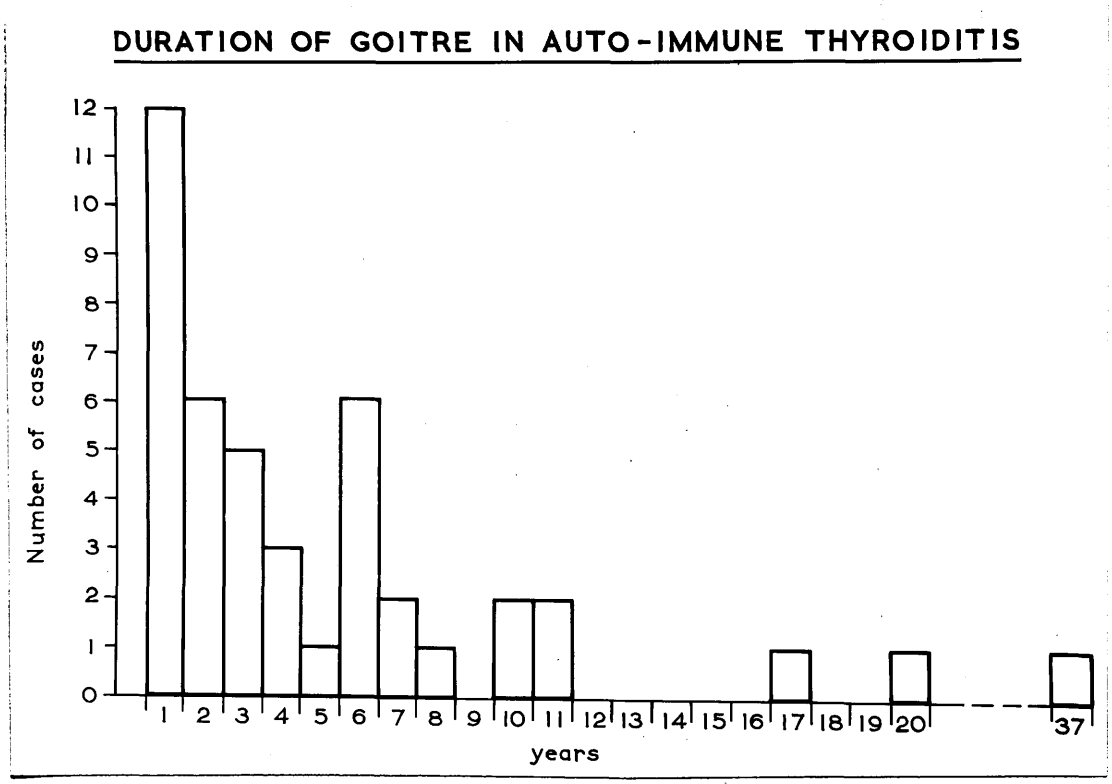
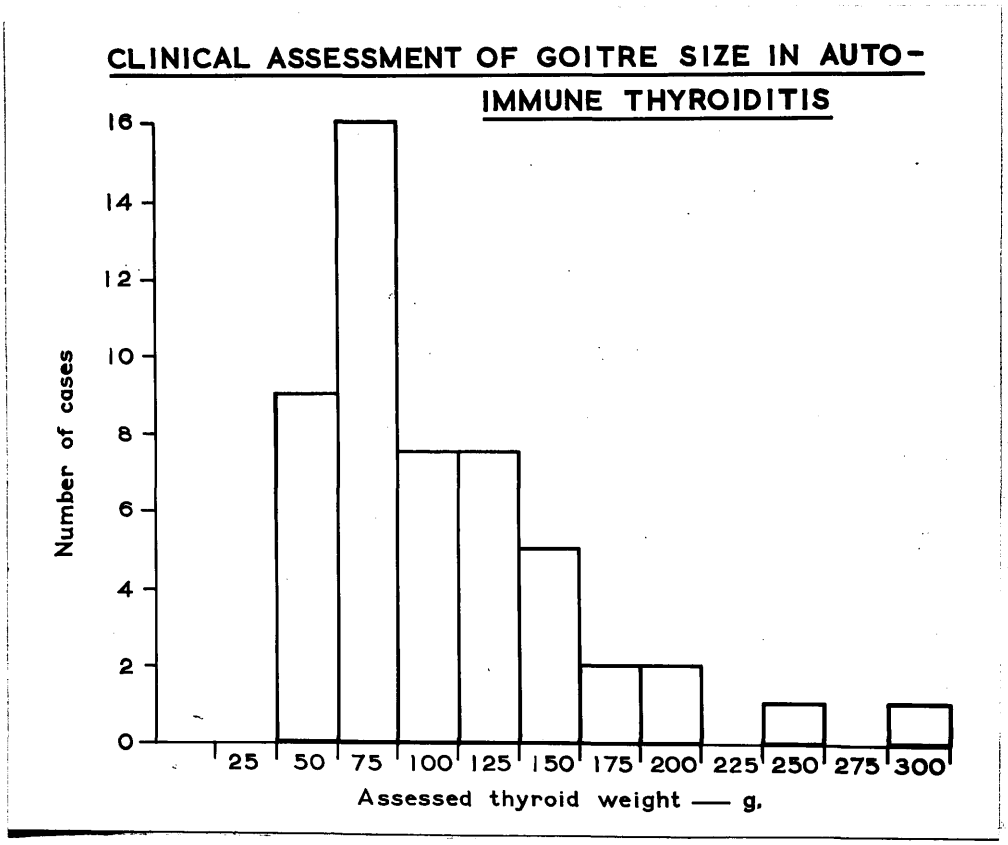

DURATION OF GOITRE IN AUTO-IMMUNE THYROIDITIS
Number of cases
0
1
2
3
4
5
6
7
8
9
10
11
12
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 37
years

Fig.6.


CLINICAL ASSESSMENT OF GOITRE SIZE IN AUTO-IMMUNE THYROIDITIS
Number of cases
0
2
4
6
8
10
12
14
16
25
50
75
100
125
150
175
200
225
250
275
300
Assessed thyroid weight — g.

/thyroiditis is insidious in most patients and without systemic upset (14). Occasionally, however, the onset of the goitre may be associated with feverishness and local discomfort in the gland (16) and this was present in 2 patients of the present series. The possibility of a virus infection has been suggested by Doniach et al. (16) but in neither of these 2 patients was there a history of contact with mumps, which is a known cause of thyroiditis (56). Furthermore, histology of the thyroid in one of these patients revealed uncomplicated auto-immune thyroiditis.

The duration of the goitre in the present series varied between 6 weeks and 37 years (Fig. 5); and 12 patients had had a goitre of a year or less. These findings are in general agreement with those of Crile (57), although a higher proportion of patients with goitres of short duration have been reported by other workers (12,14). Occasionally the goitre may reach a considerable size within a few weeks or months (14,58) and this was seen in 4 patients of the present series. Twelve per cent. of the patients studied by Furr and Crile (13) had had a goitre of 20 years or more; but this was seen in only one patient of the present series, who had had her goitre for 37 years. Histological examination of the thyroid in this patient suggested that auto-immune thyroiditis had been superimposed on a simple colloid goitre. However, a pre-existing goitre is probably unusual in auto-immune thyroiditis, except perhaps in endemic areas (17).

(3) <u>Size.</u> From Fig. 6 it can be seen that in the present series there/

/there was a wide variation of the size of the goitre, although moderatly enlarged (75 g.) goitres were most common. This is in agreement with the recorded weights in surgical specimens (see Chapter I, Section 2, p.21).

(4) Type. Diffuse enlargement of the thyroid was present in 28 patients of the present series, and in 6 patients the pyramidal lobe was palpable. Generally true adenomatous formation in auto-immune thyroiditis is inconspicuous (59), although one patient in the present series had numerous discreet nodules of normal colloid-containing acini encircled by whorls of fibrous tissue present in the thyroid. The apparent nodularity in the remaining patients can probably be attributed to the exaggeration of the normal lobulated surface.

(5) Consistency. The most characteristic feature of the goitre in auto-immune thyroiditis is its "firmness" on palpation. All but 4 patients of the present study had "firm" goitres; two of these 4 patients had "hard" goitres and in the remaining 2 the thyroid was "soft" in consistency.

(6) Fixation. In none of the patients of the present study was there fixation of the thyroid to skin or neck structures on clinical examination. This is in contrast to the fixation frequently present in thyroid neoplasm. However, extension beyond the capsule into the surrounding tissues was present in one patient with a fibrous variant of auto-immune thyroiditis.

(7) Tenderness. This was present in 12% of the patients studied by Lindsay et al. (12) but was not observed in any of the patients in this study.

(8) Bruit. A thyroid bruit was recorded in one patient.

(9) Associated lymphadenopathy. The cervical lymph nodes are frequently found to be hypertrophied at operation (60), presumably because they are producing thyroid auto-antibodies (60). Occasion-:ally these nodes are palpable (44) and this was observed in one patient in this study. In this patient the "sentinel" or "Delphic" lymph node of Cope (61) was also thought to be present. Werner (34) has stressed the diagnostic value of the finding of this node, but this has not been confirmed in the present study.

Symptoms associated with the goitre

Mild pressure symptoms, including dysphagia, are not infrequent in auto-immune thyroiditis (11,12,44,62). Sensations of "tightness" or "choking" were present in 11 patients of this study and 6 had slight dysphagia. One patient complained of pain in her thyroid, and 3 others admitted to having occasional "discomfort". Hoarseness was attributed to hypothyroidism in 12 patients, but was also present in 7 patients who were euthyroid. One of these euthyroid patients also had dysphonia and a temporary vocal cord paralysis. This latter feature has previously been reported in auto-immune thyroiditis (13,57) and is presumably due to involvement of the recurrent laryngeal nerve in the disease process. Cough and stridor were present in one patient who had a very large goitre. However, none of the patients had a mediastinal syndrome, such as reported by Sholl and Black (63).

Systemic Symptoms

(1) Hypothyroidism. Vague systemic complaints, such as lack of feeling/

/feeling of well-being and lassitude, have been frequently recorded by many authors in the past (11,13,17,31,44,52,57), but it is clear that they now can be attributed to thyroid insufficiency. Hypo-:thyroidism has been reported in 10 per cent. or less of surgical patients (11,12,25,39,64,65), but was present in 18 patients (36%) of the present study. However, of the 28 euthyroid and 4 equivocally hypothyroid patients, 10 had raised serum cholesterol values, 8 had lowered basal metabolic rates, and 7 had abnormal electrocardiograms consistent with hypothyroidism. Furthermore, the mean serum protein-bound iodine (PBI) was significantly lower in the euthyroid patients with auto-immune thyroiditis than in a control group (see Section 4, p.175). Thus, classification according to clinical status is arbitrary, since varying degrees of thyroid insufficiency are present and there is no clear-cut division between the euthyroid and hypothyroid state.

(2) Thyrotoxicosis. The possible role of thyrotoxicosis in the pathogenesis of auto-immune thyroiditis has been given much attention in the past (12,65-67), and Graham and McCullagh (68) believed that "if it could be found in the past history the basic lesions for the changes in the thyroid would have been found". A history suggestive of thyrotoxicosis was elicited in 8 patients, but in only 3 was it convincing. This is in agreement with the finding of Eason (69) and it may be that these patients represent the end result of a "burnt-out" thyrotoxicosis.

Mild thyrotoxic symptoms have also been observed at the onset of auto-immune thyroiditis (65,70-72) and Lindsay et al. (12) reported/

TABLE III

Results of Precipitation and Complement - Fixation (C.F.) Tests in Auto-immune Thyroiditis.

FIGURE 7

Clear Line Precipitin Test

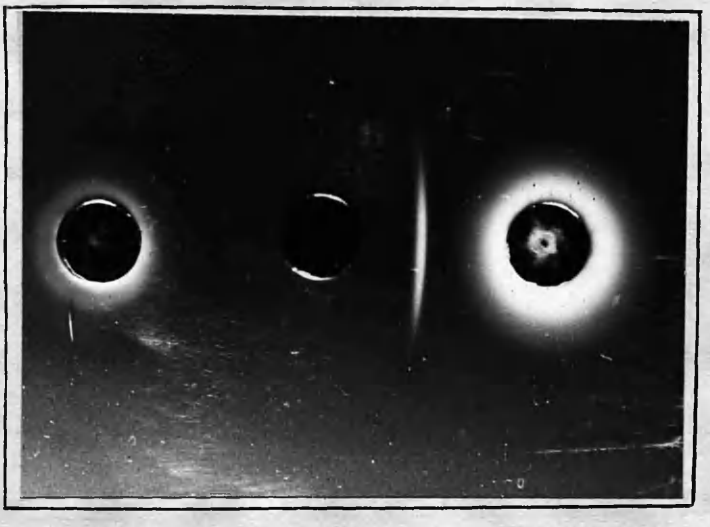
Table III.

Results of Precipitation and Complement-Fixation (CF) Tests in Auto-immune Thyroditis.

Authors	Year	Ref. No.	Total No. of Cases	Positive Thyroid Precipitin	Auto-antibody Tests CF
Roitt and Doniach	1958	75	106	71	98
Anderson et al.	1959	20	60	42	52
Belyavin and Trotter	1959	76	64	27	15
Blizzard et al.	1959	77	3	1	
Hubble	1959	15	18	15	
Present Series			50	38	46

FIG. 7.

Left



Right

A clear line is seen in the agar on the left
and a positive precipitate for comparison on the right.

/reported an incidence of 12 per cent. in their series of 170 patients. Five patients in the present study presented in this way, but were subsequently shown to be euthyroid. The diagnostic and theoretical implications of these findings will be discussed later in greater detail in Chapter III.

Eye Signs

McSwain and Moore (31) and others (42,73) have reported mild degrees of exophthalmos in patients with auto-immune thyroiditis. Exophthalmos was present in 9 of the 50 patients of the present study; an incidence which does not differ significantly ($P < 0.1$) from that described by Wayne (74) using the same criteria in 7 of 90 hospital controls. One patient was, however, of considerable interest since she had exophthalmic ophthalmoplegia and was hypo-:thyroid.

The Clinical Significance of the Thyroid Auto-antibodies

The results of the precipitin and CF tests obtained in the present study are summarised in Table III and compared with the results obtained by other workers (15,20,75-77). The overall results are in surprisingly close agreement, considering the variations in techniques used and the choice of material. Positive precipitin tests were found in 38 patients in the present study, including one patient who had had a subtotal thyroidectomy performed 5 years previously. A clear line developed in the agar instead of the usual dense white precipitate (Fig. 7) in 1 patient with a "positive" precipitin test. Goudie et al. (78) interpreted this as indicating the formation of non-aggregating antigen antibody complexes/

FIGURE 8

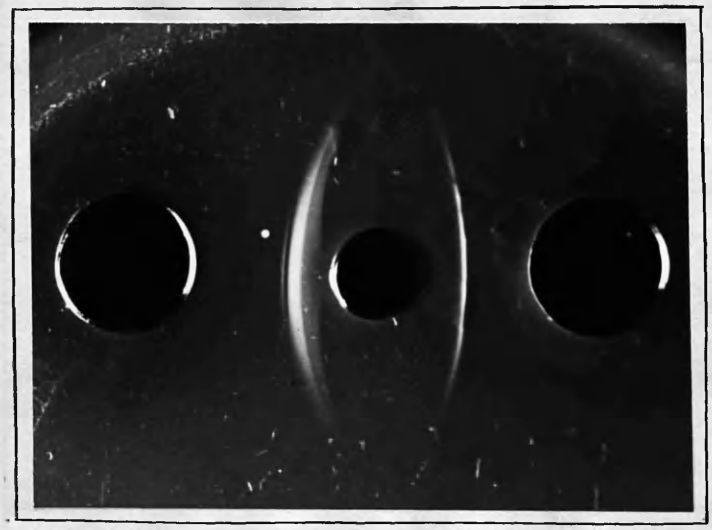
Double-line Precipitin Test

TABLE IV

Relation between the Precipitin Test and the Clinical Features in Auto-immune Thyroiditis.

FIG. 8

Left



Right

A double precipitin test is seen on the left,
with a single-line precipitate for comparison on the right.

Table IV.

Relation between the Precipitin Test and the Clinical Features in Auto-immune Thyroiditis.

Precipitin Test	(-)	(+)
Total No. of Patients	12	38
Sex ration (M/F)	1/11	3/35
Age (yrs)		
mean	52.9	52.5
range	37 - 70	28 - 67
Age at onset of goitre(yrs)		
mean	46.0	47.6
range	15 - 70	28 - 68
Assessed goitre size (g.)		
mean	104	102
range	50 - 300	50 - 200
Duration of goitre (yrs)		
mean	4.5	3.5
range	4m - 37	6 wks. - 19
Nodular goitre	8	14
Clinical status		
euthyroid	10	17
equivocally hypothyroid	0	3
hypothyroid	2	14

/complexes and suggested that this might also hold for the double-line precipitate (Fig. 8) which was seen in another patient. No untoward clinical features were noted in either of these patients and the histology of the thyroid in the patient with the clear-line precipitate was unremarkable.

No correlation was found between the results of the precipitin test and the clinical features of the disease (Table IV). However, patients with negative precipitin tests had a higher prevalence ($P < 0.1$) of nodular goitres and hypothyroidism was more frequent ($P < 0.5$) in patients with positive precipitin tests.

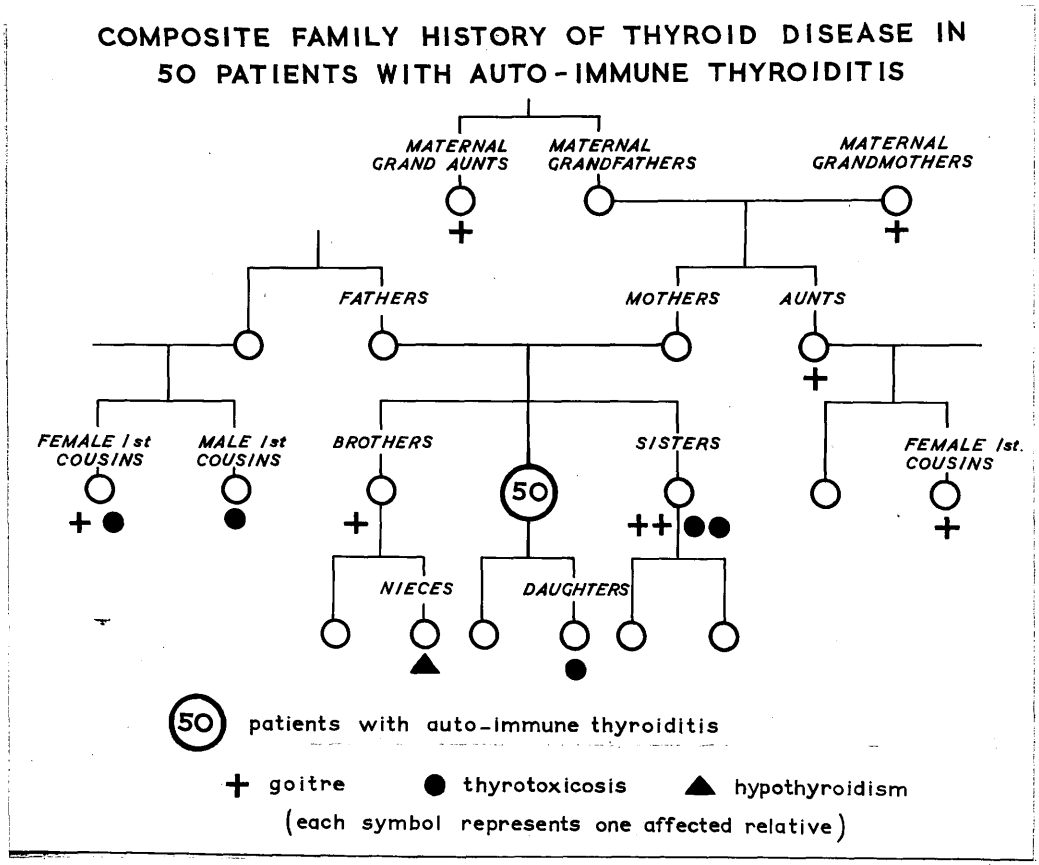
No definite correlation could be established between the presence or absence of a positive precipitin test and the natural progress of the disease. Thus, several patients with positive precipitin tests were observed for periods ranging from 4 to 18 months (mean 12.6 months) without any appreciable change in the size of the goitre and without the development of hypothyroidism (Appendices see). On the other hand, 2 patients with negative precipitin tests became hypothyroid 6 and 18 months respectively after their first visit to the clinic. These findings are in agreement with those of Roitt and Doniach (75), and lend support to the view that the precipitating auto-antibodies are not in themselves the direct cytotoxic agent.

The CF test was positive (+) in 3 patients (6%) and strongly positive (++) in 43 (86%); 2 patients (4%) had negative tests, and 2 had AC reactions. In general, patients with a positive precipitin test also had a positive CF test, but there were 2 exceptions - one with a negative CF test, and another with an AC reaction. Since most/

FIGURE 9

Composite Family History of Thyroid Disease in 50 Patients with Auto-immune Thyroiditis.

Fig. 9.


COMPOSITE FAMILY HISTORY OF THYROID DISEASE IN 50 PATIENTS WITH AUTO-IMMUNE THYROIDITIS
MATERNAL GRAND AUNTS
MATERNAL GRANDFATHERS
MATERNAL GRANDMOTHERS
FATHERS
MOTHERS
AUNTS
FEMALE 1st COUSINS
MALE 1st COUSINS
BROTHERS
50
SISTERS
FEMALE 1st. COUSINS
NIECES
DAUGHTERS
50 patients with auto-immune thyroiditis
goitre
thyrotoxicosis
hypothyroidism
(each symbol represents one affected relative)

/most patients had a positive CF test no conclusions can be drawn regarding its correlation with the clinical features of the disease. The findings are, however, consistent with 2 separate immune systems in auto-immune thyroiditis.

Only one patient had both a negative precipitin and CF test. This patient had a fibrous variant of auto-immune thyroiditis. Low titres of thyroid auto-antibodies have been reported in 4 patients with this condition by Roitt and Doniach (75). It is of interest that in the patient in this study high levels of gamma-globulins and abnormal serum flocculation tests were present and it is possible that a colloid antibody distinct from thyroglobulin might have been detected as described by Balfour et al. (79).

Familial and Genetic Aspects

It has long been recognised that different thyroid diseases, such as primary hypothyroidism, thyrotoxicosis, and non-toxic goitre, may arise in the same family (80). Dunning (81) has reported 3 patients with auto-immune thyroiditis in one family, and Lindsay et al. (12) found an increased prevalence of a family history of goitre in patients with auto-immune thyroiditis. A family history of thyroid disease was obtained in a much higher ($P < 0.05$) proportion of the patients (8 of 50) in the present study than in a control group (2 of 70); no common association was found with any particular thyroid disease (Fig. 9), although female relatives were, as expected, predominantly affected (see Appendices for further details).

Circulating/

/Circulating thyroid auto-antibodies were demonstrated by Hall et al. (82) in 22 of 39 siblings of 11 patients with auto-immune thyroid disease and this finding was interpreted by these authors as indicating that the predisposition to develop thyroid auto-antibodies is inherited as a dominant characteristic. Roitt and Doniach (83) similarly studied 64 close relatives of patients with auto-immune thyroiditis and found that of 33 with clinical evidence of thyroid disease 91 per cent. had thyroid auto-antibodies. In the remaining 61 relatives thyroid auto-antibodies were demonstrated in 30 per cent. In the present study precipitin and CF tests were performed in 17 female relatives of 8 patients with auto-immune thyroiditis (Appendices see). None of the sera had demonstrable precipitins, but 6 had positive CF tests; an incidence which is much higher ($P<0.02$) than that in a series of female hospital controls (27 of 243) studied in the same laboratory by the same methods (98).

Associated Illnesses

In the past most surgical studies have revealed little evidence of previous serious ill-health in patients with auto-immune thyroiditis (10,11,17,53); although isolated cases were reported in association with a wide variety of disorders, including disseminated tuberculosis (84), rheumatoid arthritis (63), iritis (84), Vitamin B deficiency (85), pemphigus (86) and pseudo-xanthoma elasticum (44). However, Furr and Crile (13) observed a frequent association with other ailments, in particular with hypertensive and ischaemic heart/

TABLE V

Associated Illnesses in Auto-immune Thyroiditis in the Present Study.

Table V.

Associated Illnesses in Auto-immune Thyroiditis.

Disease	No. of Cases	Disease	No. of Cases
Rheumatoid arthritis	7	Gastric carcinoma	1
Acquired haemolytic anaemia	1	Tuberculosis	1
Diabetes mellitus	2	Syphilis	1
Hypertension	1	Urticaria	1
Angina	2	Hay fever	3
Mitral stenosis	1	Vasomotor rhinorrhoea	2
Chronic Bronchitis	4	Drug allergy (penicillin)	1
Duodenal ulcer	1	Unexplained hepato-splenomegaly	1

/heart disease and "arthritis of undetermined aetiology". Beare (87) found a considerable proportion of his patients gave an antecedent history of rheumatic fever, rheumatoid arthritis, nephritis, and skin allergy. In a study of 24 patients reported by Luxton and Cooke (2) 6 patients had splenomegaly and 2 had a histologically-proven cirrhosis of the liver.

Recent study of the role of auto-immunisation in the pathogenesis of several diseases has aroused interest in the clinical associations of auto-immune thyroiditis. The co-existence of auto-immune thyroiditis with other diseases of suspected auto-immune aetiology has been reported. Thus, auto-immune thyroiditis has been associated with progressive hepatitis (2,88-90), nephrosis (91), acquired haemolytic anaemia (92-93), primary adrenal atrophy (94), and the connective tissue diseases (95). The associated illnesses in the 50 patients of the present study are summarised in Table V. It can be seen that an unexpectedly high incidence of rheumatoid arthritis was found (7 of 50 patients), and the significance of this will be discussed further in Chapter IV of the thesis. One of the patients had a Coombs-negative acquired haemolytic anaemia; another with a past history of gastric carcinoma had an unexplained hepato-splenomegaly. Two patients developed diabetes during the course of their illness, but precipitating pancreatic auto-antibodies of the type described by Thal et al. (96) were found in neither. The association of auto-immune thyroiditis with Paget's disease of the bone was brought forward by Luxton (97), but none of the patients of the present study had either radiological (i.e. X-ray of the skull, pelvis,/

/pelvis, lumbo-sacral spine and tibiae) or biochemical (i.e. raised serum alkaline phosphatase levels) evidence of the disease. Blizzard et al. (77) noted that penicillin-hypersensitivity is more frequent in patients with auto-immune thyroiditis, but the prevalence of allergic manifestations in the patients of the present study was no higher than would be expected in a random sample of the general population of similar age and sex distribution (99).

SUMMARY

The clinical features of auto-immune thyroiditis have been discussed in the basis of a study of 50 patients with the disease. The principle conclusions were as follows:-

(1) Auto-immune thyroiditis can no longer be regarded as a rare thyroid disease; it accounted for 4.5 per cent of all thyroid disorders in the present study.

(2) The disease predominantly affects middle-aged females, but the onset does not appear to be directly related to ovarian function.

(3) The commonest presentation is a complaint of neck swelling. The goitre is usually of insidious onset and may be associated with mild pressure symptoms. It is usually moderately enlarged and is characteristically "firm" in consistency. It may be either diffuse or nodular.

(4) Classification according to clinical status is arbitrary. Eighteen per cent. of the patients in the present study were obviously hypothyroid, but many of the clinically euthyroid patients had laboratory evidence of hypothyroidism.

(5) Auto-immune thyroiditis may occasionally represent the end-result of a "burnt-out" thyrotoxicosis and 6 per cent. of the patients in the present study gave a convincing history of thyrotoxicosis in the past.

(6) No correlation was found between the clinical features and progress of the disease and the results of the precipitin and CF thyroid auto-antibody tests; this is consistent with the view/

/view that these auto-antibodies are not the direct cytotoxic agent.

(7) A family history of thyroid disease and an increased prevalence of thyroid auto-antibodies in relatives of patients with auto-immune thyroiditis suggest that a genetic factor is involved in the pathogenesis of the disease.

(8) A variety of illnesses was associated with auto-immune thyroiditis in the present study, but only rheumatoid arthritis had an unexpectedly high prevalence (7 of 50).

Section 2.

A Skin Test in Auto-immune Thyroiditis.

TABLE I.

Clinical and Immuno-pathological Features of the Three Types of Skin Reactions.

Table I.

Clinical and Immuno-pathological Features of the Three Types of Skin Reactions.

Type of Skin	Immediate	Arthus	Delayed
Macroscopic appearance	Wheal and Erythema	Erythema and Induration	Erythema and Induration
Time of onset and of maximal intensity	0 - 60 minutes	6 - 24 hours	18 - 48 hours
Microscopic appearances	Vascular permeability and oedema, due to release of histamine or allied H-substance	Polymorphonuclear reaction with fibrinoid necrosis, haemorrhage and oedema. Occasional eosinophilic infiltration	Mononuclear reaction with occasional fibrinoid necrosis
Associated clinical condition	Hay fever, asthma	Serum sickness	Tuberculosis, brucellosis, histoplasmosis, lymphogranuloma, poison ivy and nickel dermatitis
Sensitizing material	Pollens	Soluble proteins and carbohydrates	Bacteria, viruses, plant materials, simple chemicals
Antibody	Present in serum as reagin. Non-precipitable and heat-labile	Precipitating antibody present in serum	Absent in serum, believed to be "cell-bound"
Transfer of sensitivity	With serum-Prausnitz-Kustner reaction	With serum	Not with serum, but with cells
Pharmacology	Antihistamines inhibit	Antihistamines do not inhibit	Antihistamines do not inhibit

INTRODUCTION.

The credit for first reporting the value of skin tests must go to Blackley (1), who, in 1873, showed that grass pollen rubbed into a scratch on the skin of a hay-fever patient caused local swelling, erythema, and irritation. Some 30 years later Dunbar (2) confirmed this observation and in 1915 Cooke (3) introduced the intradermal method of skin testing. Since these earlier observations skin reactions have been demonstrated to a wide variety of substances and appear to fall into 3 main types: firstly, the immediate type of skin response; secondly, the Arthus phenomenon; and thirdly, delayed-type hypersensitivity. The relevant details of these 3 types of skin responses are summarised in Table 1 and will now briefly be outlined.

Immediate-type Response

The immediate type of skin response is characterised by a wheal and flare appearing usually within one hour of injection of the allergin; it is commonly associated with the clinical syndromes of hay-fever and asthma and classically provoked by plant pollens. Histologically, the lesion is characterised by vascular permeability and oedema due to the release of histamine or allied H-substance as it can be inhibited by antihistamines. Circulating antibody is present in this type of reaction and is known as reagin; the response can only be transmitted by serum using the Prausnitz-Kustner reaction.

Arthus Phenomenon

The Arthus phenomenon was first described in the rabbit in 1903 (4)/

/(4). The skin response is usually of maximum intensity between 6 and 24 hours and is characterised histologically by an intense polymorphonuclear inflammation accompanied by haemorrhages, oedema, and fibrinoid necrosis. The Arthus reaction is invariably assoc-:iated with circulating precipitins, and can be transmitted by serum or plasma by technique of direct or reversed passive cutaneous anaphylaxis in the guinea-pig (5). The Arthus reaction is rare in clinical practice, but is seen after repeated injections of foreign serum.

Delayed Hypersensitivity Reactions

Skin reactions of the delayed type are classically seen in the tuberculin reaction, but also occur in a wide variety of bacterial, viral, and spirochaetal infections and with contact with certain plant substances and other chemical compounds (6). The term "delayed" stems from the latent period, usually 24 to 48 hours, which elapses from the time of application of the antigen until the appearance of the skin reaction. Histologically, this type of response is characterised by a mononuclear infiltration with little or no tissue destruction. Unlike the other 2 types of skin responses it is not associated with humoral antibodies and passive transmission cannot be achieved using either serum or plasma. "Cell-bound" antibodies are, however, present in delayed hypersensitivity and passive transfer can be carried out using cells of the leucocyte series (7). Delayed-type responses have been demonstrated in vascular tissues such as the cornea (8).

Skin Tests to Homologous or Autologous Antigens

Despite the wide application of skin-testing, little study has been done in skin sensitivity to homologous or autologous tissue antigens. In 1948 McPherson and Woods (9) using beef iris-pigment extracts as antigen demonstrated skin reactions in patients with sympathetic ophthalmia. Several workers have failed to demonstrate cutaneous allergy to synovial fluid in rheumatoid arthritis (10) and to extracts of colon in ulcerative colitis (11), but apart from these studies no other investigations of similar nature have been carried out in humans.

Cutaneous sensitivity to homologous testicular extracts was observed by Freund et al. (12) in experimental aspermatogenesis in guinea-pigs; and delayed skin to spinal cord antigen reactions have been reported by Waksman and Morrison (13) in experimental encephalo-:myelitis in rabbits. In experimental thyroiditis in rabbits Witebsky et al. (14) carried out skin tests and "in several instances positive reactions were observed with the thyroid extracts. The reactions belonged to the delayed type, being strongest about 3 days after injection". No other details were, however, given.

Personal Observations

The present investigation was undertaken in order to determine whether skin reactions might follow the intradermal injections of thyroid antigens in patients with auto-immune thyroiditis. In order to assess the diagnostic value of any such reactions skin tests were also carried out in patients with other thyroid diseases and in control subjects.

TABLE II.

Results of Precipitin Tests and Skin Reactions to Sterile Thyroid Extract in 56 Patients.

TABLE II.

Results of Precipitin Tests and Skin Reactions to Sterile Thyroid Extract in 56 Patients.

Diagnosis	Case No.	Precipitin Test	Skin Reaction
Auto-immune Thyroiditis	1 - 8	+	+ +
	9	+	+
	10	+	-
	11	-	+
	12	+	-
Primary Hypo-thyroidism	13, 14	+	+ +
	15	+	-
	16, 17	-	+
	18 - 21	-	-
Thyrotoxicisis	22	+	-
	23 - 31	-	-
Simple Non-toxic Goitre	32 - 35	-	-
Thyroid Cancer	36	-	-
Unclassified	37	-	+
Controls	38	-	+
	39 - 56	-	-

Skin Reaction: (-) negative; (+) weakly positive; (++) strongly positive.

Skin Tests

Subjects. Skin tests were performed on 56 patients, of whom 37 (3 males and 34 females), aged 20 to 68 years, had thyroid disease, and 19 (3 males and 16 females), aged 41 to 82 years, served as controls. The 37 patients with thyroid disease included 12 patients with auto-immune thyroiditis, 9 with primary hypothyroidism, 10 with thyrotoxicosis, 4 with simple goitre, and one with thyroid carcinoma. The clinical and histological criteria for diagnosis of auto-immune thyroiditis were as described in the previous section. One patient did not readily fit into any of the diagnostic groups and was recorded as "unclassified". (Table II). This patient (case 37) had been treated for 35 years with thyroid extract. She was euthyroid when I saw her but she gave a history typical of hypothyroidism before treatment. The clinical details of the 56 patients studied are summarised in the appendices.

Antigen for skin testing.* A sterile saline extract was prepared from the surgical excised thyroid of a thyrotoxic patient by the method previously described by Goudie et al. (15). The extract was then passed through a Seitz filter, dispensed in volumes of 0.5 to 1.0 ml., and stored at -15 degrees C. Samples were cultured under both aerobic and anaerobic conditions at 20 degrees C. and 37 degrees C. for 7 days to ensure sterility.

Skin tests. The tests were carried out on the volar aspect of the forearms. Thirty-five patients received 3 intradermal injections; (a)/

* I am grateful to Dr. R.B. Goudie for the preparation of this antigen.

TABLE III.

Relationship of Precipitating Antithyroid Antibodies to Results of Skin Tests with Saline Extract of Thyroid Tissue.

TABLE III.

Relationship of Precipitating Antithyroid Antibodies to Results of Skin Tests with Saline Extract of Thyroid Tissue.

Precipitin Test	Skin reaction (no. of cases)		
	Negative	Weakly Positive	Strongly Positive
+	4	1	10
-	36	5	0

/(a) containing 0.2 ml. of antigen, (b) containing 0.2 ml. of antigen to which had been added 0.05 ml. of a suspension of cortisone acetate ('Cortelan'), and (c) containing 0.2 ml. of sterile 0.9% saline solution and 0.05 ml. of cortisone acetate. This procedure was based on the modification of the tuberculin test described by Citron and Scadding (16). The remaining 21 patients received the first injection only. The tests were read after 24 hours, since the reaction was usually maximal at this time. The results were classified as negative (no reaction or an area of erythema of less than one centimetre diameter), weakly positive (an area of erythema one centimetre or more in diameter), or strongly positive (an area of erythema one centimetre or more in diameter with central induration). Because the outline of the skin reaction was irregular, the size of the response was recorded as the mean of the maximum and minimum diameters.

Thyroid Auto-antibody tests. Precipitin and CF tests were performed by the methods described earlier, and were carried out in all patients on the serum obtained before skin testing and also in 46 patients one to 24 weeks after the skin test.

Results

The results of the skin reactions in relation to the precipitin and CF tests in 56 patients tested are summarised in Tables II and III respectively. Table IIIshows that of the 15 patients with positive precipitin tests, 10 had strongly positive skin tests and 1 had a weakly positive reaction. Of the remaining 4 precipitin positive/

TABLE IV.

Results of Complement-Fixation (C.F.) Tests to Sterile Thyroid Extract in 56 Patients.

TABLE V.

Relationship of Complement-fixing (C.F.) Antithyroid Antibodies to Result of Skin Tests with Saline Extract of Thyroid Tissue.

TABLE IV.

Results of Complement-Fixation (CF) Tests to Sterile Thyroid Extract in 56 Patients.

Diagnosis	Case No.	C.F. Test	Skin Reaction
Auto-immune Thyroiditis	1	+	+ +
	2 - 8	+ +	+ +
	9	+	+
	10	+ +	-
	11	+ +	+
	12	+ +	-
Primary Hypothyroidism	14	-	+ +
	15, 20, 21	-	-
	13	+	+ +
	18, 19	+	-
	16, 17	+ +	+
Thyrotoxicosis	22	+ +	+
	23	-	-
	24 - 26	+	-
	27 - 31	+ +	-
Simple Non-Toxic Goitres	32 - 35	-	-
Thyroid Cancer	36	-	-
Unclassified	37	-	+
Controls	38	+	+
	39, 40	+	-
	41	+ +	-
	42 - 56	-	-

Footnote: Skin Reaction: (-) negative; (+) weakly positive; (++) strongly positive.

TABLE V.

Relationship of Complement-fixing (CF) Antithyroid Antibodies to Result of Skin Tests with Saline Extract of Thyroid Tissue.

C.F. Test	Skin Reactions (no. of cases)		
	Negative	Weakly Positive	Strongly Positive
+ +	8	4	7
+	7	2	2
-	24	1	1

/positive patients with negative skin reactions, 3 are of special interest. One patient with histologically proven auto-immune thyroiditis (case 10) had an atypicalpH-dependent precipitin reaction (17). The second (case 15) who had primary hypothyroidism, had a skin reaction which was delayed for 48 hours. Because of the criteria laid down, this response was classified as negative. The third patient (case 22) was unequivocally thyrotoxic.

Of the 41 patients with negative precipitin tests, 36 had negative skin reactions and 5 had weakly positive skin reactions (Table III). The details of this latter group are as follows. One patient (case 11) had had a partial thyroidectomy performed twice previously, and auto-immune thyroiditis was diagnosed histol-:ogically on the second occasion. After the second operation the patient became hypothyroid and was treated with thyroxine. Cases 16 and 17 had primary hypothyroidism; case 37 was unclassified but gave a past history of hypothyroidism; and case 38, a female of 82 years with pernicious anaemia, was one of the control series.

A less clear association was found between the results of the skin reactions and the CF auto-antibody tests (Tables IV and V). Thus, 2 of the 26 patients with negative CF tests had positive skin reactions and one of these (case 14) with primary hypothyroidism and a positive precipitin test had a strongly positive skin reaction. Moreover, of the 30 patients with positive (+ and ++) CF tests only 15 had positive skin tests.

The effect of adding cortisone to the inoculum was variable. There was a tendency for the skin reaction to be enhanced, as shown/

FIGURE 1.

Comparison of Mean Diameters of Skin Reactions to Injections of Thyroid Extract with and without Cortisone Acetate.

FIGURE 2.

Examples of Strongly Positive Skin Reactions.

FIGURE 3.

Example of a Weakly Positive Skin Reaction.

FIGURE 4 (a and b)

Histological Features of a strongly Positive Skin Reaction.

FIG. 1

Comparison of Mean Diameters of Skin Reactions to Injections of Thyroid Extract with and without Cortisone Acetate.

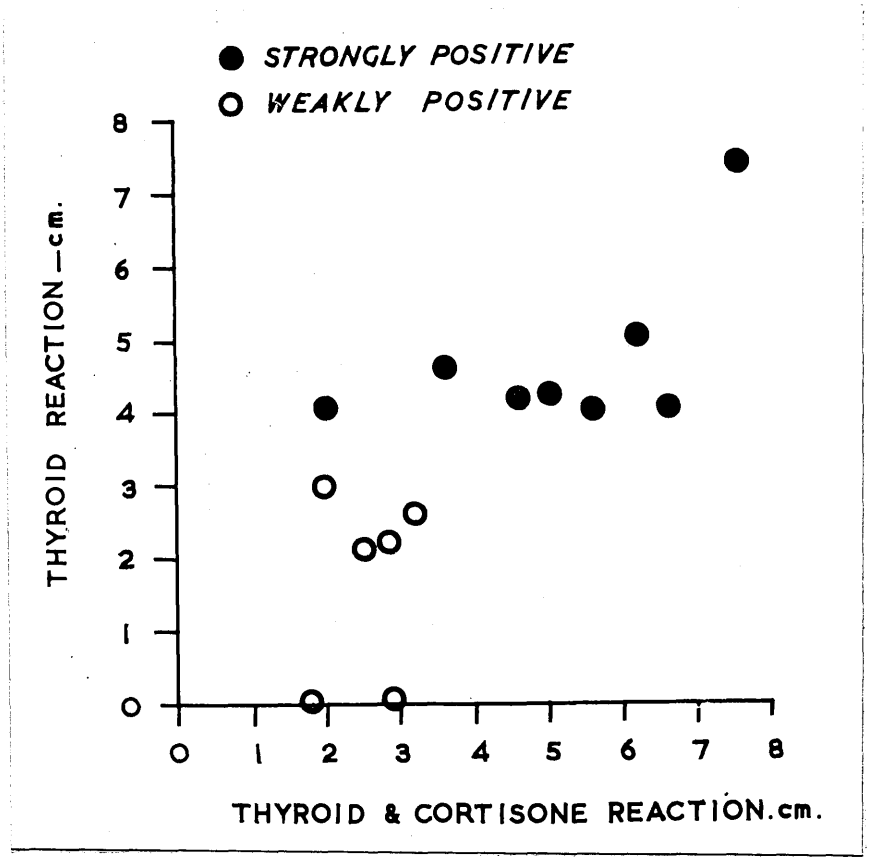
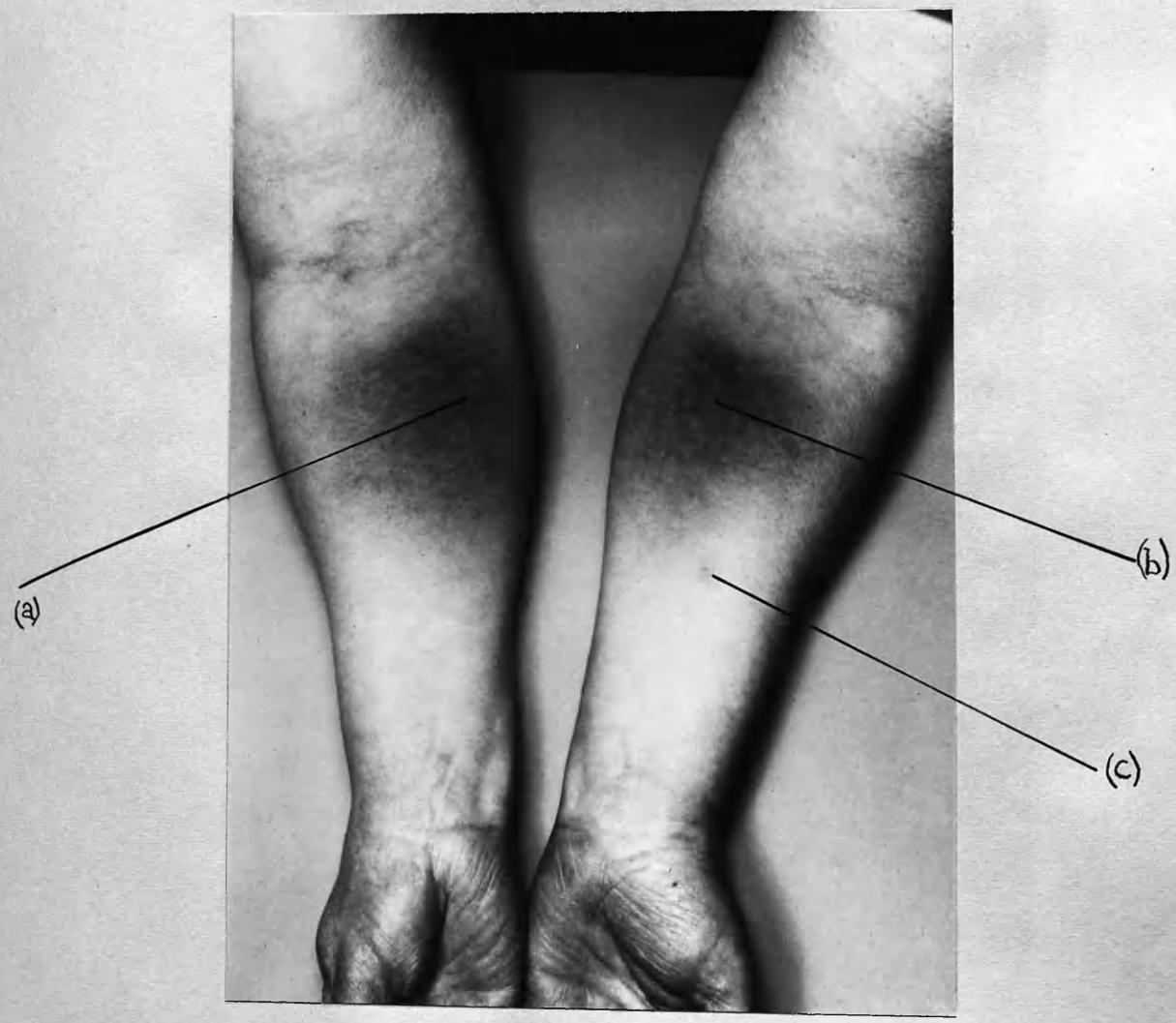


FIG. 2

Examples of a Strongly Positive Skin Reaction



(a) Strongly positive with antigen alone.

(b) Strongly positive with antigen plus cortisone.

(c) Effect of control injection of cortisone acetate in saline.

FIG. 3.

Example of a Weakly Positive Skin Reaction.

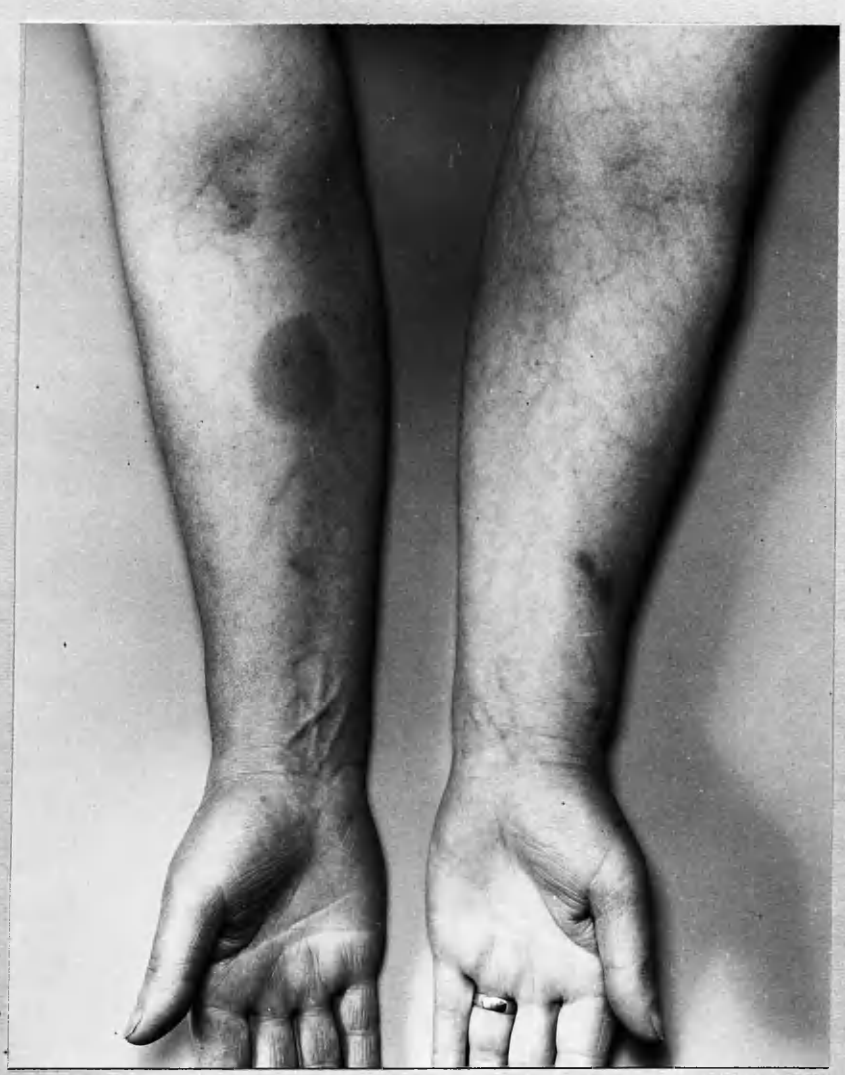


FIG. 4 (a) Low Power view of dermis, showing diffuse infiltration with inflammatory cells. (Haematoxylin and eosin x 90).

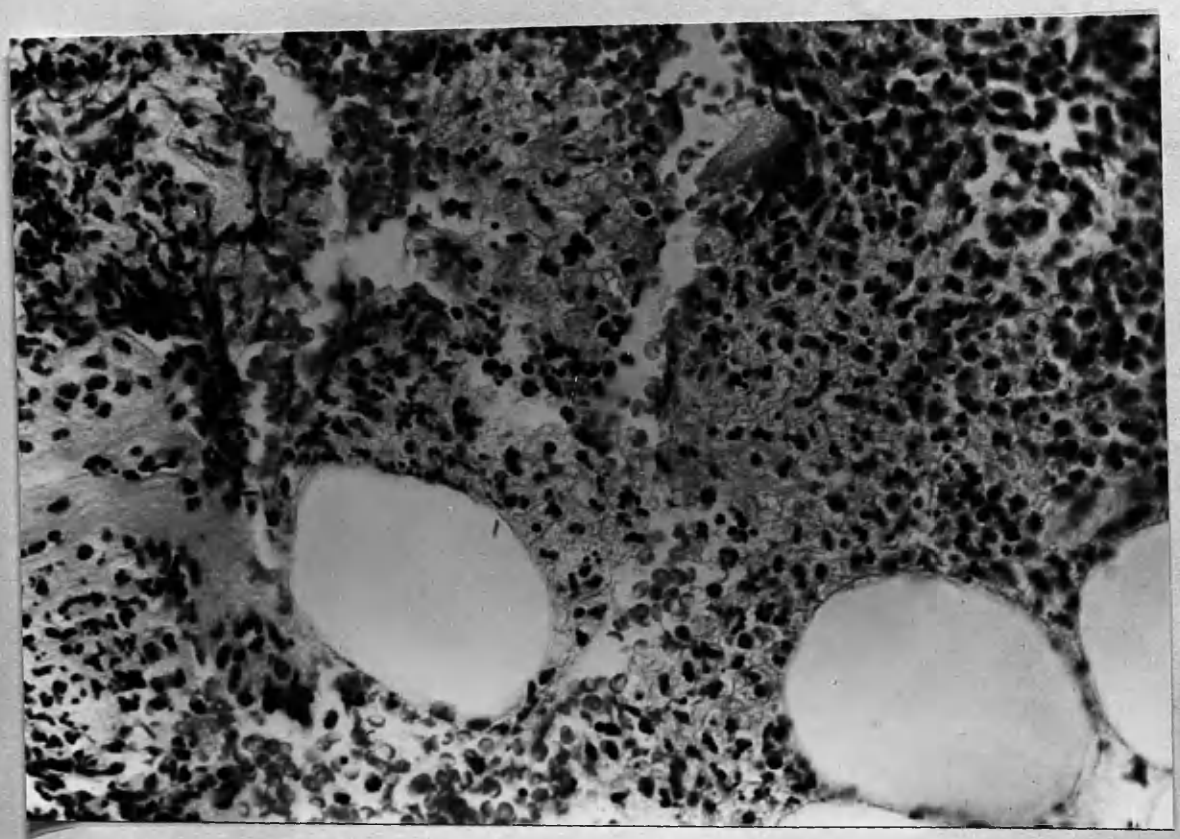


FIG. 4(b) High power view of dermis, showing dense inflammatory cell infiltration, haemorrhages, tissue necrosis, and fibrinous exudates. Inflammatory cells consist mainly of polymorpho-nuclear leucocytes, many of which are dead or have pyknotic nuclei. (Haematoxylin and eosin x 520).

/shown in Fig. 1 where the mean diameters of the reaction to thyroid extract alone have been plotted against the measurements obtained when cortisone was added. In 2 subjects (cases 12 and 22) a weakly positive reaction was produced with thyroid extract and cortisone, whereas there was a negative reaction with thyroid alone. In no instance did the intradermal injection of cortisone acetate and saline produce a skin reaction.

An example of a strongly positive response is shown in Fig. 2 and of a weakly positive reaction in Fig. 3. When indurated, the lesions were often painful and tender. The diameters of the indurated areas varied between 2.5 and 7.25 cm. (average 4.3 cm.), and in those reactions where erythema alone was present the diameters of the lesions were between 1.7 and 3.5 cm. (average 2.5 cm.). Resolution was rapid, being complete in most instances in 48 to 72 hours. In no case was there vesication, suppuration, or ulceration, and no local sequelae were observed. An immediate erythematous flare which faded rapidly was noted in several patients including controls. This bore no relationship to the clinical or serological findings, or to the type of skin reaction at 48 hours, and was not amenable to passive transfer by the Prausnitz-Kustner reaction in 4 patients studied.

Biopsy of a strongly positive skin reaction showed extensive oedema and haemorrhage into the dermis and subcutis. There was marked emigration of polymorph neutrophils, many of which were necrotic, together with a few eosinophil leucocytes (Fig. 4). Histologically, weakly positive and negative skin reactions were much less extensive/

/less extensive but they were qualitatively similar to the strongly positive reaction seen in figure 4. The intradermal injection of 0.2 ml. of 0.9% saline solution, or of an equal volume of an individual's own plasma, produced a similar histological reaction to that following the injection of antigen in a control subject with a negative skin test.

Discussion

Strongly positive skin reactions characterised by both erythema and induration after intradermal injections of human thyroid tissue extract were seen only in patients with thyroid disease who had precipitating thyroid auto-antibody in the serum. A weakly positive reaction with erythema only was also seen in one such patient. Presumably the skin reaction in all these patients was a manifest-:ation of a local antigen antibody reaction occurring between the thyroglobulin in the inoculum and the circulating precipitins. This interpretation may also hold for the 5 patients who gave a weakly positive reaction but who had no demonstrable precipitinsin the serum; 4 of these had a form of thyroid disease in which precipitins are known to occur and the fifth (case 38) possibly had latent focal Hashimoto-like changes in the thyroid since she was a euthyroid, elderly female with a positive thyroid CF test (18). The lack of association between the skin reaction and precipitating antibody in these patients may thus be due to the known insensitivity of the precipitin reaction. Circulating antibodies might have been demonstrated in these patients by the TRC method, since this is more/

/more sensitive in detecting thyroglobulin auto-antibodies.

The association between the skin reactions and the CF auto-antibodies (Tables IV and V) was less clear than with the precipitin test, and makes it unlikely that anti-microsomal auto-antibodies were involved. Thus it is probable, but not certain, that the skin changes seen are those of an Arthus phenomenon. Precipitating antibody is essential for this phenomenon; as shown above, this type of antibody was present in all the patients with strongly positive skin reactions and it may well have been present even though undetected in those patients showing a weakly positive reaction. The relatively slow development, the macroscopic appearance, and the histological features of the skin response are in keeping with the Arthus phenomenon, but the validity of the histological evidence is doubtful since the control studies using either saline, autologous plasma, or thyroid tissue extract produced a qualitatively similar, but less marked, microscopic lesion. Attempts to transmit sensitivity passively to the rabbit have been unsuccessful (19), although Ovary et al. (20) and Lessof et al. (21) have demonstrated passive cutaneous anaphylaxis in the guinea-pig with precipitating anti-thyroglobulin sera but not with complement-fixing thyroid sera.

As shown in Fig. 1, the addition of cortisone to the intradermal injection enhanced the skin reaction. Citron and Scadding (16) observed a similar effect in tuberculin skin testing, and they suggested that cortisone prolonged the retention of the inoculum at the site of injection, thus increasing the sensitivity of the test.

This/

/This explanation might also apply to the results in the present investigation; particularly those of the 2 precipitin positive patients in cases 11 and 20 in whom weakly positive skin reactions developed when cortisone was included in the injection.

This study was the first in which local reactions were observed after the intradermal injection of thyroid extract in patients with spontaneous thyroid disease although, as previously mentioned, Witebsky et al. (14) had noted a delayed type of skin reaction in rabbits immunised with homologous thyroid tissue. Witebsky (22) and Barwell and White (23) have since confirmed my findings. However, Witebsky (22), and also the Lancet (24), and Scottish Medical Journal (25), have inclined to the view that the reactions are manifestations of "cell bound" or delayed hypersensitivity, although there is nothing in the present study which supports such an interpretation.

Although the intradermal test may help to elucidate the auto-immune phenomena of human thyroid disease it should not be used as a diagnostic test. The precipitin test is equally effective, and there is a small but appreciable risk of transmitting homologous serum jaundice by the injection of human thyroid extract (26). Furthermore, such an injection in a susceptible individual may induce thyroid antibody formation. Precipitin tests were performed one to four weeks after skin testing in 46 patients, and in 6 of these with thyroid disease changes were observed in the precipitin reaction. Three patients with auto-immune thyroiditis (cases 1, 4, 8) the reaction became weaker or negative. In one patient with thyrotoxicosis/

/thyrotoxicosis (case 30) a weak precipitin reaction developed 3 weeks after the skin test, but this was no longer present 2 weeks later. Case 15 with primary hypothyroidism and case 22 with thyrotoxicosis both had weakly positive precipitin reactions which became stronger after the skin test. Unfortunately, the significance of the changes in the precipitin reaction in these patients is doubtful since adequate serial studies to ascertain the constancy of the reaction before skin testing were not made.

SUMMARY

Intradermal tests, using a saline extract of human thyroid tissue as antigen, were carried out on 56 subjects of whom 37 had thyroid disease. The skin reactions were classified as strongly positive or weakly positive. There was a close correlation between the presence of circulating thyroid precipitins and strongly positive skin reactions.

In general, positive skin reactions were observed in patients with auto-immune thyroiditis or with primary hypothyroidism. With one exception positive reactions did not occur in individuals without clinical evidence of thyroid disease. The skin reaction was compatible with an Arthus phenomenon, and the addition of cortisone acetate to the inoculum tended to increase the size of the reaction.

These findings show that thyroid antigen is capable of producing an abnormal tissue reaction in certain patients with auto-immune thyroid disease. The demonstration of tissue damage at the site of inoculation of the thyroid antigen might be interpreted as indicating that some of the changes seen in the thyroid in auto-immune thyroiditis might be the result of an antigen antibody reaction. No evidence has been found that "cell bound" or delayed hypersensit-:ivity is present in auto-immune thyroiditis.

Section 3.

Biochemical Studies

Historical Aspects

In 1952 Fromm et al. (1) described raised gamma-globulins in 4 patients with auto-immune thyroiditis. Abnormal colloidal gold curves were reported in 2 patients with auto-immune thyroiditis by Cooke and Wilder (2) - an observation which was later extended by Skirpan et al. (3). These authors studied the colloidal gold curves and serum cholesterol levels in 19 patients with auto-immune thyroiditis and found abnormal colloidal gold tests in 15; they concluded that the colloidal gold test seemed "to be more sensitive than serum cholesterol determinations in establishing a diagnosis of thyroid failure without goitre".

In 1956 Luxton and Cooke (4) reported that in 21 of 24 patients suffering from auto-immune thyroiditis the colloidal gold and thymol turbidity tests yielded abnormal results which reverted to normal after treatment with thyroid extract in from 4 to 26 months. They considered that these flocculation tests might prove of value in the diagnosis of goitre, as they had "not seen positive results in simple, toxic, or malignant goitres".

Luxton and Cooke (4) also studied the serum albumin and globulin levels in 20 patients with auto-immune thyroiditis; 6 showed an increase in globulin. They also carried out electrophoresis of the serum proteins in 6 patients and found high gamma-globulin levels in 6.

Changes in the electrophoretic pattern of the serum proteins were/

/were observed in 16 of 20 patients with auto-immune thyroiditis studied by Skillern et al. (5) in 1956; these consisted of decreases in the serum albumin to low or low-normal levels and elevation of the gamma-globulins. Treatment with desiccated thyroid induced a decrease in the gamma-globulins although not usually to normal levels, and an increase in the value of the serum albumin. Skillern et al. (5) also found abnormal colloidal gold curves in 20 of 25 patients, abnormal thymol turbidity tests in 7 of 12 patients, and abnormal zinc sulphate turbidity levels in 6 of 12 patients. These changes were attributed by these authors to the effects of thyroxine deficiency.

In 1957 Roitt and Doniach (6) correctly associated the biochemical disturbances with the auto-immune process. Empirical liver function tests and differential serum protein determinations were carried out by Doniach and Hudson (7) in 11 patients with auto-immune thyroiditis, in 21 patients with simple non-toxic goitre, 4 patients with thyro-:toxicosis, and 8 patients with primary or secondary hypothyroidism who acted as controls. Raised gamma-globulins were found in almost all the patients with auto-immune thyroiditis, although the total serum albumin and globulin levels were normal. The colloidal gold, thymol turbidity, and zinc sulphate turbidity tests also yielded abnormal results in almost all the patients with auto-immune thyroid-:itis. In general, these tests gave concordant results although "in a few patients the colloidal gold results disagreed with other flocculation reactions and with the results of electrophoresis". Normal gamma-globulins and serum flocculation tests were found in the/

/the 21 patients with simple goitre and in 3 patients suffering from thyroid neoplasms. On this evidence Doniach and Hudson (7) concluded that "paper electrophoresis in combination with flocculation tests provide diagnostic help and distinguish lymphadenoid goitre from simple non-toxic goitre and from carcinoma of the thyroid".

Doniach and Hudson (7) also studied the serum flocculation tests and serum protein changes in a post-operative group of 25 patients suffering from auto-immune thyroiditis. They found that the serum proteins were normal in most patients although "there was a lag of several months before this reversal took place". Similarly the serum flocculation tests were found to return to normal after removal of the goitre.

In 1958 Greene et al. (8) reported their experience with serum flocculation tests and electrophoresis of the serum proteins in thyroid diseases. These authors found the colloidal gold curve abnormal in 87.5% of their patients with auto-immune thyroiditis as compared with 37.3% in other thyroid diseases, and concluded that this test was "a fairly good, but not invariably reliable criterion of Hashimoto's disease when other causes of abnormality have been excluded". Greene et al. (8) also found raised gamma-globulin levels and decreased serum albumin values on electrophoresis of the sera of 8 patients with auto-immune thyroiditis, and suggested that the albumin/gamma-globulin ratio might be a useful diagnostic criterion for the disease. The results of the findings in a post-operative group of patients with auto-immune thyroiditis confirmed the previous observation of Doniach and Hudson (7) that thyroidectomy causes the electrophoretic pattern to return to normal.

Shulman et al. (9) could find no specific abnormality in the electrophoretic pattern in 51 patients whom they studied; thus, 20 had elevated gamma-globulins, 6 raised beta-globulins, 23 raised alpha-2 and 10 raised alpha-1 globulins, and the serum albumin was lowered in 6. Moreover, these workers could find no correlation between the gamma-globulin levels and the titres of TRC auto-antibodies and concluded that "such analyses are of no real clinical value".

Personal Observations

Although consistent abnormalities have been described in auto-immune thyroiditis by a number of workers, it is difficult to evaluate their extent because in most of the studies the number of patients has been small and the control data inadequate for statistical assessment. The purpose, therefore, of the present section of the thesis is to study the serum protein abnormalities in this disease and to compare them with the changes occurring in other thyroid diseases which may occasion diagnostic difficulty, notably simple non-toxic goitre and thyroid neoplasm. Since many patients with auto-immune thyroiditis are hypothyroid and since a few present with the clinical features of thyrotoxicosis the serum protein changes in primary hypothyroidism, and thyrotoxicosis have been studied. Also, since changes in the serum proteins are reflected in the standard serum flocculation tests and the diagnostic use of the latter has been advocated (4,7,10), this group of tests has also been evaluated. Opportunity has also been taken to assess the value of the erythrocyte sedimentation rate (ESR) in the diagnosis of auto-immune thyroiditis,/

TABLE I.

Results of Determinations and Electro-phoresis of of the Serum Proteins in Thyroid Disease.

TABLE II.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rates in Thyroid Disease.

TABLE I.

Results of Determinations and Electrophoresis of the Serum Proteins in Thyroid Disease.

Clinical Group.	Total No. of Cases	Albumin (g./100 ml.)		Globulin (g./100 ml.)		Globulin Fractions (g./100 ml.).							
						α_1		α_2		β		γ	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Normals.	26	5.2	± 0.4	1.9	± 0.3	0.20	± 0.05	0.43	± 0.09	0.55	± 0.11	0.74	± 0.15
Auto-immune Thyroiditis.	41	4.2	± 0.4	2.4	± 0.6	0.20	± 0.09	0.44	± 0.13	0.57	± 0.12	1.25	± 0.50
Primary Hypothyroidism.	40	4.3	± 0.4	2.0	± 0.5	0.18	± 0.07	0.40	± 0.18	0.65	± 0.24	0.83	± 0.23
Simple Goitre	33	4.9	± 0.5	1.9	± 0.3	0.20	± 0.12	0.40	± 0.09	0.51	± 0.10	0.79	± 0.14
Thyrotoxicosis.	37	4.1	± 0.4	1.9	± 0.4	0.18	± 0.04	0.37	± 0.17	0.52	± 0.13	0.82	± 0.19
Thyrotoxicosis with Exophthalmic Ophthalmoplegia.	16	4.1	± 0.4	1.9	± 0.4	0.20	± 0.06	0.43	± 0.16	0.50	± 0.08	0.82	± 0.19
Treated Thyrotoxicosis.	16	4.7	± 0.4	1.8	± 0.2	0.19	± 0.04	0.37	± 0.15	0.50	± 0.07	0.77	± 0.19
Thyroid Neoplasm.	15	4.5	± 0.6	1.9	± 0.2	0.21	± 0.05	0.50	± 0.10	0.46	± 0.06	0.78	± 0.10

TABLE II.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rates in Thyroid Disease.

Clinical Group.	Thymol Turbidity. (normal 0 - 2 units).					Thymol Flocculation. (normal 0 units).					Cephalin Cholesterol (normal 0).				
	0 - 2	3 - 5	5	Total No.	% Abnormal	0	1 - 2	3 - 4	Total No.	% Abnormal	0	+ and ++	+++	Total No.	% Abnormal
Auto-immune Thyroiditis.	11	16	14	41	73.2	18	8	15	41	56.1	8	6	8	22	63.6
Primary Hypothyroidism.	42	13	0	55	23.6	48	5	2	55	12.7	26	5	1	32	18.8
Simple Goitre.	118	9	0	127	7.1	125	2	0	127	1.6	44	15	1	60	26.7
Thyrotoxicosis.	153	13	0	166	7.8	150	12	0	162	7.4	56	31	12	99	43.4
Thyrotoxicosis with Exophthalmic Ophthalmoplegia.	15	0	0	15	0	14	1	0	15	6.7	2	1	0	3	33.3
Treated Thyrotoxicosis.	11	3	0	16	18.8	15	1	0	16	6.3	4	2	1	8	37.5
Thyroid Neoplasm	15	1	0	16	6.3	15	1	0	16	6.3	2	0	0	2	0

Clinical Group.	Colloidal Gold (normal 0 - 1 units).					Zinc Sulphate Turbidity (normal 5 - 12 units).					E.S.R. (normal 0 - 12 mm./first hr.)			
	0 - 1	2 - 3	4 - 5	Total No.	% Abnormal	5 - 12	12 - 25	25	Total No.	% Abnormal	Mean	Range	Total No.	% Abnormal.
Auto-immune Thyroiditis.	13	6	21	40	67.5	5	16	7	28	82.1	23	4 - 78	41	68.3
Primary Hypothyroidism.	19	15	7	41	53.7	11	12	0	23	52.2	19	3 - 55	43	62.8
Simple Goitre.	50	33	21	104	51.9	28	15	1	44	36.4	7	1 - 20	106	6.7
Thyrotoxicosis.	58	46	34	138	58.0	36	21	0	57	36.9	6	1 - 19	134	7.5
Thyrotoxicosis with Exophthalmic Ophthalmoplegia.	7	4	3	14	50.0	6	6	0	12	50.0				
Treated Thyrotoxicosis.	7	6	3	16	56.3	6	2	0	8	25.0				
Thyroid Neoplasm	5	4	3	12	58.3	7	3	0	10	30.0	26	5 - 68	15	66.7

/thyroiditis, since this has been found either normal (11,12) or moderately elevated (7,13-15).

Materials and Methods

Serum protein analyses were carried out in 28 normal controls and 182 patients with thyroid disease listed in Table 1 (see Appendices for further details). The latter included: 41 patients with auto-immune thyroiditis, 40 patients with primary hypothyroidism, 33 patients with simple non-toxic goitre, 69 patients with thyrotoxicosis, including 16 patients with exophthalmic ophthalmoplegia and 16 euthyroid patients after various forms of therapy, and 15 patients with thyroid neoplasm. Serum flocculation tests were also carried out in a total of 420 patients with thyroid disease (Table II) who included: 41 with auto-immune thyroiditis, 55 with primary hypothyroidism, 127 with simple non-toxic goitre, 181 with thyrotoxicosis including 15 with exophthalmic ophthalmoplegia, and 16 euthyroid after treatment, and 16 patients with thyroid neoplasm (see Appendices for further details). The ESR was carried out in a total of 339 patients with thyroid disease. (Table II).

The diagnosis of auto-immune thyroiditis, simple non-toxic goitre and thyroid neoplasm, was based on the criteria described in this Chapter of the thesis. The diagnosis of thyrotoxicosis (16,17) and primary hypothyroidism (17) were based on the methods described elsewhere. Patients with systemic disease, which might have been associated with changes in the serum proteins, were excluded from the study.

Serum protein estimations*/

/Serum protein estimations* were carried out by the biuret method of Gornall et al. (18). Filter paper electrophoresis was performed on serum using the horizontal strip method; after staining, quantitative evaluation of the protein pattern was carried out using an "E.E.L." scanner. The percentage value thus found was expressed as g. per 100 ml. of serum from the total value of the serum globulin.

The serum flocculation tests were carried out by the standard laboratory methods and included thymol turbidity (19) and flocculation (20), zinc sulphate turbidity (21), cephalin cholesterol (22), and colloidal gold (23) reactions. The ESR was performed by the method of Westergren (24).

Tests for thyroid auto-antibodies were carried out by both precipitin and CF methods as described in Section 1 of this Chapter.

Results

The results of the serum protein determinations are summarised in Table 1 and the serum flocculation tests and the ESR in Table II.

Auto-immune thyroiditis. The mean serum albumin in the patients with auto-immune thyroiditis was 4.2 g. per 100 ml. (SD $\pm$ 0.4) which was significantly lower ($P < 0.001$) than the mean value of 5.2 g. per 100 ml. (SD $\pm$ 0.4) found in the normal subjects. The mean serum globulin of 2.4 g. per 100 ml. (SD $\pm$ 0.6) in the former was significantly higher ($P < 0.001$) than the normal mean value of 1.9 g. per 100 ml. (SD $\pm$ 0.3). This increase in total globulins was entirely due/

* I am grateful to Dr. E.B.Hendry and his staff of the Biochemistry Department of the Western Infirmary for carrying out all the serum protein estimations and serum flocculation tests reported in this section.

/due to an increase in the gamma-globulin fraction ($P < 0.001$). Twenty-two of the 36 patients (61 per cent.) in whom electrophoresis was performed had gamma-globulin values which exceeded the highest value (1.0g. per 100 ml.) found in the normal group (see Appendices). There was a highly significant correlation between the goitre size and the levels of gamma-globulin ($r = 0.34$, $P < 0.001$).

The various serum flocculation tests were abnormal in 56 to 82 per cent. of patients with auto-immune thyroiditis (Table II) and the mean ESR (23 mm. in the first hour) was raised. The ESR exceeded the upper limit of the normal range (12 mm. in the first hour) in 27 of the patients (68.3 per cent.). There was a correlation between the thymol turbidity results and the levels of gamma-globulins ($r = 0.385$, $P = 0.02$).

Primary Hypothyroidism. The mean serum albumin in the patients with primary hypothyroidism was 4.3 g. per 100 ml. (SD $\pm$ 0.4), which was significantly lower ($P < 0.001$) than the normal mean value of 5.2 g. per 100 ml. (SD $\pm$ 0.4). The total serum globulin, on the other hand, was only slightly increased, although there was a suggestive increase in the beta ($P < 0.1$) and gamma ($P < 0.1$) globulins. The trends were present to a greater extent in patients with a positive precipitin test, but the small number (8 patients) does not permit statistical analysis. Seven of the 40 patients (17 per cent.) had a serum gamma-globulin value which exceeded 1.0 g. per 100 ml.

The various serum flocculation tests were positive in 12.7 to 53.7 per cent. of the patients (Table II) and the mean ESR (19 mm. in the/

/the first hour) was increased. The ESR exceeded the upper limit of the normal range in 27 of 43 patients (62.8 per cent.). The finding of a raised ESR in some cases of primary hypothyroidism is in agreement with the observations of MacAlpine (25) and Lillington et al. (26).

Simple Non-toxic Goitre. The mean serum albumin was 4.9 g. per 100 ml. (SD $\pm$ 0.5) in patients with simple non-toxic goitre, which was slightly, but significantly, lower ($P < 0.02$) than the mean value of the control series. The total globulins and the different globulin fractions did not, however, differ significantly from the normal. Only 2 of the 33 patients (6 per cent.) had gamma-globulin levels exceeding 1.0 g. per 100 ml.

The serum flocculation tests were abnormal in only a few patients with the exception of the cephalin cholesterol, zinc sulphate turbidity, and colloidal gold tests, which were abnormal in 26.7 per cent., 36.4 per cent., and 51.9 per cent., respectively (Table II). The ESR (mean 7 mm. in the first hour) lay within the normal range in the majority of the patients although in 11 (.6.7 per cent.) it was slightly elevated.

Thyrotoxicosis. The mean serum albumin (4.1 g. per 100 ml. SD $\pm$ 0.4) was more markedly ($P < .001$) in this disease than in any other thyroid disorder (Table I). The total serum globulins were normal; but there was a slight increase in the gamma-globulins ($P < 0.1$). Four of the 37 patients (11 per cent.) had gamma-globulin values exceeding 1.0 g. per 100 ml.

The serum flocculation tests were abnormal in a high proportion of the/

/of the patients; in particular the zinc sulphate turbidity (36.9 per cent.), the cephalin cholesterol (43.4 per cent.), and colloidal gold (58.0 per cent.) tests (Table II).

The ESR (mean = 6 mm. in the first hour) was within the normal range in the majority of the patients, although in 19 (7.5 per cent.) it was slightly raised.

Patients with thyrotoxicosis complicated by severe exophthalmos had similar abnormalities to those found in uncomplicated thyrotoxic-:osis and do not merit separate consideration.

The thyrotoxicosis was treated by either antithyroid drugs or by I^{131} therapy and this tended to reverse the serum protein abnormalities; the mean serum albumin in the group of treated and euthyroid patients being 4.7 g. per 100 ml. (SD $\pm$ 0.4) as compared with 4.1 g. per 100 ml. (SD $\pm$ 0.4) in the untreated group.

Thyroid neoplasm. These patients had an abnormally ($P < 0.001$) decreased serum albumin (mean 4.5 g. per 100 ml. SD $\pm$ 0.6), whereas the total serum globulins were normal. However, the alpha-2 globulins were increased ($P < 0.05$) and the beta globulins decreased ($P < 0.01$). None of the patients with thyroid neoplasm had gamma-globulin levels exceeding 1.0 g. per 100 ml.

The thymol turbidity and flocculation tests and the cephalin cholesterol were normal in most cases, although the zinc sulphate turbidity and colloidal gold tests gave abnormal results in 30 and 58.3 per cent. respectively (Table II). The mean ESR (26 mm. in the first hour) was increased and exceeded the upper limit of the normal range in 9 (66.7 per cent.) of the patients.

Discussion

An increase in the gamma-globulin fraction of the serum proteins in auto-immune thyroiditis has been reported by other workers (1,4,5,7-9); and in this study the levels found have been compared statistically with those in other thyroid diseases. When systemic disorders associated with serum protein abnormalities are excluded the finding of an elevated gamma-globulin i.e. exceeding 1.0 g. per 100 ml. can be considered as strong supportive evidence of auto-immune thyroiditis. On the other hand a normal level of gamma-globulin does not exclude the diagnosis since in about half of the patients in the present study the gamma-globulin level was below 1.0 g. per 100 ml. A slight increase in the gamma-globulins was also found in patients with primary hypothyroidism and this was particularly marked in those with precipitating antibodies to thyroglobulin. This is consistent with the view that the rise in the gamma-globulins is associated with the auto-immune response and not with hypothyroidism per se (27).

Doniach et al. (28) have reported that the levels of precipitins in auto-immune thyroiditis are in the region of 700 mg. per 100 ml. although higher levels up to 1890 mg. per 100 ml. have been reported (29). The finding of a mean rise of 510 mg. per 100 ml. in patients with auto-immune thyroiditis is consistent with most, if not all, of the increase in the gamma-globulin concentration being due to the circulating precipitins. However, Humphrey and his colleagues (30,31) have shown that the rise in gamma-globulins to an antigenic stimulus/

/stimulus may also be partly attributed to the syntheses of non-specific antibody.

The finding of a low serum albumin in all forms of thyroid disease eliminates this determination as a diagnostic test for auto-immune thyroiditis. The low levels found in auto-immune thyroiditis and primary hypothyroidism may be associated with diminished albumin synthesis by the liver due to occult or overt hypothyroidism (32), and Kline (33) has demonstrated diminution in the liberation of nitrogen and amino-acids from liver slices of hypothyroid rats. The striking decrease in serum albumin in thyrotoxicosis confirms previous observations (32, 34, 35) and is probably accounted for by an increased breakdown of albumin in the peripheral tissues (36), although impairment of hepatic synthesis has also been invoked (32,35). The low levels of serum albumin may be a reflection of the poor intake of protein in these patients (37), but the low levels in simple non-toxic goitre is not as yet explained.

As previously mentioned, several authors (4,7,10) have advocated the use of serum flocculation tests in the diagnosis of auto-immune thyroiditis. In the present study the cephalin cholesterol, colloidal gold, and zinc sulphate turbidity tests were found of little practical value since they were frequently positive in patients with simple non-toxic goitre and thyroid neoplasm. On the other hand the thymol turbidity and thymol flocculation tests were found to be more specific. Although negative in about a quarter of the patients with auto-immune thyroiditis these tests were rarely positive in simple non-toxic goitre and thyroid neoplasm, conditions most likely to be confused with auto-immune thyroiditis.

Finally,/

/Finally, the value of the ESR determination should not be underestimated; this was normal in 93 per cent of patients with simple non-toxic goitre and elevated in 68 per cent of patients with auto-immune thyroiditis.

SUMMARY

Serum protein electrophoresis, flocculation tests, and ESR determinations, were studied in 28 healthy control subjects, 41 patients with auto-immune thyroiditis, and a large number of patients with various other forms of thyroid disease. The striking findings were the raised gamma-globulin level in auto-immune thyroiditis and the decreased serum albumin level in thyrotoxicosis. It is concluded that a raised gamma-globulin, abnormal thymol turbidity and flocculation tests, and an elevated ESR, are of diagnostic value in auto-immune thyroiditis.

Section 4.

Iodine Metabolism in Auto-immune Thyroiditis.

INTRODUCTION

In recent years 3 developments have facilitated the study of iodine metabolism and thyroid function in man: firstly, the use of radioisotopes of iodine; secondly, the perfection of accurate methods for the separation, identification, and chemical determination of the extremely small amounts of iodinated compounds in the thyroid and extra-thyroidal tissues; and thirdly, the discovery of the antithyroid drugs, which, by interfering with certain specific steps in the biosynthesis of the thyroid hormones, have enabled a more detailed study of thyroid function. Much of this work has been reviewed (1 - 7) and need not be reiterated here; only these aspects dealing with quantitative measurements of iodine metabolism will be outlined.

Stable Iodine Metabolism

In a brilliant theoretical review on the quantitative aspects of iodine metabolism in man Riggs (8) stated that: "A sharp distinction must be drawn between the kind of information obtained with tracer doses of radioactive iodine and the kind of information obtained with chemical methods of analysis. Tracer studies are ideal for the measurement of the proportion of the iodine in the body which follows a particular metabolic pathway and for the study of the rate of turnover of iodine within the various compartments. By themselves, however, tracer studies cannot indicate the actual amounts of iodine which are being metabolised". Koutras et al. (9) have clearly demonstrated that the radioiodine uptake depends not only on the level of/

/of thyroid activity, but also on the concentration of iodine in the plasma (PII); and likewise that the PBI^{131} not only depends on the amount of hormone being produced, but also on the rate of turnover of the isotope by the thyroid and ths size of the intrathyroidal exchangeable iodine (IEI) pool.

Measurement of PII and Absolute Iodine Uptake (AIU).

In normal circumstances the level of PII is too small to be measured directly by chemical methods (10). Stanley (11) in 1949 was the first to use an indirect method of measuring both the PII and the absolute (stable) uptake of iodine by the thyroid (AIU) based on the principle of isotopic dilution. Since the thyroid and kidney cannot distinguish between radioactive and stable iodine atoms, the specific activity of the iodine (i.e. the proportion of the radioactive to the total iodine atoms) going into the thyroid is the same as the specific activity of the inorganic iodine present in plasma and urine. The stable amount of iodine accumulated by the thyroid is expressed as AIU, the uptake of radioiodine during the same period of time as I^{131}, the level of plasma and urinary inorganic and radioiodine as PII and PII^{131}, and UII and UII^{131}, respectively, then:

$$\frac{PII}{PII^{131}} = \frac{UII}{UII^{131}} = \frac{AIU}{I^{131}}.$$

$$\text{Therefore,} \quad PII = \frac{PII^{131} \times UII}{UII^{131}}$$

$$\text{and,} \quad AIU = \frac{UII \times I^{131}}{UII^{131}}$$

Alternatively the AIU can be derived from knowledge of the volume of plasma cleared of its iodine content in unit time (i.e. the thyroid clearance) and the concentration of iodine in this volume of plasma. Thus:-

AIU = thyroid clearance x PII.

Several workers (10, 12-17) have used methods based on these principles for studies of stable iodine metabolism, although German workers (18-20) have preferred saliva to urine. These authors have claimed that salivary iodine is entirely inorganic, whereas urinary iodine also contains some inorganic compounds. However, with the exception of rare cases of dehalogenase defect (21, 22), administration of organic iodine compounds (23), nephrosis (24), and in some thyrotoxic patients (25), the iodine normally present in the urine is almost entirely in the inorganic form (7). Furthermore, collection of urine is both easier and more accurate than that of saliva and is on the whole preferable.

Measurement of IEI

Similarly on the basis of isotopic dilution, the IEI can be measured (26). After the administration of a tracer dose of radioiodine, the specific activity of hormone in the blood-stream will gradually approach that in the thyroid gland. When the two specific activities become equal: then,

$$\frac{\text{PBI in the thyroid (IEI)}}{\text{PBI}^{131} \text{ in the thyroid}} = \frac{\text{PBI in the blood}}{\text{PBI}^{131} \text{ in the blood}}.$$

From this equation it can be seen that organic iodine in the thyroid/

/thyroid (PBI in the thyroid) or IEI can be derived:

$$IEI = \frac{PBI\ (blood) \times PBI^{131}\ (thyroid)}{PBI^{131}\ (blood)} .$$

Measurement of Serum PBI

Estimation of the amount of iodine (chiefly in the form of thyroxine) which is bound to plasma proteins (PBI) is also necessary if a complete picture of iodine metablism is to be obtained. It is probably the best test of thyroid function currently available (5) and has an overall accuracy of over 90 per cent (27). The principle steps in the estimation of the serum PBI include: (1) separation of PBI from inorganic iodine, (2) protein digestion and isolation of bound iodine in a form suitable for estimation, and (3) colorimetric determination using the iodide catalysed ceric-arsenite reaction. Alkaline ashing and digestion with distillation have been widely used for protein digestion, but are technically difficult. Zak et al. (28) simplified this latter procedure by using a chloric acid digestion method. Farrell and Richmond (29) have modified the chloric acid digestion method, improved the initial separation of inorganic iodine from protein-bound iodine by using an anion-echange resin column, and simplified the final colorimetric measurement by applying a brucine catalytic inhibitor. Farrelland Macgregor (30) and Richmond et al. (31) have reported consistent and reliable results using this method.

Measurement of Butanol-extrable Iodine (BEI).

Although the PBI is generally regarded as a measure of the circulating/

/circulating thyroid hormone, it is nevertheless the result of 2 parameters of thyroid hormone production, namely the rate of formation and the rate of peripheral degradation. Furthermore, included in the estimation of the total PBI are other iodinated protein complexes. Since both thyroxine and triiodothyronine are soluble in butanol (32), the butanol extractable protein-bound iodine (BEI) gives a more accurate determination of the circulating thyroxine level (33). A similar extraction procedure can also be used to recover labelled-thyroxine from the total PBI^{131} (34).

A full picture of iodine metabolism can only be obtained by simultaneous measurement of the various aspects of thyroid function; a point first emphasised by Riggs (8): "Chemical methods on the other hand give valuable information concerning the quantities of iodine with which the body deals, but by themselves provide no more than a dim outline of the dynamics of iodine metabolism. Only by the combined use of radioactive iodine tracers and of chemical methods can a clear picture of the over-all metabolism of iodine be obtained."

Historical Aspects of Iodine Metabolism in Auto-immune Thyroiditis.

In 1949, Werner (35) first observed that the radioiodine uptake may be either low or normal in auto-immune thyroiditis. This finding was confirmed by others (36-48), although in several patients without clinical evidence of thyrotoxicosis the thyroid uptake was noted to be in the thyrotoxic range (36,39,40,42,44,45, 47,48).

In general a poor correlation was found between the thyroid gland uptake of radioiodine and the clinical status; and Skillern et al. (40), Doniach and Hudson (47), and Murray and McGirr (48), concluded that the measurement of the thyroid gland uptake alone was of no diagnostic value in this disease.

Goodwin et al. (49) observed a high PBI^{131} (2.3%/dose/litre) in one patient with auto-immune thyroiditis, but Werner (36) appears to have been the first to draw attention to this anomaly. Beare (42) recorded a PBI^{131} value in the thyrotoxic range (0.66% dose/litre) in a patient who was hypothyroid, and Doniach and Hudson ((47) observed high values in 4 of their patients. Doniach and Hudson (47) interpreted these findings as indicating that "in lymphadenoid goitre there is a small intrathyroidal iodine pool with a high specific activity"; and in support of this these authors found a much shorter biological half-life of a tracer dose of radioiodine (2.8 to 12 days) in 4 patients with auto-immune thyroiditis as compared with 30 to 180 days in 10 patients with simple non-toxic goitre. Other workers (6,7,48) accepted this interpretation, although Hubble (45) suggested that it might also be due to the formation of an abnormal iodinated protein such as had been described by Owen and McConahey (43). These authors showed that more than 10 per cent of the total PBI^{131} was butanol-insoluble in 30 of 38 patients with auto-immune thyroiditis, and that in approximately one-third of the patients the butanol insoluble fraction exceeded the value of radio-thyroxine.

Owen/

/Owen and McConahey (43) were, however, unable to identify the nature of the butanol-inextrable iodo-protein as only tracer doses of radioiodine were given and the concentration of radioiodine in the serum was inadequate for detailed analysis. Butanol-insoluble iodo-proteins have also been reported by others in both stable (40,41) and radioiodine (47) fractions of the PBI. Chromatographic investigations in auto-immune thyroiditis have demonstrated the formation of abnormal iodinated proteins in the thyroid (43) and in an electrophoretic study of the thyroid proteins Watson et al. (50) demonstrated a "Q" band of unknown significance, present at or close to the starting point of electrophoretic strips in all of 5 thyroids from patients with auto-immune thyroiditis.

Murray and McGirr (48) found a significant fall in the thyroid gland uptake in 6 patients with auto-immune thyroiditis following the administration of 0.2 to 0.3 mgm. thyroxine daily for periods varying from 10 and 20 weeks, and Owen and McConahey (43) observed a fall in the uptake in one patient with triiodothyronine. In one patient with auto-immune thyroiditis, who presented with thyrotoxic manifestations and had both an elevated thyroid uptake and PBI^{131} value, Doniach et al.(47) demonstrated the value of the triiodo-:thyronine suppression test in excluding thyrotoxicosis.

Beare (42) observed that a scintigram of the thyroid in one patient with auto-immune thyroiditis showed a uniform distribution of the radioiodine which followed the outline of the goitre; and this/

/this observation was confirmed by both Doniach and Hudson (47) and Murray and McGirr (48) in a small number of patients. These authors (47,48) suggested that this procedure may help to differentiate auto-immune thyroiditis from either non-toxic nodular or malignant goitre in which the radioiodine distribution is irreg-:ular. Autoradiography of the thyroid was carried out in one patient studied by Doniach and Hudson (47) who showed that the radioiodine was "taken up in fairly evenly scattered small foci", and Statland et al. (38) showed that the radioiodine was concentrated mainly in the epithelial areas. Owen (6) and Décourt et al. (52) on the other hand reported an irregular distribution of the isotope in the thyroid in auto-immune thyroiditis.

In 1956 Skillern et al. (40) showed that a single injection of 4 units of TSH did not significantly increase the rate of I^{131} uptake in 23 patients with histologically proven auto-immune thyroid-:itis in contrast to a significant increase observed in 18 patients with non-toxic goitre. These authors suggested that this test might therefore prove valuable in the pre-operative differentiation of auto-immune thyroiditis from simple non-toxic goitre and also perhaps from thyroid neoplasm. However, Werner (36) noted that the thyroid gland uptake in auto-immune thyroiditis "may occasionally respond" to TSH stimulation, and both Owen and McConahey (43) and Skillern and Evans (41) confirmed this in a few patients given larger doses of TSH (10 to 20 units). In a study of "low thyroid reserve"/

/reserve" Jefferies et al. (53) noted the failure of the PBI to rise after TSH stimulation in one patient with auto-immune thyroiditis.

In 1957 Morgans and Trotter (54) made the interesting observation that when potassium perchlorate was administered following a tracer dose of radioiodine to normal patients the thyroid counting rate rose slightly and then remained constant, whereas in 12 patients with auto-immune thyroiditis whom they studied the administration of potassium perchlorate caused a significant dis-:charge of radioiodine. The test was negative in all but one of 25 patients with simple goitre and Morgans and Trotter (54) suggested that it might be of additional diagnostic value. Hubble (45) found the test positive in 10 patients with auto-immune thyroiditis and negative in 3 normals and one patient with a simple nodular goitre; and concluded that the test was "nearly specific". In addition, Hubble (45) observed that: "the degree of discharge correlated with the degree of hypothyroidism, i.e. with the extent of destruction of the thyroid gland. The greater the degree of hypothyroidism the greater the discharge of iodine from the gland". Murray and McGirr (48) also reported favourably on this test and found it positive in all of 7 patients with auto-immune thyroiditis and negative in all of 14 controls.

Estimation of the PBI in auto-immune thyroiditis has been reported by several American workers. Thus in 1951, Statland et al. (38) noted PBI values of 0.9, 2.5, and 4.4 µg. per 100 ml. in 3 patients/

/patients with auto-immune thyroiditis. In 1956 Skillern et al. (40) recorded PBI values in 12 patients; the results of which were in the low normal range in 9 and in the high normal in 3. In the following year Skillern and Evans (41) reported normal values of PBI in 13 of 14 patients with auto-immune thyroiditis and concluded that the test was of little value in the diagnosis of this disease. On the other hand Owen (6) took the view that when there was a disparity between the results of the PBI and the radioiodine tests this might direct suspicion towards auto-immune thyroiditis. Low or normal values of PBI have been recorded by most authors (44,46,55) with the exception of Gribetz et al. (56) who in a study of 6 children found high values in 3 (8.8, 9.6, and 9.3 per 100 ml.), the first 2 of whom had normal BEI values (3.7 and 4.2 mg. per 100 ml.).

Personal Observations

Despite the large number of publications on various aspects of auto-immune thyroiditis in recent years, comparatively little attention has been given to the mechanism of the disturbances in iodine metablism in this disease. The purpose of the present section of the thesis is to determine the nature of the abnormality in iodine matbolism in this condition. By using the combination of chemical and isotopic techniques, previously described in the introduction of this section, a very full picture of iodine metabolism in auto-immune thyroiditis has been obtained and an explanation/

/explanation is provided for the abnormal radioiodine tests frequently found in the disease. The diagnostic implications of the various tests using radioactive iodine are also discussed.

Materials and Methods

Fifty patients with auto-immune thyroiditis have been studied. The diagnostic criteria were as described in Section 1 of this Chapter of the thesis. The patients were clinically assessed by the procedures described by Wayne (57) and classified as euthyroid, equivocally hypothyroid, or clearly hypothyroid. As discussed in Section 1 of this Chapter, it was fully appreciated that such a distinction was arbitrary, as there was no sharp dividing line between the groups. Radioactive iodine was used both as I^{131} and as the short-lived isotope I^{132}. The radioactive iodine (supplied by the Radiochemical Centre, Amersham) was proved to be free from carrier I^{127}. Inaccuracy in the thyroid uptake measurements due to back-scatter radiation was eliminated by checking the results with a "phantom" thyroid. The thyroid gland uptake measurement using I^{131} and I^{132} were comparable.

Standard Radioiodine Tests*, including 4 and 48 low thyroid uptake measurements and PBI^{131} at 48 hours, were carried out by the methods described by Wayne (57); PBI^{131} estimation was, however, simplified by using an ion exchange column (58).

The potassium perchlorate discharge test (54) was performed as modified/

* I am grateful to Miss E.M. Macdonald, B.Sc., and Mrs. S.R. Johnston, A.I.M.L.T., for carrying out tests involving the use of radioiodine.

/modified by Koutras et al. (58). The thyroid gland uptake was measured 60 minutes after an oral dose of 25 μc I^{132}. Immediately thereafter 500 mg. potassium perchlorate was given by mouth and 40 minutes later the thyroid uptake was again measured. The result was expressed as a percentage of the initial reading; a value of less than 90% was considered positive.

The thyroxine suppression tests were performed by estimating the $2\frac{1}{2}$ hour I^{132} uptake by the thyroid/ before and after the administration of 0.2 mg. thyroxine sodium daily for 3 weeks. Thyrotrophin stimulation tests were performed in two ways. In 10 patients the $2\frac{1}{2}$ hour thyroid gland uptake of I^{132} was estimated before and 24 hours after the administration IOUSP units TSH (Armour). In patients who did not respond by an increased gland uptake another measurement was made after two further injections of TSH at 24-hourly intervals (59). In 13 patients the PBI^{131} was measured before and 24 hours after 10 units of TSH given 9 days after a tracer dose of I^{131} (26).

The PBI* was measured by the chloric-acid-digestion method of Zak et al. (28) as modified by Farrell and Richmond (29).

The thyroid clearance rate of radioiodine was measured according to the method of Myant et al. (60) between 1 and $2\frac{1}{2}$ hours after the oral administration of 25 μc of I^{131} or 50 μc of I^{132}. Simultaneous estimation of the radioiodine and stable iodine content of/

* I am grateful to Mr. M.H. Richmond, B.Sc., and Mr. T. McGhie, A.I.M.L.T., for the PBI measurements.

/of the urine excreted over the same period provided data for the estimation of the PII and the AIU by the thyroid gland, using the method of Stanley (11). The PII (in μg. per 100 ml.) was calculated from the formula:

$$PII = \frac{I\ urine \times I^{131}\ (or\ I^{132})\ plasma}{I^{131}\ (or\ I^{132})\ urine}$$

where I urine represents the stable iodine of the urine in μg. per 100 ml., I^{131} plasma the radioiodine content of the plasma in per cent. of dose per ml. plasma, and I^{131} urine the radioiodine content of the urine in per cent. of dose per ml. urine.

The accuracy of the indirect estimation of PII was confirmed by direct chemical determination (29) in 6 patients in whom it was large enough to estimate. The difference between the direct and indirect estimate did not exceed 15 per cent.

The AIU (in μg. per hour) was calculated from the formula:

AIU = PII (μg. per ml.) x Thyroid Clearance of Radioiodine (ml. per hr.)

The renal clearance was calculated in the same way as the thyroid clearance, using the urinary excretion instead of the thyroid uptake of radioactive iodine.

The IEI was estimated by the method of Nodine et al. (26) using an injection of 10 units of TSH given on the tenth day after administration of 75 μc of I^{131}.

Urinary iodine was estimated on 0.5 - 1.0 ml. aliquots by the same/

Table I

Measurements of Stable and Radioactive Iodine in Auto-immune Thyroiditis

Figure 1.

Correlation between 4 hour Thyroid Gland Uptake I^{131} and PBI in Auto-immune Thyroiditis

Figure 2.

Correlation between 4 hour Thyroid Gland Uptake I^{131} and BMR

Table I

Measurements of Stable and Radioactive Iodine in Auto-immune Thyroiditis.

Measurements.	No. of Cases.	Mean S.E.	Range	Normal Range
2½ hr. uptake of I^{132} (% dose).	15	25.7 ± 2.4	10.3 - 46.6	10.0 - 35.0
4 hr. uptake of I^{131} (% dose).	49	37.4 ± 2.3	7.5 - 77.1	15.0 - 45.0
48 hr. uptake of I^{131} (% dose).	49	40.1 ± 3.1	10.2 - 79.8	20.0 - 60.0
Thyroid clearance (ml./min.).	15	22.7 ± 3.7	2.9 - 52.9	8.0 - 40.0
Plasma inorganic iodine (ug.%).	14	0.20 ± 0.04	0.02 - 0.58	0.08 - 0.60
Absolute iodine uptake (ug./hr.).	14	2.0 ± 0.4	0.4 - 5.9	0.5 - 6.0
48 hr. PBI^{131} (% dose/l.).	49	0.38 ± 0.08	0.05 - 2.74	0.00 - 0.2
BII^{131} (% of PBI^{131})	9	31.0 ± 9.0	0.00 - 95.0	0.00 - 20.0
Serum PBI (ug.%).	45	2.6 ± 0.4	0.5 - 5.3	3.0 - 7.5
Iodine Utilisation Index.	14	1.7 ± 0.3	0.6 - 6.0	1.0 - 10.0
Intrathyroidal exchangeable iodine (mg.).	11	1.2 ± 0.2	0.05 - 3.8	1.5 - 15.0
Renal clearance of iodine (ml./min.).	14	28.1 ± 1.9	16.5 - 43.5	15.0 - 55.0

Fig. 1.

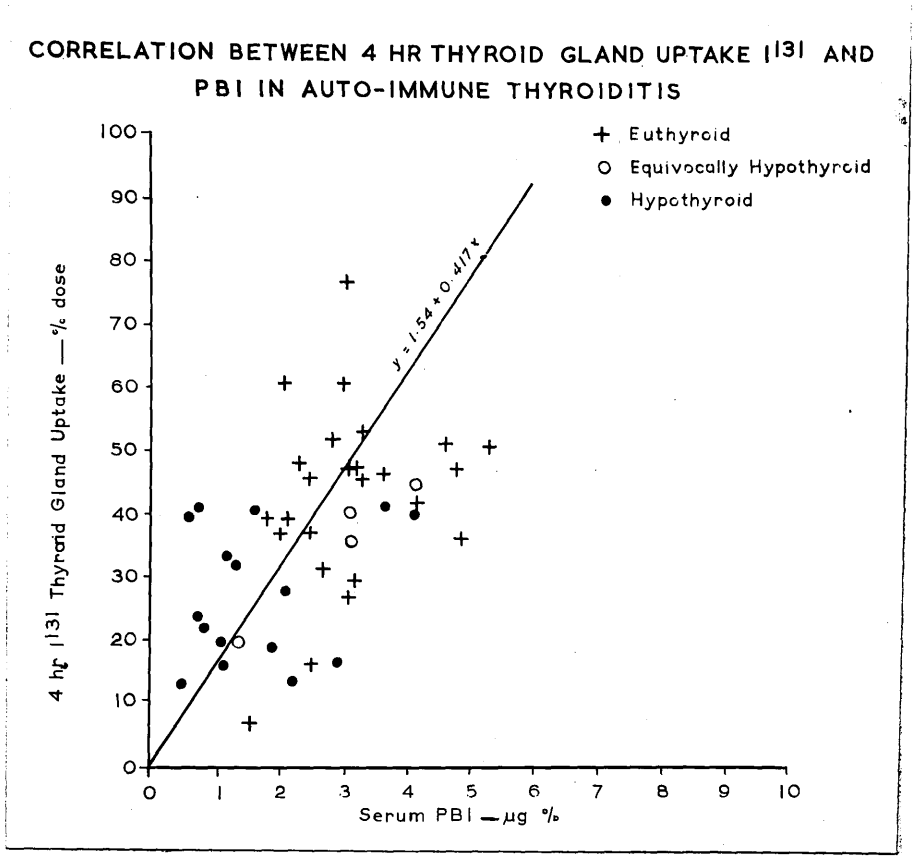
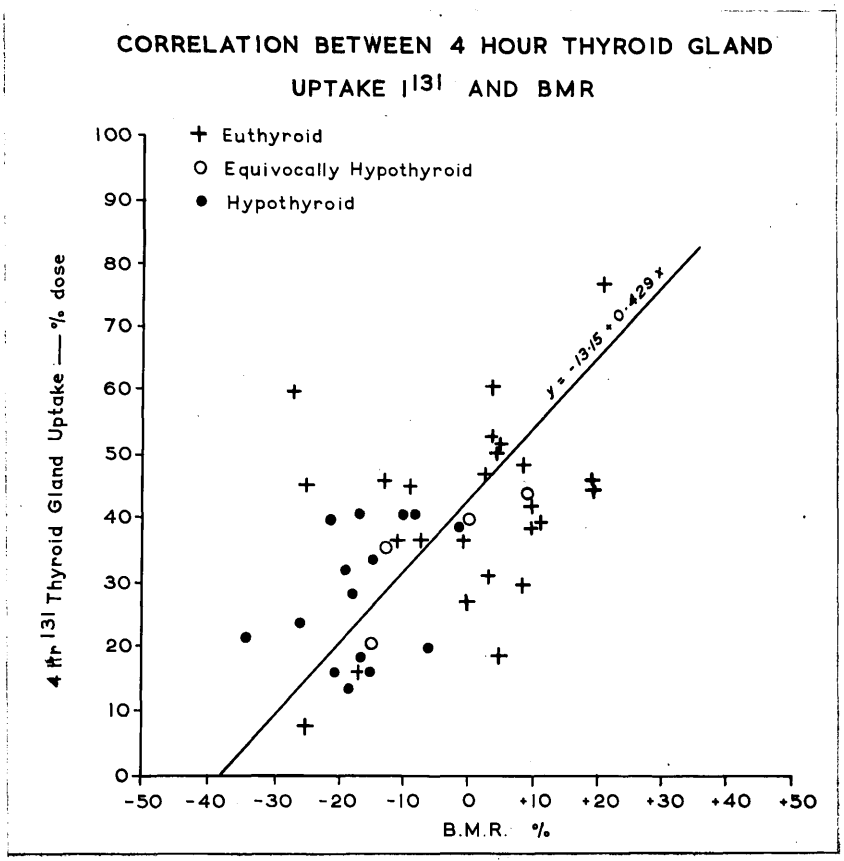

CORRELATION BETWEEN 4 HR THYROID GLAND UPTAKE I131 AND PBI IN AUTO-IMMUNE THYROIDITIS
+ Euthyroid
O Equivocally Hypothyroid
● Hypothyroid
y = 1.54 + 0.417x
4 hr I131 Thyroid Gland Uptake — % dose
Serum PBI — µg %
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
7
8
9
10

Fig. 2.


CORRELATION BETWEEN 4 HOUR THYROID GLAND UPTAKE I131 AND BMR
Euthyroid
Equivocally Hypothyroid
Hypothyroid
y = -13·15 + 0·429 x
4 hr I131 Thyroid Gland Uptake — % dose
B.M.R. %
100
90
80
70
60
50
40
30
20
10
0
-50
-40
-30
-20
-10
0
+10
+20
+30
+40
+50

/same chemical reaction as used in determination of the PBI results but without prior treatment. The mean recovery of iodine added to urine was found by Farrell and Richmond (29) to be 99.3% (SD ± 3.7%). The absence of significant amounts of organic iodine in the urine was confirmed by the use of an anion-exchange column (29).

The butanol inextractable radioiodine (BII^{131}) was estimated using 5 ml. samples of plasma. The inorganic I^{131} was removed by an ion exchange column (28) and the precipitate remaining after butanol extraction was assayed for radioactivity.

Results.

The results of the studies of the metabolism of both stable and radioactive iodine are summarised in Table 1.

In most cases the radioiodine uptake by the thyroid at $2\frac{1}{2}$, 4, and 48 hours and the thyroid clearance rate lay within the normal range, but in several cases these values were above, and in a few below, the normal range; the standard deviation was therefore large. High values were found frequently in the 4 hour measurements, which exceeded the 48 hour uptake in 20 of the 49 patients. This is consistent with the short biological half-life of radioiodine in auto-immune thyroiditis found by Doniach and Hudson (47). The 4 hour thyroid gland uptake correlated significantly ($P<0.001$) with both the PBI ($r = 0.371$, Fig. 1) and BMR ($r = 0.436$, Fig. 2). From these scattergrams it can be seen that in general euthyroid patients had a higher uptake of radioiodine than those who were hypothyroid,/

Figure 3.

Correlation between 4 hour Thyroid Gland Uptake I^{131} and Serum Cholesterol.

Figure 4.

Correlation between 4 hour Thyroid Gland Uptake I^{131} and Goitre Size in Auto-immune Thyroiditis.

Figure 5.

Correlation between PBI^{131} and Serum PBI in Auto-immune Thyroiditis.

Figure 6.

Serum PBI in Euthyroid Patients with Auto-immune Thyroiditis.

Fig. 3.

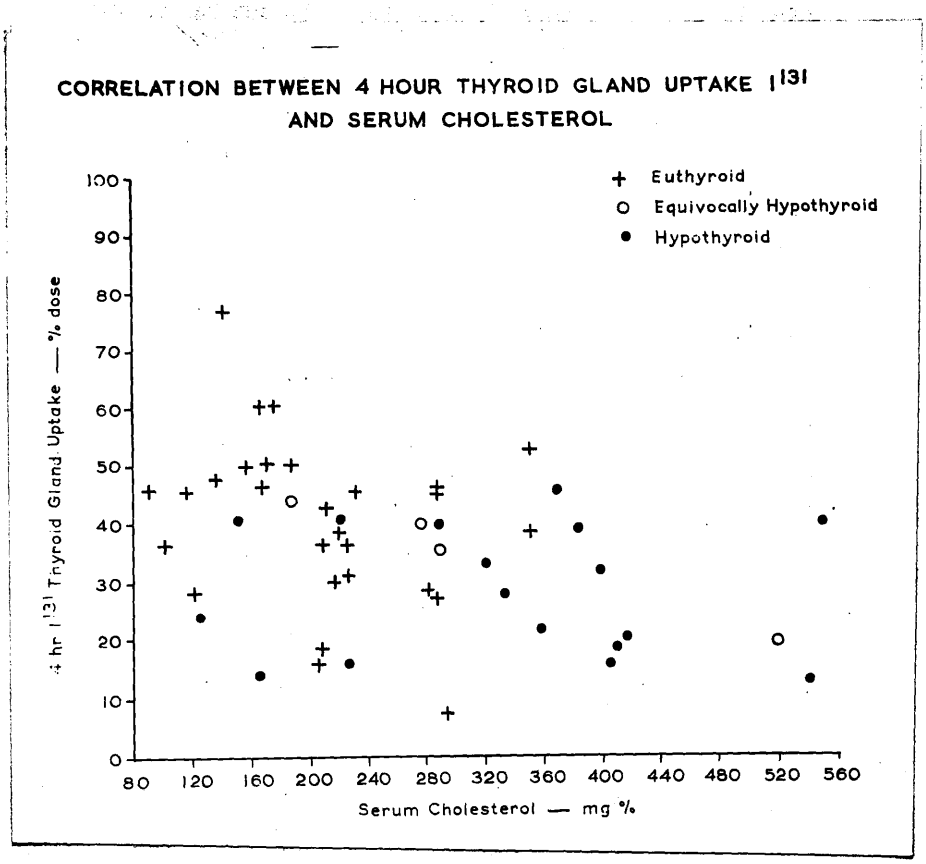

CORRELATION BETWEEN 4 HOUR THYROID GLAND UPTAKE I131
AND SERUM CHOLESTEROL
+ Euthyroid
O Equivocally Hypothyroid
● Hypothyroid
4 hr I131 Thyroid Gland Uptake — % dose
100
90
80
70
60
50
40
30
20
10
0
80 120 160 200 240 280 320 360 400 440 480 520 560
Serum Cholesterol — mg %

Fig. 4.

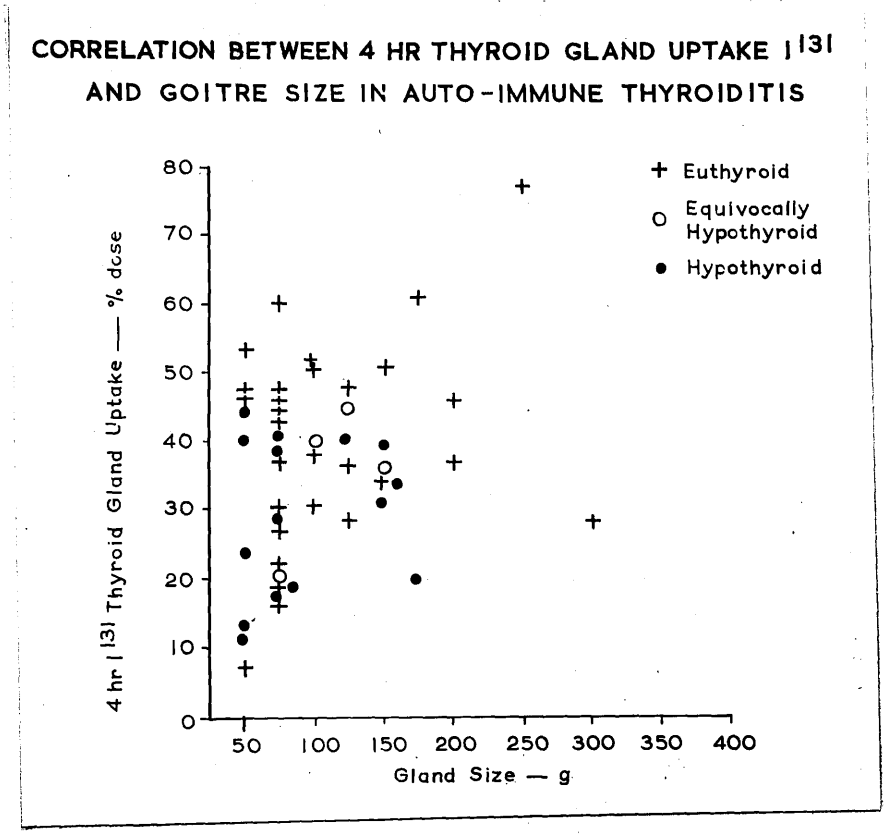

CORRELATION BETWEEN 4 HR THYROID GLAND UPTAKE I131
AND GOITRE SIZE IN AUTO-IMMUNE THYROIDITIS
4 hr I131 Thyroid Gland Uptake — % dose
Gland Size — g
+ Euthyroid
o Equivocally Hypothyroid
• Hypothyroid
0
10
20
30
40
50
60
70
80
50
100
150
200
250
300
350
400

Fig. 5.

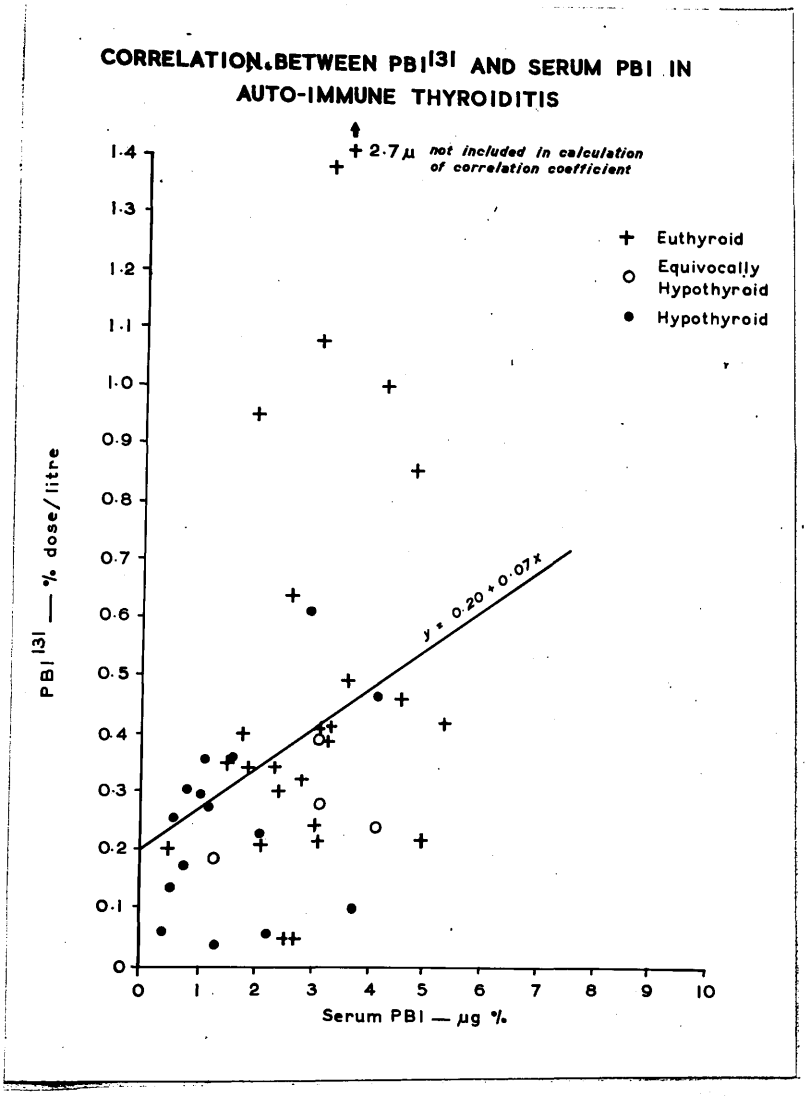
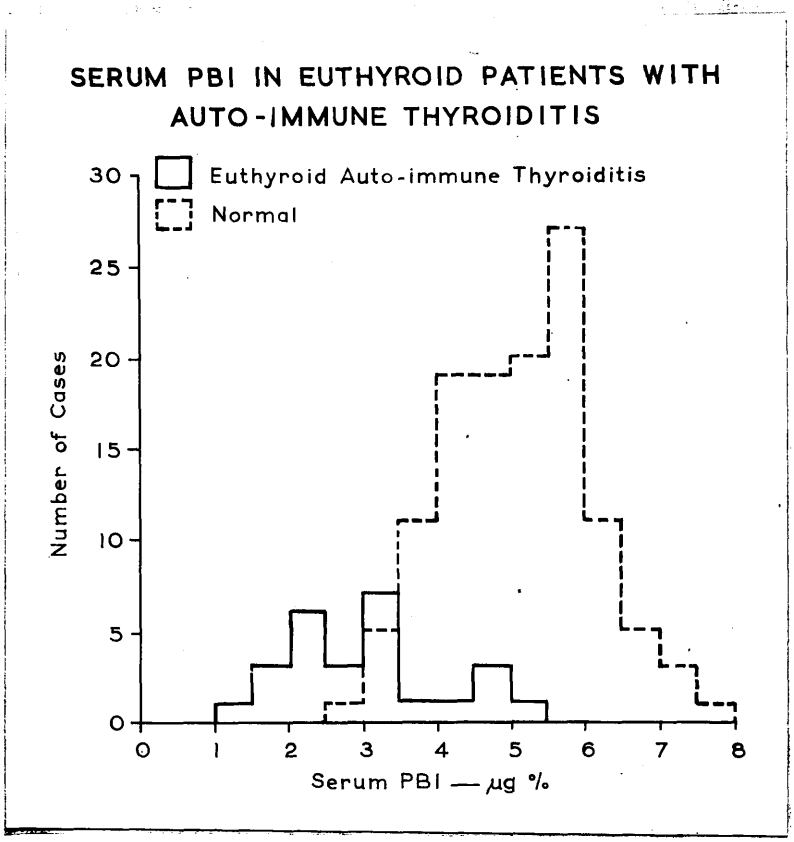

CORRELATION BETWEEN PBI[131] AND SERUM PBI IN AUTO-IMMUNE THYROIDITIS
+ 2·7 μ not included in calculation of correlation coefficient
Euthyroid
Equivocally Hypothyroid
Hypothyroid
y = 0·20 + 0·07x
PBI[131] — % dose/litre
Serum PBI — μg %
0
0·1
0·2
0·3
0·4
0·5
0·6
0·7
0·8
0·9
1·0
1·1
1·2
1·3
1·4
0
1
2
3
4
5
6
7
8
9
10

Fig. 6.


SERUM PBI IN EUTHYROID PATIENTS WITH AUTO-IMMUNE THYROIDITIS
Euthyroid Auto-immune Thyroiditis
Normal
Number of Cases
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
Serum PBI — µg %

/hypothyroid, but that there was a considerable overlap in the results. No significant correlation ($P<0.1$) was found between the 4 hour uptake and the serum cholesterol values ($r = 0,191$, Fig. 3). There was no correlation between the 4 hour uptake and the goitre size ($r = 0.226$, Fig. 4) and this is in agreement with the previous observations of Doniach and Hudson (47).

The PII values lay within the normal range, with the exception of 2 patients who had values of 0.02 and 0.06 µg. per cent respectively.

The AIU was within the normal range with the exception of one hypothyroid patient who had a value of 0.4 µg. per hour.

The mean value of the PBI^{131} lay above the upper limit of the normal and in 20 patients (40.8%) this value was in the thyrotoxic range (i.e. exceeding 0.39% per dose per litre). From Fig. 5 it can be seen that euthyroid patients tended to have a higher PBI^{131} than hypothyroid patients.

The BII^{131} varied from 0 - 95% with a mean of 31% of the PBI^{131} values. Five of the 9 patients had values of BII^{131} exceeding 20% of the total PBI^{131}.

The PBI values lay in the hypothyroid or in the low normal range (mean 2.6 µg. per cent., highest value 5.3 µg. per cent.). The mean PBI in the clinically euthyroid patients (3.1 µg. per cent.) was significantly lower ($P< 0.001$) than the mean normal (5.2 µg. per cent.) value (Fig. 6). Confirmatory evidence of subclinical hypothyroidism in these patients included: a low BMR in 5, a raised serum/

Figure 7.

Effect of TSH Stimulation on Thyroid I^{132} Uptake and PBI^{131} Discharge

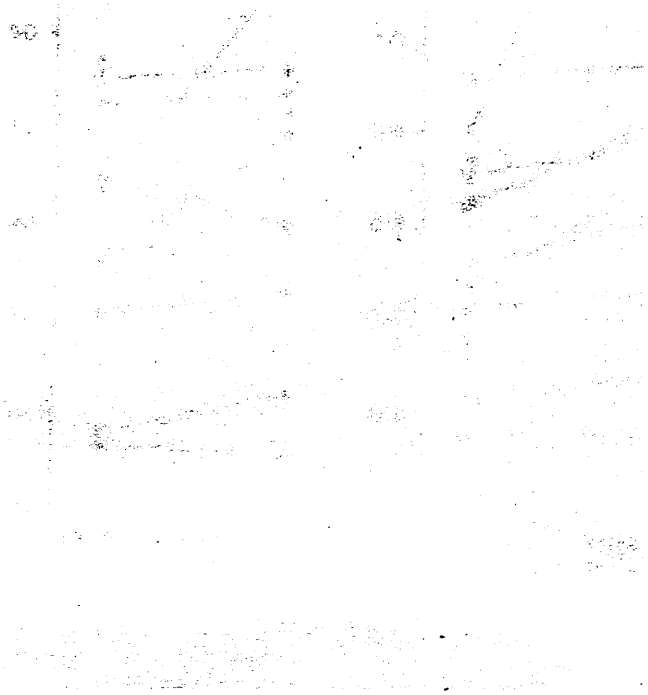
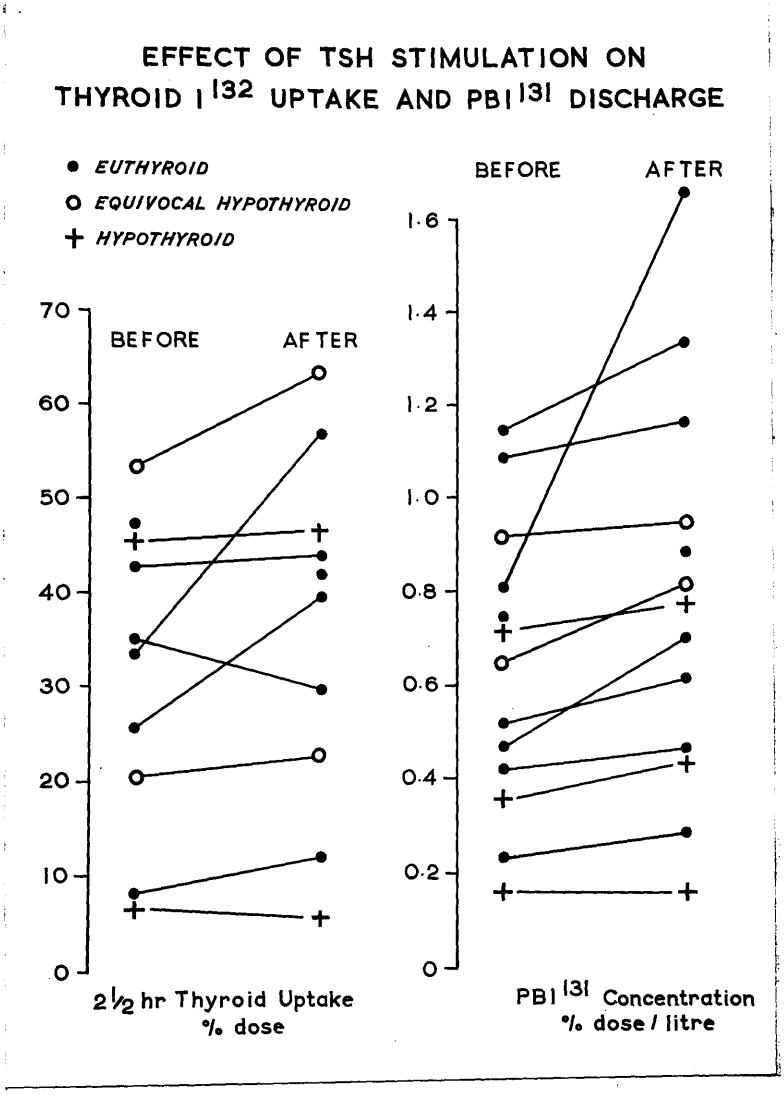


Fig. 7.


EFFECT OF TSH STIMULATION ON
THYROID I 132 UPTAKE AND PBI 131 DISCHARGE
EUTHYROID
EQUIVOCAL HYPOTHYROID
HYPOTHYROID
BEFORE
AFTER
70
60
50
40
30
20
10
0
2 1/2 hr Thyroid Uptake
% dose
BEFORE
AFTER
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
PBI 131 Concentration
% dose / litre

/serum cholesterol in 6, and an ECG suggestive of hypothyroidism in 5. From figures 1 and 5 it can be seen that the clinical status agreed more closely with the PBI than with the PBI^{131} or the 4 hour thyroid gland uptake of radioiodine. The PBI correlated significantly ($P < 0.05$) with the PBI^{131} ($r = 0.309$, Fig. 5).

The ratio of PBI to AIU is a measure of the capacity of the thyroid gland to utilise the iodine presented to it and this has been termed the iodine utilisation index (58). Six of 15 patients with auto-immune thyroiditis had ratios below the lower limit of the normal. The mean index (1.7) was significantly lower ($P < 0.02$) than the mean of a normal series (3.4) studied in the same laboratory by the same methods; the iodine utilisation index tended to be lower in hypothyroid patients.

In 10 of 12 patients with auto-immune thyroiditis in which the IEI was calculated, abnormally low values were obtained (Table 1). In 2 patients the discharge of protein-bound radioactivity after TSH was insufficient to allow calculation of the intrathyroidal iodine; presumably in the 2 patients it was extremely low.

The mean value of the renal clearance of iodide was within the normal range, although a little lower than the mean of a normal group (34.0 ml. per min.). The difference, however, was not statistically significant.

The results of the TSH tests are summarised in Fig. 7. Of 10 patients in whom the thyroid uptake was measured before and after/

/after TSH administration the thyroid radioiodine uptake increased by 10% or more in only 3 patients. The discharge of PBI^{131} was measured after TSH administration in 13 patients, during estimations of the IEI (26). All 8 euthyroid patients responded with a rise in the PBI^{131}, but only in one was the rise comparable with that found in normal patients. On the other hand, only 1 of 3 hypothyroid patients showed a rise in the PBI^{131}. All 34 patients tested showed a normal suppression of thyroidal uptake of radioiodine following thyroxine administration.

A positive potassium perchlorate discharge test was found in 12 of 27 patients (44.4%). There was no correlation between the clinical status of the patient and the result of the test. The mean discharge of those with a positive test was 17% with a maximum of 23%.

Discussion

The patients with auto-immune thyroiditis had, as a group, a low plasma PBI, although the absolute (or stable) iodine uptake (AIU) by the thyroid was normal. The low PBI reflects decreased thyroid hormone production. The alternative explanation - increased peripheral degradation of thyroxine - is very unlikely since the group tended to by hypothyroid (61). The results thus imply that the thyroid gland, in spite of retaining the normal amount of iodine, cannot utilise this iodide in the normal way to produce hormone. The same pattern of iodine metabolism has been found in patients with congenital/

/congenital dyshormonogenesis (58), although the abnormality was more severe and the AIU was greater than normal. From the point of view of handling of iodine, auto-immune thyroiditis may thus be considered as a form of "acquired dyshormonogenesis" in which the thyroid displays a diminished capacity for utilising the iodine presented to it.

Other indices of iodine metabolism in auto-immune thyroiditis suggest that the defects in hormone synthesis are multiple. Thus, a deficiency of organic binding of iodine is indicated by the discharge of iodine from the gland following the administration of potassium perchlorate (47,48,54) which was observed in 12 of the patients in the present study. Furthermore, 5 of 9 patients had an abnormal butanol-insoluble iodinated protein which exceeded 20 per cent. of the total PBI^{131} concentration. Both abnormalities were present in some of the patients. Butanol-insoluble iodinated proteins have previously been reported in auto-immune thyroiditis (40,41), congenital dyshormonogenesis (58,62-64), and thyroid cancer (65,66). Preliminary studies in 3 of the patients have failed to show that the butanol-insoluble protein has the immunological specificity of thyroglobulin (67). The possibility exists that the patients had dyshormonogenesis before developing auto-immune thyroiditis; but this seems very unlikely, since thyroid auto-antibodies are only rarely encountered in congenital dyshormonogenesis (68)/

Figure 8

Influence of Small Intrathyroid Exchangeable Iodine Pool on PBI^{131}.

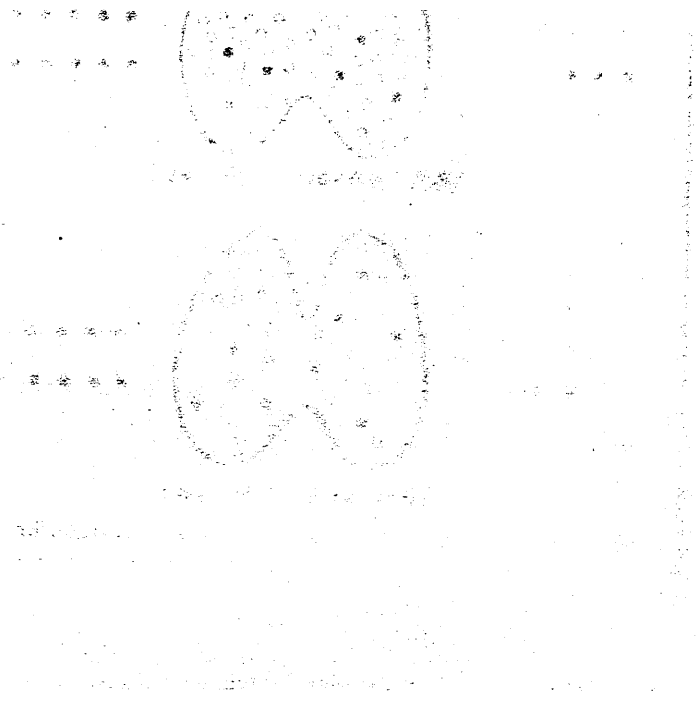
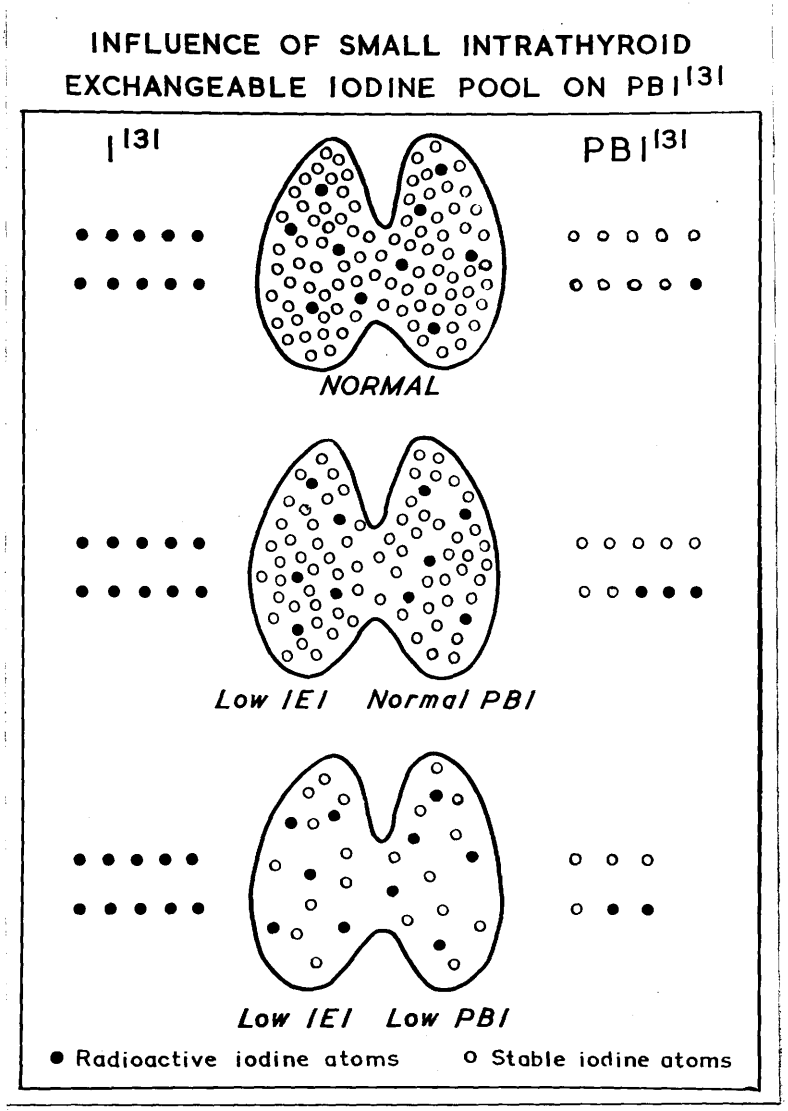


Fig. 8.


INFLUENCE OF SMALL INTRATHYROID EXCHANGEABLE IODINE POOL ON PBI[131]
I[131]
PBI[131]
NORMAL
Low IEI Normal PBI
Low IEI Low PBI
● Radioactive iodine atoms
o Stable iodine atoms

/(68). Moreover, Carr et al. (69) have found normal activity of iodotyrosine dehalogenase in auto-immune thyroiditis.

In many patients with simple non-toxic goitre a discrepancy is found between the clinical status and the radioiodine uptake. In iodine-deficiency goitre the discrepancy is more apparent than real, since the high radioiodine uptake is not associated with a high AIU and can be explained on the basis of a dilution phenomenon (10). In such patients the actual amount of iodide retained by the thyroid (AIU) and the quantity of hormone produced are both normal. On the other hand, in congenital dyshormonogenesis and in auto-immune thyroiditis there is an actual dissociation between the amount of iodide retained and the amount of hormone synthesised. This explains a normal or even high radioiodine uptake in a hypothyroid patient with auto-immune thyroiditis.

In almost all the patients suffering from auto-immune thyroiditis who have been examined, the IEI was abnormally low and this is consistent with the reduction in the biological half-life of radioiodine in this disease (47). Koutras et al. (9) have shown that the PBI^{131} is inversely related to the size of the IEI pool. This implies that the high PBI^{131} levels in patients with auto-immune thyroiditis is due to dilution of the radioactive atoms taken up by the thyroid in a smaller pool of intrathyroidal iodine than normal. Thus, the hormonal iodine released has a higher specific activity, although the total amount may be normal or reduced (Fig. 8). From this/

/this figure it can be seen that the PBI^{131} is in fact related not only to the amount of thyroid hormone released, but also to its specific activity which is inversely related to the IEI pool. This mechanism would account for the high PBI^{131} observed in many of the patients. Since the proportion of butanol-insoluble material is the same, both in chemical PBI and in radioactive PBI^{131} (43), its degradation rate is presumably not very different from that of the normal hormone. It follows that the butanol-insoluble iodoprotein, although it contributes to the PBI^{131} in some patients, cannot be responsible for the discrepancy between the high PBI^{131} and the low PBI. This discrepancy can only be explained by postul-:ating that the high PBI^{131} does not reflect an increased production of thyroid iodoproteins but a rapid turnover rate of iodine within the thyroid. This rapid turnover is probably the result of an increased TSH stimulation. This is consistent with the finding of a poor response to exogenous TSH (Fig. 7), presumably because these patients are already under maximal or near maximal stimulation by endogenous TSH. The assumed increase in endogenous TSH can be attributed to the low level of circulating PBI since the radioiodine uptake by the thyroid is suppressed by thyroxine administration.

Apart from these theoretical considerations the standard radioiodine tests may be of value in the diagnosis of auto-immune thyroiditis. Thus, a pattern of some diagnostic value is the combination of a high PBI^{131} with either a low or normal radioiodine uptake and a low PBI. The routine radioiodine tests show, however, marked/

/marked variability and may be completely misleading since euthyroid patients may show results consistent with thyrotoxicosis (51). In these circumstances the triiodothyronine or thyroxine suppression test will prove of value in differentiating the "pseudo-toxic" auto-immune thyroiditis from the mild thyrotoxic (see Chapter III, Section 2, for further discussion of this problem.). The TSH test is of no help in this particular problem (40), although it is of value in differentiating auto-immune thyroiditis from simple non-toxic goitre, in which an invariably normal response occurs (41). The IEI is also normal in simple non-toxic goitre (10,70) but this test is too elaborate and time-consuming to be of practical help. In contrast to the findings of Morgans and Trotter (54), and others, (45,48) the potassium perchlorate discharge test gave normal results in about only half of the patients; nevertheless a positive test is diagnostically valuable, since it is, with the exception of dyshormonogenesis of the peroxidase deficiency type (71), rarely positive in other forms of thyroid disorder.

The finding of a low PBI in clinically euthyroid patients confirms the previous observations of Skillern et al. (40), and provides a rationale for treatment of all patients with thyroxine sodium therapy.

The defects in iodine metabolism in auto-immune thyroiditis are essentially those which would be expected if a form of dyshormonogenesis occurred along with a decreased IEI. The standard radioiodine tests which are usually used in clinical practice often give abnormal/

/abnormal results in this condition, but they can be explained if the whole picture of iodine metabolism is known.

SUMMARY

A detailed and comprehensive investigation of iodine metabolism has been carried out in 49 patients with auto-immune thyroiditis. The results show a disassociation between the uptake of iodine by the thyroid, i.e. AIU, which is normal, and the PBI level which is significantly decreased. These findings indicate that the thyroid gland in auto-immune thyroiditis traps a normal quantity of iodine, but lacks the capacity to utilise it efficiently to form thyroid hormone. This faulty utilisation of iodine may be considered to be a form of "acquired dyshormonogenesis". Evidence of its nature is provided by the frequent discharge of iodine from the thyroid gland following administration of potassium perchlorate and the presence of a butanol-insoluble iodinated protein in the plasma in many patients.

The markedly reduced IEI values, and not the presence of BII, explains the frequent discrepancy between the high PBI^{131} and the low PBI.

A pattern of some diagnostic value is the combination of a high PBI^{131} with either a low or normal radioiodine uptake and a low PBI. The thyroxine (or triiodothyronine) suppression and TSH tests are of value in the differential diagnosis of auto-immune thyroiditis, and thyrotoxicosis and simple non-toxic goitre respectively. A positive potassium perchlorate discharge test is presumptive evidence of auto-immune thyroiditis.

The/

/The finding of a low PBI in many clinically euthyroid patients indicates an early degree of hypothyroidism and provides a rationale for the treatment of all patients suffering from auto-immune thyroid-:itis with thyroxine substitution therapy.

Section 5.

The Differential Diagnosis of Auto-immune Thyroiditis.

Most physicians would agree that the clinical diagnosis of auto-immune thyroiditis presents little difficulty when the patient is a middle-age female with a firm goitre and hypothyroidism. Diagnostic difficulty usually arises in the euthyroid patient; the thyroid swelling being mistaken for a simple goitre or a thyroid neoplasm. Euthyroid patients with auto-immune thyroiditis may have anxiety symptoms which lead the physician to suspect thyro-:toxicosis, and the results of routine radioiodine tests may apparently confirm this diagnosis. Less common diagnostic difficulties include dyshormonogenesis, goitre due to iodide or goitrogen administration, and subacute thyroiditis.

In this section I shall discuss the differential diagnosis of auto-immune thyroiditis. I have compared the clinical and laboratory findings in the 50 patients with auto-immune thyroiditis with those in other thyroid diseases which may give rise to diagnostic difficulty. The methods used have been described in the preceding sections of this Chapter of the thesis.

(1) Simple Goitre

Auto-immune thyroiditis is probably most commonly misdiagnosed as simple goitre than any other thyroid disorder. This is due to the fact that, apart from hypothyroidism, no absolute clinical distinction can be drawn between the 2 conditions. In the present study 509 patients have been diagnosed as having simple goitre, and/

Table I.

Summary of the Clinical Findings in Auto-immune Thyroiditis, Simple Goitre, and Thyroid Neoplasm.

Table II.

Effect of Thyroxine Sodium Therapy on Goitre Size in Auto-immune Thyroiditis and Simple Goitre.

Table I.

Summary of the Clinical Findings in Auto-immune Thyroiditis, Simple Goitre, and Thyroid Neoplasm.

		Auto-immune Thyroiditis (50 cases).	Simple Goitre (79 cases).	Thyroid Neoplasm (18 cases)
Age	Range	28 - 70 years	16 - 27 years	19 - 78 years
	Mean	52.5 years	36.6 years	55.7 years
Sex		92% females	96% females	72% females
Clinical Features of Goitre	Duration : Range	6 weeks - 37 years	2 weeks - 37 years	3 months - 30 years
	Mean	4.6 years	7.3 years	2.9 years
	Recent increase in size	4 (8%)	11 (13.9%)	13 (72.7%)
	Size : Range	50 - 300 g.	50 - 300 g.	50 - 200 g.
	Mean	108 g.	100 g.	102 g.
	Nodularity	22 (44%)	24 (30%)	13 (72%)
	Consistency	"firm" : 46 (92%)	"firm" : 24 (30%)	"firm" : 7 (38.8%)
		"hard" : 2 (4%)	"hard" : 0 (0%)	"hard" : 8 (44.4%)
		"soft" : 2 (4%)	"soft" : 55 (70%)	Not palpable 3 (16.8%)
	Pain or tenderness	1 (2%)	0 (0%)	3 (16.7%)
	Pressure effects	Mild 11 (22%)	Mild 14 (18%)	Mild 2 (11.1%)
		Severe 0 (0%)	Severe 2 (2.5%)	Severe 5 (27.8%)
	X-ray of trachea	Compression 4 (8%)	Compression 8 (10.1%)	Compression 7 (38.9%)
		Deviation 8 (16%)	Deviation 15 (18.9%)	Deviation 4 (22.2%)
	Laryngeal palsy	1 (2%) temporary	0 (0%)	2 (11.1%)
	Fixation	0 (0%)	0 (0%)	9 (50%)
Cervical adenopathy		1 (2%)	0 (0%)	6 (33%)
? Thyrotoxicosis		5 (10%)	13 (16.5%)	0 (0%)
Hypothyroidism		18 (36%)	0 (0%)	0 (0%)

Table II

Effect of Thyroxine Sodium Therapy on Goitre Size

in Auto-immune Thyroiditis and Simple Goitre

Clinical Condition	No. of Cases	Duration of Therapy (months).	Mean Neck Circumference (inches)		Significance
			Before Mean S.D.	After Mean S.D.	
Auto-immune thyroiditis	19	mean 14.6	14.78 ± 1.11	13.63 ± 1.06	$p < 0.001$ } $p < 0.05$
Simple goitre	23	mean 9.1	13.53 ± 0.96	12.98 ± 0.81	$p < 0.05$ }

The p values have been calculated from the mean difference of the values before and after treatment and its standard error, and not from the differences between the means.

/and the clinical findings in 79 of these patients are summarised in Table I. It can be seen that the consistency of the goitre is of some importance in differentiating auto-immune thyroiditis and simple goitre. Thus, a "soft" goitre was present in only 4 per cent of the patients with auto-immune thyroiditis, whereas it was found in 70 per cent of those with simple goitre. Moreover, patients with simple goitre are on the average younger, and have a longer history of goitre. (Table I).

Shrinkage of the thyroid swelling with dried thyroid extract or thyroxine sodium therapy has been observed in both auto-immune thyroiditis (1-8) and simple goitre (9-14), and has been confirmed in the present study (Table II). Although the goitres in auto-immune thyroiditis had as a group a much greater ($P < 0.05$) reduction in size than the simple goitres, this observation cannot be applied as a diagnostic test in an individual patient because of the variations in shrinkage of the goitre in the 2 groups.

In the present study the precipitin test has been found to provide a valuable means of differentiating the 2 disorders. None of the 509 patients diagnosed as having simple goitre had a positive precipitin test, including 38 patients who later came to surgery and were confirmed histologically. This contrasts with the findings in auto-immune thyroiditis, where the precipitin test was positive in 76 per cent. of the patients. On the other hand the CF test was of less value in differentiating the 2 conditions, since/

Table III.

Prevalence of Thyroid Auto-antibodies in Simple Goitre.

Figure 1.

Biochemical Studies in Auto-immune Thyroiditis, Simple Non-Toxic Goitre, and Thyroid Neoplasm.

Table IV.

Iodine Metabolism in Auto-immune Thyroiditis and Simple Goitre.

Table V.

Perchlorate Discharge Tests, BII^{131} determinations, and TSH tests in Auto-immune Thyroiditis and Simple Goitre.

Table III.

Prevalence of Thyroid Auto-antibodies in Simple Goitre.

Authors	Year	Ref. No.	No. of Cases.	Positive Thyroid Auto-antibody Tests		
				Prec.	CF	TRC
Paine et al.	1957	15	20			1
Roitt and Doniach	1958	16	198	1+	17	144
Anderson et al.	1959	17	44	0	4	
Belyavin and Trotter	1959	18	33	0	4	
Blizzard et al.	1959	19	19	3+		8
Cline et al.	1959	20	5			0
Hackett et al.	1960	21	16			10
Schade et al.	1960	22	26		2	8
Present Series			509	0	46	

+Diagnosis not confirmed by histological examination.

Fig. 1.

BIOCHEMICAL STUDIES IN AUTO-IMMUNE THYROIDITIS SIMPLE NON-TOXIC GOITRE AND THYROID NEOPLASM

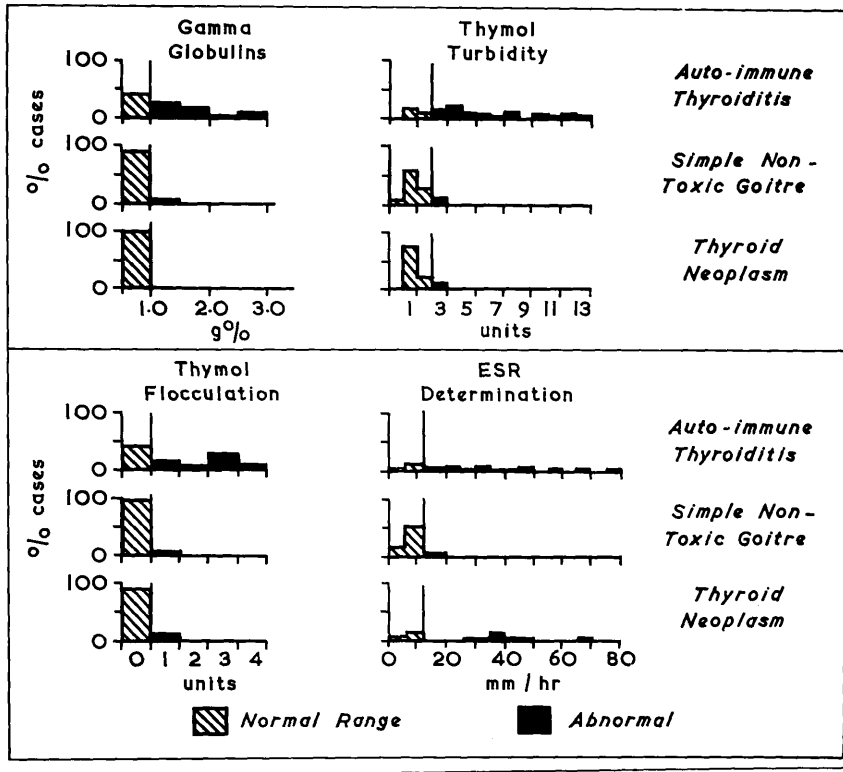


Table IV

Iodine Metabolism in Auto-immune Thyroiditis and Simple Goitre.

Measurements.	Auto-immune Thyroiditis		Simple Goitre	
	No. of Cases.	Mean and S.E.	No. of Cases.	Mean and S.E.
2½ hr. uptake I^{132} (% dose).	15	25.7 ± 2.4 (10.3 - 46.6)	53	32.8 ± 1.85 (21.7 - 76.4)
4 hr. uptake I^{131} (% dose).	49	37.4 ± 2.3 (7.5 - 77.1)	107	46.8 ± 4.1 (17.1 - 75.2)
48 hr. uptake I^{131} (% dose).	49	40.1 ± 3.1 (10.2 - 79.8)	107	49.3 ± 4.9 (16.0 - 81.2)
Thyroid clearance (ml./min.).	15	22.7 ± 3.7 (2.9 - 52.9)	53	50.2 ± 5.2 (6.6 - 155.4)
Plasma inorganic iodine (ug.%)	14	0.20 ± 0.04 (0.02 - 0.58)	53	0.08 ± 0.008 (0.02 - 0.19)
Absolute iodine uptake (ug./hr.)	14	2.0 ± 0.4 (0.4 - 5.9)	53	1.8 ± 0.16 (0.7 - 5.9)
48 hr. PBI^{131} (% dose/l.).	49	0.38 ± 0.08 (0.05 - 2.74)	107	0.06 ± 0.02 (0.05 - 0.35)
Serum PBI (ug.%).	45	2.6 ± 0.4 (10.5 - 5.3)	53	5.1 ± 0.17 (2.8 - 8.2)
Intrathyroidal exchangeable iodine (mg.)	11	1.2 ± 0.2 (0.05 - 3.8	3	10.3 (6.2 - 14.6)
Renal clearance of iodine (ml./min.).	14	28.1 ± 1.9 (16.5 - 43.5)	21	37.8 ± 2.6 (16.0 - 63.7)

Range is given in Brackets below mean and S.E.

Table V.

Perchlorate Discharge Tests, BII^{131} determinations, and TSH tests in Auto-immune Thyroiditis and Simple Goitre.

Measurements		Auto-immune Thyroiditis	Simple Goitre
Perchlorate Discharge Tests	No. Tested	32	13
	No. Positive	12	0
	% Positive	37.5	0
48 hr. BII^{131} (% PBI^{131})	No. Tested	9	-
	No. Abnormal	5	-
	% Abnormal	55.6	-
TSH Tests (both I^{131} Uptake and PBI^{131} Discharge)	No. Tested	16	7
	No. Normal	2	7
	% Normal	12.5	100

/since it was positive (both + and ++) in 9 per cent. in simple goitre and in 92 per cent. in auto-immune thyroiditis. The results of the precipitin and CF auto-antibody tests obtained by other workers (16-18,22) are summarised in Table III, and are in general agreement with my own observations. However, both Roitt and Doniach (16) and Blizzard et al. (19) reported positive precipitin tests in patients with simple goitre, but it is to be noted that the diagnosis was not confirmed by histological examination.

As previously discussed in Section 3 of this Chapter of the thesis, the finding of raised gamma-globulin levels, abnormal thymol turbidity and flocculation tests, and an elevated ESR, is presumptive evidence of auto-immune thyroiditis in a goitrous patient who has no systemic or connective tissue disease. The value of these determinations in the differentiation of auto-immune thyroiditis from simple goitre is illustrated in Fig. 1.

The results of radioiodine and stable iodine studies in auto-immune thyroiditis and simple goitre* are compared in Tables IV and V. It can be seen that neither the radioiodine uptake nor AIU help to differentiate the 2 disorders, but the finding of a high PBI^{131} or BII^{131} in association with a normal uptake and low PBI favours auto-immune thyroiditis. On the other hand, a low PII with a high thyroid clearance indicates iodine deficiency, and favours simple goitre. The IEI is low in auto-immune thyroiditis, and is/

* I am grateful to Dr. D.A. Koutras for the results of the studies in iodine metabolism in simple goitre.

/is normal in simple goitre, but this test is too elaborate as a routine diagnostic procedure.

From Table V it can be seen that the potassium perchlorate discharge test is helpful in differentiating the 2 diseases. Although positive in only half the patients with auto-immune thyroiditis, it is nevertheless invariably negative in simple goitre. The TSH test also provides a good test for distinguishing the 2 conditions. This is especially so now that I^{132} is readily available. In auto-immune thyroiditis the response of the gland is impaired, whereas it is normal in simple goitre. A normal suppression of uptake with thyroxine or triiodothyronine therapy occurs in both conditions and is therefore of no value as a differential test.

(2) Thyroid Neoplasm.

Although thyroid neoplasm is a rare disease its differentiation from auto-immune thyroiditis is of considerable practical importance. The 2 diseases may be confused clinically and on histological criteria (23). In auto-immune thyroiditis, both carcinoma, usually papillary (24), and non-epithelial lymphoid tumours (25,26), are said to occur more frequently than expected.

Experience of this problem in the present study is limited to 18 patients with histologically proven thyroid neoplasms (see Appendices for further details). Little difficulty was experienced in these patients in differentiating thyroid neoplasm from/

Table VI

Prevalence of Thyroid Auto-antibodies in Thyroid Neoplasm.

Table VI.

Prevalence of Thyroid Auto-antibodies in Thyroid Neoplasm.

Authors	Year	Ref. No.	No. of Cases.	Positive Thyroid Auto-antibody Tests		
				Prec.	CF	TRC
Paine et al.	1957	15	6	0		2
Doniach et al.	1958	29	36	0	4	9
Stuart and Allan	1958	27	6	2		3
Belyavin and Trotter	1959	48	25	0	6	
Blizzard et al.	1959	19	2			0
Cline et al.	1959	20	1			0
Hackett et al.	1960	21	2			1
Present Series			18	1	2	

/from auto-immune thyroiditis - the presence of a rapidly enlarging goitre of short duration, associated with pain and tenderness, severe pressure effects including vocal cord paralysis, or cervical lymphadenopathy, drawing attention to the neoplastic process (Table I).

The precipitin test was positive in one patient with a papillary adeno-carcinoma of the thyroid; sections of the gland in this patient also revealed the presence of severe chronic thyroid-:itis. Positive precipitin tests have been reported in 2 patients by Stuart and Allen (27) and in one patient by Smart and Owen (28), although in the majority of patients the test has been negative (Table VI). The prevalence of positive CF tests in the present series (2 of 18) corresponds with the expected incidence of 10 per cent. of focal thyroiditis in thyroid neoplasms (30).

As previously discussed in Section 3, the results of the thymol turbidity and flocculation tests and electrophoresis of the serum proteins are of some value in differentiating the 2 diseases, although the ESR is raised in both conditions (Fig. 1).

Routine radioiodine tests have been carried out in patients with thyroid neoplasms. High normal PBI^{131} values, due perhaps to associated thyroiditis or to the production of abnormal butanol-insoluble iodinated proteins (31), were found in 3 patients, and might have led to diagnostic difficulties had the clinical features been atypical. Doniach and Hudson (32) and Murray and McGirr (33)/

/McGirr (33) have suggested that topographical survey of the goitre might be helpful in differentiating the 2 diseases;/ insufficient experience has been gained with this and other ancillary radioiodine tests to make any comment on their diagnostic value.

In conclusion, it is clear that in differentiating auto-immune thyroiditis from thyroid neoplasm, the results of the precipitin test must be interpreted with caution and only in conjunction with careful clinical assessment and other laboratory investigations. If the clinical findings are at all suggestive of neoplasm, then biopsy should be performed.

(3) Thyrotoxicosis.

Euthyroid patients with auto-immune thyroiditis may simulate mild thyrotoxicosis and have radioiodine tests which confirm this diagnosis. In the present study 5 of the 50 patients suffering from auto-immune thyroiditis presented in this way. This problem will be fully dealt with in Section 2, Chapter III of the thesis.

(4) Dyshormonogenesis.

Dyshormonogenesis may rarely present as a goitre and hypothyroidism in adult life (34) and so simulate auto-immune thyroiditis. Radioiodine tests may be misleading since the PBI^{131} and BII^{131} may be elevated due to the formation of abnormal iodinated proteins (35). The PBI may be low and the response to TSH stimulation impaired. Moreover, the potassium perchlorate discharge test is positive in the peroxidase-deficiency type of dyshormonogenesis (36).

Four/

/Four adult patients with dyshormonogenesis were encountered in the present study who might have been misdiagnosed as auto-immune thyroiditis, although in all 4 the goitre was "soft" in consistency. Three of the patients had peroxidase defects and deaf-mutism (Pendred's syndrome) and the fourth had a dehalogenase defect (37). All 4 were readily differentiated from auto-immune thyroiditis by stable iodine studies and the finding of a greatly increased AIU (37). The precipitin and CF tests, serum flocculation tests, gamma-globulin values, and ESR determination, were all normal.

(5) "Iodide" Goitre.

The protracted use of iodides for asthma or bronchitis may occasionally be complicated by the development of a goitre with or without hypothyroidism (40-46), and so be confused with auto-immune thyroiditis. Paris et al. (45) have recently summarised the differential diagnosis between the 2 conditions. Little help can be obtained from the consistency of the goitre or the clinical status, and the PBI^{131} and BII values may be elevated in both conditions. On the other hand, the PBI is low or normal in auto-immune thyroiditis and high during iodide administration, and this serves to differentiate the 2 diseases. Only one patient was observed during the course of the present investigation who presented with a goitre and hypothyroidism due to the taking of "Felsol" powders; the precipitin and CF tests and the serum flocculation tests and gamma-globulin values were normal and spontaneous recovery occurred with stopping the powders.

The/

/The differential diagnosis of iodide goitre and auto-immune thyroiditis rests primarily on the history of ingestion of iodides or iodine containing compounds, but the application of stable iodine measurements will greatly facilitate the differentiation of the 2 diseases. Further experience is necessary in order to assess the diagnostic value of the serological and biochemical tests.

(6) Goitre due to Goitrogens.

Goitre with or without hypothyroidism may result from the ingestion of a goitrogen or from its application to the skin (47). One such case due to the prolonged application of a resorcinol-containing cream to a varicose ulcer in the leg was observed in the present study. The precipitin, CF, and serum flocculation tests were negative and the gamma-globulin and ESR values normal. Stable iodine studies showed a normal accumulation of iodine (i.e. AIU) by the thyroid gland with a low level of PBI - a pattern similar to that seen in auto-immune thyroiditis. Confirmation of the diagnosis was obtained by shrinkage of the goitre and disappearance of hypothyroidism with withdrawal of the ointment.

(7) Subacute Thyroiditis.

This is a rare disease in this country, but occasionally may cause difficulty in differential diagnosis. The onset of auto-immune thyroiditis may be abrupt and associated with pain in the goitre and fever, and thyroid auto-antibodies may be temporarily present/

/present in subacute thyroiditis (15,19,20). However, in subacute thyroiditis the radioiodine uptake by the thyroid is depressed during the acute stage of the disease, and this differentiates the 2 conditions.

SUMMARY

The differential diagnosis of auto-immune thyroiditis is discussed in relation to simple non-toxic goitre, thyroid neoplasm, dyshormonogenesis, "iodide" goitre and goitre due to goitrogens, and subacute thyroiditis. Auto-immune thyroiditis and simple non-toxic goitre can be readily differentiated on the basis of a combination of clinical and laboratory findings including serological, biochemical and radioiodine tests. Most cases of auto-immune thyroiditis can be differentiated from thyroid neoplasm, but the occasional occurrence of a positive precipitin test in the latter makes it necessary to carry out thyroid biopsy when the clinical findings are equivocal. The differential diagnosis of auto-immune thyroiditis with dyshormonogenesis, "iodide" goitre, and goitre due to goitrogens, can be made on the basis of a careful history and laboratory tests, but further experience will be required to assess the value of the immunological and biochemical tests. Subacute thyroiditis can usually be differentiated on the clinical history and the results of radioiodine tests.

Section 6.

The Treatment of Auto-immune Thyroiditis.

Surgical treatment of the goitre in auto-immune thyroiditis leads to a high incidence of post-operative hypothyroidism (1). For this reason, recommendations for surgery are generally limited to the relief of pressure effects or to the elimination of an associated neoplasm (2-5), although both Keleher (6) and Priebe and Patterson (7) have recently advocated subtotal thyroidectomy as the treatment of choice.

A variety of conservative measures, including treatment with radium (8-9), X-rays (10-13), steroids (2,13-16), thiouracil (17) and methylthiouracil (18), and bismuth (19) have been tried in the past with variable success. All have, however, been largely superseded by treatment with desiccated thyroid extract, which has proved satisfactory in both reducing goitre size and correcting hypothyroidism and the serum biochemical abnormalities (12-14, 20-26).

Personal Observations.

Macgregor (27) has suggested a more extensive use of the pure and synthetic thyroid compounds in view of the variable efficacy of dried thyroid preparations, but so far no study has been reported of the use of thyroxine sodium in the treatment of auto-immune thyroiditis. Opportunity has, therefore, been taken to study the effect of thyroxine sodium 0.1 mg. twice daily by mouth in 19 of the patients of the present study. The duration of treatment varied from 2 to 36 months with a mean follow-up of 15.4 months.

The/

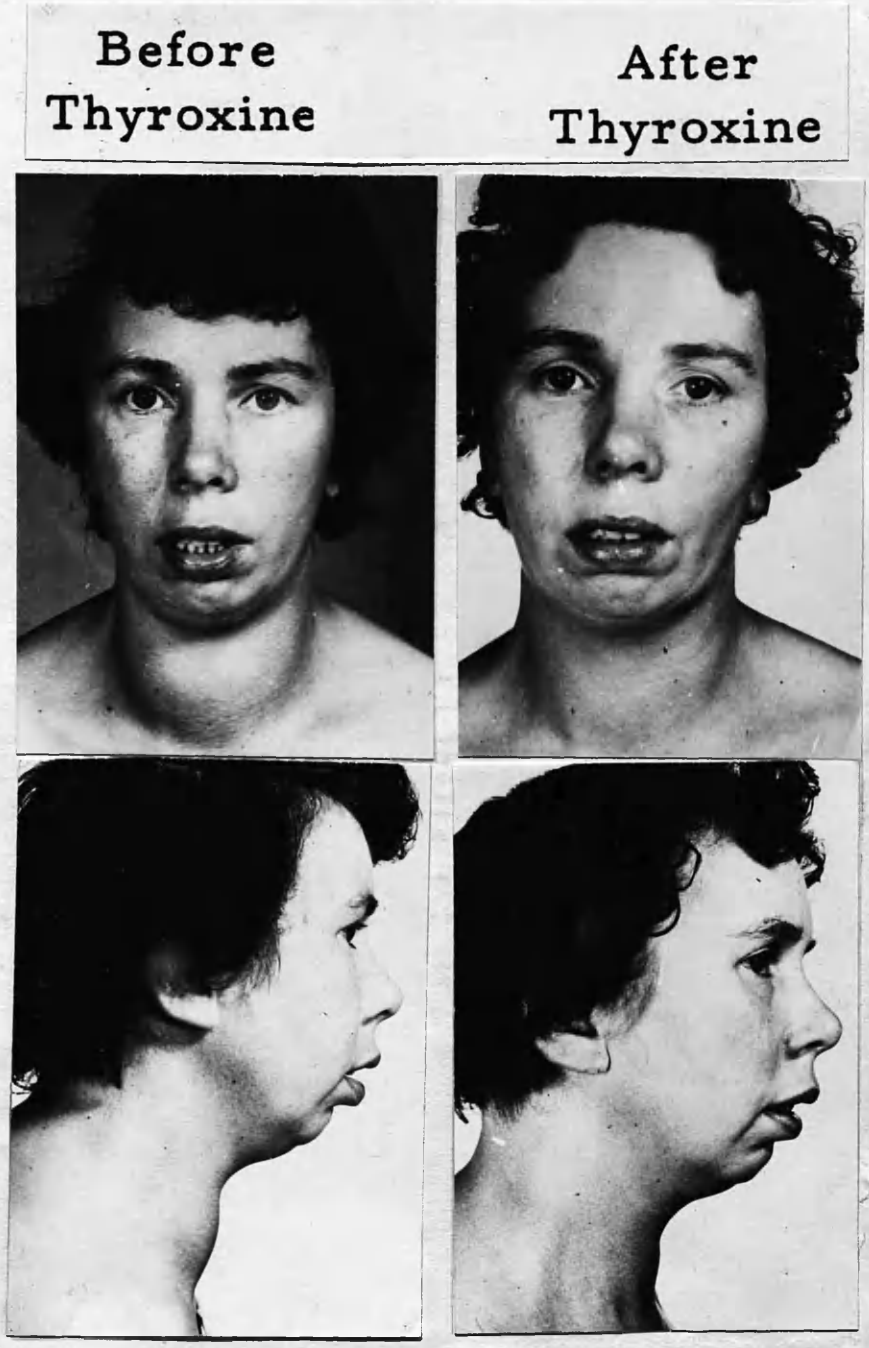
FIGURE 1.

Effect of Thyroxine Sodium Therapy on Goitre Size.

TABLE I.

Effect of Treatment with Thyroxine Sodium in 19 Patients with Auto-immune Thyroiditis.

Fig. 1.



Woman, aged 40 years (Thesis No. 16). Marked shrinkage of goitre after 36 months thyroxine sodium therapy. Initial neck circumference 15.5 inches; final neck circumference 13.5 inches.

TABLE I.

Effect of Treatment with Thyroxine sodium in 19 patients with Auto-immune Thyroiditis.

	Mean Neck Circumference (inches). Mean S.D.	Thyroid Auto-Antibody Tests: Precipitin No. Pos.	Precipitin % Pos.	Complement-Fixation No. Pos.	Complement-Fixation % Pos.	Serum Proteins (g./100 ml.): Albumin Mean S.D.	Globulin Mean S.D.	γ Globulin Mean S.D.	Serum Flocculation Tests (units): Thymol Turbidity Mean S.D.	Thymol Flocculation Mean S.D.	E.S.R. (mm./first hr.) Mean S.D.
Before	14.78 ± 1.11	16	84.2	19	100	4.23 ± 0.40	2.66 ± 0.67	1.41 ± 0.57	7.0 ± 4.5	2.0 ± 1.5	25 ± 15
After	13.63 ± 1.06	13	68.4	19	100	4.59 ± 0.36	2.34 ± 0.62	1.00 ± 0.39	4.0 ± 2.2	1.0 ± 0.1	15 ± 9
P values	< 0.001					< 0.001	< 0.001	< 0.001	< 0.001	< 0.01	< 0.01

The P values have been calculated from the mean difference of the values before and after treatment and its standard error and not from the differences between the means.

/The results of this investigation are summarised in Table 1 and are given in more detail in the Appendices. There was a variable but significant ($P < 0.001$) reduction in goitre size, which was quite marked in several patients (Fig. 1) and particularly so in those with small goitres of recent onset. There was also a significant restoration of the biochemical abnormalities with thyroxine sodium therapy (Table 1), although with 3 exceptions, the precipitin and CF tests remained unchanged. Changes in the biochemical and serological tests were even more pronounced in patients treated by surgery (see Appendices).

The indications for treatment with thyroxine sodium in the euthyroid patient with auto-immune thyroiditis remains debatable, although Hubble (26) and Crile (13) are in agreement in recommending thyroid replacement therapy even when the patient is not hypothyroid. In the preceding sections of this Chapter of the thesis it was emphasised that the clinical division between euthyroid and hypothyroid was entirely arbitrary, since many of the euthyroid patients had laboratory evidence of thyroid underactivity, e.g. low BMRs, raised serum cholesterol levels, and abnormal electrocardiograms. Furthermore it was shown that the clinically euthyroid patients had as a group a significantly lower level of serum PBI than a normal control group. It is, therefore, concluded that thyroxine sodium in physiological replacement dosage is indicated in all patients with auto-immune thyroiditis irrespective of their clinical status.

SUMMARY

The effect of treatment with thyroxine sodium 0.1 mg. twice daily by mouth has been studied in 19 patients with auto-immune thyroiditis.

A variable but significant shrinkage of the goitre was associated with a return to normal of the biochemical abnormalities, although there was little change in the results of the precipitin and CF auto-antibody tests.

Mild degrees of hypothyroidism detected only by laboratory procedures are not infrequent in auto-immune thyroiditis; consequently, thyroxine sodium should be prescribed in all patients irrespective of their clinical status and the treatment continued for life.

Rarely surgical intervention may be necessary to relieve pressure symptoms when thyroxine sodium therapy has failed to reduce the size of the goitre. X-ray or steroid therapy may provide alternative methods of treatment in these circumstances if surgery is contraindicated.

C H A P T E R III.

The Relationship of Auto-immune Thyroiditis to Primary Hypothyroidism and Thyrotoxicosis.

Section 1.

The Relationship of Auto-immune Thyroiditis to Primary Hypothyroidism.

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VOLUME II.

Sir William Gull (1) first described a "cretinoid condition supervening in adult life in women" in 1874, and the disease was named "myxoedema" by W.M. Ord (2) in 1877, on account of the abnormal amount of mucin in the subcutaneous tissues. In 1893 Halliburton (3) pointed out that "myxoedema" was by no means a constant feature and suggested the term "hypothyroidism", which has been favoured by recent writers on the subject (4).

Hypothyroidism may result from a number of conditions giving rise to thyroid destruction or dysfunction or be secondary to pituitary failure but it is the spontaneous "primary" form of the disease with which the following account is concerned.

Past views regarding Aetiology and Pathogenesis of Primary Hypothyroidism.

In 1951 McGavack (5) voiced the opinion of most writers of textbooks on Diseases of the Thyroid (6-8) when he considered that "the majority of cases of spontaneous hypothyroidism are due to an atrophy of the thyroid gland, the aetiology of which is still undetermined". There is an undoubted genetic factor (9-12) and Draper (13) considered that patients with the disease "tend to be broad shouldered, short-necked, and stocky, to have a sunny disposition and a sense of humour". On the other hand, Werner (8) considered emotional depression or "apathetic withdrawal" as a possible predisposing cause. Females are predominantly affected, especially multiparae (14), but the role the ovarian hormones/

Figure 1.

Illustration of histological appearances in the thyroid gland in myxoedema. Committee appointed by the Clinical Society of London (1888).

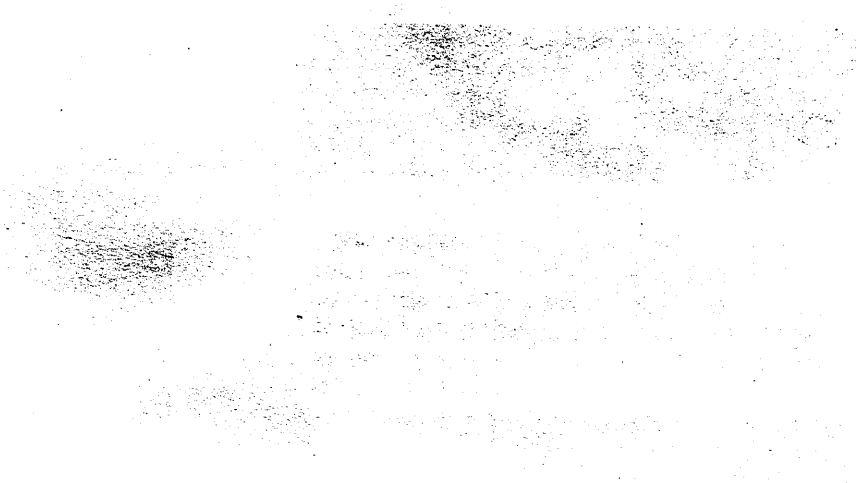
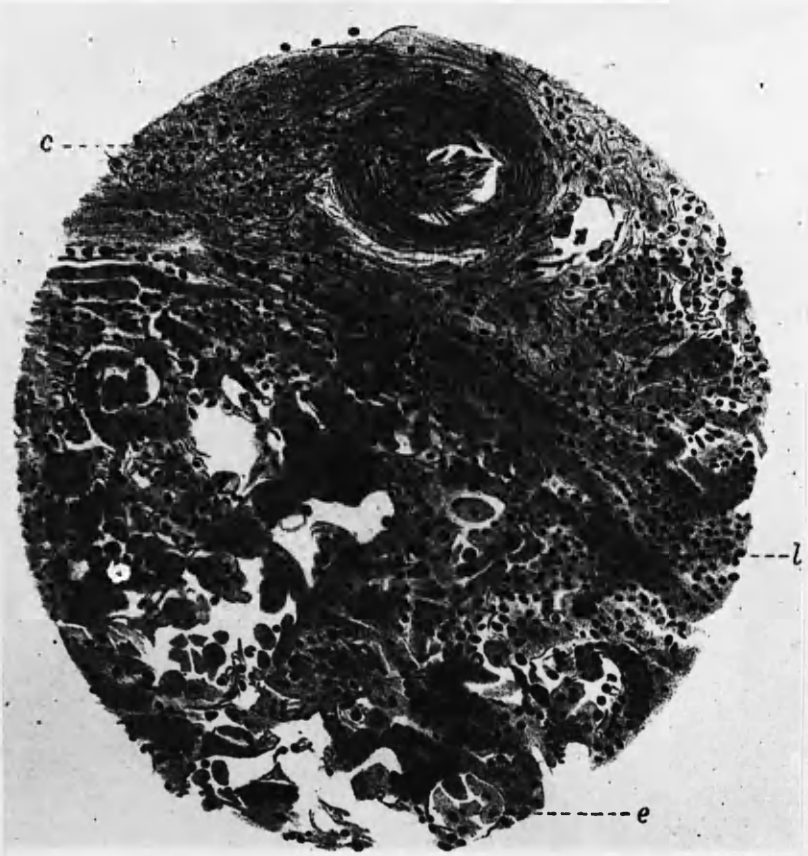


Fig. 1.



The remnant of a lobule is seen undergoing atrophic changes. The epithelium (*e.*) is proliferating and at the same time atrophying, as seen specially at the margin of the lobule. The destruction is secondary to the invasion of the interstitial capsular tissue (*c.*), which is thickened by leucocytes (*l.*). The process is apparently one of contractile or atrophic cirrhosis.

/hormones play in the pathogenesis is obscure. Occasionally the onset of the disease may be preceded by some years with a history of thyrotoxicosis (15-17), and Eason (18) considered that in these cases primary hypothyroidism might represent the final end result of a "burnt-out" thyrotoxicosis.

The Relation of Auto-immune thyroiditis to Primary Hypothyroidism.

Historical Aspects.

The historical aspects of the possible relationship between the 2 diseases can be considered under 3 headings: (1) Morbid Anatomy, (2) Iodine Metabolism and Biochemical aspects, and (3) Immunology. These will now be briefly outlined.

(1) Morbid Anatomy. Opportunities to study the morbid anatomy of the thyroid in primary hypothyroidism have been infrequent, and in most reports the gland is reported as showing "a variable degree of atrophy and fibrosis". However, in a histological study based on 13 cases, the Committee appointed by the Clinical Society of London (19) in 1888, reported, "lymphocytic infiltration, scattered epithelial cells, disappearance of acini and of colloid" in addition to fibrotic replacement of the parenchyma. In one of the illustrations in this report (Fig. 1) the appearances appear to be very similar to those seen in auto-immune thyroiditis. Indeed, Jaffé (20) and Bastenie (21) both concluded that from a histological point of view there was no essential difference between the 2 diseases; this view has also been supported by recent studies (22, 23).

(2) Iodine Metabolism and Biochemical Aspects. In 1956 Skillern et al. (24) proposed that auto-immune thyroiditis was "primary thyroid failure with compensatory thyroid enlargement", whereas primary hypothyroidism without a goitre represented "de-compensated thyroid failure", on the grounds that the thyroid was insensitive to stimulation by TSH in both conditions. The reason for the inability of the thyroid to enlarge in response to TSH stimulation in patients with primary hypothyroidism was however obscure. In addition, Skillern et al. (24) drew attention to hypergammaglobulinaemia and abnormal colloidal gold curves which occurred in both diseases.

(3) Immunology. In 1942, Lerman (25) observed that rabbits experimentally immunised against human thyroglobulin developed antibody to their own thyroids, and that they became hypothyroid over the course of about 6 months. The possible relevance of these facts to the pathogenesis of primary hypothyroidism escaped attention until 1957, when Doniach and Roitt (26) described thyroid auto-antibodies in patients with the disease. This finding supported the earlier histological studies, and the hypothesis of Skillern et al. (24), of a basic unity between the 2 diseases.

Personal Observations.

The present investigation confirms and extends these earlier observations, and supports the belief that auto-immune thyroiditis and primary hypothyroidism share a common pathogenetic basis.

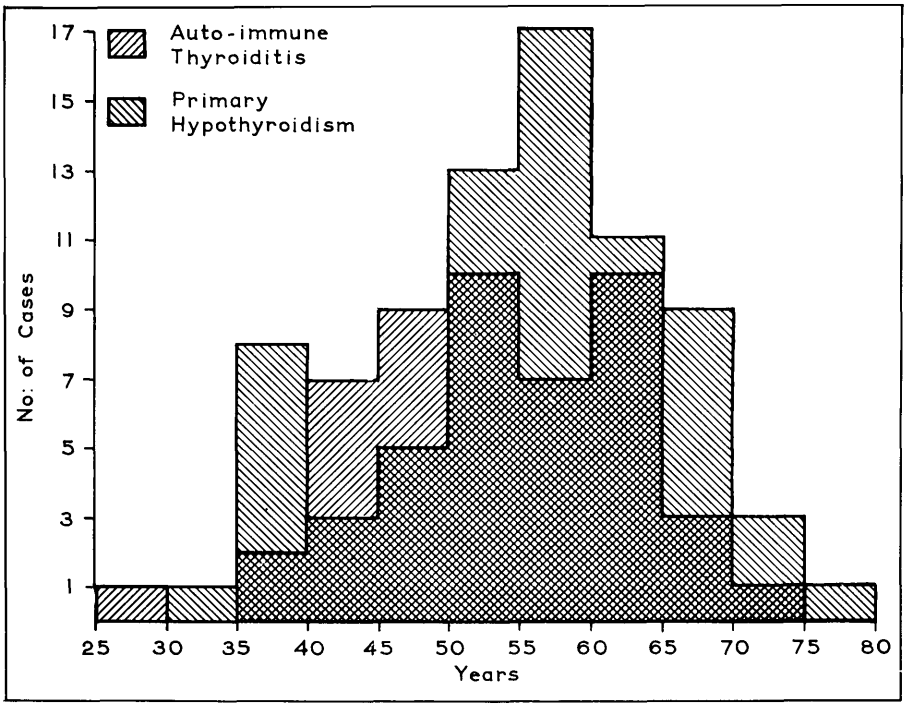
The/

Figure 2.

Comparison in Age Distribution in Auto-immune Thyroiditis and Primary Hypothyroidism.

Fig. 2.

COMPARISON IN AGE DISTRIBUTION IN AUTO-IMMUNE THYROIDITIS AND PRIMARY HYPOTHYROIDISM



/The clinical, serological and biochemical features have been studied in 71 patients with primary hypothyroidism and compared with those in 50 patients with auto-immune thyroiditis.

Materials and Methods

The clinical details of the 71 patients with primary hypothyroidism are summarised in the Appendices. The diagnosis of primary hypothyroidism was based on clinical features of hypothyroidism (4) in an agoitrous subject with no evidence of hypopituitarism. The diagnosis was confirmed by serum cholesterol and BMR determinations, 13-lead ECGs, routine radioiodine tests, and serum PBI estimations. The methods used have been described in detail in Chapter II.

Results

(1) Clinical Features

Age. The age distribution in the 2 diseases was strikingly similar (Fig. 2). The age range for patients with primary hypothyroidism was 34 to 73 years (mean age 55.0 years), and 28 to 70 years (mean age 52.5 years) in auto-immune thyroiditis.

Sex. Females were predominantly affected in both diseases, although the proportion of males (18.3 per cent) was higher in primary hypothyroidism than in auto-immune thyroiditis (8 per cent).

Past History of Thyrotoxicosis. This was elicited on careful enquiry/

Table I

Prevalence of Thyroid Auto-antibodies in Primary Hypothyroidism.

Figure 3.

Biochemical Studies in Auto-immune Thyroiditis and Primary Hypothyroidism.

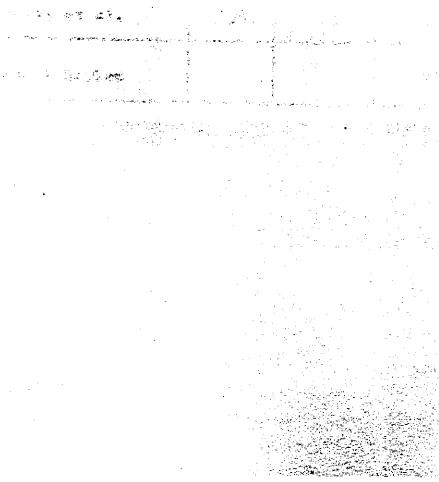


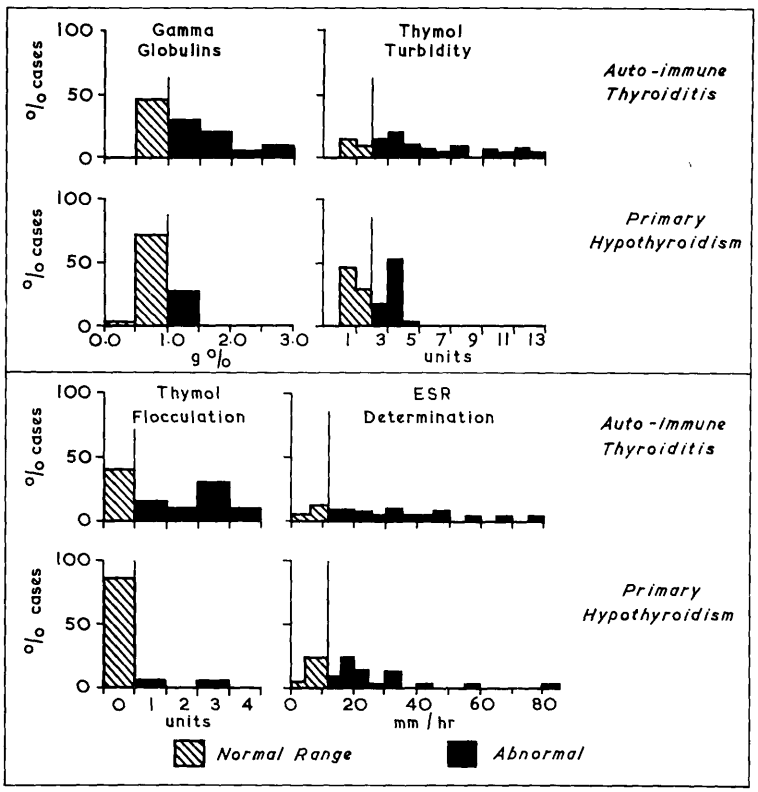
Table I.

Prevalence of Thyroid Auto-antibodies in Primary Hypothyroidism.

Authors	Year	Ref. No.	No. of Cases.	Positive Thyroid Auto-antibody Tests		
				Preo.	CF	TRC
Murray	1958	29	45	9	30	
Owen and Smart	1958	30	78			63
Roitt and Doniach	1958	28	101	19	64	66
Anderson et al.	1959	31	90	13	48	
Belyavin and Trotter	1959	32	19	4	10	
Blizzard et al.	1959	33	4	0		7
Cline et al.	1959	34	2			0
Hackett et al.	1960	35	20			12
Present Series			71	11	36	

Fig. 3.

BIOCHEMICAL STUDIES IN AUTO-IMMUNE THYROIDITIS AND PRIMARY HYPOTHYROIDISM



/enquiry in 5 patients (7.0 per cent.) with primary hypothyroidism, as compared with 6 per cent. in auto-immune thyroiditis.

Family History of Thyroid Disease. A family history of thyroid disease was obtained in 8 patients (11 per cent.) with primary hypothyroidism as compared with 16 per cent. in patients with auto-immune thyroiditis. A family history of thyroid disease was obtained particularly in those patients with primary hypothyroidism who had positive precipitin tests.

(2) Immunology

The prevalence of positive precipitin and CF tests (15.5 and 46.5 per cent. respectively) in the 71 patients with primary hypothyroidism in the present study is in close agreement with the results obtained by other workers (28-35) (Table I), but contrasts with the much higher prevalence of these auto-antibodies in the 50 patients with auto-immune thyroiditis - 76 and 92 per cent. respectively. Positive skin tests are found in both conditions (see Chapter II, Section 2).

(3) Biochemistry

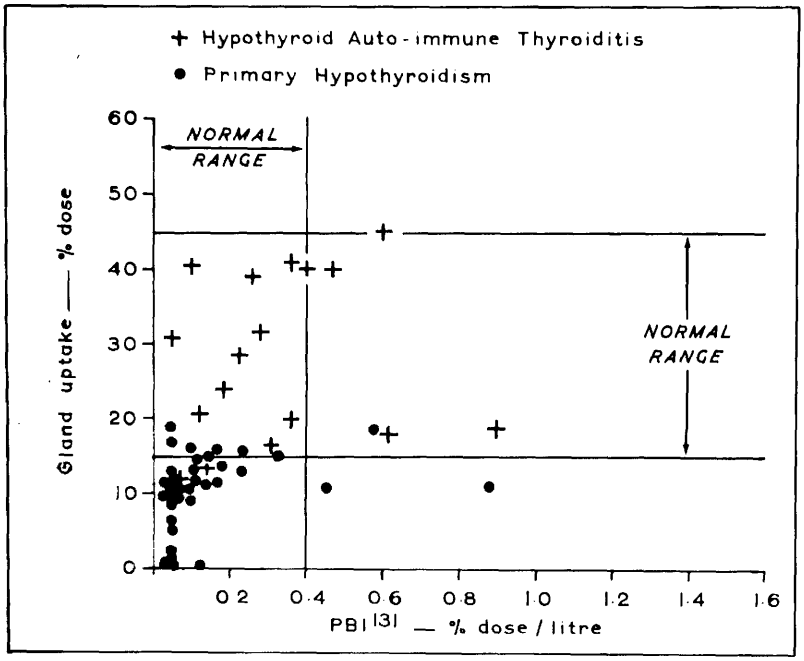
In Section 3 of Chapter II of the thesis it was shown that raised gamma-globulins, abnormal thymol turbidity and flocculation tests, and elevated ESR values, were found in patients with both primary hypothyroidism and auto-immune thyroiditis. These abnormalities were, however, more pronounced in patients with auto-immune thyroiditis (Fig. 3) and in patients with primary hypothyroidism with positive precipitin/

Figure 4.

Results of Routine Radioiodine Tests in Hypothyroid Auto-immune Thyroiditis and Primary Hypothyroidism.

Fig. 4.

RESULTS OF ROUTINE RADIOIODINE TESTS IN HYPOTHYROID AUTO-IMMUNE THYROIDITIS AND PRIMARY HYPOTHYROIDISM



/precipitin tests, suggesting that they were associated with the auto-immune process and not with the hypothyroidism per se.

(4) Iodine Metabolism

Radioiodine tests. These are summarised in Fig. 4. It can be seen that in general patients with primary hypothyroidism had both a low 4-hour uptake and low PBI^{131}, whereas hypothyroid patients with auto-immune thyroiditis had a normal uptake and elevated PBI^{131}. Some overlap, however, does occur.

Potassium perchlorate discharge tests. These were performed in 7 patients and positive tests similar to those found in auto-immune thyroiditis were present in 2.

TSH tests. These were carried out in 15 patients with primary hypothyroidism. No increase was noted in the $2\frac{1}{2}$-hour uptake of I^{132} in any of the patients. This corresponds with the findings in auto-immune thyroiditis (see Chapter II, Section 4).

BII^{131}. This was estimated in 2 patients with primary hypothyroidism who had high PBI^{131} values. High values were found in both - 35 and 40 per cent. respectively of the total PBI^{131} values.

(5) Intermediate Syndromes

Several patients in the present study with primary hypothyroidism had what might be described as an "intermediate" syndrome between this disease and auto-immune thyroiditis. The following is an illustrative case:-

A woman, aged 60 years, complained of increasing physical tiredness/

/tiredness, mental lethargy, acroparaesthesiae, deafness, cold intolerance, and hoarseness of a year's duration. She had also been aware of loss of hair, dryness of the skin, and weight increase, but had not been constipated. There was no past history of thyroid disease and no family history of thyroid disorder. On physical examination she presented the typical appearances of hypothyroidism but had no palpable thyroid tissue. Additional investigations included: precipitin test (+), CF test (++), thymol turbidity 3 units, thymol flocculation 1 unit, gamma globulin 1.2 g. per 100 ml., ESR 40 mm. in the first hour, radioiodine tests: 4-hour uptake 18.8 per cent per dose, 48-hour PBI^{131} 0.58 per cent per dose per litre, potassium perchlorate discharge test positive, BII^{131} 35 per cent. of PBI^{131}, and serum PBI 3.0 µg. per 100 ml. Investigations confirmed the diagnosis of hypothyroidism: BMR-6 per cent., serum cholesterol 370 mg. per 100 ml., and ECG consistent with hypothyroidism.

Comment

The findings in the present investigation show that no clear dividing line can be drawn between primary hypothyroidism and auto-immune thyroiditis; this supports the histological evidence that the 2 diseases are variants of the same fundamental process. The pathogenesis of primary hypothyroidism is associated auto-immunisation in a proportion of cases, but the fundamental problem of causation remains obscure. The actual lesion which provokes thyroid auto-immunisation/

/immunisation has not been identified, although it is probable that approximately 5 per cent. of cases of primary hypothyroidism represent a "burnt-out" thyrotoxicosis. The low prevalence of thyroid auto-antibodies in primary hypothyroidism may be due to the small shrunken gland containing little or no colloid and a meagre quantity of antibody forming cells (36).

SUMMARY

The clinical and laboratory features in 71 patients with primary hypothyroidism have been compared with these in 50 patients with auto-immune thyroiditis. The features common to both diseases included:-

(1) Clinical - age distribution, female preponderance, past history of thyrotoxicosis, and family history of goitre.

(2) Immunological - precipitin and complement-fixation (CF) thyroid auto-antibody tests, and skin tests.

(3) Biochemical - raised gamma-globulins, abnormal thymol turbidity and flocculation tests, and elevated ESR determinations.

(4) Radioiodine studies - raised 48-hour PBI^{131} and BII^{131} values, positive perchlorate discharge, and unresponsiveness to TSH stimulation.

Several patients had "intermediate" syndromes between the 2 diseases.

It is concluded that primary hypothyroidism and auto-immune thyroiditis are variants of the same pathological process.

Section 2.

The Relationship of Auto-immune Thyroiditis to Thyrotoxicosis.

That a possible association exists between auto-immune thyroiditis and thyrotoxicosis has long been suspected, and the demonstration of thyroid auto-antibodies in the blood serum of patients with both diseases strengthens this view. The following historical review outlines the speculation and fact concerning the association between the 2 diseases.

Historical Outline

(1) Round-cell infiltration in the Thyrotoxic Gland and its relation to the Pathological changes of Auto-immune Thyroiditis.

Focal lesions of chronic thyroiditis have long been recognised as an integral part of the histological picture in thyrotoxicosis. Thus, Greenfield (1) in his Bradshaw lecture in 1893, noted that "proliferative change is liable to be followed by fibrous overgrowth" in the thyrotoxic gland, and the presence of lymphocytes attracted the attention of several workers at the beginning of the century (2-12). However, it was not until Brunger's report of 2 patients in 1914 (13), that chronic thyroiditis in the thyrotoxic gland became generally recognised (14-16). In 1934 Smith et al. (17) noted the similarity between this focal lesion and the changes seen in auto-immune thyroiditis, and 2 years later Broders (18) pointed out that chronic thyroiditis in varying degrees was present in the majority of thyrotoxic glands. Chronic thyroiditis of an unspecified degree was found in 75 per cent. of thyrotoxic glands by Simmonds (9), in 83 per cent. by Kocher (19), in 90 per cent. by/

/by Wegelin (20), and in 100 per cent. by Warthin (12) and Hertz (21). In the majority of cases the degree of round-cell infil-:tration was slight although both Hellwig (22) and Greene (23) found "severe" thyroiditis in a quarter of their cases. These "severe" degrees of round-cell infiltration were considered by Hellwig (22) to be characteristic of auto-immune thyroiditis, "a fact of particular interest that has been overlooked by most authors". Beattie et al. (24) went further and stated: "Thus the latter stages of a primary hyperplastic toxic (primary exoph-:thalmic) goitre, there may be degeneration and general atrophy of the epithelium as a result of exhaustion. In some cases, the degeneration and atrophy are focal, and around and obscuring the degenerating acini, collections of lymphocytes appear, sometimes forming lymph nodes. The name lymphadenoid goitre has been applied to this type of change". Lindsay et al. (25) also considered that auto-immune thyroiditis might be focal in its distribution since they could find no significant qualitative difference between the lesion seen in thyrotoxic glands and the slightly more extensive lesion classified as auto-immune thyroiditis. Friedman (26) also supported this view and found transformation to Hürthle cells so uniform in tissue removed after operation for thyrotoxicosis that he concluded "that some of the gland remnants were indisting-:uishable histologically from Hashimoto's disease". Contrary opinions were, however, expressed by Joll (27), Statland et al. (28), and Harland and Frantz (29), but it is to be noted that these workers/

/workers arbitrarily defined auto-immune thyroiditis as a diffuse and generalised process and excluded all cases showing thyrotoxic features from their series.

(2) Clinical Significance of Round-cell Infiltration in Thyrotoxic Glands.

Whatever the pathological significance of the round-cell infiltration in thyrotoxic glands and its association with auto-immune thyroiditis it appears from the studies of Whitesell and Black (30) at the Mayo Clinic, and workers in this country (23,31), that it may be of clinical importance. Thus, Whitesell and Black (30) found the incidence of post-operative hypothyroidism in a series of 86 thyrotoxic patients with varying degrees of lymphocytic and fibrocytic replacement to be 24 per cent. in those with lymphocytic infiltration only, and 34 per cent. in those with mixed fibrolymphocytic lesions; in patients showing 40 to 50 per cent. replacement the incidence of post-operative hypothyroidism approached 70 per cent. In a study of 2,114 thyroidectomies reported by Levitt (31) the incidence of post-operative hypothyroidism in glands showing "epithelial hyperplasia" only was 0.3 per cent., whereas the incidence was 27 per cent. in glands showing "diffuse lymphoid hyperplasia". These results were even more striking in the series of 570 cases studied by Greene (23), - 0.3 per cent. with "no lymphadenoid changes", 38.5 per cent. with "mild lymphadenoid changes", and 83.3 per cent with "advanced lymphadenoid changes"; this author concluded that "hypothyroidism occurs extremely/

Table I.

Summary of the Findings in Cases allegedly Illustrating the Co-existence of Auto-immune Thyroiditis and Thyrotoxicosis.

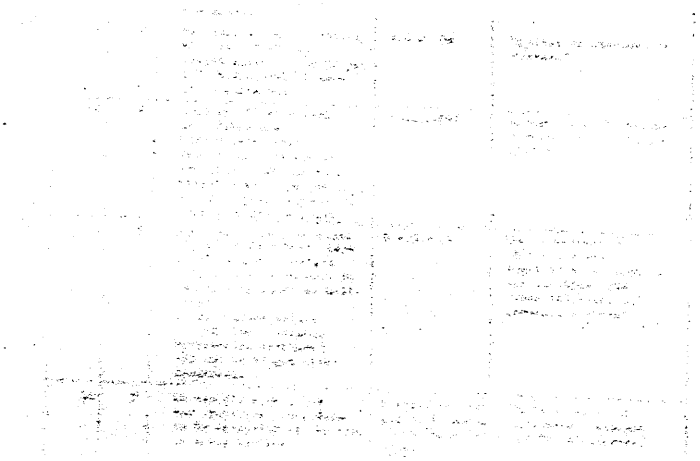


TABLE I. Summary of the Findings in Cases allegedly Illustrating the Co-existence of Auto-immune Thyroiditis and Thyrotoxicosis.

Authors	Year	Ref. No.	Age.	Sex.	Clinical Details and Response to Therapy.	Laboratory Investigations	Thyroid Histology
Pelowe	1934	32	26	F	Excessive sweating. Unable to gain weight. Slight enlargement of right lobe of thyroid. Pulse rate 120 per minute. No improvement with treatment.	B.M.R. +43% Serum cholesterol 195mg%.	"Areas of "hypertrophic" (toxic) struma and enormous lymphoid infiltration"
Poor et al.	1934	33	35	F	Nervousness and recent weight loss. Goitre, warm moist palms, tremor of fingers. Pulse rate 86 per min. No mention of response to treatment.	B.M.R. -2%	"Typical of Hashimoto's disease"
Boyden et al.	1935	34	20	F	No details given.	B.M.R. +30%	"Typical of Hashimoto's disease"
			27	M	Diabetes Mellitus. Weight loss. Exophthalmos and tremor. Responded to anti-thyroid therapy and gained 40 pounds in weight. B.M.R. fell to -5%	B.M.R. +47%	"Typical of Hashimoto's disease"
			30	F	Tiredness and sweating. Goitre present. B.M.R. fell to +0% with treatment.	B.M.R. +25%	"Typical of Hashimoto's disease"
Eden and Trotter	1942	35	35	F	General ill-health with weight loss and ankle swelling for 3 months. Goitre moderately enlarged and firm and Von Graefe's sign positive in each eye. Periorbital oedema and pretibial myxoedema. Generalised pigmentation. Skin warm and moist. Atrial fibrillation 90 to 100 per min. Became hypothyroid 4 months after operation.	B.M.R. +48%, + 44% +37% on 3 occasions.	Areas showing "epithelial hyperplasia together with wide-spread chronic thyreditis"
McSwain and Moore	1943	36	3 cases age & sex not given		Complained of nervousness and palpitations. All had a goitre and 1 had exophthalmos. Response to treatment not recorded.	B.M.R. +26% +16% -15%	"Typical of Hashimoto's disease" in all 3.
Gurkan	1945	37	56	M	Dyspnoea, nervousness, weight loss, and diarrhoea. Hard diffuse goitre. Exophthalmos, lid retraction and lid lag. Tremor of hands and legs. Pulse 130 per min. Increased weight with treatment.	B.M.R. +76%, + 87% and +80% on three occasions.	"Areas typical of thyrotoxicosis and of thyroditis of Hashimoto's type"
Hori	1946	38	41	F	Tiredness and palpitations Goitre for 30 years. B.M.R. -11% 8 days after operation	B.M.R. +8%	"Typical of Hashimoto's disease"
			35	F	Weakness and nervousness. Goitre present. "Slight widening of the palpebral fissures" Pulse 100 per min. B.M.R. 0% 7 days after operation.	B.M.R. +26% serum cholesterol. 119mg%	"Typical of Hashimoto's disease"
			60	F	Nervousness and sensation of heat. Goitre and exophthalmos. Pulse 90 per min. B.M.R. -19% 12 days after operation.	B.M.R. -5%	"Typical of Hashimoto's disease"
Pedigo and Abramson	1947	39	48	M	Acutely ill with fever and arthralgia. Nervousness, heat intolerance, excessive sweating, good appetite, weight loss. Firm goitre. No eye signs. Response to treatment not recorded.	B.M.R. +69%	"Hashimoto's thyroiditis supervened on a simple goitre"
Rabson and Arata	1949	40	27	F	6 months history of rapid thyroid enlargement. Loss of 55 pounds in weight (attributed by authors to co-existing diabetes mellitus). Firm, diffuse goitre, Exophthalmos, tremor. Nervousness decreased and gained weight with treatment.	B.M.R. +47%	"Areas typical of thyrotoxicosis, together with lymphoid infiltration with lymph follicles and germinal centres"
Hubble	1959	42	30	F	No details given, but had proptosis. Considered to be euthyroid at the time of investigation.	Precipitin test positive. Serum floculation tests normal. I^{131} tests 4-hr uptake 29%/dose 48-hr PBI^{131} 0.44%/dose/l. Potassium perchlorate discharge test positive. PBI 4.9µg%. BMR +8%	"Characteristic of Hashimoto's disease and Thyrotoxicosis."
Lawton	1957	41	42	F	Lost one stone in weight in 4 months and had sweating, tremor and upper lid lag	B.M.R +38% after 4 months treatment with methyl-thiouracil became hypothyroid. Thyroid extract prescribed and gland disappeared.	"Biopsy showed Hashimoto's disease". No mention of thyrotoxic epithelium.

/extremely rarely (perhaps never) after removal of thyroids which have no lymphadenoid changes, short of total thyroidectomy".

In these 3 studies the clinical severity of the thyrotoxicosis was less in those patients whose glands showed severe thyroiditis; Whitesell and Black (30) found a trend towards a reduction in the BMR and the incidence of atrial fibrillation. Neither Levitt (31) nor Greene (23) found a correlation between the degree of thyroiditis present and the age and sex of the patient, although Whitesell and Black (30) found the mean age of patients with fibrolymphocytic replacement to be 5.4 years less than those with lymphocytic infiltration, and that males had consistently less thyroiditis than females in corresponding decades. Greene (23) could find no correlation between the degree of thyroiditis found and the goitre type, although Levitt (31) noted less thyroiditis in diffuse goitres. Exophthalmos was found in these 3 studies to be increased in patients with thyroiditis present in their glands; Whitesell and Black (30) observed an incidence of 60 per cent. of exophthalmos in their patients showing more than 50 per cent. fibrolymphocytic replacement.

(3) <u>Clinical Association between Auto-immune thyroiditis and thyrotoxicosis.</u>

The alleged co-existence of auto-immune thyroiditis and thyrotoxicosis has been frequently reported (32-42). In general the patients in these reports fall into 2 main groups (Table 1). Firstly, there are the patients with histologically proven diffuse thyroiditis,/

/thyroiditis, i.e. auto-immune thyroiditis, who have manifested features, often mild and usually transient, of thyrotoxicosis (33,34,36,38,39,41). The evidence of thyrotoxicosis in these patients is unconvincing, and Joll (27) who discussed this problem at some length attributed the alleged toxic features to "local pressure, apprehension of cancer, etc." In the second group (32, 35,37,40,42) the diagnosis of thyrotoxicosis is more certain although by no means unequivocal (Table 1). In this group subsequent histological examination of the excised thyroid revealed various degrees of chronic thyroiditis, but it is difficult from the textual descriptions to decide whether the thyroiditis was sufficiently extensive to justify the description auto-immune thyroiditis.

As mentioned in Chapter II a past history of thyrotoxicosis can be elicited in a small proportion of patients with auto-immune thyroiditis. Fraser and Nordin (43) reported a patient with confirmed thyrotoxicosis who spontaneously developed hypothyroidism within 3 years; unfortunately no histological examination was carried out.

(4) Evidence of Progression of thyrotoxicosis to Auto-immune thyroiditis.

Many writers have supported the proposition of a progression of thyrotoxicosis to auto-immune thyroiditis. Thus, in 1927, in his address to the Edinburgh Medico-Chirurgical Society, Eason (44) presented both clinical and histological evidence (but not serial studies)/

/studies) that auto-immune thyroiditis had antecedent thyrotoxicosis. In 1938 Vaux (45) suggested that "the clinical evidence of thyrotoxicosis, especially in early cases, correlated with the histological findings of decreasing degrees of epithelial hyperplasia and increasing destruction of the acini as the condition progresses, points to some excessive evolution following a thyrotoxicosis of mild degree", and in 1948 Goldberg and Davson (46) concluded that "a toxic phase is sufficiently frequent (in auto-immune thyroiditis) to count as an important factor in the pathogenesis".

In 1951 Levitt (31) traced an apparently continuous pathological process from toxic diffuse goitre through auto-immune thyroiditis to struma fibrosa: "the thyrotoxic gland undergoes a gradual transition from epithelial hyperplasia characteristic of classical Graves' disease through successive phases of lympho-epithelial hyperplasia, focal and then diffuse lymphoid hyperplasia (lymphadenoid goitre), and fibro-lymphoid hyperplasia (Hashimoto's disease) to the final stage of fibrosis (Riedel's thyroiditis)". Levitt (31,48,49) postulated that these 2 apparently separate diseases - auto-immune thyroiditis and thyrotoxicosis were, in fact, successive stages of a single disease of the thyroid. Goetsch and Kamner (49) and Chesky et al. (50) supported this view and the latter authors went further and included subacute thyroiditis as a stage in the process.

Lennox (51) and others (52,53) strongly criticised Levitt's concept/

Table II

Histological Progression of Thyrotoxicosis to Auto-immune Thyroiditis: Summary of Findings in Cases Reported in the Literature with Twice-removed Thyrotoxic Glands.

Table II.

Histological Progression of Thyrotoxicosis to Auto-immune Thyroditis: Summary of Findings in Cases Reported in the Literature with Twice-removed Thyrotoxic Glands.

Authors	Year	Ref No.	No. of Cases	Interval between operation	Comments
Warthin	1929	54	2	15 years 7 operations during 18 years	"Lymphoid Hyperplasia"found in later specimens.
Reinhoff et al.	1934	55	10	Not Stated	No evidence of progression
Roussy et al.	1934	56	2	2 and 7 years	Lymphocytes and fibrosis in the second specimens.
Levitt	1951	31	22	Not Stated	16 progressed: 4 retrogressed and 2 remained unchanged
Spjut et al.	1957	57	57	3 months to 25 years	No convincing progression. 5 cases judged as "near misses",but changes interpreted as "exhaustion atrophy"
Curran et al.	1958	58	7	1 and 14½ years	No evidence of progression
Sclare	1959	59	2	15 and 20 years	Convincing evidence of progression in one case. First biopsy specimen not available in other.

/concept on the grounds that if it were correct proved progression from thyrotoxicosis to auto-immune thyroiditis should be common, and this was certainly not so far from the evidence given by Levitt (31). In 22 of the patients in Levitt's study in whom thyroid biopsy had been carried out following a previous operation, only 16 showed histological progression to a more advanced phase, whereas 4 had regressed, and 2 had remained unchanged. Histological details were unfortunately not provided, but the "progression" in the 16 patients was slight. Furthermore, in twice-removed thyrotoxic glands studied by other workers (54-59) few have manifested progression to auto-immune thyroiditis (Table II). Thus, it appears that most of the evidence of a natural progression of thyrotoxicosis to auto-immune thyroiditis is based on the clinical side (43,44) and only isolated patients, such as the one reported by Sclare (59), provide pathological support for such a concept.

(5) Immunological Studies in Thyrotoxicosis.

As early as 1908, Marinesco (60) demonstrated a positive CF reaction between aqueous extracts of thyrotoxic gland and the serum of patients from whom the glands were taken. Papazolu (61) in 1911 extended these observations, and demonstrated positive CF reactions in 26 of 38 thyrotoxic patients, but not in normal controls, and concluded on this evidence that the thyroid gland had acted as an antigenic stimulus and caused the formation of antibodies. In 1915/

Table III

Prevalence of Thyroid Auto-antibodies in Thyrotoxicosis.

Table III.

Prevalence of Thyroid Auto-antibodies in Thyrotoxicosis

Authors	Year	Ref No.	Total no. of cases	Positive thyroid Auto-antibody tests		
				Precipitin	CF	TMC
Paine et al.	1957	67	4			1
Roitt and Doniach	1958	68	181	2	67	103
Anderson et al.	1959	69	247	5	128	
Belyavin and Trotter	1959	70	66	6	28	
Blizzard et al.	1959	71	94	1		34
Cline et al.	1959	72	11	0	0	2
Blagg	1960	73	263			155
Schade et al.	1960	74	28		8	10
Hales et al.	1961	75	98			43
Present Series			468	5	231	

/1915 Beebe (62) attempted to treat patients with thyrotoxicosis with thyroid antisera, and from his report appeared to have a modicum of success. In 1942, Lerman (63) attempted to immunise a thyrotoxic patient against sheep thyroglobulin. Although a low antibody titre developed, no clinical improvement resulted.

These earlier observations appear to have aroused little interest and it was not until 1957, one year after the discovery of thyroid auto-antibodies in auto-immune thyroiditis (64) that positive CF (65) and precipitin (66) tests were described in thyrotoxicosis. These observations have since been confirmed and extended by a number of workers (67-75) and positive TRC auto-antibody tests have also been described in thyrotoxicosis (67,68, 71-76). The prevalence of positive thyroid auto-antibody tests reported in the literature is summarised in Table III and compared with those found in 468 thyrotoxic patients in the present study. It can be seen that the prevalence of positive precipitin tests is extremely small (approximately 2 per cent.), whereas positive CF and TRC auto-antibody tests are present in approximately 50 per cent. of thyrotoxic patients . The titres of CF and TRC auto-antibodies in thyrotoxicosis are, however, much lower than those found in auto-immune thyroiditis and primary hypothyroidism (68).

It was originally suggested by Doniach and Roitt (77) and Goudie et al. (66) that the thyroid auto-antibodies in thyrotoxicosis might bear a relation to the degree of round-cell infiltration in the gland. Some evidence for this has recently been found by Schade/

/Schade et al. (74) using the TRC test. Furthermore, Doniach and Roitt (77) suggested that if this lesion "represented a localised immune response, then thyroglobulin released at operation might be expected to act as a boosting dose and to stimulate increased antibody production, with consequent destruction of the residual thyroid". Similarly, they suggested that "after therapeutic doses of I^{131} thyroglobulin is known to be released, suggesting that auto-immunisation may play a role in the onset of hypothyroidism, particularly when it occurs after treatment with relatively small doses of the isotope". In support of the first of these hypotheses Witebsky et al. (78) reported the development of thyroid auto-antibodies in the serum of a thyrotoxic patient after subtotal thyroidectomy, although Roitt and Doniach (68) more often found a fall in titres of thyroid auto-antibodies following operation. In support of the second hypothesis Blizzard et al. (70) reported that none of 6 patients with thyrotoxicosis requiring more than 25 mc I^{131} to achieve cure had thyroid auto-antibodies in their serum. Roitt and Doniach (68) could find no difference in the prevalence of thyroid auto-antibodies in patients in prolonged remission after carbimazole treatment than in a control untreated series.

In an admirable review of the thyroid and auto-immunity in December 1960 the Scottish Medical Journal (79) concluded that there was as yet no adequate data relating serum antibody levels in thyrotoxicosis to the subsequent natural history of the disease or to/

/to the results of treatment. However, later in the same month Blagg (73) reported a correlation between the TRC auto-antibody titres and the outcome of I^{131} therapy.

The purpose of the present investigation was to assess the clinical significance of both the precipitin and CF thyroid auto-antibody tests in thyrotoxicosis. The investigation is based on a study of 468 thyrotoxic patients and the problem has been approached by studying the results of the thyroid auto-antibody tests in relation to the clinical features of the disease, to the degree of round-cell infiltration found in the thyroid gland at operation, and to the outcome of antithyroid drug, radioiodine, and surgical treatment. The results of these investigations help to elucidate the nature of the auto-immune reaction in thyrotoxicosis, and also have important practical implications in the management of the thyrotoxic patient.

Section 2 (a)

The Clinical Significance of the Precipitin test in Thyrotoxicosis.

In Chapter II of the thesis it was shown that circulating precipitating thyroid auto-antibodies are present in a large proportion of patients with auto-immune thyroiditis. In this section it is shown that the application of these immunological tests in patients with symptoms suggestive of thyrotoxicosis is of considerable practical importance, since 2 groups of patients have been identified, in whom the correct diagnosis could not otherwise have been made, and where mismanagement might have occurred.

In the first group evidence of auto-immune thyroiditis was found in patients with undoubted thyrotoxicosis. Only one fully documented case of this association has been previously described (80,81). The second group of patients had been referred to the clinic because of suspected thyrotoxicosis and radioiodine tests had appeared to confirm this diagnosis. Further investigations, however, showed that these patients were in fact euthyroid and that the presence of auto-immune thyroiditis explained the abnormal laboratory findings.

Materials and Methods

The patients were assessed clinically by the procedure described by Crooks et al.(82). By this method a numerical value is given to clinical symptoms and signs; a total value called the "clinical diagnostic index" is thus obtained. When less than 11, this index is normal; between 11 and 19 the diagnosis is equivocal; an index of 20 and above indicates thyrotoxicosis. The radioiodine, thyroid/

Table I.

Summary of Clinical Details and Results of Investigations in Five Cases of Thyrotoxicosis with Positive Precipitin Tests (Group 1).

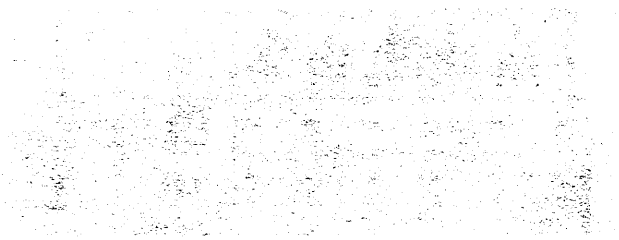


TABLE I.—*Summary of Clinical Details and Results of Investigations in Five Cases of Thyrotoxicosis with Positive Precipitin Tests (Group 1)*

Case No.	Age and Sex	Diagnostic Index	Goitre	Eye Signs	Radioiodine Tests				B.M.R. (%)†	P.B.I. (μg./100 ml.)	Thyroid Auto-antibodies		Serum Flocculation Tests	Gamma-globulin	Progress
					4-Hour Uptake (% Dose)	P.B. I-131 (% Dose/l.)	Thyroid Suppression Test	$KClO_4$ Discharge Test			C.F.T.	T.R.A.			
1	38 F	25	Firm, diffuse, 50 g.*	Bilateral exophthalmos	69·0	0·48			+21		++		Abnormal	Raised	Hypothyroid 3 months after operation
2	20 F	37	Firm, diffuse, 75 g.	Right-sided exophthalmos	78·5	5·47	Not suppressed	—	+40	12·8	++	+ 1/10,000	Normal	Normal	Euthyroid 1 year after operation
3	36 F	31	Firm, nodular, painful, 75 g.	None	97·0	1·43	,,				++		,,	,,	Hypothyroid 2 months after operation
4	66 F	42	Firm, diffuse, 75 g.	Bilateral exophthalmos	95·0	1·09			+70	10·3	++	+ 1/320	,,	,,	Required high dose of $KClO_4$ to produce remission
5	49 F	34	Firm, nodular, 100 g.	None	86·5	4·85	Not suppressed	—		17·9	++	+ 1/640	,,	,	Euthyroid 1½ years after I-131 therapy

C.F.T. = Complement-fixation test. T.R.A. = Tanned-red-cell agglutination. * Assessed gland size is recorded in each case. † Robertson and Reid standards.

/thyroid auto-antibody, and biochemical tests were performed by the methods described in Chapter II of the thesis. The TRC auto-antibody tests were kindly performed by Dr. A.E. Stuart of the Department of Pathology, University of Edinburgh.

Results

1. Thyrotoxicosis with severe chronic thyroiditis.

The findings in 5 patients with unequivocal thyrotoxicosis and positive precipitin tests (Group 1) are summarised in Table I. The case reports of these patients are summarised below. The diagnostic index lay within the thyrotoxic range in every patient.

Patient No. 1, a woman, aged 38 years, complained of painless thyroid enlargement gradually increasing for 1 year and associated with tiredness and loss of approximately $2\frac{1}{2}$ stones (16 kg.) in weight, despite a good appetite. On examination, she was extremely nervous and had a sinus tachycardia of approximately 120 beats per minute. A firm slightly enlarged goitre with a bruit was present and bilateral exophthalmos was noted. The movements were hyperkinetic and there was a fine finger tremor. The skin was warm and moist.

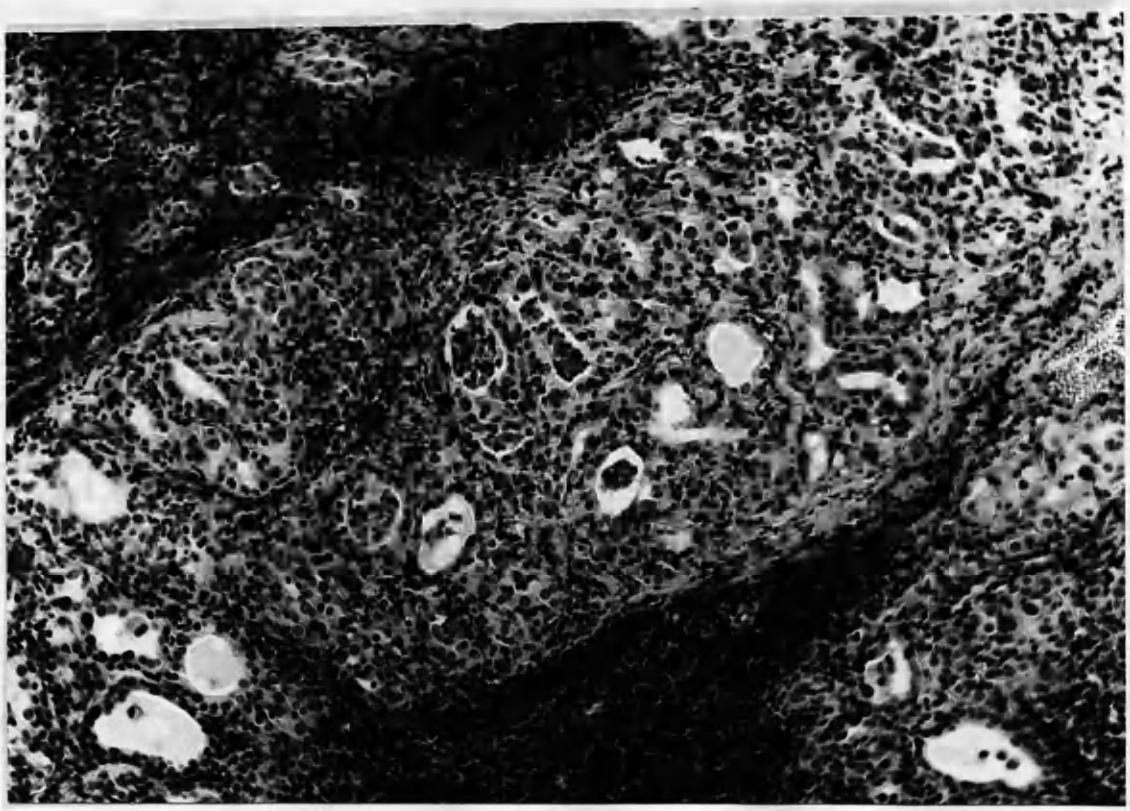
Subtotal thyroidectomy was carried out after preparation with carbimazole and potassium iodide. During the pre-operative preparation the patient gained 14 lb. (6.4 kg.) in weight and became clinically euthyroid.

The/

Figures 1 - 3.

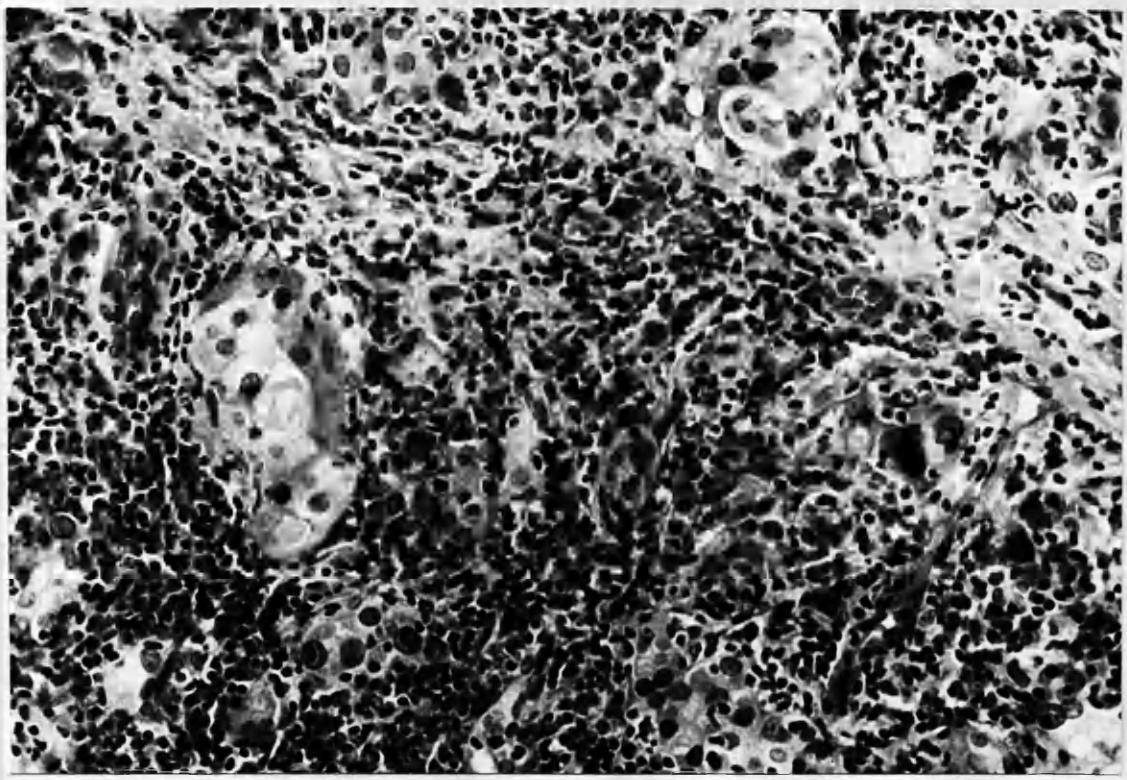
Histological appearances of the thyroid gland in a thyrotoxic patient with a positive precipitin test.

Fig. 1.



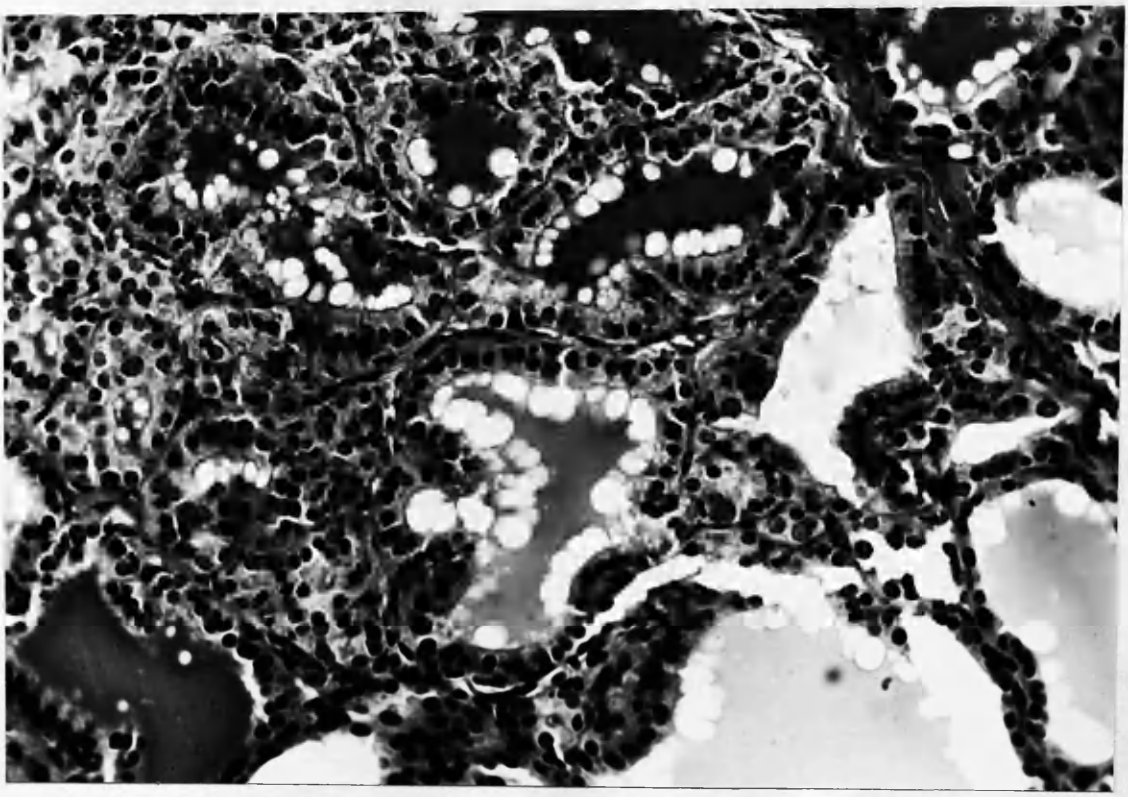
Patient No. 1. Area showing chronic thyroiditis with diffuse round-cell infiltration, colloidophagy, and dense lymphocytic aggregates. (Haematoxylin and eosin. x50).

Fig. 2.



Patient No.1. Severe chronic thyroiditis showing dense and intimate interacinar infiltration with round cells. Thyroid acini are partly destroyed, and those remaining show Askanazy-cell change. (Haematoxylin and eosin x 110).

Fig. 3.



Patient No. 1. Area of thyroid showing usual features of thyrotoxicosis. Chronic thyroiditis is absent. Such areas were scanty and small. (Haematoxylin and eosin. x 110).

/The excised thyroid tissue weighed 40 g. and was smooth, pink and lobulated. Microscopy* revealed severe and extensive chronic thyroiditis, together with features suggestive of thyro-:toxicosis. The chronic thyroiditis consisted of numerous large lymphoid follicles with large germinal centres, and extensive inter-acinar infiltration with lymphocytes and plasma cells. This latter change varied in intensity in different areas and occasional small areas smounting to a small proportion of the thyroid tissue remained unaffected. The thyroid epithelium was arranged in small acini, or solid clumps, and showed variations in nuclear size, increase of cytoplasm and eosinophilia, amounting in places to fully developed Askanazy-cell change. Some of these features are illustrated in Figs. 1 and 2. Colloidophagy was present in many of the acini. In some areas, and particularly where chronic thyroiditis was mild or absent, the acini showed features typical of thyrotoxicosis - hyperplastic columnar epithelium forming small acini containing poorly-staining colloid with scalloping at the edges (Fig. 3). The appearances were compatible with a thyrotoxic gland showing in addition changes of severe chronic thyroiditis.

The patient made an uneventful post-operative recovery, but 3 months after the operation she had gained a further 17 lb. (7.7 kg.) in weight and complained of lethargy and cold intolerance. The symptoms/

* I am grateful to Dr. J.R. Anderson of the University Department of Pathology for the interpretation of the pathological findings in these patients and for the photomicrographs in this section.

/symptoms improved with thyroxine sodium therapy and the patient was well and euthyroid when seen 3 months later.

Patient No 2, a female, aged 20 years, gave a history of thyroid enlargement and prominence of the eyes of 3 months' duration. She had also noticed increasing dyspnoea on exertion, palpitations, tiredness, heat intolerance, nervousness, excessive sweating and an increase in appetite, although her weight was constant. The goitre was diffuse and firm with a bruit over both lobes. There was exophthalmos, lid retraction and lid lag, hyperkinesis and fine finger tremor were present. The skin was hot and moist and the resting pulse rate was 103 beats per minute.

After pre-operative treatment with potassium iodide, subtotal thyroidectomy was performed.

The excised thyroid tissue weighed 60 g. Microscopy showed accentuation of the lobular architecture, with rather less than half of the thyroid lobules showing changes typical of thyrotoxicosis with little or no thyroiditis. The remainder of the lobules showed varying degrees of superimposed chronic thyroiditis which included interfollicular infiltration with plasma cells and smaller numbers of lymphocytes, occasional lymph follicles, colloidophagy, and changes in the epithelium from the columnar type typical of thyrotoxicosis to Askanazy cell type, sometimes with loss of follicular arrangement and aggregation of the cells in small clumps. The degree of these changes varied in different lobules and in different/

/different parts of the same lobule. Many lobules were, however, diffusely and severely involved.

The patient made an uneventful post-operative recovery. When last seen 1 year after the operation she was well and euthyroid. The precipitin test at this time was negative.

Patient No. 3, a female, aged 36 years gave a history of a sudden onset of a tender and painful goitre which appeared "overnight". The pain in the thyroid lasted only a few days, but the goitre persisted and progressively increased in size over the next 8 months. At her first attendance the patient complained of fatigue and irritability, and had no dyspnoea on exertion, palpitations, heat intolerance, excessive sweating or change in appetite or weight. On examination, a moderately enlarge, firm, nodular goitre was present. A sinus tachycardia of 93 beats per minute was recorded and the skin was warm and moist. A therapeutic trial with methylthiouracil was commenced and some initial improvement was noted. Three months later the thyroid precipitin test was found to be positive and methylthiouracil therapy was discontinued. Six months later the patient returned complaining of excessive tiredness, palpitations, dyspnoea on exertion, excessive sweating and recent preference for cold weather. The goitre had not changed noticeably in size or consistency but a bruit was now present over the whole gland. Hyperkinesis and a fine finger tremor were present. The skin/

/skin was warm and moist and a sinus tachycardia of 96 beats per minute was recorded.

The patient received a pre-operative course of methylthiouracil and Lugol's iodine and with this symptomatic improvement occurred, the signs of thyrotoxicosis disappeared, and the patient gained 7 lb. (3.2 kg.) in weight.

A subtotal thyroidectomy was performed; the excised thyroid tissue weighed 65 g. and was firm and lobulated. The histological features were complex. The appearance in some areas was that of thyrotoxicosis with columnar epithelium lining the vesicles which contained scalloped and poorly-staining colloid and showed numerous papillary projections into the vesicles. Marked nuclear pleomorphism of the thyroid epithelium was seen and nuclear debris and phagocytes occupied some of the vesicles. The colloid varied considerably in amount and in intensity of staining. Numerous foci of plasma cells and lymphocytes and lymph follicles were present, and some areas of Askanazy cell change were found. In addition, several foci of necrosis of up to 0.5 cm. in diameter were seen in areas which were not adenomatous and there were also patches of fibrosis with thick walled vessels, some of which showed acute inflammatory infiltration of the wall and some chronic periariteritis. The appearances were consistent with thyrotoxicosis and superimposed vascular changes and chronic thyroiditis affecting approximately 25 per cent. of the thyroid tissue.

Two months after the operation the patient developed hypothyroidism./

/hypothyroidism. When last seen 2 years later, she was well and euthyroid and taking 0.1 mg. of thyroxine sodium daily. The precipitin test at this time was negative.

Patient No. 4, a woman, aged 66 years, gave a history of protrusion and excessive lacrimation of the eyes, and painless thyroid swelling of 5 years duration. In 1954 she developed symptoms of thyro-:toxicosis and treatment with methylthiouracil produced remission of symptoms. Methylthiouracil therapy was discontinued in September, 1957. Following this the patient had a relapse and when seen in December 1957, she complained of dyspnoea on effort, palpitations, excessive tiredness, nervousness and heat intolerance, and excessive sweating. She had lost approximately 28 lb. (12.8 kg.) in weight, despite an increased appetite. On examination the thyroid gland was diffuse and moderately enlarged, firm but not tender. A bruit was present over both lobes. Bilateral exophthalmos was present, which was more obvious on the right side. Lid retraction was present on the right and bilateral lid lag was noted. There was some limitation of outward and upward movement of the right eye, and conjunctival injection was present at the outer isthmus, although there was no chemosis or periorbital oedema. A cataract was present in the right eye, which was blind. Hyperkinetic movements and fine finger tremor were present and the skin was hot and dry. A sinus tachycardia of 95 beats was recorded.

Treatment with potassium perchlorate 400 mg. 6-hourly was commenced/

/commenced but a few weeks later congestive cardiac failure developed which improved with digoxin and diuretic therapy. Four months later the dose of potassium perchlorate was reduced to 250 mg. 4 times daily, and 2 months later she was considered to be euthyroid and the dose was further reduced to 250 mg. twice daily. The patient remained well and euthyroid on this maintenance dose of potassium perchlorate but when seen 7 months later she was complaining of severe pain and aching in the region of the thyroid gland which radiated upwards into both sides of her neck. This pain had kept her awake at night and was only partly relieved by aspirin tablets. On examination the thyroid gland was firm, but not tender. There was no pyrexia; the fauces were normal and there was no cervical lymphadenopathy. A repeat precipitin test was negative and the serum flocculation tests were again normal. The ESR (Westergran) was 48 mm. in the first hour, although the total and differential white cell count were normal. Mumps complement-fixation test was negative. The pain in the thyroid gland persisted intermittently and gradually disappeared over a period of 3 weeks, while the sedimentation rate fell to 5 mm. in the first hour a month later. With a maintenance dose of 250 mg. potassium perchlorate 250 mg. twice daily the patient has remained euthyroid. She was last seen in March, 1960, when the precipitin test was negative.

Patient No. 5, a woman, aged 49 years had first noticed a goitre 5 months previously and for 10 months had complained of excessive tiredness,/

Table II.

Summary of Clinical Details and Results of Investigations in Five Cases of Auto-immune Thyroiditis presenting as Thyrotoxicosis (Group 2).

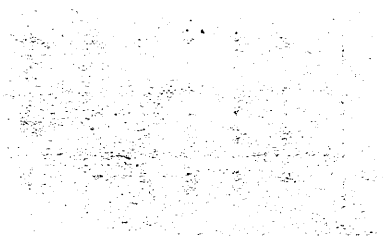


TABLE II.—*Summary of Clinical Details and Results of Investigations in Five Cases of Auto-immune Thyroiditis Presenting as Thyrotoxicosis (Group 2)*

Case No.	Age and Sex	Diagnostic Index	Goitre	Radioiodine Tests				P.B.I. (μg./100 ml.)	B.M.R. (%)	Thyroid		Serum Flocculation Tests	Gamma-globulin
				4-Hour Uptake (% Dose)	P.B. I-131 (% Dose/l.)	Thyroid Suppression Test	$KClO_4$ Discharge Test			Precipitin Test	C.F.T.		
I	62 F	17	Firm, diffuse, 50 g.	45·6	0·41	Suppressed	—	3·3		+	++	Abnormal	Normal
II	34 F	19	Firm, nodular, 50 g.	46·4	0·49	..	—	4·6	+19	—	++	..	Raised
III	48 F	16	Firm, diffuse, 75 g.	50·6	0·42	..	+	5·3	+28	+	++	..	..
IV	63 M	14	Firm, nodular, 75 g.	51·3	0·46	..	+	4·6	+7	+	++	..	..
V	45 F	18	Firm, diffuse, 50 g.	46·2	0·40	..	+	4·2	−2	+	++	..	..

/tiredness, nervousness, heat intolerance, and weight loss, despite an increased appetite; there had been no pain in the thyroid gland and no pressure symptoms. On examination the thyroid gland was markedly enlarged, firm and nodular. A bruit was present over both lobes. Exophthalmos was absent, but bilateral lid retraction and lid lag was noted. Hyperkinetic movements and fine finger tremor were present and the skin was hot and moist. The pulse rate was 87 beats per minute.

In view of the patient's age, it was decided that she was suitable for radioactive iodine therapy. Accordingly, 16 mc. of radioactive iodine (I^{131}) was given by the method described by Crooks et al. (79) and 5 months later the patient was still thyrotoxic, although improved. A further 12 mc. of radioactive iodine was given and when next seen [redacted] 3 months later the patient was euthyroid. When last seen 18 months following the first therapeutic dose of radioiodine, the patient was well and euthyroid. At that time the precipitin test was still strongly positive.

2. Auto-immune thyroiditis simulating thyrotoxicosis.

Five patients suspected of thyrotoxicosis on clinical grounds who had radioactive iodine tests consistent with this condition (Group II) are summarised in Table II. The final diagnosis was shown to be euthyroid auto-immune thyroiditis. The case reports are given below. The diagnostic index lay within the equivocal range in every patient. The Thesis Numbers of the 5 patients in this Group are respectively: 31, 11, 12, 21 and 43. For further details see Appendices, Chapter II, Section 1.

Patient No 1, a woman, aged 62 years, gave a history of thyroid enlargement of 6 years duration. During the previous 2 years she had complained of palpitations, tiredness, and slight preference for cold weather. On examination, a small, firm, diffuse goitre without a bruit was present. There were no eye signs. Movements were hyperkinetic and the hands were warm and moist. No finger tremor was observed and the pulse rate was 84 beats per minute.

No antithyroid therapy was prescribed and the patient's symptoms gradually disappeared with reassurance. Thyroxine therapy was later prescribed and with this the goitre diminished in size. Patient No. 2, a woman, aged 34 years gave a history of goitre, dyspnoea on effort, palpitations, tiredness, preference for cold and nervousness of 3 years' duration. On examination, a small, firm, nodular, goitre without a bruit was present, but no lid retraction or lid lag was noted. Hyperkinesis was present, but there was no finger tremor. The skin was dry and moist and the resting pulse rate was 89 beats per minute. Treatment with potassium perchlorate 250 mg. 4 times daily was begun and there was slight symptomatic improvement. When see 3 months later the patient had developed hypothyroidism, which was confirmed by electrocardiography, BMR, and serum cholesterol determinations. Treatment was discontinued and she recovered spontaneously. Following this the patient remained euthyroid and 4 months later a surgical biopsy of the thyroid was carried out.

The/

/The excised tissue showed widespread chronic thyroiditis, with lymphoid follicles, plasma cell infiltration, and Askanazy cell changes. There was also irregular fibrosis.

Six weeks after the surgical biopsy the patient developed hypothyroidism. This responded to replacement therapy with thyroxine sodium 0.1 mg. twice daily and the goitre diminished in size.

Patient No 3, a woman, aged 48 years gave a two-year history of goitre and increasing dyspnoea on exertion, tiredness, nervousness and loss of weight despite a normal appetite. On examination the thyroid gland was moderately enlarged, diffuse, and firm. There was no bruit. Bilateral exophthalmos was present, but there was no lid retraction or lid lag and no hyperkinesis. Fine finger tremor was present and the hands were warm and moist. The resting pulse rate was 112 beats per minute. Thyroxine sodium was prescribed and the goitre became smaller.

Patient No 4, a man, aged 63 years, gave a history of goitre of 6 months duration and a history of increasing dyspnoea on exertion, excessive tiredness, intolerance of heat and nervousness of 1 year's duration. On examination, a firm, moderately enlarged, nodular goitre was present and accompanied by a bruit. Exophthalmos was noted, but there was no lid retraction or lid lag. There was no hyperkinesis, or fine finger tremor and the skin was cool and moist. The resting pulse rate was 81 beats per minute.

The patient was treated with potassium perchlorate 250 mg. orally/

/orally 4 times daily. This treatment was continued for 12 weeks but there was no symptomatic improvement and the patient has since remained well and euthyroid. The patient was given 0.2 mg. thyroxine sodium daily which produced a reduction in the size of the goitre.

Patient No 5, a woman, aged 45 years, gave a 3 year history of nervousness, excessive sweating, intolerance of heat and weight loss. The patient had been aware of a goitre of 11 years duration but had noticed no recent increase in size. On examination the thyroid was slightly enlarged, diffuse and firm and without a bruit. Slight bilateral exophthalmos was present. There was no hyperkinesis and no finger tremor. The skin was hot and dry. The resting pulse rate was 97 beats per minute.

No antithyroid therapy was prescribed, and the symptoms gradually disappeared with reassurance. She remained well until 2 years later, when hypothyroidism developed. Thyroxine sodium 0.2 mg. daily was prescribed and the goitre diminished in size.

DISCUSSION

A positive precipitin reaction is almost invariably associated with extensive destructive thyroiditis such as is found in auto-immune thyroiditis or in some patients with primary hypothyroidism (68,69,81). In 3 of the proved thyrotoxic patients in Group I, in whom subtotal thyroidectomy was carried out, histological examination of the gland showed features of thyrotoxicosis and, in addition, focal chronic thyroiditis of far greater extent and severity than is usually seen in a thyrotoxic thyroid. The features/

/features were similar to those described by Doniach and Hudson (80) in their patient. These findings demonstrate that auto-immune thyroiditis and thyrotoxicosis can be present simultaneously in the same patient, and may be the explanation for the spontaneous development of hypothyroidism in patients with thyrotoxicosis reported in the literature (43). They might also explain the past history of thyrotoxicosis obtained from a small proportion of patients with auto-immune thyroiditis (44). The low incidence of both positive precipitin tests and the severer degrees of lymph-:adenoid change in thyrotoxicosis probably explains why this particular sequence of events is relatively uncommon.

These patients reveal the interesting combination of a hyper-:plastic and destructive lesion occurring simultaneously and on the basis of the findings one can speculate on the aetiological factors involved. It is possible that thyrotoxicosis might predispose to the occurrence of auto-immune thyroiditis. Alternatively, both conditions might have a predisposing constitutional factor (83). The first possibility is supported by the work of Long and Shewell (84) who have demonstrated the enhanced immunological reactions in thyroxine-fed guinea-pigs, and by the demonstration by Stuart and Allan (76) of the loss of integrity of the basement membrane in the human thyrotoxic gland. The association of the 2 diseases in these patients does not, however, necessarily support the general concept popularised by Levitt (31) that there is a natural prog-:ression from thyrotoxicosis to auto-immune thyroiditis.

The/

/The finding of a positive precipitin test in a thyrotoxic patient may have practical significance, since it has been shown that when partial thyroidectomy is performed on glands with severe degrees of chronic thyroiditis, there is an increased liability to the development of post-operative hypothyroidism (23,30,31, 85). Although the therapeutic response was variable in these patients (Group 1) the unusually rapid development of hypothyroidism in Patients No. 1, and 3, at 3 and 2 months respectively after operation suggests that the chronic thyroiditis was sufficiently severe to impair the function of the thyroid remnant. On the other hand, patient No. 2 remained well and euthyroid one year after her operation, and the remaining 2 patients of this Group (Patients No. 4 and 5) were both severely toxic and relatively resistant to other forms of therapy. I therefore believe that until further experience has been gained of this type of patient the treatment of choice should be antithyroid drug therapy, since treatment by surgery or radioactive iodine might hasten the onset of hypothyroidism.

In contrast to these patients with unequivocal thyrotoxicosis and associated auto-immune thyroiditis (Group 1), there is the further group of patients with auto-immune thyroiditis who are of particular importance in that the clinical findings and the results of laboratory investigations may lead to an incorrect diagnosis of thyrotoxicosis. The 5 patients of this type (Group II), were all suspected on clinical grounds of having thyrotoxicosis, and this suspicion appears to be confirmed by radioiodine studies. The diagnosis/

/diagnosis of auto-immune thyroiditis in this group was confirmed by positive precipitin tests or by histological examination of the gland, and thyrotoxicosis was excluded on the basis of serum PBI determinations and normal thyroxine suppression tests. This is, in my opinion, the type of patient frequently reported in the literature as demonstrating the association of thyrotoxicosis with auto-immune thyroiditis (33,34,36,38,39,41) and I agree with Joll (27), that the alleged thyrotoxic features in these patients, with the exception of the goitre, can be attributed to anxiety or apprehension. The value of routinely performing precipitin tests and serum flocculation tests or electrophoresis of serum proteins in patients with suspected thyrotoxicosis is clearly demonstrated in this group, since, if the diagnosis had been reached on the basis of the clinical findings and the standard radioactive iodine tests alone, destructive antithyroid therapy might have been prescribed. It might be argued that the 4 patients of Group II, with positive precipitin tests, in whom the thyroid was not examined histologically, were examples of thyrotoxicosis associated with auto-immune thyroiditis in which the latter had been sufficiently extensive to produce spontaneous remission of thyro-:toxicosis. This possibility, however, does not affect the therapeutic implications of the finding. Furthermore, if thyro-:toxicosis had previously been present the remnant of functioning thyroid tissue in some of the patients, at least, should have behaved like toxic glands and have had negative suppression tests; all/

/all in fact were normally suppressed. In the fifth patient of this group with a negative precipitin test there was no histological evidence of thyrotoxicosis.

It is concluded that auto-immune thyroiditis and overt thyrotoxicosis can co-exist and that these patients can be recognised by a combination of immunological and biochemical procedures. It is probable that patients with truly 'thyrotoxic' auto-immune thyroiditis, if left untreated, would ultimately become euthyroid or even develop hypothyroidism. They do not present a diagnostic problem in so far as their hyperthyroidism is concerned, but the association of the 2 diseases clearly contraindicates destructive therapeutic measures. Antithyroid drugs should be used to control the symptoms in these patients. On the other hand, the 'pseudo-toxic' patient with auto-immune thyroiditis presents primarily a diagnostic problem because of possible confusion with thyrotoxicosis, and their existence makes it necessary not to place too much reliance on the results of the routine radioiodine tests, especially if the clinical features are atypical. The most helpful tests in these patients are the thyroxine (or triiodothyronine) suppression test and the chemical estimation of the PBI. Where these tests are not available a precipitin test for thyroid auto-antibodies should be performed. It is even more simple to carry out the thymol turbidity or flocculation tests or electrophoresis of the serum proteins, and this would have given adequate warning in the 5 patients of this group who have been described.

SUMMARY

A group of 5 patients is described with unequivocal thyrotoxicosis and positive precipitin tests for thyroid auto-antibodies. In 3 in whom histological examination was carried out, there were changes consistent with the co-existence of thyrotoxicosis and extensive thyroiditis, indistinguishable from auto-immune thyroiditis. A further group of 5 patients with suspected thyrotoxicosis, apparently confirmed by routine radioactive iodine tests, were subsequently shown to be euthyroid and to have auto-immune thyroiditis. It is recommended that immunological tests for thyroid auto-antibodies should be carried out in all cases of overt or suspected thyrotoxicosis to prevent unnecessary destructive therapy and the radioactive iodine studies in equivocal cases of thyrotoxicosis should be interpreted in the light of these tests.

Section 2 (b)

The Clinical Significance of the Complement-Fixation test in Thyrotoxicosis.

In the historical section it was pointed out that auto-antibodies to the "microsomal" antigen can be detected in a large number of patients with thyrotoxicosis by the CF test (68-70), but that the significance of these antibodies is not known. The present study reports a clinical and pathological assessment of the CF test in 468 thyrotoxic patients. The problem has been approached in 3 ways. Firstly, the CF test has been studied in relation to the clinical features of thyrotoxicosis and to the response to antithyroid therapy. Secondly, serial determinations of the CF test have been carried out following various forms of antithyroid therapy. Thirdly, the relation has been studied between the results of the CF test and the extent of round-cell infiltration found in the thyroid gland after operation.

Materials and Methods

468 patients with thyrotoxicosis were studied of whom 253 were untreated and 215 had received specific antithyroid therapy. The diagnosis was based on the clinical and laboratory criteria described in the previous section.

The CF test was performed as described in Chapter II of the thesis. The following clinical criteria were recorded in addition to the age and sex of the patient: the presence of a goitre, its consistency (diffuse or nodular), its size (slightly enlarged, approximately 50 g. - moderately enlarged, 75 g. - very large, 100 g. or more), and its duration (less than 1 year - 1 to 5 years - 5 years and more). In all patients the "clinical diagnostic index" (82)/

/(82) was recorded. This index is a quantitative estimate of the symptoms and signs and correlates with the severity of the disease. The presence of ocular signs was noted in every case, the criteria being described by Crooks et al. (82).

The type of treatment given, (if any), before the first CF test was noted in each patient. Potassium perchlorate was the most frequently used antithyroid drug. In the case of I^{131} therapy the doses were prescribed by the method of Crooks et al. (86) and the number of doses given recorded.

The response to treatment was studied. Hypothyroidism following surgery or radioiodine was recorded only if permanent (86) and was confirmed by cholesterol, BMR, or PBI determinations, and ECG studies. Resistance to I^{131} therapy was defined as persist-:ence of hyperthyroidism after 2 or more doses.

The incidence of drug reactions including skin rashes and haemotological complications was noted. A patient was considered to have a family history of thyroid disease if she was aware of a relative with a thyroid disorder.

Serial studies of thyroid auto-antibody tests (both precipitin and CF) were done in 145 of the untreated group before and after receiving various forms of therapy. In all, 416 tests were done and the patients were followed up for periods varying from 1 to 23 months. (mean follow-up 6.7 months).

The histological sections were available for study in 56 cases and the degree of round-cell infiltration was related to the result of the/

/the CF test. Round cell infiltration was assessed by counting the number of low-power fields containing round-cell aggregates out of 50 fields examined for each gland. This examination was done by Dr. R.B. Goudie (of the University Department of Pathology, Western Infirmary, Glasgow) who had no knowledge of the results of the CF tests.

Statistical Methods*

The data are presented in contingency tables showing the distribution of patients with each characteristic by the reaction to the CF test. Any apparent variations in the CF test results with the other classifications were examined for statistical significance. The usual chi-square test of association in contingency tables is insensitive when the groupings are in some natural order of measurement and any relations may be expected to vary consistently with this natural order. Here, tests more sensitive than chi-square can be devised to examine the hypothesis that the distribution of patients with a characteristic changes progressively with increasing positiveness of the CF reaction. There are a number of tests of this kind (87-89). A simple but reasonably efficient method was used in the present analysis. Negative, positive and double positive CF reactions were scored 0, 1 and 2 respectively and the analysis was carried out as if there/

* I would like to thank Dr. W. Brass, M.A., of the Statistics Department, University of Aberdeen, who kindly performed the statistical analyses in this section.

Table I.

Correlation between the Complement-Fixation Test and Sex in Thyrotoxicosis (468 cases).

Table I.

Correlation between the Complement-Fixation Test and Sex in Thyrotoxicosis (468 cases)

Complement-Fixation Test	Females		Males	
	No.	%	No.	%
(-)	201	84.8	36	15.2
(+)	80	80.8	19	19.2
(++)	110	83.3	22	16.7

/there were scale measurements. When the other characteristic considered was a dichotomy the null hypothesis of no association was then examined by a t test of the difference between 2 mean scores. When the other characteristic was also an ordered classification it was likewise treated as a scale measurement with the groups at equal intervals apart and the regression of the CF score on this measurement was tested. In general, only a t test of the linear component of regression was applied but for 1 relationship (with age) the quadratic component, which was clearly important, was tested also. The standard criteria of statistical significance are used, i.e. t deviations which would have been exceeded by chance in less than 5% and 1% of trials on the null hypothesis of no association are called "significant" and "highly significant" respectively.

Results

1. Clinical Significance of Single Determinations of the CF test

Since no correlation was found between the sex of the patient and the result of the CF test (Table I), male and female patients were analysed together. On the other hand, antithyroid therapy was found to influence the results of the test (see below), therefore patients who had received no previous treatment (253 patients) and those previously given antithyroid therapy (215 patients) were analysed separately. For convenience these groups are referred to below as "untreated" and "treated" respectively.

(A) "Untreated" Group (253 patients).

The/

/The results are summarised in Table II (Appendices).

Age. There were no significant differences in the mean ages of the groups with a (-) test (43.2 years), with a (+) test (41.4 years), and with (++) test (42.7 years). However, as can be seen from Table III, the positivity of the CF test was increased in the middle-aged group (30 to 60 years). Consequently the quadratic component of this change in mean score with age was highly significant. The mean gland sizes in the groups aged 60 years or more (49.0 g.) and less than 30 years of age (69.9 g.) were lower than in the group aged between 30 and 60 years (70.0 g.), but this did not wholly account for the higher incidence of positive tests in the middle age group.

Table III

Relation between Age and Complement-Fixation Test

Age in years	No. of Cases with CF Test				Mean Score
	-	+	++	Total	
Under 30	30	7	7	44	0.48
30-39	35	17	18	70	0.76
40-49	32	16	20	68	0.82
50-59	26	8	14	48	0.75
60-69	9	1	2	12	0.42
70 and over	9	2	0	11	0.18
Total	141	51	61	253	0.68

Goitre. The positivity of the CF test was directly related to goitre size ($P<0.05$) and inversely related to the duration of/

/of the goitre ($P < 0.05$). The results of the CF test did not vary significantly with the consistency of the goitre.

Table IV

Relation between Size and Duration of Goitre and Complement-Fixation Test.

	No. of Cases with CF Test				Mean Score
	-	+	++	Total	
Size (g) Absent	13	2	4	19	0.53
50	48	20	11	79	0.53
75	45	18	24	87	0.76
100	35	11	22	68	0.81
Total	128	49	57	234	0.70
Duration (months) 0-11	40	18	33	91	0.92
12-59	34	8	14	56	0.64
60 and over	10	3	2	15	0.47
Total	84	29	49	162	0.78

Intensity and Duration of Symptoms. There was no indication that the results of the CF test were related to either the severity of the illness, as assessed by the clinical diagnostic index, or the duration of the symptoms.

Eye Signs. There was no correlation between the result of the CF test and the presence of the exophthalmos of Graves' disease or of exophthalmic ophthalmoplegia. This is in contrast to the findings of a relationship of TRC antibody titres to exophthalmos by Hales et al. (75).

Family History./

Family History. Patients with a family history of thyroid disease had a higher incidence of positive CF tests (P approx-:imately 0.1). The same trend was also found in the group with previous antithyroid treatment, and when the evidence from both groups is considered together the results are significant ($P < 0.05$). (Table V).

Table V

Relation between Family History of Thyroid Disease and Complement-Fixation Test.

Family History	No. of Cases with CF Test				Mean Score
	-	+	++	Total	
	"Untreated"				
With	36	17	22	75	0.81
Without	105	34	39	178	0.63
Total	141	51	61	253	0.68
	"Treated"				
With	25	10	29	64	1.06
Without	71	38	42	151	0.81
Total	96	48	71	215	0.88

Drug Reactions. Reactions to antithyroid drugs, either mild or severe, did not vary with the results of the CF test.

Response to treatment. In patients treated with surgery the positivity of the CF test was found to increase in the order: relapse after operation, euthyroid and hypothyroid (Table VI).

This/

/This trend was just on the borderline of significance. (P approximately 0.05). In the case of radioiodine therapy the reverse effect was found and the test became less positive in the order: hypothyroid, euthyroid, euthyroid with 1 dose, and resistant ($P < 0.01$). (Table VI). Further analysis showed that this was partly due to the fact that the mean gland size was smaller in the group with negative tests (59 g.) than in the group with (+) (65 g.) or (++) (80 g.) tests, although the residual trend when gland size had been allowed for was still significant.

Table VI

Relation between Outcome of Treatment and Complement-Fixation Test.

Response to Treatment	No. of Cases with CF Test				Mean Score
	-	+	++	Total	
Surgery					
Relapse	7	2	2	11	0.55
Euthyroid	16	9	14	39	0.95
Hypothyroid	0	2	2	4	1.50
Total	23	13	18	54	0.91
Radioiodine Therapy					
Resistant	7	3	13	23	1.26
Euthyroid (One dose)	31	11	16	58	0.74
Hypothyroid	8	4	1	13	0.46
Total	46	18	30	94	0.83

No definite conclusions could be reached regarding the relationship/

Table VIII.

Relation between Previous Treatment and Complement-Fixation Test.

Table VIII

Relation between Previous Treatment and Complement-Fixation Test.

	No. of Cases with CF Test				Mean Score
	-	+	++	Total	
"Untreated"	141	51	61	253	0.68
"Treated"					
Drugs + Surgery	23	10	15	48	0.83
Drugs only	47	19	21	87	0.70
Radioiodine	26	19	35	80	1.11
Total Treated	96	48	71	215	0.88
No. of Doses I131					
One	18	13	18	49	1.00
Two	7	4	7	18	1.00
Three or more	1	2	10	13	1.69
Total	26	19	35	80	1.11

/relationship of the CF test to the results of antithyroid therapy (Table VII Appendices) because of the short period of follow-up (mean approximately 10 months).

(B) "Treated" Group (215 patients).

There was a significantly higher number of patients with positive CF tests in the "treated" group than in the "untreated" group ($P<0.02$). From Table VIII it can be seen that this was largely due to the patients who had been previously treated with radioiodine. The CF test results for these were substantially more positive than the corresponding measurements for other patients ($P< 0.01$), but the latter did not differ significantly from the values for the untreated patients. Furthermore there was a significant correlation ($P<0.05$) between the positivity of the CF test and increasing doses of I^{131} (Table VIII). The "treated" group as a whole was similar to the "untreated" group with respect to mean age, consistency of the goitre and clinical severity. (Table IX Appendices).

Table X.

Changes in Complement-Fixation Test After I^{131} and Antithyroid Drug Therapy.

Table X

Changes in Complement-Fixation Test after I^{131} and Anti-Thyroid Drug Therapy.

I^{131} Therapy

	after Treatment			
	-	+	++	Total
Before Treatment -	33	2	6	41
+	4	4	3	11
++	2	0	22	24
Total	39	6	31	76

Change in mean C.F. score = +0.12

Anti-Thyroid Drugs

	after Treatment			
	-	+	++	Total
Before Treatment -	21	1	1	23
+	8	2	4	14
++	3	1	13	17
Total	32	4	18	54

Change in mean C.F. score = -0.15

2. The Effect of therapy on the results of the CF test.

The effect of therapy on serial measurements of the CF test is shown in Table X. It can be seen that the incidence of negative tests is higher following antithyroid drug treatment and the incidence of positive (++) tests is higher following radioiodine therapy. Neither of these trends is significant when considered separately, but when taken together this difference in trends is significant ($P < 0.02$). This is consistent with the finding of a higher incidence of positive tests in patients who had been treated with radioiodine therapy. It is possible that had the follow-up period been longer, the trend towards a positive test in those who had received radioiodine therapy would have been more apparent.

Figure 1.

Relation between the CF test and the degree of round-cell infiltration in the thyroid.

Figure 2.

Relation between complement-fixation Test, Round-cell Infiltration and Response to Therapy.

Fig. 1.

RELATION BETWEEN COMPLEMENT-FIXATION TEST
AND ROUND-CELL INFILTRATION IN THYROTOXIC GLANDS

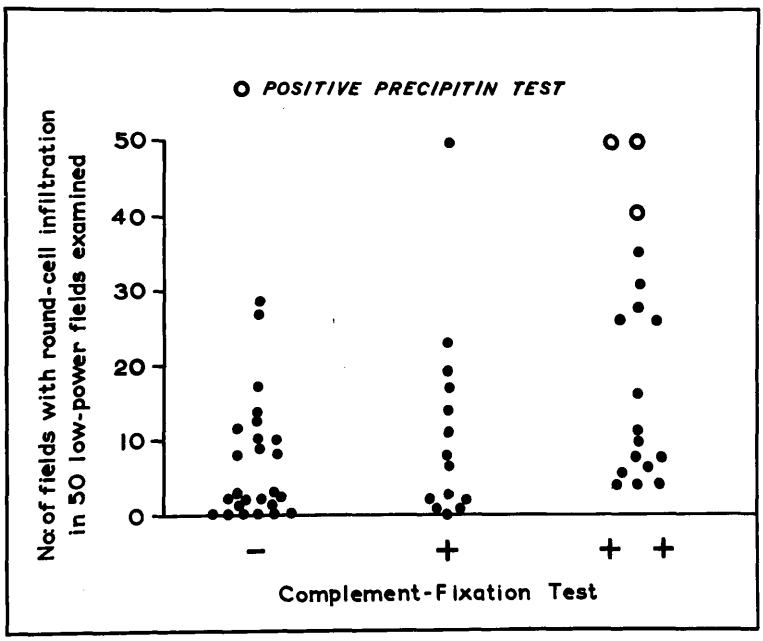
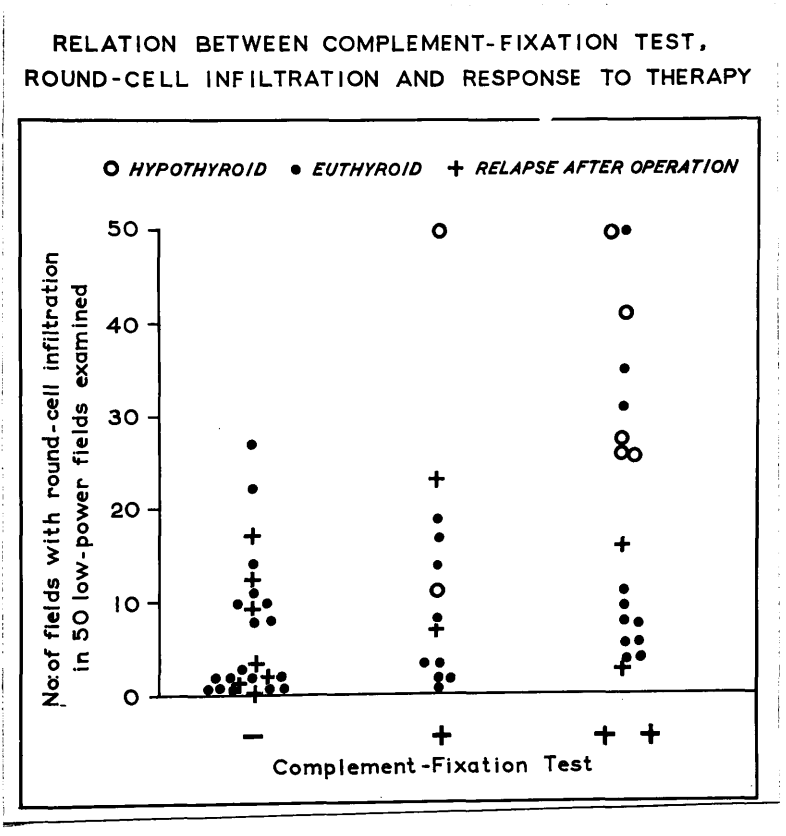


Fig. 2.


RELATION BETWEEN COMPLEMENT-FIXATION TEST,
ROUND-CELL INFILTRATION AND RESPONSE TO THERAPY
O HYPOTHYROID • EUTHYROID + RELAPSE AFTER OPERATION
No: of fields with round-cell infiltration in 50 low-power fields examined
50
40
30
20
10
0
−
+
+ +
Complement-Fixation Test

3. Relation between the CF test and the degree of round-cell infiltration in the thyroid.

From Fig. 1, it can be seen that there is a direct relation between the degree of round-cell infiltration in the thyroid and the positivity of the CF test. There is, however, a wide scatter in the distribution of the infiltration measurements in the 3 CF test categories. To reduce the erratic effects of the extreme observations the analysis was carried out on the square roots of the measurements of round-cell infiltration. The relation with the CF test results was then found to be highly significant ($P < 0.001$). From Fig. 2, it can be seen that hypothyroidism occurred exclusively in patients with positive CF tests, and especially in those with severer degrees of round-cell infiltration, whereas relapse after operation occurred in those with negative tests and lesser degrees of lymphoid replacement. It can also be seen that 3 of the 4 patients with extensive lymphocytic infiltration (present in 50 out of 50 fields examined) became hypothyroid after surgery. Two of these patients had positive precipitin tests and were described in greater detail in the previous section.

DISCUSSION

In the present study a significant correlation has been demonstrated between the results of the CF test and the degree of round-cell infiltration in the thyroid gland (Fig. 1). This may be of practical importance since the incidence of post-operative hypothyroidism/

/hypothyroidism is greater with increasing lymphocytic replacement in the thyrotoxic gland (23,30,31,85). These observations have been confirmed in the present study and moreover, the CF test has been shown to correlate with the degree of round-cell infiltration in the thyroid gland ($P < 0.001$), and so to be of some predictive value in the outcome of surgical treatment ($P < 0.05$). It is concluded that thyrotoxic patients with a positive CF test are best treated initially with a course of antithyroid drugs unless there is a definite indication for surgery.

Schade et al. (1960) have reported a correlation between the degree of round-cell infiltration in thyrotoxic glands and the level of TRC auto-antibodies but concluded that there was no relationship with the CF test. This conclusion seems unjustified since these authors found a higher incidence of positive CF tests in patients with lymphoid infiltration in the thyroid gland; the absence of statistical significance can be attributed to the small number of cases (8 positive CF tests in total). Furthermore, these authors carried out their serological tests at varying intervals after thyroidectomy which is known to produce a fall in the circulating antibody levels (Owen and Smart, 1958).

A much higher incidence ($P < 0.01$) of positive CF tests was found in patients who had received treatment with radioiodine (Table VIII). Furthermore, serial determinations of the CF test in patients receiving I^{131} therapy showed a significantly greater increase in positive CF tests than in those receiving antithyroid drugs/

/drugs (Table XI); but the precipitin test showed no change. The increased positivity of the CF test after I^{131} therapy may be related to the histological lesions resembling auto-immune thyroiditis which have been found by various workers in the thyroid gland after I^{131} therapy (90-92). It has therefore been suggested that destructive forms of antithyroid therapy might predispose the thyroid to the development of auto-immunity (71,77). Profound morphological changes are found in the thyroid epithelial cells after I^{131} therapy (93) which may initiate an auto-immune process due to leakage of microsomal antigen. However, an interesting finding is the absence of correlation between the result of the CF test and the success of treatment with radioactive iodine; this may be attributable to lack of uniformity of irradiation by the gland affected by chronic thyroiditis.

Correlation of the results of a positive CF test with age shows a striking similarity to the age distribution of "focal thyroiditis" found in a large series of thyroid glands by Woolner et al. (94). The low incidence of positive CF tests in the patients under 30 years of age might conceivably be due to persistence of immunological tolerance to thyroid antigens. In view of the observations of blood group iso-antibodies by Thomson and Kettel (95) and of antibodies to influenzal viruses by Sabin et al. (96), the low incidence of positive CF tests in patients over the age of 60 years may be due to a diminished antibody forming potential. The absence of significant sex difference in the/

/the incidence of positive CF tests in thyrotoxicosis is in striking contrast to the increased incidence of positive CF tests in euthyroid females without overt thyroid disease. Although there is an increased prevalence of all types of thyroid disease in the female, it appears that there is no immunological difference in affected males and females.

Doniach et al. (98) invoked an auto-immune reaction to explain the pathogenesis of severe exophthalmos on the basis of the lymphocytic infiltration, oedema, and fragmentation of muscle found in the ocular tissue. The incidence of positive precipitins found by these workers (99) was nearly 10 per cent. in a group of 90 malignant exophthalmos sera, whereas it was only 0.5 per cent. in over 300 thyrotoxic sera from patients with benign or absent eye signs. Hales et al. (75) also found a positive correlation between the TRC auto-antibodies and the exophthalmos of Graves' disease, but no correlation has been found with either the precipitin test (positive in only 1 of 42 patients with severe exophthalmos) or CF test in the present study.

Approximately 5 per cent. of patients receiving antithyroid drugs for treatment of thyrotoxicosis develop delayed hypersensitivity allergic reactions (100). Blizzard et al. (71) reported an increased prevalence of penicillin reactions in patients with thyroglobulin auto-antibodies, but no such correlation has been found in the present study between the results of the CF test and the onset of drug allergies. This is perhaps not so surprising,/

/surprising, since the 2 immunological systems are quite distinct (101).

Hall et al. (102) have produced evidence of a genetically determined predisposition to the formation of thyroid auto-antibodies. It has been shown that patients with a family history of thyroid disease have a higher incidence of positive CF tests. These findings are comparable to the higher prevalence of rheumatoid arthritis found in relatives of patients with positive Rose-Waaler tests (103). This comparison between the 2 diseases is particularly relevant in view of the association which has been found between auto-immune thyroiditis and rheumatoid arthritis (see Chapter IV, Section 1). These considerations suggest that the familial factor in the inheritance of thyroid disease may be associated with a predisposition to the development of thyroid auto-antibodies.

SUMMARY

The significance of a positive thyroid complement-fixation (CF) test in thyrotoxicosis has been investigated by studying the correlation between various features of the disease in 468 patients. A significant correlation was found between the positivity of the CF test and (1) the degree of lymphocytic infiltration in the gland, (2) the incidence of post-operative hypothyroidism, (3) size of the goitre, (4) previous treatment with radioiodine, and (5) a family history of thyroid disease. No correlation was found between the results of the test and the incidence of reactions to antithyroid drugs. The results suggest that thyrotoxic patients with positive CF tests should be treated initially with antithyroid drugs unless there is a definite indication for surgery.

CHAPTER IV.

The Clinical Associations of Auto-immune Thyroiditis.

Introduction.

Introduction.

For many years only foreign proteins were considered to be true antigens. Horse serum, for instance, was long known as a potent antigen when injected into humans but did not provoke antibody formation in the horse. In 1901 Landsteiner (1) made his important discovery of the blood group substances and drew attention to the fact that agglutinating antibodies against these blood group substances may develop in humans, but not in the individual himself. These antibodies were called isoantibodies. Ehrlich and Morgenroth (2) were able to produce isoantibodies by injecting goats with red blood cells from other goats, but not against the goat's own blood cells. This inability to produce antibody to oneself was interpreted by Ehrlich as a fundamental biological law of nature and enunciated as "horror autoxicus".

In recent years a group of diseases has emerged which has proved an exception to this general law of immunity and in which auto-immune mechanisms may play a vital role. Witebsky et al. (3) have laid down certain criteria which should be fulfilled before implicating the role of an auto-antibody in the pathogenesis of a disease. These include:"(1) The direct demonstration of free circulating antibodies that are active at body temperature or of cell-bound antibodies by indirect means, (2) The recognition of the specific antigen against which this antibody is directed. (3) The production of antibodies against the same antigen in

experimental/

/experimental animals. (4) The appearance of pathological changes in the corresponding tissues of an actively sensitized animal that are basically similar to those in the human disease."

It has been seen that these criteria have come to be fulfilled in auto-immune thyroiditis. Auto-immune processes are also clearly evident in certain acquired haemolytic anaemias, in which antibodies reacting against red cells may be present, which can be shown to be cytotoxic in vivo (4). Thrombocytopenia and leucopenia may be associated with auto-immune haemolytic anaemia and cytotoxic antibodies to platelets (5) and leucocytic agglutinins (6) have been demonstrated. Auto-immune mechanisms have also been suspected in the connective tissue disorders and in systemic lupus erythematosus the LE cell test has led to the discovery of several factors which react with cell nuclei (7), and in rheumatoid arthritis the serological factor underlying the Rose-Waaler test has been shown to be a macroglobulin which behaves somewhat akin to an auto-antibody (8). In Sjögren's disease, rheumatoid arthritis often co-exists and a positive LE cell test is occasionally found (9); precipitating antibodies have been described to lachrymal and salivary glands (10). Similarly precipitating antibodies have been described in chronic pancreatitis (11), and Broberger and Perlmann (12) have reported the existence of antibodies against normal colonic extract in the blood-serum of children with ulcerative colitis. Complement-fixing adrenal antibodies have also been described in primary adrenal atrophy (13), and sperm agglutinating antibodies have/

/have been demonstrated in some patients with orchitis (14) and oligospermia (15). Auto-immunity has also been suspected in a variety of other conditions including progressive hepatitis (16), chronic renal (17) and cardiac (18) diseases, and in the encephalomyelitides (19) and multiple sclerosis (20), although the evidence in these diseases is less convincing.

Although circulating thyroid auto-antibodies can readily be demonstrated in the blood sera of a high proportion of patients with auto-immune thyroiditis, little is known regarding the factors which predispose certain patients to develop these auto-antibodies. Accordingly it would be of interest to determine whether these factors operate only for thyroid tissue antigens, or whether the individuals concerned are prone to develop auto-antibodies to tissue antigens in general. This problem may be approached in 2 ways; firstly, patients with auto-immune thyroiditis may be examined for the presence of auto-antibodies other than those specific for thyroid tissue; and secondly, the clinical association of immune thyroiditis with "auto-immune" diseases can be studied. The first approach was adopted by White et al. (21) who demonstrated antinuclear factors in the serum of a proportion of patients with auto-immune thyroiditis . The second approach is the one adopted in the present investigation, in which the clinical associations of auto-immune thyroiditis with the connective tissue disorders, acquired haemolytic anaemia, and cirrhosis of the liver have been studied. The immune response in patients with these various conditions/

/conditions has also been studied by measuring the antitoxin titres after primary immunisation to tetanus toxoid. The results of these investigations are discussed in relation to current concepts of antibody formation and immunological tolerance.

Section 1.

The Association of Auto-immune thyroiditis and the Connective tissue diseases, with particular reference to Rheumatoid Arthritis.

Our present concept of the diseases of connective tissue springs largely from the work of Klinge (1) who in 1933 first drew attention to the systemic character of the connective tissue lesions and their similarity to the tissue changes in the hyper-:sensitivity state; from Klemperer et al. (2) who in 1942 first conceived the nosological unity of the connective tissue or "collagen" diseases; and from Hench et al. (3) who in 1949 discovered the therapeutic efficiency of the adrenal steroid hormones. The diseases which so far have been suggested as belonging to this group of diseases include: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, scleroderma, polyarteritis nodosa, rheumatic fever, and acute nephritis. Rheumatic fever and acute nephritis are in a rather special category in view of their aetiological relation to streptococcal infection and their predominant attack on children, and for these reasons will not be considered further. The role of auto-immunity in the pathogenesis of the connective tissue diseases will now be briefly outlined together with the historical aspects of the association of these diseases and auto-immune thyroiditis.

Auto-immunity in the Connective Tissue Diseases.

Review

The theory of hypersensitivity as the pathological basis of the connective tissue diseases has attracted much attention during the past 2 decades. The evidence for this theory is largely based on the observations made by Rich (4) that histologically identical

focal/

/focal collagen and necrotising vascular lesions to those found in the connective tissue disorders, can be caused in animals by immunisation with foreign proteins. Experimentally amyloid, with its locus in the connective tissue, can be produced by hyperimmunisation (5) and its relatively frequent occurrence in rheumatoid arthritis (6-8) has suggested to some workers the participation of hypersensitivity in the pathogenesis of this disease (5). Moreover, the hypergammaglobulinaemia in rheumatoid arthritis has also been invoked as evidence of a hyperimmune response in this disease (10,11). However, the outstanding problem in invoking hypersensitisation to explain the pathogenesis of the connective tissue diseases is that no sustained hyper-:sensitivity state has as yet been described in man or in the experimental animal (5), and the search for an exogenous antigen has so far proved unrewarding (12).

The possibility that auto-immunisation to components of body tissues may play a role in causation of the connective tissue diseases, has been considered by several workers (5,12-14). In the experimental animal immunisation with homologous tissues conjugated with streptococcal vaccine results in the formation of auto-antibodies to heart, connective tissue, and muscle, and pathological changes in the same organs which resemble those in rheumatic fever (15). In the human, it is the newer work with the rheumatoid and L E cell factors, which points more particularly to the role of auto-immunity in the pathogenesis of the connective tissue/

/tissue disorders.

The rheumatoid factor, first described by Waaler in 1940 (16) and then re-discovered 8 years later by Rose et al. (17), has been shown to be a gamma-globulin (18) which belongs to the category of macroglobulins with a sedimentation coefficient of 19S as compared with the sedimentation coefficient of 7S for normal gamma-globulin (19). Normally, however, in whole serum the rheumatoid factor exists as a loose combination of several molecules of 7S gamma-globulin, which forms a complex with a sedimentation coefficient of 22 S (20).

Several modifications of the Rose-Waaler test have now been developed (18), and it is clear that the reaction is in the nature of an antigen-antibody reaction (18) and that the rheumatoid factor can combine with its own naturally occurring 7S gamma-globulin (5). The possibility that the Rose-Waaler test represents an auto-immune reaction thus becomes a tenable hypothesis, and the demonstration of rheumatoid factor by fluorescent antibody techniques in the antibody-forming plasma cells (21) supports such a hypothesis. However, it is necessary to postulate a high degree of non-specificity, since reactant gamma-globulin may be obtained in a wide variety of animal species (22). Glynn and Holborow (14) have put forward the attractive hypothesis that the rheumatoid factor is the result on the part of the rheumatoid patient to alteration in autogenous proteins, which is ignored by the immunological mechanisms of the normal individual. These workers also/

/also considered that the pattern of tissue damage in rheumatoid arthritis resembled a delayed-type of hypersensitivity reaction and that, therefore, the disease was probably independent of circulating antibodies; this might provide an explanation for the occurrence of a generalised arthritis of rheumatoid type in patients with agammaglobulinaemia (23).

A striking number of autologous tissue components to which circulating antibodies can be found are present in patients suffering from systemic lupus erythematosus. Thus, gamma-globulins which react with red blood cells occur frequently (24) and leucocytic agglutinins may arise without previous transfusions (25). Platelet agglutinins may be found in association with thrombocyto-:penic purpura (26), and a gamma-globulin may be present which has antithromboplastic activity (27). Another gamma-globulin which may be present is one which gives rise to a false positive Wassermann reaction (24). There is also a gamma-globulin which is deposited in large amounts in the fibrotic lesions of the spleen (28) and in the glomerular lesions in lupus nephritis (29).

A manifestation of systemic lupus erythematosus of great current interest of immunological nature is the "L E cell" test. The discovery of this test by Hargraves et al. (30) in 1948 has led to the identification of a group of factors which react with different constituents of the cell nucleus (31). Separate factors are present which react with pure DNA and histone (32) and cyto-plasmic factors have also been demonstrated (31). Like the rheumatoid/

/rheumatoid factor, the L E cell factor has been shown electro-:phoretically and ultra-centrifugally to be a gamma-globulin (33) and also to be inactivated and quantitatively precipitated by antiserum to normal human gamma-globulin (34). Immunologically it has the characteristics of the 7S gamma-globulin (35) although occasionally a small amount of high molecular weight gamma-globulin may also be present (34). Positive L E cell tests have also been reported in dermatomyositis (36), scleroderma (37), and polyarteritis nodosa (38), which also have a clinical and pathological overlap with each other and with rheumatoid arthritis and systemic lupus erythematosus (39).

Thus, there is at present evidence for the role of auto-immunity in the pathogenesis of the connective tissue diseases. Both the serum factors underlying the Rose-Waaler test in rheumatoid arthritis and the L E test in systemic lupus erythematosus possess the character-:istics of human antibody gamma-globulin, and also share some of the features of auto-antibodies. However, infusions of Rose-Waaler positive sera (40) and L E cell-positive sera (41) into human volunteers have been without significant effect, and infants born to mothers with systemic lupus erythematosus seem to suffer no ill effects despite the detection of positive L E cell tests, which may last up to 7 weeks following delivery (42-44). Moreover, the known isolated connective tissue components, with the exception of reticulin (45), are virtually non-antigenic (46-52), and tissue culture experiments using sera from patients suffering from systemic lupus/

/lupus erythematosus have been unable to detect cytotoxicity (34). Hence, while no evidence has appeared which directly contradicts the hypothesis that auto-immunisation is involved in the pathogenesis of the connective tissue diseases, the supportive evidence must be considered incomplete.

The Association of Auto-immune Thyroiditis and the Connective Tissue Diseases.

That an association exists between thyroid disease and the connective tissue diseases has long been suspected. Low BMRs (53-59) and clinical hypothyroidism (60-61) have been observed in a number of patients with rheumatoid arthritis, although Baggenstoss et al. (62) were unable to find histological evidence of hypothyroidism in 30 patients dying from rheumatoid arthritis. The association of thyrotoxicosis and rheumatoid arthritis has been reported (59,60,63-65), and the presence of lymphorrhages in the muscles in both conditions suggested to Levitt (66) that these 2 diseases might share a common pathogenesis. Short et al. (59) found a much higher prevalence of non-toxic goitre in patients with rheumatoid arthritis/ than in a control series (7 of 293) and Jones (63) considered that rheumatoid arthritis was more common in regions where simple goitre was prevalent. The association of auto-immune thyroiditis with rheumatoid arthritis has been recorded in only a few patients (67-69), although 2 of the 293 patients studied by Short et al. (59) had an unspecified type of thyroiditis. Thyroid disease (70), including auto-immune thyroiditis (71) has also been observed in other/

/forms of connective tissue disease, and histological abnormalities chiefly consisting of fibrosis (72), have been described in scleroderma. L E cells have been reported occasionally in patients with thyroid disease (73), and Heaton (74) has recently brought together evidence for the association of Sjögren's disease with systemic lupus erythematosus and rheumatoid arthritis, and auto-immune thyroiditis.

Thus, at present there is sufficient evidence to suggest a relationship, of a type as yet undetermined, between the connective tissue diseases and thyroid abnormalities in general.

Personal Observations

In the present investigation I have studied the possible relationship between auto-immune thyroiditis and rheumatoid arthritis by studying 2 groups of patients. The first group presented primarily with the thyroid disease and was examined for evidence of rheumatoid arthritis. I have compared the prevalence of arthritis in this series and in patients attending clinics of the same hospital dealing with other diseases. The second group consisted of patients with rheumatoid arthritis; the prevalence of positive tests for thyroid auto-antibodies was studied. Seven patients illustrating the clinical association between the 2 conditions have been selected for fuller presentation.

I have also studied the prevalence of positive thyroid auto-antibody tests in a small number of patients with a variety of connective tissue diseases, including Sjögren's disease.

Materials and Methods

Patients in the first group (Group 1A) presented primarily with auto-immune thyroiditis, and those in the second (Group 2A) with rheumatoid arthritis. Group 3 comprised patients with other connective tissue diseases, including Sjögren's disease.

Group 1A comprised 50 patients with auto-immune thyroiditis (46 women, 4 men). Their ages ranged from 28 to 70 years with a mean age of 51.9 for women and 59 for men. The clinical findings in this group are given in detail in the Appendices. The diagnosis of auto-immune thyroiditis was based on the criteria previously described in Chapter II of the thesis. These patients had all been referred because of the thyroid abnormality; they were examined for clinical evidence of rheumatoid arthritis by the methods suggested by Kellgren and Lawrence (75), and for radiological evidence of diseased hands (76). Rose-Waaler tests were also performed in all patients of this group, by the method described by Greenbury (77). The Rose-Waaler test was considered positive when the serum titres exceeded 1/16. L E cell tests were also carried out in 37 patients of this group.

A control series (Group 1B) was examined in the same way for evidence of rheumatoid arthritis. This group included 179 women patients attending other clinics in the hospital; 125 patients from the diabetic clinic, and 54 patients with dyspeptic symptoms from a general surgical clinic. The mean age (55 years) was similar to that in Group 1A.

Group 2A/

Group 2A consisted of 73 unselected patients with rheumatoid arthritis (49 women, 24 men) who attended the clinics associated with this hospital. Their ages ranged from 17 to 74 years, with a mean for women of 53 years and for men of 52 years. The diagnosis of rheumatoid arthritis in these patients was based on the presence of typical arthritic deformities, and was confirmed by an X-ray of the hands which satisfied the criteria given by Kellgren (76) and/or a positive Rose-Waaler test. The patients in this group were examined for evidence of thyroid disease by the clinical and laboratory methods described in Chapter II of the thesis. The clinical details in this group are summarised in the Appendices. Tests for thyroid auto-antibodies (both precipitin and CF) were performed by the methods described in Chapter II. Non-specific CF tests excluded 3 patients, reducing the number available for analysis to 70.

The results of the thyroid auto-antibody tests in this group were compared with the prevalence of positive tests in a series of hospital patients (Group 2B) previously reported from the same laboratory (78).

Group 3 consisted of 21 patients (18 females, 3 males) with various connective tissue diseases, including 9 with systemic lupus erythematosus, 6 with scleroderma, 2 with dermatomyositis, 2 with periarteritis nodosa, and also 2 patients suffering from Sjögren's disease. Their ages ranged from 22 to 67 years, with a mean age of 48.8 for women and 44 for men. The clinical details in this group/

Table I.

Investigations in 7 patients with Auto-immune Thyroiditis and Rheumatoid Arthritis

Table I.

Investigations in 7 patients with Auto-immune Thyroiditis and Rheumatoid Arthritis.

Case No.	Radioiodine Studies: 4 hr. uptake (% dose)	Radioiodine Studies: 48 hr. PBI ^{131}I (% dose/l.)	Radioiodine Studies: Pot. perchlorate Discharge Test	PBI (µg. %)	BMR (%)	Serum Cholesterol (mg. %)	Thyroid Auto-antibody Tests: Prec.	Thyroid Auto-antibody Tests: C.F.	Thymol Turbidity (units)	γ Globulin (mg. %).	Rose-Waaler Test	X-ray Hands	LE-cell Test	E.S.R. (mm./first hr.)
1	77.1	2.74	-	3.1	+21	140	+	++	4	1.40	+	+	-	82
2	45.6	0.41	-	3.3	+ 9	285	+	++	7	0.68	+	+	-	15
3	36.0	0			-19	398	+	+	2	0.73	+	+	-	50
4	64.4	0	-	2.1	+ 4	175	-	++	3	0.93	+	+	-	48
5	43.0	1.0	+	4.3	+ 5	310	+	anti-complementary	3	0.90	+	+	-	27
6	30.0	0.40			+ 9	215	+	++	8	1.35	-	+	-	13
7	14.0	0.14	+	0.5	-18	165	+	++	3	1.30	+	+	+	26

/group are summarised in the Appendices. The diagnosis of systemic lupus erythematosus was based on the clinical features and was confirmed in each patient by a positive L E cell test. The diagnosis of scleroderma, dermatomyositis, and periarteritis nodosa, was confirmed by histological examination of affected tissues. The diagnosis of Sjögren's disease was based on the clinical findings of xerostomia and kerato-conjunctivitis sicca, and was confirmed by positive Schirmer (79) and Rose Bengal (80) tests. Several of the patients in this group had received steroid therapy and were in remission when examined.

Results

Group 1A; Auto-immune thyroiditis.

Six of 46 women had an arthritis of rheumatoid type confirmed by either a positive Rose-Waaler test or by radiological evidence of the disease, or both (Table I). A further 3 women in this group had positive Rose-Waaler tests without clinical or radiological evidence of rheumatoid arthritis. Equivocal clinical and radiological signs were present in one woman patient with a negative Rose-Waaler test. As these 4 patients did not satisfy the strict diagnostic criteria of the present investigation they were not counted as cases of rheumatoid disease in the statistical analysis. One of the 4 men in this group had rheumatoid arthritis and also had a positive L E cell test (Table I). The prevalence of rheumatoid arthritis in the women patients with auto-immune thyroiditis (Group 1A; 6 of 46 cases) is much higher ($P < 0.01$) than in the control/

/control cases (Group 1B; 2 of 179 cases).

The case histories of the 7 patients of group 1A with clinical and laboratory evidence of auto-immune thyroiditis and rheumatoid arthritis are described below. The results of the investigations in these patients are summarised in the accompanying table (Table I).

Case Reports

Patient No. 1. (Thesis No. 13), a woman, aged 67 years, had had a goitre for 8 months. The goitre appeared shortly after a febrile illness and at the onset was associated with discomfort in the region of the thyroid, especially on swallowing. She complained of nervousness and irritability and her doctor prescribed carbimazole without significant effect. The patient also had had arthritis of 9 years' duration which had been treated with salicylates. On examination a large, firm, nodular goitre was present. There were no signs of hyper- or hypo-thyroidism. Typical severe rheumatoid arthritis was present in the hands, feet, wrists, elbows, knees and ankles. Subcutaneous nodules were present. A thyroid biopsy was carried out and the histological findings were consistent with auto-immune thyroiditis. Treatment with thyroxine sodium in a dose of 0.2 mgm. daily was followed by diminution in the size of the gland.

Patient No. 2. (Thesis No. 31), a woman, aged 61 years, had had a goitre for the past 6 years. During the previous two years she had complained of excessive tiredness, palpitations and preference for/

/for cold. She also suffered from stiffness and painful swelling in the joints of the hands, wrists and elbows. On examination a small, firm, nodular goitre was present. The hands were warm and moist and showed classical rheumatoid arthritis. The resting pulse rate was 85 beats per minute. Investigations (Table I) showed, however, that the patient was euthyroid (PBI 3.3 µg. per cent., BMR +9 per cent.). The precipitin and complement-fixation tests confirmed the diagnosis of auto-immunising thyroiditis. Thyroxine sodium was prescribed and the goitre diminished in size.

Patient No. 3. (Thesis No. 32), a woman, aged 65 years, had had rheumatoid arthritis for 17 years and a goitre for 3 years. A thyroid neoplasm was suspected and a subtotal thyroidectomy was performed; histological examination showed auto-immune thyroiditis. Two years later the patient developed hypothyroidism and on exam-:ination the right lobe of the thyroid was just palpable and firm. Characteristic rheumatoid arthritic deformities were present in the hands, wrists, elbows, shoulders and knees, and subcutaneous nodules at the left elbow and left wrist. Treatment with thyroxine sodium was followed by diminution of the size of the gland remnant.

Patient No. 4. (Thesis No. 40), a woman, aged 52 years, was referred because of a recent increase in the size of a goitre which had been present for 37 years. The patient had generalised arthritis of 3 years' duration which had been treated with salicylates and phenylbutazone. On examination she was euthyroid with/

/with a large, diffuse, soft goitre. Rheumatoid arthritis of moderate severity was present in the hands, wrists, elbows, knees and ankles. Thyroid biopsy showed severe and extensive auto-immune thyroiditis in addition to areas of normal epithelium. Treatment with thyroxine sodium was followed by diminution in the size of the remnant.

Patient No. 5. (Thesis No. 41), a woman, aged 66 years, had had rheumatoid arthritis for 3 years and a thyroid swelling for 18 months. On examination the thyroid gland was moderately enlarged, diffuse and firm. There were no signs of hyper- or hypo-thyroidism. Moderately severe rheumatoid arthritis was present affecting mainly the hands, wrists, elbows and knees. Treatment with thyroxine sodium was followed by diminution in the size of the gland.

Patient No. 6. (Thesis No. 46), a woman of 57 years complained of discomfort and "tightness" in her throat associated with a thyroid swelling of 2 months' duration. She also gave a history of painful hands, wrists, elbows, and knees of 2 years' duration. On examination the thyroid was moderately enlarged, diffuse and firm. There were no signs of hyper- or hypo- thyroidism. Moderately severe rheumatoid arthritis was present affecting mainly the hands, wrists, elbows, and knees. Treatment with thyroxine sodium was followed by diminution in the size of the gland.

Patient No. 7. (Thesis No. 4), a man, aged 62 years, was referred because of suspected hypothyroidism. He also gave a history/

/history of joint pains particularly in the hands and wrists of several years' duration. On examination he was obviously hypothyroid, with a small firm goitre. Typical rheumatoid changes were present in the hands and wrists and there was limitation of movement and stiffness of the elbows and shoulders. In addition the patient had small irregular pupils, which, however, reacted normally to light. The Wassermann reaction and treponemal immobilisation test were both strongly positive, but there was no other evidence of syphilitic disease. Following treatment with thyroxine sodium the goitre became impalpable.

Group 2A: Rheumatoid Arthritis.

Twelve of 46 patients with rheumatoid arthritis had positive CF tests. This incidence is much higher ($P<0.01$) than in female control cases (27 of 243). Two of the cases with rheumatoid arthritis and positive CF tests also had positive precipitin tests. Both were hypothyroid without a goitre. None of the remaining 10 cases with positive CF tests had clinical evidence of thyroid disease, although one had a high normal 48-hour PBI^{131} (0.33 per cent dose/litre). No correlation was found between the CF test results and the duration of the arthritis, or the results of the Rose-Waaler and L E cell tests. None of the 24 male cases with rheumatoid arthritis had clinical evidence of thyroid disease and all had negative thyroid auto-antibody tests. Six out of 292 male controls had positive CF tests.

Group 3: Connective Tissue Diseases, and Sjögren's disease.

Four/

Table II.

Thyroid Auto-antibodies in Connective Tissue Diseases, and Sjögren's Disease.

Table II.

Thyroid Auto-antibodies in Connective Tissue Diseases, and Sjögren's Disease.

Clinical Condition	Sex	No. of Cases.	Thyroid Auto-antibody Tests			
			Prec. (+)	Complement-fixation (+ and ++)		Anti-Complementary
				Specific	Non-specific	
Systemic lupus Erythematosus.	F M	9		1	4	1
Scleroderma.	F M	4 2		1	1	
Dermatomyositis.	F M	2		1		
Periarteritis Nodosa.	F M	1 1				
Sjögren's Disease.	F M	2	1	1		
Totals.		21	1	4	5	1

Four of the 21 patients in this group had positive thyroid-specific CF tests (Table II). This incidence is higher than in the control cases (Group 2B), but the small numbers do not permit statistical conclusions to be drawn. The findings in these 4 patients are of interest. One, a woman of 60 years with Sjögren's disease and rheumatoid arthritis, had a large firm goitre and a positive precipitin test; thyroid biopsy revealed extensive Askanazy-cell change but no chronic thyroiditis. Another, a woman of 64 years with dermatomyositis, developed hypothyroidism without a goitre one year after the onset of her illness. The third, a woman of 49 years developed primary hypothyroidism 15 years after the onset of Raynaud's phenomenon and scleroderma. The fourth patient, a woman of 60 years, with systemic lupus erythematosus, had no clinical or laboratory evidence of thyroid disease.

Discussion.

The present study provides statistical evidence of an association between auto-immune thyroiditis and rheumatoid arthritis. The patients with auto-immune thyroiditis (Group 1A) had all been referred because of thyroid disease being suspected, and an unexpectedly high proportion had evidence of rheumatoid arthritis. This prevalence is very much higher ($P<0.001$) than that of rheumatoid arthritis reported by Miall et al. (81) in females in an urban and rural population in South Wales. In the group of patients studied by Miall et al. the criteria for diagnosis/

Table III.

Survey Estimates of the Prevalence of Rheumatoid Arthritis.

Table III.

Survey Estimates of the Prevalence of Rheumatoid Arthritis.

Authors and Ref. No.	Year	Country	Prevalence/100. Males	Prevalence/100. Females	Age Group (years)	Diagnostic Criteria
Holsti and Rantasalo (82)	1936	Finland	0.3	0.9	All	"Chronic arthritis" known to Public Health Nurses in their districts.
Edström (83)	1944	Sweden	1.3	2.7	All	"Chronic arthritis" recognised by specially trained medical students in the home.
Kellgren et al. (84)	1953	England	1.4	3.3	over 15	Clinical - based on brief examination in the home.
Kellgren and Lawrence (75)	1956	England	2.5	11.0	55 to 64	Clinical, confirmed by positive X-ray and/or Rose-Waaler test.
Cobb et al. (85)	1957	U.S.A.	0.6	4.7	over 15	A.R.A. definitions, probable and definite by clinical and X-ray findings.
Miall et al. (81)	1958	Wales	1.3	0.7	between 15 and 35	Clinical, confirmed by X-ray and/or Rose-Waaler test.

/diagnosis and the age distribution were the same as in Group 1A. The prevalence of rheumatoid arthritis in Group 1A is also higher than that reported by workers in other countries using various criteria (75,81-85) - Table III.

Conclusions derived from hospital populations, however, often give a biased picture of the association between diseases (86), because the occurrence of 2 diseases in the same person gives an increased probability of being referred to hospital (Berkson's fallacy). For this reason it was thought desirable to compare the incidence of rheumatoid arthritis in Group 1A with that of a group of patients (Group 1B) from the same area referred to the same hospital with diseases in which either a positive or negative correlation with rheumatoid arthritis seemed highly improbable. The incidence of rheumatoid arthritis was much higher in the group of patients with auto-immune thyroiditis than in the control group ($P < 0.01$). It is therefore unlikely that the high incidence of rheumatoid arthritis in Group 1A has arisen from errors due to biased sampling.

An association between auto-immune thyroiditis and rheumatoid arthritis is also strongly supported by the finding in Group 2A. The incidence of positive thyroid-specific CF tests in female patients with rheumatoid disease (Group 2A) was much higher ($P < 0.01$) than that found in a hospital control population (Group 2B). Twelve patients in Group 2A had a positive CF test; Goudie et al. (78) have shown that histological examination of

thyroid/

/thyroid gland in such cases will reveal focal lesions of auto-immune thyroiditis. Two of these patients had, in addition, positive precipitin tests and were hypothyroid. There is thus good evidence that they had diffuse auto-immune thyroiditis since it has been shown that classical auto-immune thyroiditis and "primary" hypothyroidism are clinical variants of the same pathological process. (See Chapter III, Section 1).

The high prevalence of rheumatoid arthritis in the patients with auto-immune thyroiditis and the high prevalence of both positive precipitin and CF tests in the patients with rheumatoid arthritis are highly suggestive evidence in favour of a true association between these diseases. The study included only 20 men with rheumatoid arthritis, and this number is too small to draw conclusions regarding the association of auto-immune thyroiditis and rheumatoid arthritis in this sex. The findings in Group 3 also suggest that an association might exist between auto-immune thyroiditis and the connective tissue diseases, including Sjögren's disease; but the high incidence of non-specific CF tests in patients with systemic lupus erythematosus and the small number of patients studied precludes statistical evaluation. Since the completion of this work Holborow (87) and others (71,88) have demonstrated serum anti-nuclear factor in patients with auto-immune thyroiditis, thus suggesting an association with systemic lupus erythematosus, and Anderson et al. (89) using the TRC method have demonstrated a significant increase in/

/in thyroglobulin auto-antibodies in patients with all forms of connective tissue disease, including rheumatoid arthritis. On the other hand, Hijmans et al. (90) have been unable to demonstrate an increased prevalence of thyroid CF tests in patients with rheumatoid arthritis, although demonstrating a clinical and serological overlap between auto-immune thyroid disease and systemic lupus erythematosus. The discrepancy between my own findings in rheumatoid arthritis and those of Hijmans et al. (90) may partly be explained on the greater sensitivity of the CF test used in the present study in respect to serum concentration and to the amounts of complement used.

In an extensive review of rheumatoid arthritis in relation to other diseases Short et al. (59) have reported that the only associated condition which they could find was with thyroid disease. Some of their cases of simple goitre may well have been examples of auto-immune thyroiditis since at that time immunological tests were not available in this field. Both auto-immune thyroiditis and rheumatoid arthritis have certain similarities. For example, both are diseases of females of the same age (91,92). In both diseases hypergammaglobulinaemia (93,94) is associated with lymphocyte and plasma cell infiltration - in the thyroid in auto-immune thyroiditis (95) and in the synovial membrane of the joints in rheumatoid arthritis (96); and both conditions may improve with steroid therapy (97,98). The finding of a clinical assoc-:iation between these diseases provides some support for the view that auto-/

/auto-immunisation may play a part in the pathogenesis of rheumatoid arthritis. Further study of patients with both diseases may help to elucidate their inter-relationship and so throw light on the fundamental nature of the auto-immune process.

SUMMARY

The incidence of rheumatoid arthritis in 50 unselected patients with auto-immune thyroiditis was significantly higher than that in a control series of hospital patients with diseases with no known association with rheumatoid arthritis. Thyroid auto-antibodies were also demonstrated in a significantly higher number of unselected patients with rheumatoid arthritis than in a control series. Details are given of 7 patients in whom the association was present. A high incidence of thyroid auto-antibodies was also demonstrated in patients suffering from miscellaneous connective tissue diseases, including Sjögren's disease. The association between these diseases may be explained on the basis that auto-immune mechanisms play some part in their pathogenesis.

Section 2.

The Association of Auto-immune Thyroiditis and Acquired Auto-immune Haemolytic Anaemia.

The first recognition of auto-immunity in haemolytic anaemia was in 1904 by Donath and Landsteiner (1) who demonstrated a haemolysin reacting with the patient's red blood cells in paroxysmal haemoglobinuria. Auto-agglutination was also described independent-:ly by Widal et al. (2) and Chauffard and Troisier (3) in 1908, but these observations appear largely to have been overlooked. In 1936, however, Dameshek and Schwartz (4) drew attention to the presence of haemolysins in patients suffering from haemolytic anaemia and in 1946 Boorman et al. (5) reported a direct anti-globulin reaction or Coomb's test (6) in a proportion of cases. Following these latter observations a considerable amount of work has been carried out on the auto-immune aspects of the haemolytic anaemias and this has been admirably reviewed by Dacie (7). For the present purpose only conditions giving rise to a positive Coomb's test will be considered as falling into the "auto-immune" group.

It appears that auto-immune haemolytic anaemia comprises a number of disorders of varying aetiology and pathogenesis, involving warm and cold antibody types, each with idiopathic and secondary varieties (8). The serum in these anaemias contains auto-antibodies in the sense that they react with the patient's own red blood cells. The antibody is an incomplete one which can be demonstrated by the direct or indirect Coomb's test or by various modifications such as the use of trypsin-treated cells (9). There is evidence that the warm and cold antibodies are physically different (10). There also appears to be a fairly close correlation between the titre of antibody/

/antibody and the clinical severity of the haemolytic process (7).

The precise role the auto-antibodies play in the pathogenesis of the haemolysis is not clear. Dacie (7) has suggested that the antibodies may result from modification of the antigenicity of the erythrocytes by either virus, toxin or drug; or, alternatively, that they are the consequence of mutation with formation of abnormal gamma-globulins. Evidence in favour of the role of auto-immunisation in the pathogenesis of the disease includes the finding of hypergammaglobulinaemia (11), low serum complement levels (12), and associated leucopenia (7), and thrombocytopenia (13).

The Association of Auto-immune Thyroiditis and Acquired Auto-immune Haemolytic Anaemia.

Historical Aspects

A careful review of the literature has revealed only 2 reports of the co-existence of auto-immune thyroiditis and acquired auto-immune haemolytic anaemia. In the first Wasastjerna (14) described a 47-year old woman who suffered simultaneously from a severe haemolytic anaemia and had a goitre which was proved histologically to be due to auto-immune thyroiditis. Both the Coomb's test and precipitin test were positive; with more detailed studies Wasastjerna was able to demonstrate that the 2 types of antibody were distinct. In the second report by White et al. (15) the patient concerned was a woman of 48 years who had a Coombs positive haemolytic anaemia and a goitre. The precipitin test was, however, negative and no thyroid biopsy was performed and the diagnosis of auto-immune thyroiditis was based on the clinical findings.

Personal Observations

In the present investigation I have studied the possible association between auto-immune thyroiditis and acquired auto-immune haemolytic anaemia. As in the previous section I have approached the problem by first examining a group of patients with auto-immune thyroiditis for evidence of acquired auto-immune haemolytic anaemia, and secondly by studying the prevalence of thyroid auto-antibodies in patients with acquired auto-immune haemolytic anaemia.

Materials and Methods

Two groups of patients were studied; Group 1 with auto-immune thyroiditis, and Group 2 with acquired auto-immune haemolytic anaemia.

Group 1 consisted of 50 patients (46 females, 4 males) with auto-immune thyroiditis. Their ages ranged from 28 to 70 years, with a mean age of 52.5 years. The diagnosis of auto-immune thyroiditis was based on the criteria described in Chapter II of the thesis. Full blood examination, including reticulocyte counts and Coomb's tests, were carried out in all patients of this group and in addition radiochromium (Cr^{51}) studies were performed in 5 patients, by the method described by Mollison and Veall (16).

Group 2 comprised 22 patients (18females, 4 males) with acquired auto-immune haemolytic anaemia. The age range in this group was 18 to 70 years with a mean age of 52.5 for women and 54.0 for men. Each patient was examined clinically for evidence of thyroid disease and the prevalence of thyroid auto-antibodies was studied using the precipitation and complement-fixation methods described in Chapter II/

/Chapter II of the thesis.

The clinical details in this group are summarised in the Appendices; all the patients had a positive Coombs test. Three patients with complementary CF reactions and two with non-specific CF tests have been excluded from the statistical analysis, reducing the number available to 17.

Results

Group 1: Auto-immune thyroiditis

The results of the haematological investigations in this group are given in detail in the Appendices. Only one patient in this group was found to have a haemolytic anaemia, and the case-report of this patient is described below:

Thesis No. 42. A woman of 57 years had had a goitre for 2 years. On examination, the thyroid was moderately enlarged, diffuse and firm, and there were no signs of hyper- or hypo- thyroidism. Investigations confirmed the diagnosis of auto-immune thyroiditis; precipitin and CF tests positive, thymol turbidity 5 units, thymol flocculation 3 units, gamma-globulin 1.09 g. per 100 ml., 4 hour gland uptake I^{131} 60.3 per cent / dose, 48 hour PBI^{131} 0.24 per cent dose/litre, potassium perchlorate discharge test positive, and serum PBI 3.0 µg. per 100 ml. Blood examination was normal: Hb 84 per cent., PCV 40 per cent., MCH C, 31.5 per cent., and white blood count 5,100 cells per cu. mm. The ESR was 15 mm. in the first hour and the serum bilirubin 1.4 mg. per 100 ml. Treatment with thyroxine sodium in a dose of 0.2 mg. daily was

Table I.

Results of Precipitin and Complement-Fixation Test in Acquired Haemolytic Anaemia.

Table I.

Results of Precipitin and Complement-Fixation test in Acquired Haemolytic Anaemia.

Clinical Group	Sex	Total No. of Cases.	Thyroid Auto-antibody Tests	
			Precipitin (+)	Complement-Fixation (+) and (++)
Acquired Haemolytic Anaemia	F	13	1	5
	M	4		
Hospital Controls	F	243		27
	M	240		6

/followed by diminution in the size of the gland.

Six months after her first attendance the patient complained of lassitude and dyspnoea on exertion, and on examination she looked pale and slightly icteric. The tip of the spleen was just palpable. Investigations confirmed the diagnosis of haemolytic anaemia: Hb 68 per cent., PCV 31.5 per cent., MCHC 32 per cent., white blood count 4,000 cells per cu. mm., differential white blood count normal, platelet count 155,000 cells per cu. mm., reticulocyte count 5 per cent., Coombs test negative, non-specific cold agglutinins present to titre of 1 in 4 with normal group O cells, red-cell fragility normal, no abnormal haemoglobins were detected. The Cr^{51} half-life was 12 days, and sequestration of red blood cells was demonstrated in the spleen. The serum bilirubin was 2.6 per cent. Liver biopsy was normal.

The patient declined to have splenectomy and has been observed for a period of 2 years without significant alteration in the level of haemoglobin or reticulocyte count.

Group 2: Auto-immune Haemolytic Anaemia

The results of the precipitin and CF tests in this group are summarised in Table 1 and full details of investigations are given in the Appendices. From Table 1 it can be seen that 5 of 13 females with auto-immune haemolytic anaemia had positive CF tests, including one with a positive precipitin test. This incidence is higher ($P < 0.02$) than in women controls (27 of 243) studied in the same laboratory by the same methods (17). None of the 4 men with auto-immune haemolytic anaemia had positive thyroid auto-antibody tests.

Discussion

The interesting finding in the present investigation is the high prevalence of thyroid auto-antibodies in female patients with acquired auto-immune haemolytic anaemia (Group 1). Five of the 13 female patients in this group had positive thyroid-specific CF tests; an incidence which is much higher ($P < 0.02$) than that in 27 of 243 female hospital controls reported by Goudie et al. (17), from the same laboratory. However, in contrast to the high prevalence of thyroid auto-antibodies in this group none of the patients with auto-immune thyroiditis comprising Group 1 had auto-immune haemolytic anaemia, although one patient developed an acquired idiopathic Coombs negative haemolytic anaemia six months after her first attendance at the clinic.

The high prevalence of thyroid auto-antibodies in patients suffering from auto-immune haemolytic anaemia lends support to the view that auto-immunisation may be of importance in the pathogenesis of this disease. The predisposition to develop thyroid auto-immunity in patients with auto-immune haemolytic anaemia may be due to an enhanced antibody forming potential, since patients with this disease readily produce antibodies to blood group substances (7). On the other hand the development of thyroid auto-immunisation may be due to a disturbance of the mechanism of immunological tolerance operating in normal health, in which case the present findings would support the view held by Dacie (7) that the pathogenesis of auto-immune haemolytic anaemia is primarily related to a disturbance in the immunological cells of the reticulo-endothelial/

/-endothelial system.

The present investigation does not explain the nature of the association between auto-immune thyroiditis and auto-immune haemolytic anaemia, but it serves as a useful pointer to the problem, which further study may help to elucidate.

SUMMARY

Thyroid auto-antibodies were found in a much higher proportion of females with auto-immune haemolytic anaemia than in a control series of female hospital patients. The case-history of one patient with auto-immune thyroiditis who developed an acquired idiopathic Coombs negative haemolytic anaemia is described. The findings lend support to the view that auto-immunity plays a role in the pathogenesis of auto-immune haemolytic anaemia.

Section 3.

The Association of Auto-immune Thyroiditis and Cirrhosis of the Liver.

Introduction

Cirrhosis (Greek kirrhos = yellow) of the liver is a disease of world-wide distribution. It is due to a variety of causes, including chronic alcoholism, viral hepatitis, malnutrition, metabolic diseases, parasitic and spirochaetal infection, poisons and passive venous congestion; but the final end picture is the same (1). Histologically the disease is characterised by a distorted reconstruction of the normal architecture brought about by liver-cell necrosis, connective tissue proliferation, and parenchymal regeneration.

Portal cirrhosis is the commonest type of chronic liver disease in this country, but is relatively rare and accounts for approximate-:ly 0.3 per cent. of all deaths in Scotland (2). Studies of the aetiological factors involved in Great Britain (1, 3) have shown that chronic alcoholism and viral hepatitis together account for approximately half the cases, whereas in the remainder the aetiology is completely obscure. Alcoholic cirrhosis occurs predominantly in males, but other forms of the disease occur more commonly in females (1, 3).

The Role of Auto-immunity in the pathogenesis of Cirrhosis of the Liver.

Although many instances of hepatic cirrhosis can be directly related to either a preceding viral hepatitis or excessive alcoholic intake, it still remains uncertain what factors, if any, determine the onset of progressive liver damage in individual cases. In

/1944, Eaton et al. (4) first initiated speculation regarding the possible role of immunological processes in the progression of acute viral hepatitis to cirrhosis of the liver, when they described complement-fixing liver antibodies in the blood-serum of patients with acute hepatitis. Seven years later Zimmermann et al. (5) suggested that "hypergammaglobulinaemia in acute hepatitis might indicate the production of antiliver protein that continues to cause necrosis of the liver." In 1956 Mackay et al. (6) suggested that liver cells damaged by either a virus or toxic agent might be rendered antigenic and so initiate an auto-immune reaction which becoming self-perpetuating would finally lead to chronic liver damage. Later Mackay et al. (7) brought together evidence in support of an auto-immune basis for cirrhosis of the liver: marrow plasmocytosis, hypergammaglobulinaemia associated with plasma and lymphocytic infiltration in the liver, the occasional occurrence of positive LE cell tests with manifestations of systemic lupus erythematosus ("lupoid" hepatitis) (6-12), the presence of "auto-immune" complement-fixing antibodies of the type described by Gadjusek (13), and the occasional response of the liver necrotising-process to steroid therapy (14).

Most attempts to demonstrate liver auto-antibodies have so far proved unsuccessful, although Dausset and Marchal (15) described a "heat labile substance behaving as an auto-antibody" in a cirrhotic patient. Hunter et al. (16) have also recently claimed to have demonstrated auto-agglutinins to liver in patients with chronic liver disease.

The Interrelationships between the Thyroid and Liver

The liver plays an important role in the catabolism of the thyroid hormones. Not only is thyroxine selectively taken up by the liver (17), but it also penetrates the liver cells (18), and is then secreted into the bile partly conjugated as glucuronides (19) and partly in the form of α-keto derivatives (20). Some thyroxine reappears in the stools but is reabsorbed in the intestine thus establishing an entero-hepatic circulation (21). Thyroxine is also deiodinated by the liver (22). Experimental obstructive jaundice in rats, produced by ligature of the bile duct, has been shown to result in suppression of thyroid activity (23), but in acute hepatitis in man high levels of serum protein-bound iodine have been reported (24,25) which has been interpreted as being due to an increased thyroxine-binding of the serum proteins (25) similar to that in pregnancy (26) and during treatment with oestrogens (27). On the other hand the levels of serum protein bound iodine in cirrhosis have been reported as low (24), normal (28,29) or slightly elevated (25). Radioiodine studies of thyroid function in patients with cirrhosis have shown variable results; the thyroid gland uptake of radioiodine has been reported as either normal (25) or increased (28,29). With few exceptions (30), the plasma protein-bound radioactivity has been found normal in cirrhosis (25).

Conversely the thyroid hormones are known to accelerate the rate of both chemical and enzymatic reactions in the liver. In thyrotoxicosis/

/thyrotoxicosis a mild disturbance of hepatic function is not uncommon (31), and minor histological changes in the liver are frequently found (32). An increased incidence of hepatic cirrhosis in thyrotoxic patients has not, however, been confirmed by recent studies (33) although the prognosis in acute viral hepatitis is poorer when thyrotoxicosis co-exists (1). Thyroidectomy and hypo-:physectomy have been found to result in cirrhosis of the liver in dogs (34), but cirrhosis of the liver has only occasionally been reported in spontaneous hypothyroidism in man (35-39).

The Association of Auto-immune Thyroiditis and Cirrhosis of the Liver

Historical Aspects

Farrant (40) appears to have been the first to have described histological changes in the thyroid gland in patients with cirrhosis of the liver. In 1914 this author found that "the thyroid taken from 6 cases of cirrhosis of the liver all showed considerable fibrosis". In a study of the histological changes in the endocrine glands in cirrhosis in 1932 Barrelet (41) confirmed Farrant's observations, and could find no correlation between the degree of fibrosis present in the thyroid and "either the age, or the form of the cirrhosis" (translated from the French). In 1957 Barr and Sommers (42) reported an extensive clinico-pathological study of the endocrine changes in 100 patients dying with hepatic cirrhosis and found what they described as "fibrous atrophy" of the thyroid in 31 per cent. of the patients (29 of 94) as compared with 18 per cent. (15 of 108) in a control series. On the other hand the presence of sub-clinical auto-immune thyroiditis appears to have been mentioned/

/mentioned by only a few workers (43,44), although Bastenie (45) drew attention to the increased frequency of this lesion in 1937.

The co-existence of auto-immune thyroiditis and cirrhosis of the liver was first described in 1956 by Luxton and Cooke (46). These authors described 2 patients with both diseases in a series of 24 patients with the former condition, and also noted abnormal bromsulphthalein (BSP) tests in a further 5. Later Luxton (47) in drawing attention to the remarkable histological resemblances between the 2 conditions suggested that cirrhosis of the liver might be termed "Hashimotosis of the liver". These similarities had previously been noted by Shaw and Smith (48) in 1925; in describing the histological appearances of auto-immune thyroiditis these authors observed that "the change, i.e. hyperplasia is similar to the compensatory regeneration which takes place in cirrhosis of the liver". Continental workers (49) had also previously described auto-immune thyroiditis as "cirrhose de la thyroïde".

In a study of 106 patients with auto-immune thyroiditis in 1958 Roitt and Doniach (50) mentioned 4 patients who had unspecified forms of liver disease; in one of these, however, liver biopsy showed "periportal lymphoid infiltration and fibrosis". In the following year Doniach et al. (38) described the clinical details of 3 patients with cirrhosis of the liver and auto-immune thyroiditis; 2 of these patients had a goitre and were subsequently shown by biopsy to have auto-immune thyroiditis and the third had primary hypothyroidism. The clinical and laboratory details in these patients/

Table I.

Clinical Association of Auto-immune Thyroiditis and Cirrhosis of the Liver reported in the Literature.

Table I.

Clinical Association of Auto-immune Thyroditis and Cirrhosis of the Liver reported in the Literature.

Authors and Year	Ref. No.	Age	Sex	Clinical Details and Laboratory Findings
Doniach et al (1959)	37	69	M	Sudden onset of painful hard goitre, followed 15 days later by fever and jaundice. Precipitin test positive; thyroid histology confirmed auto-immune thyroditis. Liver biopsy "suggestive of recent hepatitis with progression to Cirrhosis". LE cells not looked for.
		55	F	History of jaundice at 8 years of age and of "puberty" goitre of 5 years duration. At age of 51 years developed a goitre. Precipitin test positive; thyroid histology consistent with auto-immune thyroditis. At age of 53 years became jaundiced; liver biopsy consistent with cirrhosis.
Limbosch (1959)	51	50	F	Hypothyroid with small firm goitre. Precipitin test positive; Thyroid biopsy; Auto-immune thyroditis with severe fibrosis. Liver palpable and biopsy revealed "fine fibrosis with a little lymphocytic infiltration" (translated).
McConakey and Callaghan (1960)	52	57	F	Goitre at age of 51 years, which was confirmed histologically to be auto-immune thyroditis. Jaundice at age of 54 years; liver biopsy consistent with cirrhosis. Precipitin test positive.

/patients with auto-immune thyroiditis and cirrhosis of the liver are summarised in Table 1, together with patients with both conditions described by Limbosch (50) and McConakey and Callaghan (52). From this table it can be seen that the patients are middle-aged and that only one is a male. The aetiology of the cirrhosis in this male patient is probably viral hepatitis, but the aetiology is obscure in the female patients. The onset of the goitre appeared to precede the liver disease in all the patients, with the exception of the one reported by Limbosch (51) in whom the onset of neither disease was stated. The association of primary hypothyroidism with "lupoid" hepatitis has also been reported (36).

Thyroid auto-antibodies have also been described in patients with cirrhosis of the liver without overt thyroid disease (50,53,54). In a post-mortem survey of the CF test in relation to thyroid histology, Goudie et al. (53) found this test positive in 6 of 17 patients with hepatic cirrhosis. When these results were considered separately for sex the incidence of thyroid-specific CF tests in the females (6 of 11) was significantly higher than in other female hospital patients without liver disease (27 of 243). These workers suggested that their findings should serve "as a pointer to the problem and will help to solve it only by furnishing evidence of the thyroid lesion during life, thus permitting detailed investigations in the living intact patient".

Personal Observations

The purpose of the present study is to investigate the nature of/

/of the possible association between auto-immune thyroiditis and cirrhosis of the liver. The plan of the study is similar to that described in the investigations of the association of auto-immune thyroiditis and the connective tissue diseases, and auto-immune haemolytic anaemia. A group of patients with auto-immune thyroiditis has been examined for evidence of liver disease; and the incidence of thyroid auto-antibodies in patients with cirrhosis of the liver has been investigated. The presence of thyroid auto-antibodies in patients suffering from hepatic cirrhosis has been studied in relation to the clinico-pathological features of the liver disease.

Materials and Methods

The following groups of patients were studied:

Group I consis ted of 50 patients (46 females, 4 males) with auto-immune thyroiditis. The age range of this group was 28 to 70 years, with a mean age of 52.5 years. The diagnosis of auto-immune thyroiditis was based on the criteria described in Chapter II of the thesis. Each patient was carefully screened for stigmata of liver disease and bromsulphthalein (BSP) tests (55) were carried out in 42 patients. In 6 patients who had abnormal BSP tests needle biopsy of the liver was performed.

Details of the clinical and laboratory findings in this group are summarised in the Appendices.

Group II consisted of 30 patients (16 females, 14 males) with cirrhosis of the liver. The mean age of the female patients was 51.5 years (age range 39 to 71 years) and 55.1 years for the males (age/

/(age range 37 to 71 years). The diagnosis of cirrhosis of the liver was based in 24 patients on histology of the liver. In the remainder the diagnosis was based on the clinical findings and standard liver function tests. The incidence of thyroid auto-antibodies in this group was studied by both precipitin and CF tests, using the methods described in Chapter II of the thesis. Three patients (1 female, 2 males) with non-specific CF tests (detected by testing against liver, kidney and adrenal extracts) and 3 patients (2 females, 1 male) whose sera was strongly anticomplementary, were excluded from the study, reducing the number available for analysis to 24.

Routine radioiodine tests, including measurements of the 4 hour thyroid gland uptake and 48 hour plasma protein-bound radioactivity (PBI^{131}) were performed in all patients by the methods described in Chapter II of the thesis. Additional tests of thyroid function included potassium perchlorate discharge tests and estimations of the serum PBI.

Details of the clinical and laboratory findings in this group are summarised in the Appendices.

Results

Group I. None of the patients with auto-immune thyroiditis had evidence of cirrhosis. However, 6 of the 42 patients in whom BSP tests were performed had abnormal results exceeding 6% retention at 45 minutes. Of these 6 patients, one had hepato-splenomegaly and had had a gastrectomy for gastric neoplasm; hepatic biopsy in this patient/

Table II

Incidence of Thyroid Auto-antibodies

in Cirrhosis of the Liver.

Table III

Results of Investigations of Thyroid

Function in 5 Female Cirrhotic Patients

with Thyroid Auto-antibodies.

Table II.

Incidence of Thyroid Auto-antibodies in Cirrhosis of the Liver.

Clinical Group	Sex	Total No. of cases	Thyroid Auto-antibody Tests	
			Precipitin (+)	Complement-Fixation (+) and (++)
Cirrhosis of Liver	F	13	1	5
	M	11		1
Hospital Controls	F	243		27
	M	240		6

Table III.

Results of Investigations of Thyroid Function in 5 Female Cirrhotic Patients with Thyroid Auto-antibodies.

Case	Age.	Clinical Status	Goitre	Thyroid Auto-antibody Tests.		Radioiodine Tests				Thyroid Histology
				Precipitin	Complement-Fixation	4 hour uptake (% dose)	PBI ^{131} (% dose/l.)	Perchlorate Discharge	PBI (µg./100 ml.)	
1	58	Euthyroid	None	+	++	10.2	0.22	+	3.5	
2	71	"	"	-	+	27.8	0.13	-	3.0	No post-mortem examination of thyroid performed.
3	63	"	"	-	++	24.5	0.54	+	3.6	Focal thyroiditis present.
4	45	"	"	-	++	20.2	0.21	-	4.4	Focal thyroiditis present.
5	59	"	"	-	++	43.1	0.05	-	5.5	

/patient showed no evidence of either cirrhosis or hepatic metastases; another with normal liver histology had a splenomegaly ascribed to an acquired idiopathic Coombs negative haemolytic anaemia. The case-report of the latter patient has been presented in the previous section of this Chapter of the thesis. The remaining 4 patients all had normal liver histology.

Group II. Of the 11 male patients 1 had a thyroid-specific CF test (Table II) and another with negative thyroid auto-antibody tests had primary hypothyroidism. Because of the high incidence of chronic alcoholism in the male patients (7 of 11) and the very low incidence of thyroid CF tests no further analysis of this group has been attempted.

The incidence of positive thyroid-specific CF tests in the female patients (5 of 13) was much higher ($P < 0.02$) than in a group of female hospital controls (27 of 243) matched for age and studied by the same methods in the same laboratory (53). From Table III it can be seen that histological examination of the thyroid was carried out in 2 patients, and revealed focal thyroiditis in both. Moreover, radioiodine tests in these 2 patients were consistent with the presence of this lesion: one had a 48 hour PBI^{131} in the thyrotoxic range i.e. exceeding 0.4 per cent. per dose per litre of plasma, and had the positive perchlorate discharge test found in auto-immune thyroiditis; the other had a high-normal 48 hour PBI^{131} value, i.e. exceeding 0.2 per cent. per dose per litre of plasma. A further patient in this group also had a high-normal 48 hour PBI^{131},

and/

/and a positive perchlorate discharge test.

The mean PBI (5.0 μg. per 100 ml.) in the female cirrhotic patients was not significantly different from the mean (5.2 μg. per 100 ml.) of a normal series in this laboratory. This finding is in agreement with results obtained by Shipley and Chudzik (28), but contrasts with the low values reported by Kydd and Man (24) and the high values reported by Vanotti and Béraud (25).

No correlation was found between the occurrence of thyroid specific CF tests and the clinico-pathological features of the hepatic cirrhosis (see Appendices). There was, however, a tendency for patients with thyroid auto-antibody to show evidence of excess circulating oestrogens, e.g. "ferning" of the cervical mucus in 3 of 4 post-menopausal patients (56). In contrast 0 of 7 post-menopausal patients with negative CF test showed this feature.* None of the cirrhotic patients in the present study had a positive LE cell test or clinical evidence of systemic lupus erythematosus.

Discussion

The significant finding in the present study is the high incidence of thyroid auto-antibodies in middle-aged females with cirrhosis of the liver (Group II). Five of the 13 female patients with cirrhosis had thyroid-specific CF tests; an incidence which is much/

* I would like to thank Dr. R.R. MacDonald of the University Department of Obstetrics and Gynaecology, Western Infirmary, Glasgow, who kindly carried out these tests.

/much higher ($P < 0.02$) than that in 27 of 243 female hospital controls matched for age and studied in the same laboratory (53). This finding agrees with the previous observations of Goudie et al. (53) in a post-mortem survey of the CF test and thyroid histology in cirrhosis of the liver; and with the preliminary studies of Sclare et al. (57) using the tanned red-cell haemagglutination method.

None of the 5 female cirrhotic patients with positive CF tests had clinically overt thyroid disease. Goudie et al. (53) have demonstrated that a thyroid-specific CF test is associated with the presence of lesions of Hashimoto-type thyroiditis and therefore the 5 subjects mentioned above probably all have this lesion. Indeed the existence of thyroiditis was confirmed in 2 of the 5 patients in whom post-mortem examination was performed (Table III). Furthermore, radioiodine tests in a third patient were consistent with auto-immune thyroiditis; since there was high-normal PBI^{131} value and a positive perchlorate discharge test (Table III).

In contrast to the finding in the female patients with cirrhosis only 1 of 11 males had a positive thyroid-specific CF test. However, it is of interest that one other male patient with negative antibody tests had hypothyroidism without a goitre. Presumably, had this patient's thyroid been examined the histological changes of auto-immune thyroiditis might well have been revealed, since it has been shown that primary hypothyroidism and auto-immune thyroiditis are probably variants of the same pathological process (see Chapter III, Section 1). The findings of a preponderance of thyroid auto-antibodies/

/auto-antibodies in female patients with hepatic cirrhosis may be comparable with the similar sex-distribution found in rheumatoid arthritis and auto-immune haemolytic anaemia. In contrast with the high incidence of rheumatoid arthritis in auto-immune thyroiditis cirrhosis of the liver did not occur in any of the patients with auto-immune thyroiditis comprising Group I.

The finding of an abnormally high incidence of thyroid auto-antibodies in the female patients with cirrhosis of the liver may be of fundamental importance in our understanding of the responsible underlying pathogenetic mechanism in some cases of the disease, since it supports the concept of Mackay et al. (7) that auto-immune mechanisms may be implicated. A parallel may be drawn between auto-immune thyroiditis and cirrhosis of the liver. In both diseases hypergammaglobulinaemia is associated with lymphocytic and plasma cell infiltration of the affected organ, and both disorders may be found in association with a Coombs positive haemolytic anaemia (58,59) and anti-nuclear formation (60,61). Furthermore, Murray (62) has demonstrated partial arrest of the disease with diminution in goitre size in auto-immune thyroiditis with steroid therapy, and O'Brien et al. (14) have shown that in some patients with chronic hepatitis the liver necrosing process is sensitive to cortisone. The possibility, therefore, arises that while steroid administration may confer little or no benefit in the majority of patients suffering from cirrhosis of the liver, a small group of female cirrhotic patients may exist in whom steroid therapy would

be/

/be worth a trial. It is tentatively suggested that in the cirrhotic patient in whom the presence of thyroid auto-immunity can be demonstrated, corticoid therapy might conceivably arrest the disease and thereby improve life expectancy.

SUMMARY

Thyroid auto-antibodies were found in a much higher proportion of middle-aged females with cirrhosis of the liver than in a control series of female hospital patients. No correlation was found between the presence of the thyroid auto-antibodies and the clinico-pathological features of the liver disease, although patients with thyroid auto-antibodies had evidence of oestrogen excess.

The findings lend support to the view that auto-immunity may play a role in the pathogenesis of cirrhosis of the liver, and it is suggested that steroid therapy might be beneficial in cirrhotic patients, who have thyroid auto-antibodies.

Section 4.

The Antibody-forming Potential in Auto-immune Disease.

Introduction

It has long been known that animals differ in their capacity to produce antibodies to a given antigenic stimulus (1,2), and recent experimental studies have shown that the same is also true for healthy human beings (3-5). Furthermore, a proportion of patients suffering from certain diseases, in which auto-immune mechanisms have been implicated, have been found to respond with unusual vigour to stimulating doses of foreign antigens. Thus, patients with systemic lupus erythematosus have been found to be among the most prolific producers of antibodies to blood group substances (3,6-8). They have also been reported to produce demonstrable antibodies to antibiotics more frequently than other patients (9). Similarly, patients with rheumatoid arthritis have been found to produce significantly more circulating antitoxin to tetanus toxoid immunisation than do controls (10), although normal antibody responses have been observed by other workers to heterologous blood groups (3), and pneumococcal polysaccharides (11). In cirrhotic guinea-pigs Long (12) has demonstrated enhancement of antibody formation to diphtheria toxoid and skin testing with tuberculin, and Havens et al. (13,14) have reported high antitoxin titres to tetanus and diphtheria toxoids in several patients with alcoholic cirrhosis, who had been previously immunised with these antigens. On the other hand Cherrick et al. (15) have found normal responses to tetanus immunisation in patients who had predominantly idiopathic Laennec's cirrhosis.

Personal Observations

The purpose of the present investigation was to study the antibody-forming in patients with auto-immune thyroiditis and primary hypothyroidism in order to ascertain (a) whether patients with these diseases respond normally or not on primary immunisation with a foreign antigen, and (b) whether the antibody levels found correlate with the clinical findings or with the results of the thyroid auto-antibody tests or gamma-globulin levels. Since serological hyper-reactivity might account for the association of auto-immune thyroiditis with the connective tissue diseases, and cirrhosis of the liver, the antibody response was determined in patients suffering from these conditions. The observations were controlled by measuring the antibody response in a group of normal subjects matched for age and sex.

Tetanus toxoid was chosen as the provoking antigen in these studies because accurate and well-established techniques were available for assessing the antitoxin response, and because man does not naturally have circulating tetanus antitoxin; thus the effect of primary immunisation could be studied in patients who were in the unimmunised state. Furthermore, reactions after injection of tetanus toxoid are rare and usually mild.

Materials and Methods

The following groups of patients were studied:

Clinical Condition	Total No. of Cases.	Sex		Age (yrs.)	
		Male	Female	Mean	Range
Auto-immune thyroiditis.	20	2	18	51.9	40 - 63
Primary hypothyroidism.	17	1	16	46.5	38 - 67
Cirrhosis of the liver.	16		16	55.3	39 - 71
Connective tissue diseases.	11		11	47.5	22 - 64
Controls.	13		13	53.6	35 - 69
Totals.	77	3	74	51.1	22 - 71

The diagnosis of the various diseases was based on the criteria described in earlier parts of the thesis. The clinical data of the patients is summarised in the Appendices. The aetiology in the 16 patients with cirrhosis was as follows:- 10 had cryptogenic disease, 4 had chronic hepatitis, and 2 had alcoholic cirrhosis. The group of patients with connective tissue diseases included:- 5 patients with systemic lupus erythematosus, 2 patients with scleroderma, 1 patient with dermatomyositis, and 3 patients with rheumatoid arthritis. The control group consisted of hospital patients with functional illnesses in whom I could find no evidence of organic disease.

Patients/

TABLE I.

Tetanus Antitoxin in Titres in Auto-immune Thyroiditis, Primary Hypothyroidism, Cirrhosis of the Liver, and Miscellaneous Connective Tissue Disorders.

TABLE I.

Tetanus Antitoxin Titres in Auto-immune Thyroiditis, Primary Hypothyroidism, Cirrhosis of the liver, and Miscellaneous Connective Tissue Disorders.

Clinical Group.	No. of Cases with Tetanus Antitoxin Titres. (Units per ml.).										Total
	< 0.01	> 0.01 < 0.02	> 0.02 < 0.05	> 0.05 < 0.1	> 0.1 < 0.2	> 0.2 < 0.5	> 0.5 < 1.0	> 1.0 < 2.0	> 2.0 < 5.0	> 5.0 < 10.0	
Auto-immune thyroiditis.	4	4		2	4		4		1	1	20
Primary hypothyroidism.	4	2		2	2	3	2	2			17
Cirrhosis of liver.	4	2		1	2	3	2	2			16
Connective tissue diseases.	1	4		1	1	3		1			11
Hospital controls.			1	5	5				2		13

/Patients with a previous history of tetanus toxoid injections which might have affected the antibody response were excluded from the study.

Each patient received two intramuscular injections of 1 ml. (about 9 L f) of the same batch of tetanus toxoid, at an interval of six weeks. The tetanus toxoid was stored in a refrigerator at 2° C. until used. Blood serum was taken for estimation of antitoxin titre exactly 2 weeks after the second injection. The concentration of tetanus antitoxin in the sera was determined in mice by the method of Glenny and Stevens (16), and the results were expressed in international units.* Because the patients were initially in the unsensitised state and because of the relatively short interval between the two injections the antibody response can be regarded as the result of primary immunisation (17).

Results

The results of primary immunisation to tetanus toxoid are summarised in Table 1. The wide scatter in individual antitoxin titres precludes statistical analysis. However, from Table 1 it can be seen that there is no obvious difference in the antibody response of patients with auto-immune thyroiditis, primary hypothyroidism, cirrhosis of the liver, connective tissue disorders, and the/

* I am grateful to Miss Mollie Barr, M.Sc., of the Wellcome Research Laboratories for carrying out the tetanus antitoxin titrations.

FIGURE 1.

Relationship between Tetanus Antitoxin Titres and Gamma-globulin Levels in Auto-immune Thyroiditis and Primary Hypothyroidism.

TABLE II.

Tetanus Antitoxin Titres in Relation to Results of Precipitin Test in Auto-immune Thyroiditis and Primary Hypothyroidism.

FIG. 1.

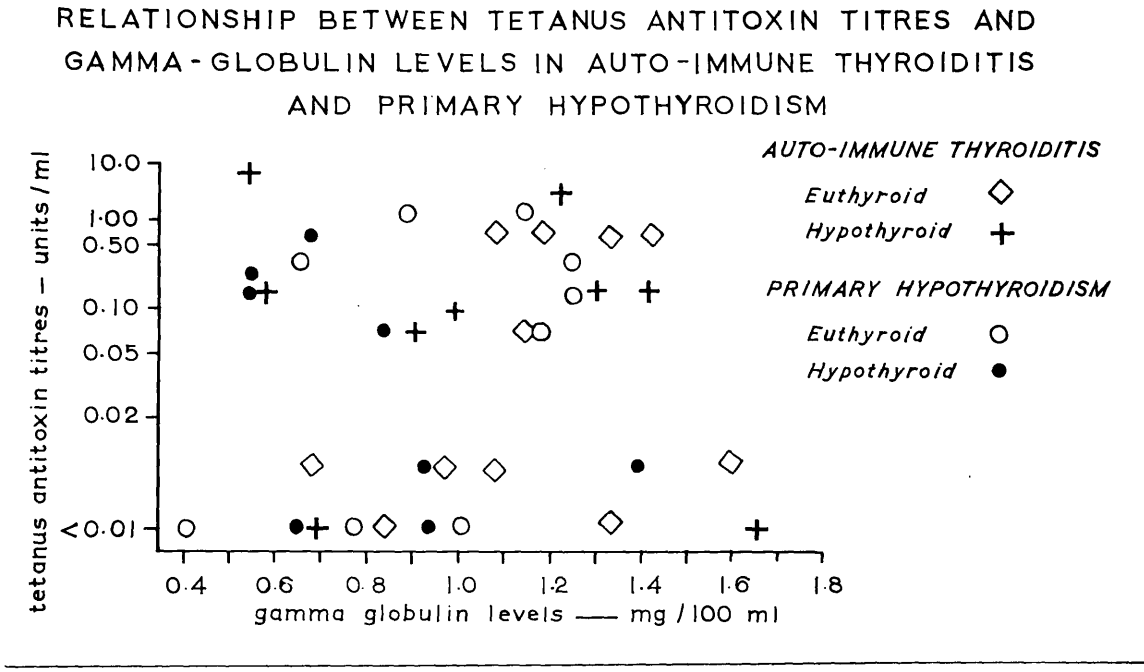

RELATIONSHIP BETWEEN TETANUS ANTITOXIN TITRES AND GAMMA-GLOBULIN LEVELS IN AUTO-IMMUNE THYROIDITIS AND PRIMARY HYPOTHYROIDISM
AUTO-IMMUNE THYROIDITIS
Euthyroid
Hypothyroid
PRIMARY HYPOTHYROIDISM
Euthyroid
Hypothyroid
tetanus antitoxin titres — units / ml
10·0
1·00
0·50
0·10
0·05
0·02
<0·01
0·4
0·6
0·8
1·0
1·2
1·4
1·6
1·8
gamma globulin levels — mg / 100 ml

TABLE II.

Tetanus Antitoxin Titres in relation to results of Precipitin Test in Auto-immune Thyroiditis and Primary Hypothyroidism.

Precipitin Test	No. of Cases with Tetanus Antitoxin Titres (units per ml.)									Total
	< 0.01	>0.01 <0.02	>0.02 <0.05	>0.05 <0.1	>0.1 <0.2	>0.2 <0.5	>0.5 <1.0	>1.0 <2.0	>2.0 <5.0	>5.0 <10.0	
(+)	3	4		3	4		4		1	1	20
(-)	5	2		1	2	3	2	2			17

/the control subjects. Furthermore, in auto-immune thyroiditis and in primary hypothyroidism no correlation was found between the antitoxin titres and the clinical status and gamma-globulin levels (Fig. 1), and the results of the precipitin tests (Table II). Patients with connective tissue diseases who were receiving steroid therapy had antitoxin titres similar to those found in patients not receiving this treatment.

Discussion

The results in the present investigation show that patients with auto-immune thyroiditis and primary hypothyroidism have a normal response to primary immunisation to tetanus toxoid. It is probable that the antitoxin titres represent the true antibody-forming potential in these patients, since no correlation was found between the levels of antitoxin and the clinical status, gamma-globulin levels (Fig. 1) or results of the precipitin tests (Table II). It follows, therefore, that hyper-immunisability cannot be primarily involved in the pathogenesis of auto-immune thyroid disease.

Havens et al. (13,14) have reported that a proportion of patients suffering from cirrhosis of the liver have a hyper-immune response to tetanus immunisation, but this has not been confirmed in the present study, or by Cherrick et al. (18) who also used tetanus toxoid as antigen. The toxoid used by Havens et al. (13,14) was alum-precipitated and the patients studied by these authors had predominantly alcoholic cirrhosis, but it seems unlikely that these differences could account for the discrepancies between the results

of/

/of these studies. A more likely explanation is that the patients studied by Havens et al. (13,14) had all been immunised to tetanus toxoid some years previously and these workers were thus testing their response to re-immunisation. Greenwood et al. (18) have shown that in sarcoidosis and in reticulosis the antibody response in patients with no previous immunity is impaired, whereas it is normal in those who have been immunised in the past. The discrepancies in the results of these studies in cirrhotic patients may therefore be due to differences between primary immunisation (as in the present study and in that reported by Cherrick et al. (15)), and re-immunisation (as in the studies of Havens et al. (13,14)).

A similar explanation may also hold for the discrepancy between the normal antibody response to primary immunisation to tetanus toxoid in patients with connective tissue diseases and the hyperimmune response observed by other workers in this group of diseases to influenzal vaccines (3), penicillin (9), and mismatched blood (3, 6-8). The unsensitised state does not strictly exist in relation to this latter group of antigens. Most adult persons have been infected with influenza in the past, and few have not had penicillin at some time. Miller et al. (19) have shown that even the first dose of Group B cells to a Group A individual represents a booster challenge to the production of isoagglutinins, and similarly Group A substance is so widely distributed in nature (20-22) that it is virtually certain that all human beings come in contact with it during their life. In the present study the criterion of the unsensitised/

/unsensitised state was strictly adhered to and the antigen used was one which patients do not normally come into contact with.

It may be that the use of a re-immunisation procedure, such as the mismatched blood technique, may have been a more appropriate means of detecting immunological hyper-reactivity in the particular group of diseases studied. Auto-antibodies may develop in susceptible individuals only after repeated exposure to the antigen concerned. Re-immunisation with further "booster" doses of tetanus toxoid might therefore have revealed immunological differences in the patients in the present study. On the other hand Lewis and Loomis (1) have demonstrated that the primary response to an antigen is the most accurate reflection of an individual to produce antibody. On the basis of the results of the present investigation it therefore seems reasonable to conolude that a general enhancement of the immunity mechanisms is not primarily involved in the pathogenesis of auto-immune thyroid disease, cirrhosis of the liver, or the connective tissue diseases.

SUMMARY

An experiment is described which was designed to measure the antibody-forming potential in auto-immune thyroiditis, primary hypothyroidism, cirrhosis of the liver, and connective tissue disease. Sixty-four patients with these clinical diseases and 13 healthy control subjects were immunised with two injections of tetanus toxoid at six-weeks interval; antitoxin titres were estimated in the blood-sera taken 2 weeks after the second injection. The results showed similar levels of immune response in all the clinical groups. No correlation was found between the tetanus antitoxin titres and the clinical status, gamma-globulin values, and precipitin tests in patients with auto-immune thyroiditis and primary hypothyroidism. It is concluded that a general hyper-immunisability is not primarily involved in the pathogenesis of auto-immune thyroid disease, cirrhosis of the liver, or connective tissue diseases.

Section 5.

The Problem of Auto-immunity.

The demonstration of a clinical association between auto-immune thyroiditis and the apparently diverse conditions of the connective tissue diseases, acquired haemolytic anaemia, and cirrhosis of the liver, in each of which there is some evidence of an auto-immune mechanism, bids us now take stock of the significance of these findings and the role of auto-immunity in the pathogenesis of disease.

Even when the presence of auto-antibody to a particular tissue can be demonstrated there still remains the question of whether the antibody is the causal agent or merely the consequence of the pathological process. At present, it appears from animal experi-:ments that auto-immunisation can certainly cause lesions in the appropriate tissue which closely resemble the corresponding naturally-occurring disease in humans. However, there is a poor correlation between the amount of humoral antibody in these experi-:ments and the extent of the lesions produced (1). It may be that the use of Freund's adjuvants in these animal studies confers a qualitative as well as a quantitative difference to the antigenic stimulus, since, with the possible exception of auto-immune haemolytic anaemia, none of the serum auto-antibodies so far described have proved cytotoxic either <u>in vitro</u> or <u>in vivo.</u> Moreover, human auto-immune disease can occur without any of the known serum auto-antibodies being demonstrable, and the clinical syndromes of systemic lupus erythematosus and rheumatoid arthritis (2,3), and acquired haemolytic anaemia (4), have been reported in patients with agammaglobulinaemia,/

/agammaglobulinaemia, in whom the production of serum antibody is greatly impaired (5,6). Thus, the evidence is at present against a direct causal relationship between the circulating auto-antibodies and tissue damage. A parallel might be drawn between serum auto-antibodies and the biochemical disturbances in metabolic disease, such as the raised serum iron levels in haemochromatosis.

If the serum auto-antibodies are not directly responsible for tissue damage, then their presence may reflect a more fundamental immunological reaction, involving the non-humoral or "cell-bound" antibody system, such as is evident in tuberculin hypersensitivity and in homograft reactions (7). Holman and Deicher (8) have demonstrated delayed-type skin reactions to autologous leucocytic extracts in patients with systemic lupus erythematosus, and Paterson (9) has achieved passive transmission of allergic encephalomyelitis in rats using lymph node extracts. As yet there is no direct evidence that delayed hypersensitivity plays a role in the patho-:genesis of auto-immune thyroiditis, and indeed skin responses to thyroid tissue extracts in patients with this condition were con-:sistent with an Arthus reaction. It is, however, extremely difficult to exclude a delayed sensitivity component in the presence of concomitant Arthus reactivity, and further analysis of skin reaction in patients with auto-immune thyroiditis would therefore be of value, in particular after injection of the individual antigens. The problem of delayed hypersensitivity in auto-immune disease might also be investigated by attempting passive/

/transfer using lymphocytes of immunologically induced disease in inbred strains of experimental animals.

What initiates the auto-immune process still remains uncertain. Gear (10) has postulated that the action of a virus, bacterial toxin, or drug, on tissue components might render them antigenic, and so lead to auto-antibody formation. Thus, this author (11) has shown that in monkeys, emulsions of normal liver are not antigenic, whereas extracts of liver from a monkey with yellow fever or from a rabbit with neoarsphenamine poisoning evoke significant antibody responses. Furthermore, the immunological basis of streptococcal infection leading to rheumatic fever or acute glomerulo-nephritis, sedormid purpura (12), and the occurrence of L E cells in hydrallazine sensitisation (13), is consistent with modification of the antigenic structure of body constituents. Such a mechanism might explain the formation of thyroid auto-antibodies in subacute (mumps) thyroiditis, although this disease does not as a rule lead to progressive auto-immunisation in spite of the fact that the infection leads to continuous acinar cell breakdown with release of colloid for several weeks. There is no <u>in vitro</u> evidence of an alteration in the antigenicity of the thyroid auto-antigens in auto-immune thyroiditis (14), and it seems unlikely that the co-existence of this disease with other auto-immune diseases can be explained on the basis of modification of the antigenicity of tissue components, unless it were postulated that a single agent, such as a virus, could initiate an auto-immune reaction in one or several different organs/

/organs simultaneously.

A more attractive explanation of the clinical association of auto-immune thyroiditis with other auto-immune diseases is that it is due to a breakdown in the mechanisms of immunological tolerance that operate in health. In 1949 Burnet and Fenner (15) proposed that except during foetal life the body was capable of distinguish-:ing between the tissues of "self" and the tissues of "not-self". In support of this hypothesis they cited the earlier observation of Owen (16) that in bovine twins each twin commonly possesses red cells of the other's blood group in addition to its own, due to mixing of their blood in the common placenta. In addition Anderson et al. (17) demonstrated that reciprocal skin grafts in non-identical bovine twins were accepted as regularly as in identical twins. In a series of brilliantly conceived experiments in inbred strains of mice, Medawar (18) was able to show that the injection of genetically foreign cells into the developing foetus produced a state of specific and "acquired immunological tolerance" which allowed the acceptance of homografts from donors of the same strain in later life.

On this foundation Burnet (19) formulated his "clonal selection" theory of antibody formation. He suggested that the capacity of an individual to produce a given antibody is a genetically determined quality of certain "clones" (Greek κλών = branch) of reticulo-endothelial cells which respond to contact with their appropriate antigen/

/antigen by the formation of antibody. A great variety of clones are normally present, each of which is capable of responding to one or a group of antigens by production of immunity. Burnet also suggested that these primitive cells are suppressed or eliminated by contact with the appropriate antigen, thus providing a mechanism whereby the immature animal can be rendered tolerant to homograft reactions. It seems reasonable, therefore, to propose that undesirable auto-immune reactions may be a consequence of a failure of a mechanism normally present for the acquisition of immune tolerance to normal body constituents during embryonic life.

It is an essential feature of Burnet's "clonal selection" theory of antibody formation that mutation of the clones of immunologically competent cells and of the immunological patterns is always in process. Random mutation is bound, therefore, to produce a proportion of immunological patterns reactive against body components, and presumably in individuals a homeostatic mechanism exists whereby these "forbidden" patterns are eliminated. The development of auto-immune disorders and in particular their clinical associations can therefore be interpreted on the basis of a partial or complete failure of this normal homeostatic mechanism, which allows the "forbidden" clones of cells to proliferate and, in reacting with the antigen involved, inflict damage on the body. "Forbidden" clones of immunologically competent cells may also be stimulated to proliferate by contact with certain antigens, such as lens protein, thyroglobulin, and spermatozoa, which for/

/for reasons of the time of their appearance and their anatomical location, the body has not acquired immunological tolerance. In these circumstances damage to the antigenic organ concerned may be necessary for initiation of the auto-immune process. Exploration of immunological tolerance to these antigens during foetal or early neonatal life in experimental animals may, therefore, prove fruitful.

Less clearly immunological but of fundamental importance are the observations of Moscona (20) of the capacity of cells to recognise and react with one another. Isolated cells in suspension can apparently recombine to form tissues similar to those of their origin, and in doing so, will avoid or reject cells of unlike origin. Moreover, mixtures of cells will segregate themselves according to tissues of origin. The mechanism of this phenomenon remains obscure, but it is conceivable that these reactions between cells are a more general expression of the function of antibody formation. Application of these observations to the tissues and immune systems of patients with auto-immune disease may be rewarding. Thus, abnormalities in the behaviour of one cell or tissue toward another in cell suspensions may be demonstrated, and abnormal tolerance mechanisms may be found, in which the patient has lost tolerance of his own cells. Perhaps also cells with different somatic composition exist in patients with auto-immune disease and react with other cells to which they normally would be compatible. A search for chromosomal abnormalities in the different cells/

/cells involved in auto-immune disease might therefore be of value.

The production of auto-antibodies is probably an inherent abnormality of the host response, in particular of the immunologically competent cells themselves. In the present thesis no evidence was found of an enhanced antibody-forming potential in patients with auto-immune thyroiditis and in other "auto-immune" diseases to primary immunisation to tetanus toxoid. The individuality in response may be linked to the patient's own ability to recognise damaged tissue as antigen and may also have a hereditary basis. In the present thesis an increased frequency of thyroid auto-antibodies has been found in relatives of patients with auto-immune thyroiditis, and in thyrotoxicosis a familial predisposition to develop anti-microsomal thyroid auto-antibodies appears to be associated with a familial predisposition to thyroid disease in general. Similarly in the connective tissue diseases serum factors similar to those found in systemic lupus erythematosus and rheumatoid arthritis have been found in unaffected relatives of patients suffering from these diseases (21). These observations suggest a hereditary presisposition to an abnormal immune response, which in some patients may manifest itself as auto-immune thyroiditis, while in others as rheumatoid arthritis or systemic lupus erythematosus, and in a few as serological reactions without clinical symptoms. A useful approach to the further study of auto-immune disease would, therefore, lie in the exploration of relatives with these various conditions, and the genetic background of patients with/

/with these illnesses, in particular in those in whom 2 or more auto-immune diseases co-existed.

Little is as yet known of the environmental factors which may predispose to the development of auto-immune disease, but a factor of some importance which has emerged in the present study is the predilection of females to develop these diseases. Thus, not only are most "auto-immune" diseases more commonly found in females, but the clinical associations of these diseases appear to occur more frequently in this sex than in the male. Dameshek (22) has suggested that the proneness of the female to develop auto-immune disease, may be due to the liberation of antigenic substances during menstruation, which because of its periodic character, may correspond to the "booster" injections of an immunising procedure. However, no direct relationship could be established between ovarian function and the onset of auto-immune thyroiditis, although it is of interest that thyroid auto-immunisation in female cirrhotic patients appeared to be associated with excess circulating oestrogens. It is possible that the proneness of the female to auto-immunity is genetically determined, but the absence of any sex difference in the incidence of complement-fixing antithyroid auto-antibodies in thyrotoxic patients/does not support such a view. Further investigation of the role of the ovarian hormones in regulation of the immune response is, however, desirable.

At present, the lack of understanding of the basic mechanisms involved in antibody formation and immunological tolerance does not permit/

/permit the formation of a well-defined hypothesis of auto-immune disease. It is uncertain whether auto-antibodies arise because of failure to acquire tolerance, because of subtle alterations in the chemical constitution of auto-antigens, or because of some derange-:ment of the antibody-forming mechanism which renders it incapable of recognising "self"; or whether the auto-antibodies merely reflect the pathological changes brought about by "cell-bound" or delayed hypersensitivity mechanisms. Nevertheless, the demonstration in the present thesis of a clinical association between auto-immune thyroiditis and the connective tissue diseases, acquired haemolytic anaemia, and cirrhosis of the liver, is consistent with the view that auto-immunisation plays a fundamental, if ill-understood, role in the pathogenesis of these conditions. The danger is one of forcing the analogy too far, and one must rest content with the observations thus far, and await the elucidation that further research may afford.

APPENDICES

APPENDICES - CHAPTER II

SECTION 1. Discussion of the Clinical Features of Auto-immune Thyroiditis based on a Study of 50 Patients.

TABLE I. Summary of Clinical Details in 50 Patients with Auto-immune Thyroiditis.

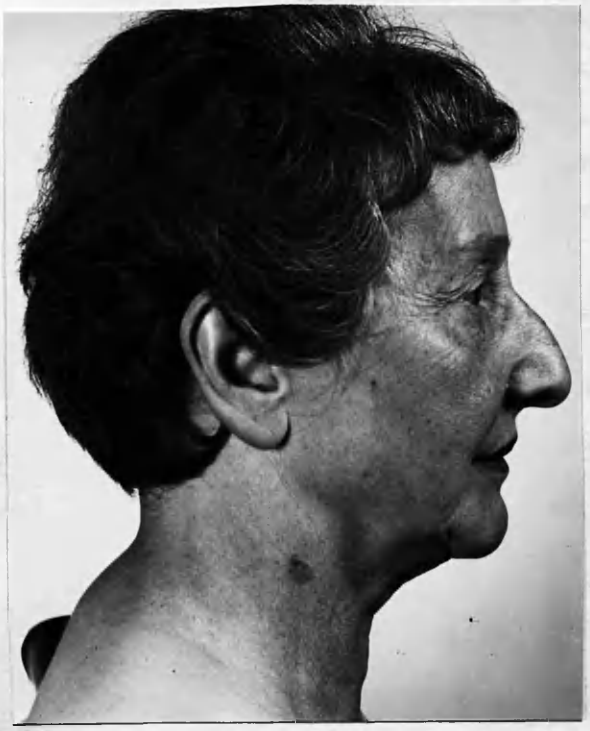
TABLE I.

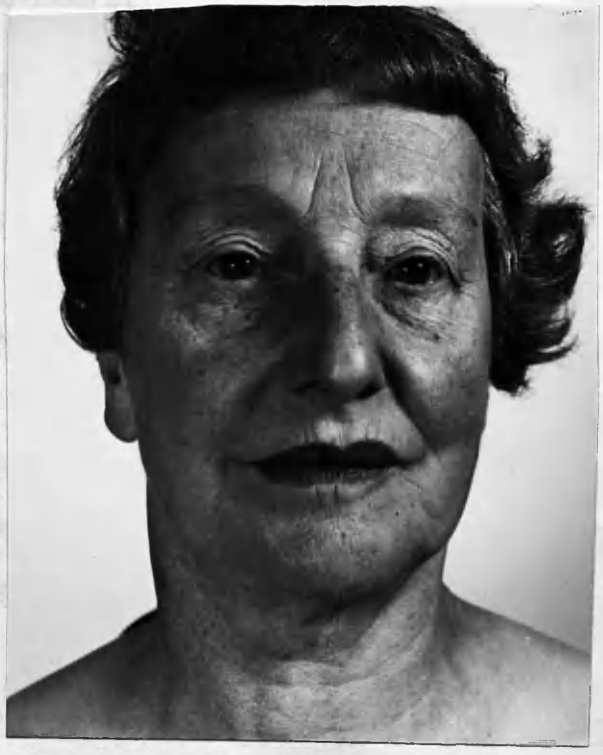
SUMMARY OF CLINICAL DETAILS IN 50 PATIENTS WITH AUTO-IMMUNE THYROIDITIS

Case No.	Age	Sex	Presenting Symptoms	Duration	GOITRE Size (g)	Type	Consistency	Local Symptoms Associated with Goitre	Other	Clinical Status (Hypothyroid Diagnostic Index	B.M.R. (%)	Serum Cholesterol (mg.%)	E.C.G.	Thyroid Auto-Antibody Tests Precp.	CFT.	Associated Illnesses.
1	70	F	Goitre with recent increase in size.	6m	300	Nodular	Firm	"Tightness" and slight dysphonia	Pyramidal lobe present.True Adenomatous formation.	+3		120	Normal	-	AC	Encapsulated hepato-splenomegaly. Gastric carcinoma three years previously.
2	56	F	Goitre with symptoms of hypothyroidism	10yr.	75	Diffuse	Firm			+84	-1	395	Hypo.	+	++	? Thyrotoxic 10 years previously
3	52	F	Goitre	6yr.	100	Nodular	Firm		Pyramidal lobe	+4	+3	225	Normal	+	+	
4	65	M	Symptoms of hypo-thyroidism	Unaware	50	Diffuse	Firm			+83	-18	165	Hypo.	+	++	Rheumatoid Arthritis. Latent syphilis.
5	41	F	"Painful" Goitre	5yr.	125	Nodular	Firm	"Choking"		+38	-10	220	Hypo.	+	++	?Thyrotoxic 5 years previously
6	63	F	Goitre	5yr.	75	Nodular	Firm	Cough and hoarseness		+1	0	285	Normal	-	++	
7	68	F	Goitre with recent increase in size	6m	75	Nodular	Firm	Slight dysphagia and hoarseness		+4	-1	225	Normal	+	++	Angina pectoris
8	49	F	Symptoms of hypo-thyroidism	Unaware	50	Diffuse	Firm			+88	-17	350	Hypo.	+	++	
9	63	F	Goitre	3yr.	100	Diffuse	Firm			+6	0	275	Normal	+	-	
10	58	F	Goitre with recent increase in size	6m	175	Nodular	Firm			+30	-6	416	Hypo.	+	++	Vasomotor rhinorrhoea
11	37	F	Goitre and thyrotoxic symptoms	3yr.	75	Diffuse	Firm			? Thyrotoxic	+19	115	Normal	-	++	
12	48	F	Goitre and thyrotoxic symptoms	3yr.	100	Diffuse	Firm	"Choking" and occasionally sore	Pyramidal lobe present. Onset with feverishness and local discomfort.	? Thyrotoxic		105	Normal	+	++	
13	67	F	Goitre with recent increase in size	8m	250	Nodular	Firm	"Choking"and slight dysphagia Occasional "ache"	Bruit present. Onset with feverishness and local discomfort.	-6	+21	140	Hypo.	+	++	? Thyrotoxic 8 months previously. Rheumatoid Arthritis.
14	80	F	Goitre	1½m	75	Diffuse	Firm	Slight dysphonia		+3	+3	160	Normal	+	++	
15	57	F	Symptoms of hypothyroidism	Unaware	50	Diffuse	Firm			+84	-86	185	Hypo.	+	++	
16	60	F	Goitre with "Tightness"	8yr.	100	Diffuse	Firm	"Tightness" and slight dysphonia		-6	+5	155	Normal	-	++	Hay fever and vasomotor rhinorrhoea.
17	45	F	Goitre with symptoms of hypo-thyroidism	5yr.	75	Diffuse	Firm			+83	-34	336	Hypo. (Double line)	+	++	
18	58	F	Goitre	1yr.	50	Nodular	Firm	"Tightness" and choking.		+1	+4	350	Normal	-	++	Chronic bronchitis
19	66	F	Goitre with increase in size	3m	75	Diffuse	Firm			+86	-9	145	Hypo.	+	++	
20	48	F	Goitre	8yr.	75	Nodular	Firm	Occasional"aching"	Histology showed fibrous variant of auto-immune thyroiditis with extension beyond capsule.	+3	-17	805	Normal	-	-	
21	63	M	Goitre and thyrotoxic symptoms	6m	150	Nodular	Firm			? Thyrotoxic	+5	170	Normal	+	++	Hypertension and angina pectoris. Chronic bronchitis.
22	56	F	Goitre and "Choking"	8yr.	150	Nodular	Hard	"Choking" and slight dysphagia		+6	-13	280	Normal	+	++	
23	44	F	Symptoms of hypo-thyroidism	Unaware	75	Diffuse	Firm			+89	-18	335	Hypo.	+	++	
24	53	F	Goitre with symptoms of hypo-thyroidism	1yr.	75	Diffuse	Firm			+85	-16	410	Hypo. (clear line)	+	++	Chronic bronchitis
25	50	F	Goitre	16yr.	125	Diffuse	Firm			+7	+9	185	Normal	+	++	
26	43	F	Goitre with "Choking"	19yr.	125	Diffuse	Soft	"Choking"	Pyramidal lobe present	-4	+9	135	Normal	+	++	
27	54	F	Goitre with recent increase in size	11 yr.	150	Diffuse	Firm	Slight dysphagia	Pyramidal lobe present	+80	-21	385	Hypo.	+	++	History of thyrotoxicosis 11 years previously.
28	50	F	Goitre with recent increase in size	8m	100	Diffuse	Firm			-80	+11	220	Normal	+	++	
29	59	M	Symptoms of hypo-thyroidism	Unaware	75	Nodular	Firm			+18	-15	225	Hypo.	-	++	Chronic bronchitis. Duodenal Ulcer.
30	65	F	Goitre with symptoms of hypo-thyroidism	5yr.	150	Nodular	Firm		Cervical lymphadenopathy present. "Delphic" node also present.	+17	-15	380	Normal	+	++	
31	61	F	Goitre and thyrotoxic symptoms	6yr.	75	Nodular	Firm	Dysphonia	Temporary laryngeal palsy.	? Thyrotoxic	+9	285	Normal	+	++	Rheumatoid Arthritis
32	65	F	Goitre with symptoms of hypo-thyroidism	10yr.	150	Diffuse	Firm	Slight dysphagia		+25	-19	398	Hypo.	+	+	Rheumatoid Arthritis
33	55	F	Goitre	5yr.	75	Diffuse	Firm			+2	+10	350	Normal	+	++	History of thyrotoxicosis 15 years previously. Urticaria
34	31	M	Goitre with increase in size	9m	200	Nodular	Hard	Dysphonia cough & strider		+8	-11	305	Hypo.	+	++	Penicillin allergy.
35	46	F	Goitre with symptoms of hypo-thyroidism	1yr.	75	Nodular	Firm			+28	-21	405	Hypo.	-	++	Diabetes Mellitus
36	50	F	Goitre	4yr.	75	Nodular	Firm			+8	-15	520	Hypo.	+	++	Exophthalmic Ophthalmoplegia
37	44	F	Goitre	1yr.	125	Nodular	Firm		Pyramidal lobe present	-7	-7	100	Normal	+	++	?Thyrotoxicosis 3 years previously Hay fever and vasomotor rhinorrhoea.
38	61	F	Goitre with recent increase in size	9m	200	Nodular	Firm	"Choking"		-9	-13	230	Hypo.	+	++	
39	45	F	Goitre	7yr.	75	Diffuse	Firm	"Choking" & dysphagia		+3	+5	208	Hypo.	+	++	Diabetes Mellitus
40	58	F	Goitre	37yr.	175	Diffuse	Soft		Histology revealed auto-immune thyroiditis superimposed on a simple colloid goitre	-16	+4	175	Normal	-	++	Rheumatoid Arthritis
41	66	F	Goitre	18m	75	Nodular	Firm									
42	57	F	Goitre with "Choking"	8yr.	75	Diffuse	Firm	"Choking"		+2	+10	210	Normal	+	AC	Rheumatoid Arthritis
43	45	F	Goitre and thyrotoxic symptoms	5yr.	75	Diffuse	Firm			-13	-27	165	Normal	+	++	Acquired idiopathic haemolytic anaemia.
44	44	F	Goitre	8yr.	90	Diffuse	Firm			?Thyrotoxic	-9	285	Normal	+	++	History of thyrotoxicosis 20 years previously. Treated with iodine.
45	36	F	Symptoms of hypothyroidism	Unaware	50	Diffuse	Firm			0	-25	295	Hypo.	+	++	Mitral stenosis with pulmonary haemosiderosis. Spinal tuberculosis.
										+19		340	Hypo.	+	++	
46	57	F	Goitre with recent increase in size	8m	75	Diffuse	Firm			-14	+9	215	Hypo.	+	++	Rheumatoid Arthritis
47	64	F	Goitre with recent increase in size	6m	100	Nodular	Firm			-14		200	Hypo.	-	++	
48	47	F	Goitre	1yr.	50	Diffuse	Firm			-14		90	Normal	-	++	
49	60	F	Symptoms of hypo-thyroidism	Unaware	50	Diffuse	Firm			+38	-25	365	Hypo.	+	++	
50	64	F	Goitre with symptoms of hypo-thyroidism.	5yr.	100	Nodular	Firm			+88	-17	566	Hypo.	-	+	? Thyrotoxicosis 5 years previously.

SOME ILLUSTRATIVE CASE-REPORTS

Patient No. 6.





This patient, aged 63 years, presented with a goitre of 5 years duration. She also complained of a cough which she attributed to the goitre, and had been aware of slight hoarseness, although she had no other symptoms of hypothyroidism. The hypothyroid diagnostic index was +1.

Investigations were as follows:-

Precipitin test: (-)
C-F test: (++)
Thymol Turbidity: 6 units.
Thymol flocculation: +2.
Gamma-globulin: 0.79 g./100 ml.
E.S.R. (Westergren): 37 mm/first hr.

I^{131} tests 4 hr. uptake: 27.8%/dose.
48 hr. PBI^{131}: 0.22%/dose/l.

Potassium perchlorate discharge test (I^{132}): negative.

BMR (Robertson and Reid): 0%.

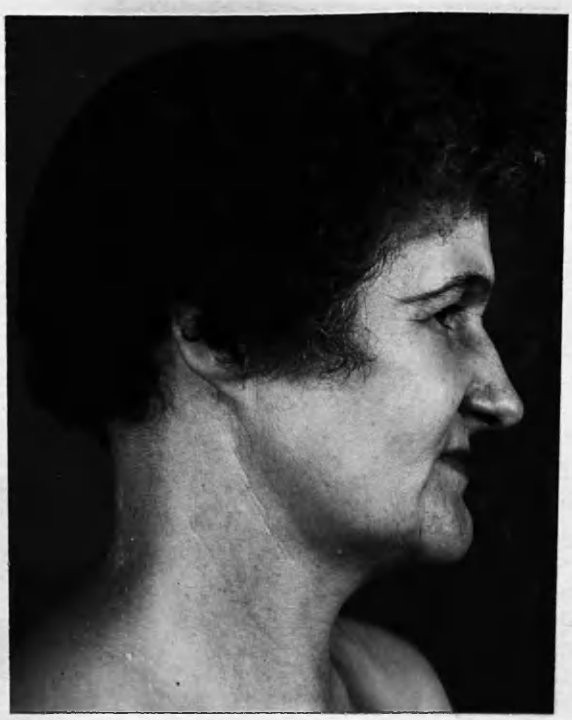
Serum Cholesterol: 285 mg./100 ml.

ECG: no evidence of hypothyroidism.

PBI: 3.1 µg./100 ml.

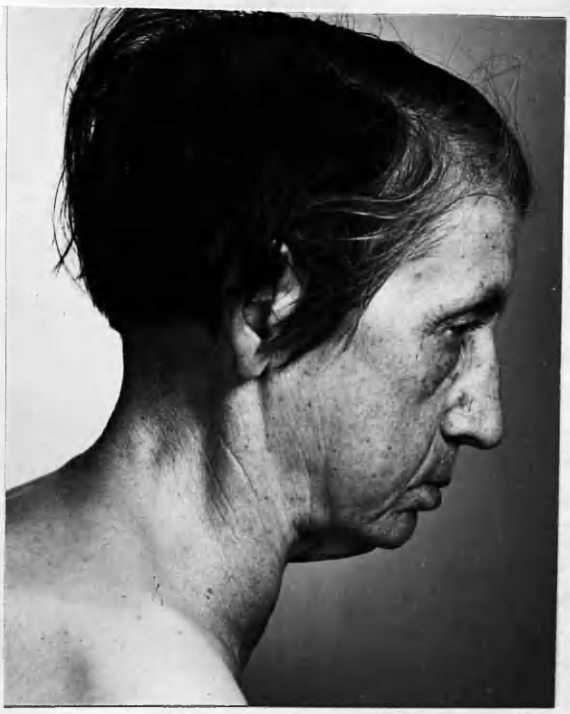
Comment: In the presence of a negative precipitin test the diagnosis of auto-immune thyroiditis could only be presumptive. Treatment with thyroxine sodium 0.1 mg. twice daily by mouth caused shrinkage of the goitre (Mean neck circumference reduced by one inch in 12 months). Subsequent thyroid biopsy confirmed auto-immune thyroiditis.

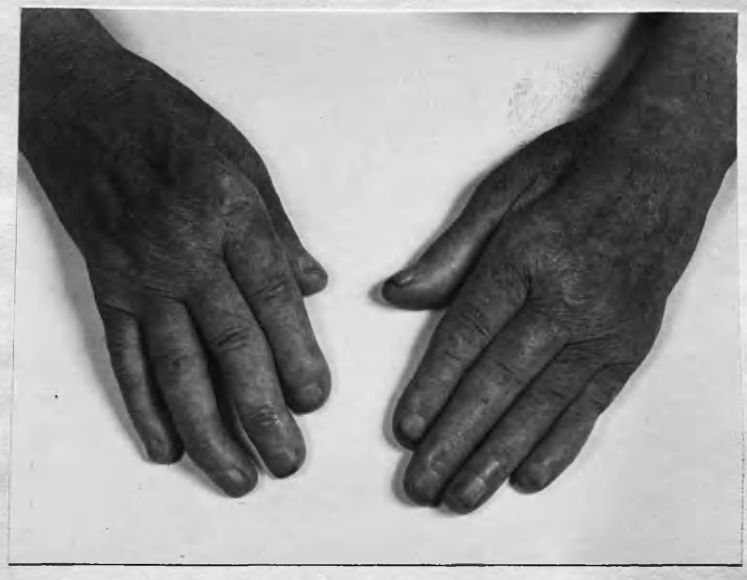
Patient No. 12.



This 48 year old woman presented with a goitre and symptoms of thyrotoxicosis. The clinical details of her illness and the results of the laboratory investigations are reported in detail in Chapter III Section 2. The results of the routine radioiodine tests (4 hr. uptake 50.6% dose, 48 hr. PBI^{131} 0.42% dose/l.) and the BMR determinations (+28%) appeared to confirm this diagnosis, although the thyroxine suppression test and estimation of the serum protein bound iodine (5.3 µg./100 ml.) showed that she was euthyroid. The precipitin test was strongly positive and the serum flocculation tests slightly abnormal (thymol turbidity 3 units, thymol flocculation +1, and it was the routine performance of these tests which first drew attention to the true state of affairs.

Patient No. 13.





This 67 year old woman had had a goitre for 8 months. She had also had severe rheumatoid arthritis for 9 years. The clinical details/

/details and the results of laboratory findings are described in detail in Chapter IV, Section 1.

Patient No. 15.

This 57 year old patient presented with symptoms of hypothyroidism. She was unaware of a diffusely-enlarged (50 g.) goitre, which was found on neck palpation. The hypothyroid diagnostic index was +24.

The results of the laboratory investigations were as follows:

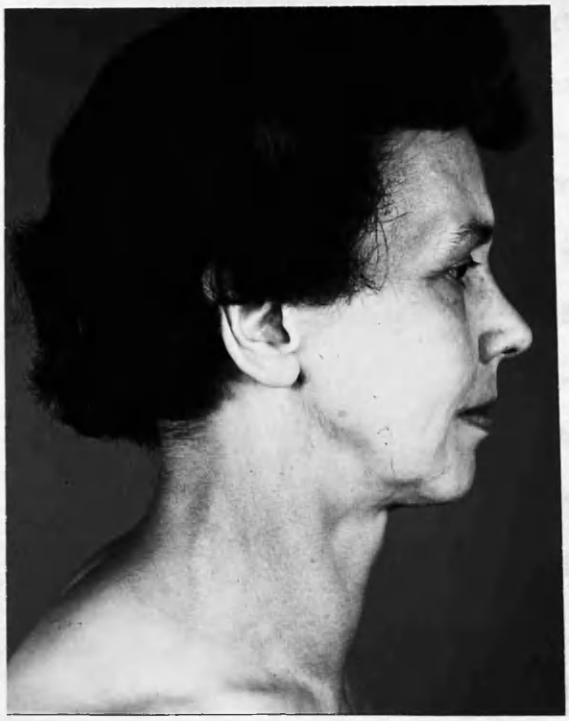
Precipitin test (+)
CF test (++)
Thymol turbidity 8 units.
Thymol flocculation +3.
Gamma-globulin 1.16 g./100 ml.
ESR (Westergren) 30 mm./first hour.
I^{131} tests 4 hr. uptake 24.3% dose
48 hr. PBI^{131} 0.18% dose/litre.
BMR (Robertson and Reid)-26%.

Serum cholesterol 125 mg./100 ml.
ECG consistent with hypothyroidism.
PBI 0.7 µg./100 ml.

Treatment and Progress With thyroxine sodium therapythe goitre in this patient has virtually disappeared, and her hypothyroidism has been corrected.

Comment. This patient draws attention to the importance of palpation of the neck for the presence of a goitre in the investiga-:tion of hypothyroidism. The finding of a firm goitre is virtually diagnostic of auto-immune thyroiditis.

Patient No. 20.



This 48 year old woman presented with a firm nodular goitre of 2 years duration. Clinically she was euthyroid and the hypothyroid diagnostic index was +3.

The results of laboratory investigations were as follows:

Precipitin test: negative.
CF test: negative.
Thymol turbidity: 7 units.
Thymol flocculation: +3.
Gamma-globulin 2.06g./100 ml.
ESR (Westergren): 12 mm./first hr.
I^{131} Tests: 4 hr.uptake: 16.5% dose.
48 hr. PBI^{131} 0.05%/dose/litre.
Potassium Perchlorate Discharge Test (I^{132}): negative.
BMR (Robertson and Reid):-17%.
Serum cholesterol 205 mg./100 ml.

PBI: 2.5 µg./100 ml.

Thyroid biopsy showed extensive fibrosis of the thyroid with extension beyond the capsule, with, in addition, chronic thyroiditis and Askanazy-cell change.

Comment. The interesting features in this patient are the negative auto-antibody tests in the presence of highly abnormal flocculation tests and gamma-globulin levels; and the histological findings in the thyroid gland. It is possible that fluorescent antibody studies might have shown an antibody to a colloid constituent other than thyroglobulin. The extension of the disease process beyond the capsule found on histological examination would lead some histologists to diagnose Riedel's struma. However, the presence of round cell infiltration and Askanazy-cell change suggest a fibrous variant of auto-immune thyroiditis.

Patient No. 23.

This 44 year old woman presented with symptoms of hypothyroidism. She had been unaware of a diffuse and moderately (75 g.) enlarged, firm goitre. The hypothyroid diagnostic score was +29.

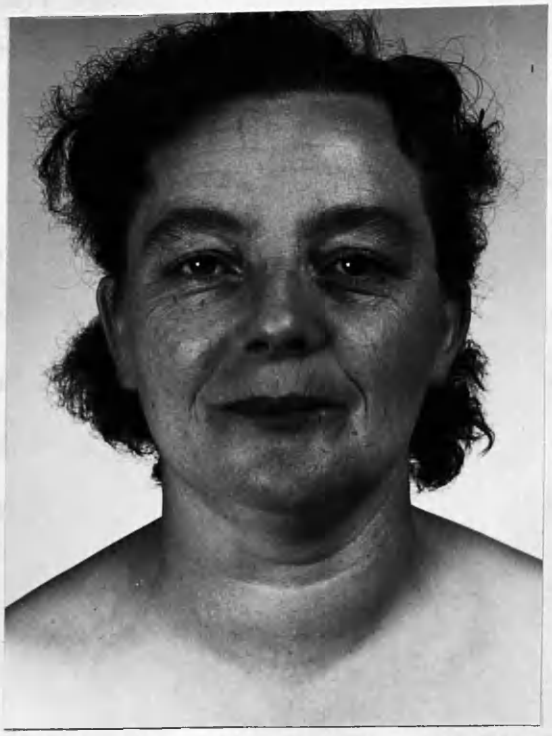
The results of the laboratory investigations were as follows:

Precipitin test: (+)
CF test: (++)
Thymol turbidity: 1 unit.
Thymol flocculation: +0.
ESR (Westergren): 8 mm./first hr.
I^{131} tests. 4 hr. uptake: 28.0% dose.
48 hr. PBI^{131}: 0.23% dose/litre.
BMR (Robertson and Reid): -18%.
Serum cholesterol: 335 mg./100 ml.
ECG: consistent with hypothyroidism.
PBI: 2.1 µg./100 ml.

Treatment and Progress./

/Treatment and Progress. Thyroxine sodium therapy completely relieved the hypothyroidism and caused the goitre to shrink considerably and to become "soft" in consistency.

Patient No. 26.



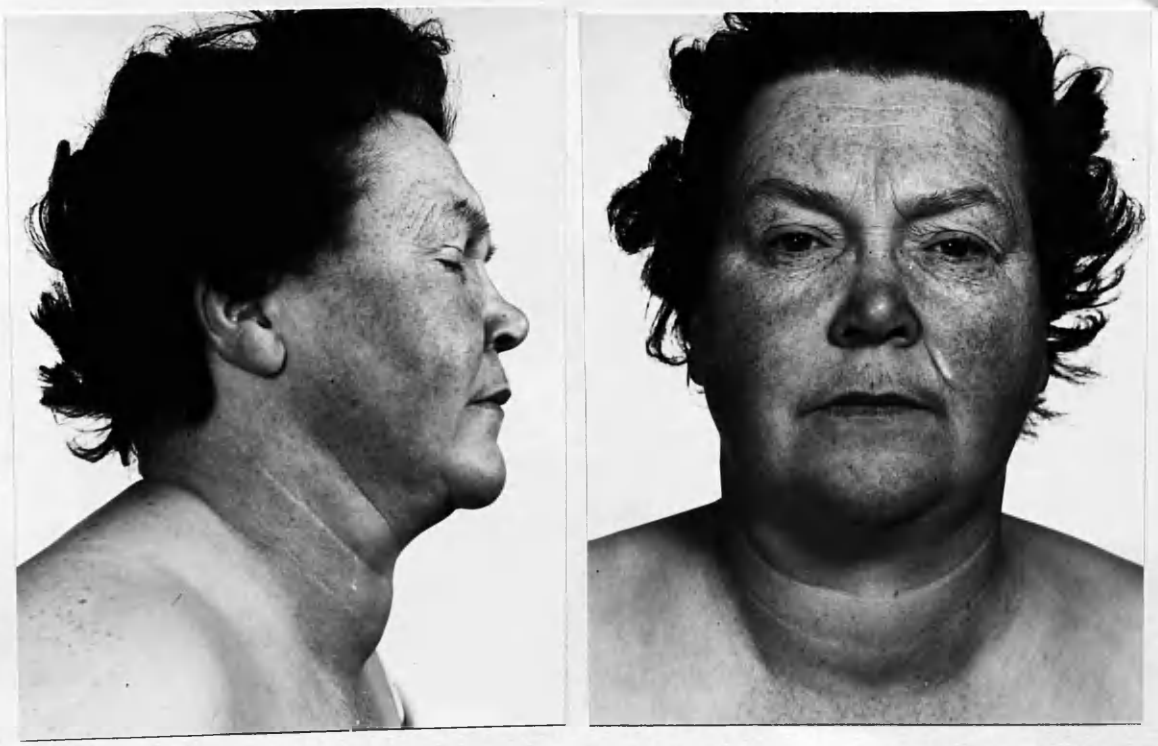
This 43 year old woman presented with a goitre associated with a "choking" sensation. She had had the goitre for 19 years. On examination the goitre was markedly enlarged (125 g.), diffuse, and "soft" in consistency, and the pyramidal lobe was clearly palpable. Clinically the patient was euthyroid - hypothyroid diagnostic index -4. The results of laboratory investigations were as follows:-

Precipitin test: (+)
CF test: (++)
Thymol turbidity: 14 units.
Thymol flocculation: +4.
ESR (Westergren): 23 mm./first hr.
I^{131} Tests 4 hr. uptake 48.3% dose.
48 hr. PBI^{131} 0.34% dose/litre.

Potassium Perchlorate Discharge Test: negative.
BMR (Robertson and Reid): +9%.
Serum cholesterol: 135 mg./100 ml.
ECG: normal.
PBI: 2.3 µg./100 ml.

Comment. A clinical diagnosis of "simple" goitre could easily have been made in this patient, especially as the goitre was "soft" in consistency. The serum PBI lay in the hypothyroid range, although clinically and by other laboratory criteria the patient was euthyroid. With thyroxine sodium 0.1 mg. twice daily there was considerable shrinkage in goitre size and restoration to normal of the biochemical abnormalities.

Patient No. 27.



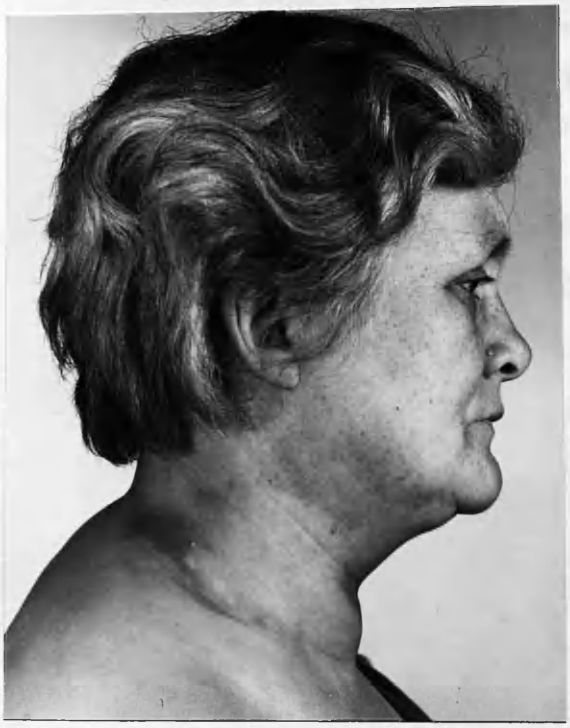
This 54 year old woman presented with a goitre of 11 years duration with recent increase in size. She also complained of slight dysphagia and had symptoms of hypothyroidism (hypothyroid diagnostic index +20). At the onset of her goitre she had manifested symptoms of thyrotoxicosis and had received a course of antithyroid drugs lasting 10 months. On examination there was clear evidence of hypothyroidism, and the goitre was diffusely enlarged (150 g.), firm, and the pyramidal lobe was palpable. Results of Investigations were as follows:

Precipitin Test: (+)
CF Test: (++)
Thymol turbidity: 3 units.
Thymol Flocculation: +2.

Gamma-globulin: 0.9 μg./100 ml.
ESR (Westergren): 9 mm./first hr.
I^{131} Tests. 4 hr. uptake: 40.0%dose.
48 hr. PBI^{131}: 0.47% dose/litre.
BMR (Robertson and Reid) - 21%.
Serum cholesterol: 285 mg./100 ml.
ECG: consistent with hypothyroidism.
PBI: 4.1 μg./100 ml.

Comment. This patient presented the classical clinical triad of auto-immune thyroiditis, namely, a middle-aged female with a firm goitre and signs of hypothyroidism. It is possible that this patient represents a "burnt-out" thyrotoxicosis.

Patient No. 33.



This 55 year old woman had had a goitre for 5 years. On examination the goitre was diffuse, firm, and moderately enlarged, and there was no evidence of hypothyroidism (hypothyroid diagnostic index +2). The patient gave a convincing history of thyrotoxicosis 15 years previously. She had also suffered from giant urticaria for many years.

The results of laboratory investigations were as follows:

Precipitin Test: (+)

CF Test: (++)

Thymol turbidity: 5 units.

Thymol flocculation: +3.

ESR (Westergren): 38 mm./first hour.

I^{131} Tests. 4 hr. Uptake: 39.0% dose.

48 hr. PBI^{131}: 0.21% dose/litre.

Potassium Perchlorate Discharge Test: negative.

BMR (Robertson and Reid): +10%.

Serum Cholesterol: 350 mg./100 ml.

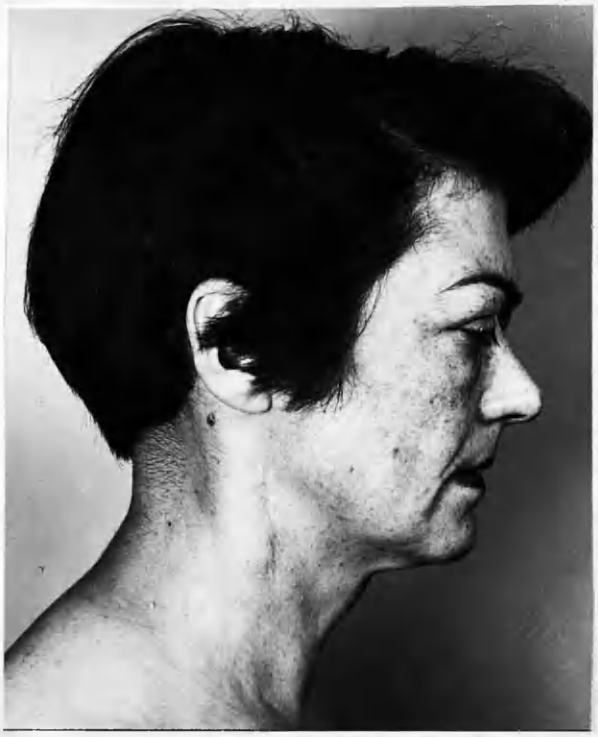
ECG: Normal.

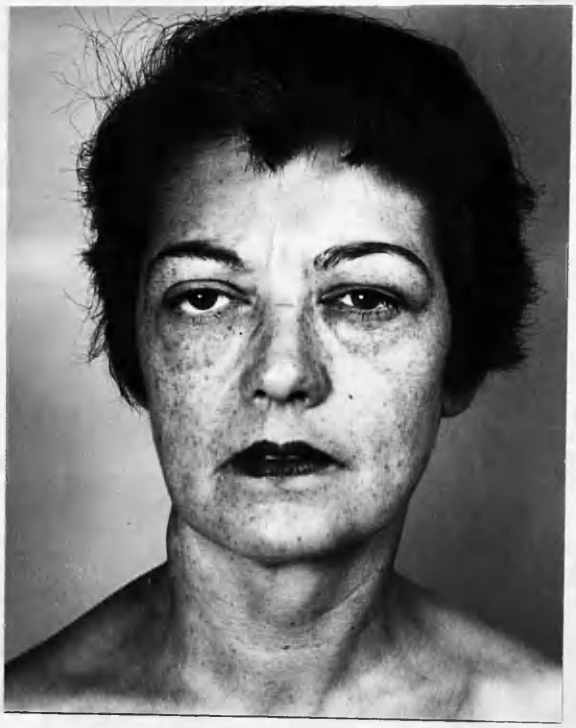
PBI: 2.1 µg./100 ml.

Comment. Although apparently clinically euthyroid it is clear from the results of the serum cholesterol and PBI determinations that this patient has mild thyroid insufficiency which is not clinically manifest. Treatment with thyroxine sodium brought about considerable shrinkage in goitre size.

Patient No. 36.

This 50 year old woman presented with a goitre of 4 years duration and symptoms suggestive of hypothyroidism. Three years previously she had been admitted to hospital for treatment of severe exophthalmic ophthalmoplegia (see over) and was given a course of corticotrophin and cortisone with good effect. At that time she had some symptoms suggestive of thyrotoxicosis, although the thyrotoxic clinical diagnostic index score was only +4.





Radioiodine (I^{131}) tests at that time showed a 4 hr. uptake of 39.4% dose and a 48 hr. PBI^{131} of 0.53% dose/litre. The BMR (Robertson and Reid) was +14% and the sleeping pulse rate 65 beats per minute. The patient was considered to be euthyroid and no specific antithyroid therapy was prescribed.

Thereafter the patient remained well up until a few months prior to my first seeing her when she developed symptoms of hypothyroidism. The patient complained of cold intolerance, acroparaesthesiae, decreased sweating, increase in weight, and hoarseness. On examination, she had a cold, dry, and yellowish skin, puffiness of the supraclavicular fossae and wrists, dry hair, and a casual pulse rate of 66 beats per minute. The goitre was moderately enlarged, firm, and nodular and there was evidence of persistent/

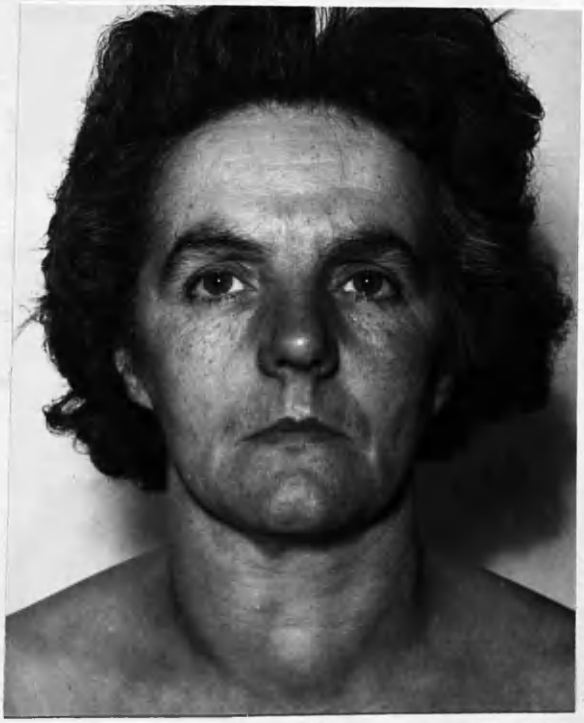
/persistent ophthalmoplegia, especially on upward converge of the eyes. It was of interest that the patient had a paternal male cousin with thyrotoxicosis and exophthalmic ophthalmoplegia, and a paternal female cousin with thyrotoxicosis.

Results of laboratory investigations were as follows:

Precipitin Test: (+).
CF Test (++).
Thymol turbidity: 1 unit.
Thymol flocculation: 0
Gamma-globulin: 1.34 g./100 ml.
ESR (Westergren): 4 mm./first hr.
I^{131} Tests. 4 hr. Uptake: 20.1% dose.
48 hr. PBI^{131}: 0.19% dose/litre.
Potassium Perchlorate Discharge Test: positive.
Thyroxine Suppression Test: normal.
BMR (Robertson and Reid): -15%.
Serum Cholesterol: 520 mg./100 ml.
ECG: consistent with hypothyroidism.
PBI: 1.3 µg./100 ml.

Comment: A proportion of clinically euthyroid patients with exophthalmic ophthalmoplegia have biochemical evidence of thyroid overactivity and autonomous thyroid function. Unfortunately, the critical investigations, i.e. a tri-iodothyronine suppression test and serum PBI estimation, were not carried out 3 years ago. It is interesting to speculate whether the orbital pathology in this patient might not also be auto-immune in nature.

Patient No. 37.



This 44 year old woman presented with a goitre of one year's duration. She had no symptoms of hypothyroidism. On examination, the goitre was markedly enlarged (125 g.), firm, and nodular, and the pyramidal lobe was palpable.

The patient had a sister who had a goitre, and another sister who had thyrotoxicosis. The results of laboratory investigations were as follows:

Precipitin Test: (+).
CF Test: (++).
Thymol turbidity: 6 units.
Thymol flocculation: +2.
Gamma-globulin: 1.5 µg./100 ml.
ESR (Westergren): 25 mm./first hr.
I^{131} Tests. 4 hr. Uptake: 36.6% dose.
48 hr. PBI^{131}: 0.22% dose/litre.
BMR (Robertson and Reid): -7%

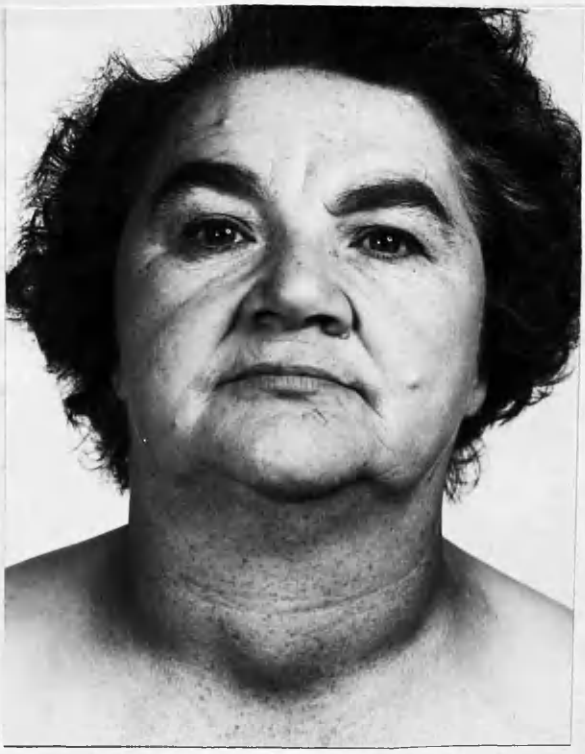
Serum cholesterol: 100 mg./100 ml.

ECG: Normal.

PBI: 4.1 µg./100 ml.

Comment. Although this patient is clinically and by laboratory criteria euthyroid, nevertheless I feel that this type of case should be treated with thyroxine sodium therapy. After 10 months' treatment in this patient there has been considerable diminution in goitre size, although little as yet alteration in the biochemical abnormalities.

Patient No. 38.



This 61 year old woman presented with a recent increase in size of a goitre of 9 months' duration. She also complained of "choking", but had no hypothyroid symptoms. On examination, the goitre was markedly enlarged (200 g.), firm, and nodular. There were some features suggestive of mild hypothyroidism, although the hypothyroid diagnostic score was within the normal range. The results of the laboratory investigations were as follows:

Precipitin test: (+).
CF test: (++).
Thymol turbidity: 14 units.
Thymol flocculation: +3.
Gamma-globulin: 1.65 g./100 ml.

ESR (Westergren): 10 mm./first hr.

I^{131} Tests: 4 hr. Uptake: 46.0% dose

48 hr. PBI^{131}: 0.29% dose/litre.

BMR (Robertson and Reid): -13%.

Serum cholesterol: 230 mg./100 ml.

ECG: consistent with hypothyroidism.

PBI: 2.4 µg./100 ml.

Treatment and Progress. After 9 months' treatment with thyroxine sodium there has been reduction in goitre size and improvement in the biochemical findings. The results of thyroxine therapy are less gratifying in patients with very large goitres.

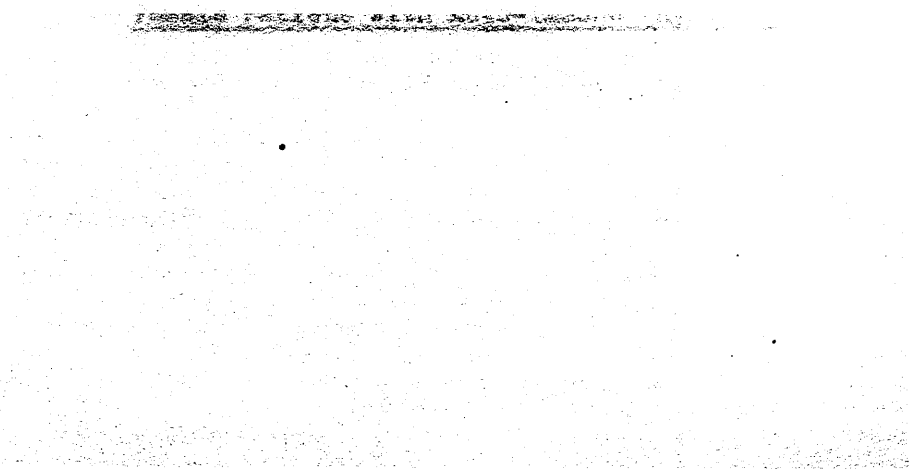


TABLE II. Details of Reproductive History in Female Patient with Auto-immune Thyroiditis.

Table II.

Details of Reproductive History in Female Patients with Auto-immune Thyroiditis.

Case No.	MENSTRUAL HISTORY			REPRODUCTIVE HISTORY				Cervical mucus Test.
	Age at Menarche (Yrs.)	History of Menorrhagia	History of Oligomenorrhoea	Age at Menopause (yrs.)	Married	No. of Children	No. of Abortions	
1	19			54	Yes	9	2	
2	13			47	Yes	4		
3	12			48	No			Negative
5	11				Yes	5		
6	14			50	No			
7	15			50	Yes	4	2	
8	14	+		49	Yes			
9	15			40	Yes	1		
10	14			41	Yes		1	
11	11		+		Yes	3		
12	12			48	Yes	3		
13	14		+	45	Yes	6		Negative
14	15				Yes			
15	14			50	Yes			Negative
16	10				No			
17	13				Yes	10		
18	16			50	Yes	3		
19	15			50	Yes	6		Negative
20	15			47	Yes	2		
22	16			50	No			
23	12				Yes	2		
24	15			45	Yes	1	2	
25	13			41	Yes	5		
26	14	+		40	Yes	2		
27	14			45	Yes	2		Negative
28	15	+		45	Yes			
30	14			44	Yes	2		
31	11			40	Yes	2	2	Negative
32	14			40	Yes			
33	16			48	Yes	4		Negative
35	14				Yes	2	1	
36	17	+		45	Yes	1		
37	14				Yes	4		
38	14			50	Yes	5	2	
39	14				Yes	2		
40	12			51	Yes			Negative
41	14			45	Yes	3		Negative
42	13		+		Yes	1	1	Negative
43	11			40	No			
44	11			38	Yes	1		
45	19			54	Yes	9	2	Negative
46	15			55	Yes	1	3	
47	14			45	No			
48	16			47	Yes	3		Negative
49	15				Yes	3	3	
50	14			49	Yes	3		

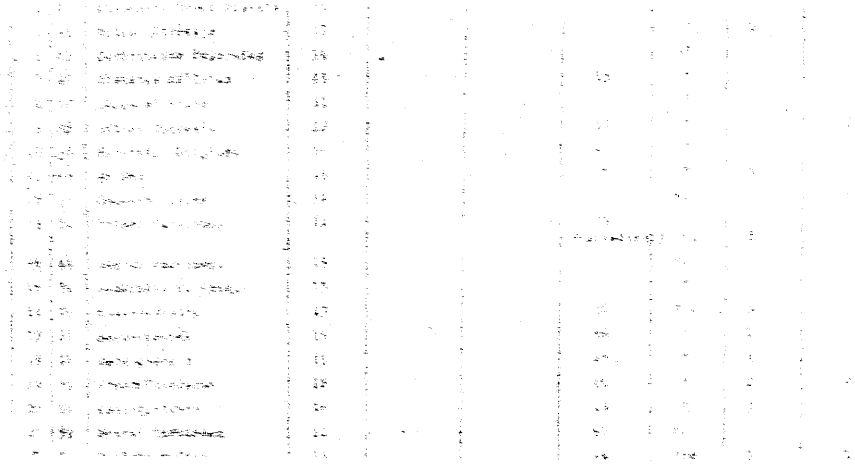


TABLE III. Details of Reproductive History in Female Hospital Controls.

Table III Details of Reproductive History in Female Hospital Controls

Case No.	Age	Clinical Condition	MENSTRUAL HISTORY			REPRODUCTIVE HISTORY		
			Age at Menarche (Yrs.)	History of Menorrhagia	History of Amenorrhoea	Age at Menopause (Yrs.)	Married	No. of Children	No. of Abortions
1	64	Cholecystitis	16			36	Yes		1
2	54	Gastric Ulcer	14			44	"	5	
3	73	Hypertension	14			47	"	2	
4	66	Rheumatic Heart Disease	14			52	"	3	
5	44	Mitral Stenosis	12				"	5	
6	46	Barbiturate Poisoning	14				"		
7	46	Diabetes Mellitus	15			45	"		
8	43	Duodenal Ulcer	11				"		
9	52	Mitral Stenosis	17			45	"	5	1
10	50	Bronchial Neoplasm	14			47	"		
11	66	Asthma	14			45	"	3	
12	31	Duodenal Ulcer	14				No		
13	74	Breast Carcinoma	12			35 (Ovariectomy)	Yes	3	1
14	46	Rectal Carcinoma	15				No		
15	34	Achalasia of Cardia	13				"		
16	74	Cholecystitis	13			50	Yes	6	
17	61	Haemorrhoids	15			56	"	2	
18	67	Osteoporosis	16			48	"	1	
19	55	Breast Carcinoma	12			49	"	2	2
20	51	Cholecystitis	16			43	"	3	
21	59	Breast Carcinoma	12	+		41	No		
22	54	Pyelonephritis	15			44	Yes	3	3
23	69	Osteoporosis	16			49	"	3	1
24	66	Osteoporosis	11			51	"	1	
25	40	Ulcerative Colitis	15			40	"	3	
26	67	Myocardiac Infarction	14	+		46	No		
27	62	Rheumatoid Arthritis	13			50	"		
28	46	Haematemesis	12			46	Yes	6	
29	68	Hypertension	12			57	No		
30	40	Ulcerative Colitis	16			40	Yes	1	
31	67	Carcinoma of Colon	14			40	"	4	1
32	72	Myocardiac Infarction	15			50	"	1	
33	58	Cholecystitis	15			48	No		
34	49	Mitral Stenosis	14	+		44	Yes	2	
35	51	Duodenal Ulcer	14			50	"	2	
36	60	Pyelonephritis	15			35	No		
37	58	Haemorrhoids	15			45	Yes	4	1
38	77	Myocardial Infarction	13			46	"	3	
39	62	Hypertension	15			51	"	2	
40	40	Haemorrhoids	12				"	5	
41	50	Varicose Ulcer	14				No		
42	42	Mitral Stenosis	14			44	Yes	2	
43	47	Hodgkin's Disease	12				No		
44	53	Duodenal Ulcer	16			46	Yes	3	1
45	51	Hypertension	15			43	"	1	
46	67	Gastric Ulcer	15			49	"	3	
47	30	Barbiturate Poisoning	13				No		
48	75	Cerebral Thrombosis	13			40	Yes	3	1
49	45	Leukaemia	13				No		
50	35	Aspirin Poisoning	15				"		
51	73	Myocardial Infarction	13			45	Yes	6	
52	60	Breast Carcinoma	16			55	"		
53	68	Steatorrhoea	15	+		49	"	3	
54	56	Iron Deficiency Anaemia	13			48	"	1	1
55	50	Bronchial Neoplasm	15			44	"	4	1
56	58	Oesophageal Neoplasm	13			40	No		
57	53	Hypertension	14			43	Yes	4	2
58	71	Leukaemia	15			48	"	2	2
59	66	Angina	12			52	"		
60	39	Fanconi's Anaemia	14			39	"	5	
61	68	Angina	14			47	No		
62	61	Reticulo-sarcoma	14			50	"		
63	47	Angina	13			46	Yes	5	
64	69	Osteoporosis	11			54	"		
65	39	Haematemesis	15	+		43	"	1	1
66	66	Myocardial Infarction	15			41	"	5	
67	73	Osteoporosis	15			39	"		
68	59	Myocardial Infarction	14			49	No		
69	48	Gastric Ulcer	15			49	Yes	3	
70	50	Hiatus hernia	14			44	"	1	

TABLE IV. **Results of Precipitation and Complement - fixation tests in Patients with Auto-immune Thyroiditis followed-up without Treatment.**

Table IV.

Results of Precipitation and Complement-Fixation Tests in Patients with Auto-immune Thyroditis Followed-up without Treatment.

Case No.	Thyroid Auto-Antibody Tests	0	1	2	3	4	5	6	W 7	E 8	E 9	K 10	11	S 12	13	14	15	16	17	18	19	20	Comments
3	Prec.	+	+		+		+			+		+			+								Remained Euthyroid
	CFT	+	+		+		+			++		+			+								
7	Prec.	+	+			+				+				+									" "
	CFT	++	++			++				++				++									
9	Prec.	+	+	+	+			+					+							+			" "
	CFT	++	++	++	++			++						++						++			
14	Prec.	+	+				−				+						+						" "
	CFT	++	++				++				++						++						
21	Prec.	+	+		+					+				+						+			" "
	CFT	+	++		++					++				++						++			
25	Prec.	+			+	+		+															" "
	CFT	++			++	++		++															
31	Prec.	+			+			+															" "
	CFT	++			++			++															
33	Prec.	+	+	+	+																		" "
	CFT	++	++	++	++																		
16	Prec.	−	−					−				−					−			−			Became hypothyroid at 72 weeks
	CFT	++	++					++				++					++			++			
18	Prec.	−	−						−						−							−	Became hypothyroid at 24 weeks.
	CFT	++	++						++						++							++	

TABLE V. Details of Familial Studies in Auto-immune thyroiditis.

Table V.

Details of Familial Studies in Auto-immune Thyroiditis.

Case No.	Thyroid Auto-antibody Tests		Details of Family History of Thyroid Disease.
	Precipitin	C.F.	
1	-	AC	Sister, 2 female first cousins and maternal grandaunt with goitre.
2	+	+ +	Daughter with thyrotoxicosis precipitin test (-), CF test (++).
13	+	+ +	Brother with thyrotoxicosis precipitin test (-).
36	+	+ +	Paternal male and female first cousins with thyrotoxicosis. Male cousin also had exophthalmic ophthalmoplegia.
37	+	+ +	Sister with goitre and another sister with thyrotoxicosis.
40	-	+ +	Maternal grandmother and aunt with goitre.
43	+	+ +	Sister with thyrotoxicosis.
50	-	+	Niece (brother's daughter) with primary hypothyroidism, precipitin test (-).

TABLE VI. Results of thyroid Auto-antibody tests in Female Relatives of Patients with Auto-immune Thyroiditis.

Table VI.

Results of Thyroid Auto-antibody Tests in Female Relatives of Patients with Auto-immune Thyroiditis.

Propositus No.	Relation	Age	Evidence of Thyroid Disease	Thyroid Auto-antibody Tests	
				Precipitin	C.F.
1	Sister	47	None	-	+
7	Sister	45	None	-	-
	Sister	51	None	-	-
	Sister	57	None	-	+
15	Sister	60	None	-	+
	Sister	62	None	-	+ +
	Half-sister	66	None	-	+ +
24	Sister	50	None	-	-
	Mother	83	None	-	-
26	Sister	27	None	-	+
	Sister	35	None	-	-
	Sister	39	None	-	-
29	Daughter	30	None	-	-
33	Sister	59	None	-	-
45	Sister	38	None	-	-
	Sister	40	None	-	-
	Sister	45	None	-	-

SECTION 2. A Skin test in Auto-immune thyroiditis.

TABLE I. Clinical Details of Patients with Auto-immune thyroiditis.

Table I.

Clinical Details of Patients with Auto-Immune Thyroditis

Case No.	Thesis No.	Age (Yrs)	Sex	Clinical Status	Thyroid Auto-antibody Tests Prec.	CFT	Skin Tests T	T+C	Contr.	Treatment
1	10	52	F	Eu	+	++	++(5)	++(6)	-	Thyroxine
2	33	55	F	Eu	+	++	++(7.25)	++(7.5)	-	None
3	30	45	F	Eu	+	++	++(4.5)	++(5)	-	Thyroxine
4	31	61	F	Eu	+	++	++(4)	++(5.5)	-	None
5	27	54	F	Hypo	+	++	++(4.5)	++(3.5)	-	None
6	19	66	F	Hypo	+	++	++(4)	++(6.5)	-	None
7	2	56	F	Hypo	+	++	++(2.5)	++(3)	-	None
8	43	45	F	Eu	+	++	++(4.5)	++(4.5)	-	None
9	3	52	F	Eu	+	+	+(2.5)		-	None
10	24	53	F	Eu	+*	++	-		-	Partial Thyroid-ectomy Thyroxine
11	50	62	F	Eu	-	+	+(1.75)		-	Partial Thyroid-ectomy Thyroxine
12	26	43	F	Eu	+	++	-	+(3)	-	None

Skin Tests: T = thyroid extract, T+C = thyroid extract plus cortisone, Contr = control injection; (-) negative, (+) positive, and (++) strongly positive skin responses. Figures in brackets refer to the mean diameter of the skin reactions in centimetres.
Clinical Status: Eu = euthyroid, hypo = hypothyroid.

* Clear-line precipitate.

TABLE II. Clinical Details of Patients with Primary Hypothyroidism.

Table II.

Clinical Details in Patients with Primary Hypothyroidism.

Case No.	Thesis No.	Age (Yrs)	Sex	Clinical Status	Thyroid Auto-antibody Tests Prec.	CFT	Skin Tests T	T+C	Contr.	Treatment
13	9	56	F	Eu	+	+	++(4)	++(2)	-	Thyroxine
14	11	64	F	Hypo	+	-	++(3)	++(2)	-	Thyroxine
15	6	44	F	Eu	+	-	-*		-	Thyroxine
16	21	38	F	Hypo	-	++	+(2.75)	+(3.25)	-	None
17	32	55	M	Hypo	-	++	+(2.25)	+(2.5)	-	Thyroxine
18	27	67	F	Hypo	-	+	-		-	None
19	61	56	F	Eu	-	+	-		-	Thyroxine
20	69	51	M	Eu	-	-	-	-	-	Thyroxine
21	15	40	F	Eu	-	-	-	-	-	Thyroxine

* Late onset of reaction at 48 hours.

TABLE III. Clinical Details of Patients with thyrotoxicosis, simple goitre, thyroid cancer, and in one Patient with "Unclassified" thyroid Disease.

Table III.

Clinical Details of Patients with Thyrotoxicosis, Simple Goitre, Thyroid Cancer, and in one Patient with "Unclassified" Thyroid Disease.

Case No.	Age	Sex	Diagnosis	Clinical Status	Thyroid Auto-antibody tests		Skin Tests			Treatment
					Prec.	CFT	T	T + C	Contr.	
22	66	F	Thyrotoxicosis	Toxic	+	++	-	+(1.75)	-	Methyl thiouracil
23	48	F	"	"	-	-	-	-	-	None
24	42	F	"	"	-	+	-	-	-	None
25	48	F	"	"	-	+	-	-	-	Potassium Perchlorate
26	76	F	"	"	-	+	-	-	-	None
27	48	F	"	"	-	++	-	-	-	None
28	38	F	"	"	-	++	-	-	-	None
29	45	F	"	"	-	++	-	-	-	None
30	20	F	"	"	-	++	-	-	-	None
31	29	F	"	"	-	++	-	-	-	None
32	37	F	Simple Non-Toxic Goitre	Euthyroid	-	-	-	-	-	None
33	27	F	"	"	-	-	-	-	-	None
34	47	F	"	"	-	-	-	-	-	None
35	31	F	"	"	-	-	-	-	-	None
36	32	M	Thyroid Cancer*	"	-	-	-	-	-	None
37	69	F	"Unclassified"	"	-	-	+(2.25)	+(2.25)	-	Thyroid Extract

* Papillary Adenocarcinoma
Skin Tests: T = Thyroid extract, T + C = Thyroid extract plus cortisone, Contr. = Control injection.
Figures in brackets refer to diameter of skin reactions in centimetres.

TABLE IV. Clinical Details in Control Patients without Overt Thyroid Disease.

Table IV.

Clinical Details in Control Patients without Overt Thyroid Disease.

Case No.	Age	Sex	Diagnosis	Thyroid Auto-antibody tests		Skin Tests		
				Prec.	CFT	T	T + C	C
38	82	F	Pernicious Anaemia	-	+	+(2.25)	+(3)	-
39	70	F	Senility Osteoporosis	-	+	-		-
40	73	F	Cor Pulmonole	-	+	-		-
41	69	F	Hypertensive Heart Failure	-	++	-		-
42	42	F	Cerebral Embolism, Mitral Stenosis, Auricular Fibrillation	-	-	-	-	-
43	68	F	Diabetes Mellitus	-	-	-		-
44	71	F	Ischaemia Heart Disease, Congestive Cardiac Failure	-	-	-		-
45	70	F	Chronic bronchitis	-	-	-	-	-
46	60	F	Congestive Cardiac Failure	-	-	-	-	-
47	82	F	Senile Dementia	-	-	-		-
48	78	F	Hemiplegia	-	-	-		-
49	42	M	Bronchial Neoplasm	-	-	-	-	-
50	56	F	Uraemia Pyelonephritis	-	-	-		-
51	52	F	Cerebral Embolism, Mitral Stenosis	-	-	-		-
52	61	M	Bronchial Carcinoma	-	-	-		-
53	69	F	Myocardial Infarction	-	-	-		-
54	79	F	Senile Dementia	-	-	-		-
55	81	F	Senility Dementia	-	-	-		-
56	41	M	Gastric Neoplasm	-	-	-		-

Skin Tests: T = thyroid extract, T + C = thyroid extract plus cortisone, C = control injection. Figures in brackets refer to diameter of skin reactions in centimeters.

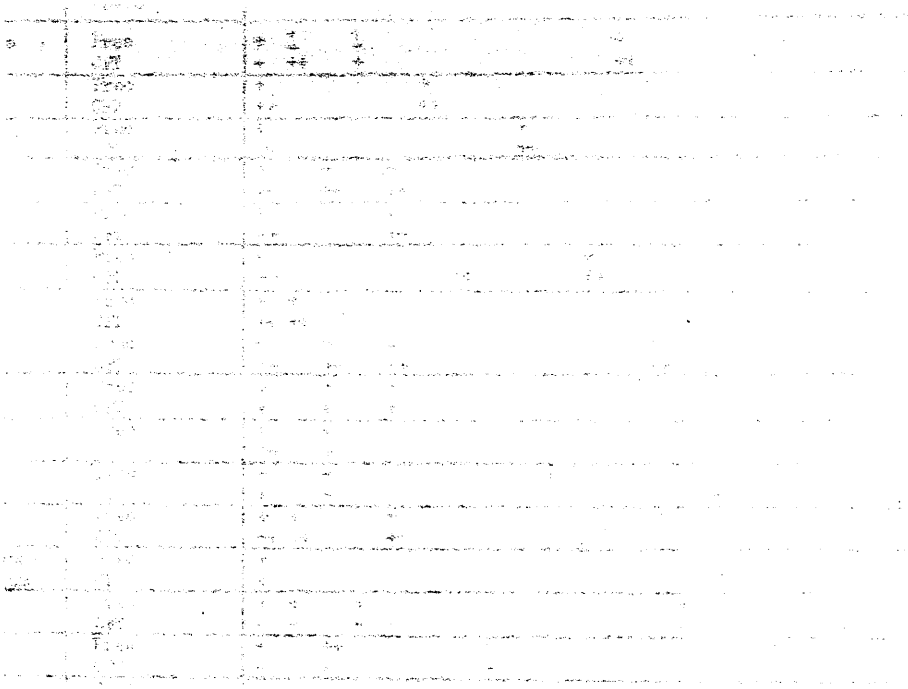


TABLE V. Results of Serial Studies of Precipitin and Complement Fixation Tests after Skin testing in thyroid Disease.

Table V. Results of Serial Studies of Precipitin and Complement-Fixation Tests after Skin Testing in Thyroid Disease

Case No.	Diagnosis	Thyroid Auto-Antibody Tests	WEEKS 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	Auto-immune Thyroditis	Prec	+	+		+								+													
		CFT	+	++		+								++													
2	"	Prec	+					+																			
		CFT	++					++																			
3	"	Prec	+								+																
		CFT	++								++																
4	"	Prec	+		-		-																				
		CFT	++		++		++																				
5	"	Prec	+				+																				
		CFT	++				++																				
6	"	Prec	+						+				+														
		CFT	++						++				++														
7	"	Prec	+	+																							
		CFT	++	++																							
8	"	Prec	+		-		-								+												
		CFT	++		++		++								++												
9	"	Prec	+		+		+																				
		CFT	+		+		+																				
10	"	Prec	+		+				-																		
		CFT	++		+																						
11	"	Prec	-		-												-										
		CFT	+		-												-										
12	"	Prec	+	+			+																				
		CFT	++	++			++																				
13	Primary Hypo-thyroidism	Prec	+																								
		CFT	+																								
14	"	Prec	+	+		+										+											
		CFT	-	-		-										-											
15	"	Prec	+		++					+																	
		CFT	-		-					-																	
16	"	Prec	-								-																
		CFT	++								-																
17	"	Prec	-				-			-										-		-					
		CFT	++				++			++										++		++					
18	"	Prec	-															-			±		-				
		CFT	+															+			+		+				
19	"	Prec	-		-		-								-												
		CFT	+		+		-								+												
20	"	Prec	-			-			-																		
		CFT	-			-			-																		
21	"	Prec	-	-													-										
		CFT	-	-													-										
22	Thyrotoxicosis	Prec	+	+	+	+																					
		CFT	++	++	++	++																					
23	"	Prec	-			-		-							-												
		CFT	-			-		-							-												
24	"	Prec	-	-		-			-								-										
		CFT	-	-		-			-								-										
25	"	Prec	-							-					-		-										
		CFT	+							++					++		++										
26	"	Prec	-				-					-															
		CFT	+				+					+															
27	"	Prec	-						-					-													
		CFT	++						++					++													
28	"	Prec	-		-		-			-					-								-				
		CFT	++		++		++			++					++								++				
29	"	Prec	-			-					-																
		CFT	++			++					++																
30	"	Prec	-			+		-		-																	
		CFT	++			++		+		+																	
31	"	Prec	-			-		-		-					-												
		CFT	++			++		+		+					+												
32	Simple non-Toxic Goitre	Prec	-	-											-												
		CFT	-	-											-												
33	"	Prec	-	-		-									-		-										
		CFT	-	-		-									-		-										
34	"	Prec	-				-								-												
		CFT	-				-								-												
35	"	Prec	-	-	-		-			-																	
		CFT	-	-	-		-			-																	

TABLE VI. Results of Serial Studies of Precipitin and Complement Fixation (CF) tests after skin testing in Control Patients without overt thyroid Disease.

Table VI.

Results of Serial Studies of Precipitin and Complement-Fixation (CF) Tests after Skin Testing in Control Patients Without overt Thyroid Disease.

Case No.	Thyroid Auto-Antibody Tests	Weeks 0	1	2	3	4	5	6
38	Prec	-	-					
	CFT	+	+					
39	Prec	-	-		-			
	CFT	+	+		+			
40	Prec	-				-		
	CFT	+				+		
42	Prec	-				-		
	CFT	-				-		
43	Prec	-	-		-			
	CFT	-	-		-			
47	Prec	-	-		-			
	CFT	-	-		-			
48	Prec	-	-		-			
	CFT	-	-		-			
50	Prec	-	-					
	CFT	-	-					
51	Prec	-					-	
	CFT	-					-	
53	Prec	-		-				
	CFT	-		-				
54	Prec	-	-		-			
	CFT	-	-		-			
55	Prec	-	-		-			
	CFT	-	-		-			
56	Prec	-		-				
	CFT	-		-				

SECTION 3. Biochemical Studies.

TABLE I.

Results of Serum Protein Investigations in Control Subjects.

Table I.

Results of Serum Protein Investigations in Control Subjects

Case No.	Age	Sex	Serum Proteins (g.100ml)					
			Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin
1	35	F	5.6	1.9	0.19	0.50	0.58	0.63
2	39	F	5.0	1.4	0.15	0.33	0.45	0.48
3	21	M	5.0	1.5	0.12	0.35	0.46	0.58
4	54	F	5.5	2.3	0.22	0.49	0.60	1.00
5	63	F	5.0	2.1	0.18	0.44	0.67	0.82
6	51	F	4.8	2.0	0.13	0.38	0.57	0.91
7	29	M	5.6	2.2	0.16	0.45	0.66	0.94
8	59	F	5.3	1.9	0.15	0.39	0.59	0.76
9	46	F	5.0	2.0	0.24	0.50	0.70	0.76
10	53	F	5.4	1.5	0.21	0.36	0.50	0.63
11	50	F	4.9	2.0	0.12	0.43	0.62	0.83
12	41	F	5.5	2.2	0.16	0.50	0.61	0.92
13	39	F	5.0	1.5	0.18	0.22	0.41	0.70
14	36	F	5.5	2.2	0.24	0.49	0.63	0.84
15	31	M	5.6	1.7	0.18	0.50	0.48	0.53
16	34	M	5.0	2.1	0.25	0.44	0.95	0.82
17	60	F	5.3	2.0	0.22	0.45	0.55	0.79
18	57	F	4.9	1.9	0.30	0.36	0.50	0.71
19	40	F	4.8	2.2	0.29	0.67	0.56	0.68
20	42	F	5.5	1.7	0.25	0.49	0.49	0.48
21	48	F	5.6	2.2	0.28	0.62	0.47	0.83
22	51	F	4.8	1.9	0.22	0.50	0.48	0.70
23	27	M	5.4	1.5	0.16	0.35	0.40	0.60
24	29	M	4.9	1.5	0.16	0.32	0.41	0.61
25	30	M	4.8	2.0	0.25	0.38	0.56	0.81
26	30	M	5.6	1.9	0.12	0.38	0.48	0.94

Mean Age 42.1 years Age Range 21 - 63 years.

TABLE II.

Results of Serum Protein Investigations in Auto-immune Thyroiditis.

TABLE III.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rate in Auto-immune Thyroiditis.

Table II.

Results of Serum Protein Investigations in Auto-immune Thyroditis

Case No.	Age	Sex	SERUM PROTEINS (g./100 ml) Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin
2	56	F	4.5	2.4	0.16	0.42	0.62	1.42
3	52	F	4.7	2.3	0.07	0.35	0.53	1.34
5	41	F	3.8	3.0				
6	63	F	3.9	2.1	0.28	0.53	0.51	0.79
7	62	F	4.3	2.2	0.19	0.35	0.59	1.08
8	49	F	4.3	1.0	0.06	0.21	0.19	0.54
9	63	F	4.3	3.2	0.16	0.59	0.47	1.98
10	52	F	4.6	2.3	0.21	0.43	0.71	0.98
11	37	F	4.5	2.0	0.16	0.34	0.60	0.70
12	48	F	4.7	2.1	0.28	0.45	0.41	0.96
14	28	F	3.9	3.0	0.26	0.42	0.58	1.74
15	57	F	3.8	2.3	0.16	0.47	0.52	1.16
16	40	F	4.2	2.2	0.36	[illegible]	[illegible]	[illegible]
17	45	F	4.0	2.0	0.12	0.30	0.38	1.22
18	52	F	4.0	2.0	0.17	0.43	0.58	0.83
19	66	F	4.3	3.5	0.31	0.83	0.70	1.66
20	46	F	3.5	2.9	0.14	0.36	0.34	2.06
21	63	M	3.7	2.3	0.15	0.40	0.56	1.18
22	56	F	3.5	3.5	0.09	0.30	0.58	2.53
23	44	F	4.7	1.8				
24	53	F	3.8	2.0	0.16	0.43	0.67	0.74
25	50	F	4.3	2.5	0.22	0.34	0.52	1.42
26	43	F	4.2	2.2	0.24	0.38	0.49	1.09
27	54	F	4.6	1.8	0.13	0.35	0.38	0.94
28	50	F	4.3	2.2	0.12	0.50	0.49	1.10
29	51	M	5.1	2.0	0.15	0.36	0.65	0.84
30	45	F	3.8	2.3	0.21	0.38	0.81	0.90
33	55	F	4.2	2.2				
34	51	M	5.0	4.6	0.33	0.79	0.80	2.68
35	46	F	4.6	1.9	0.22	0.41	0.63	0.64
36	50	F	4.6	2.9	0.15	0.69	0.72	1.34
37	44	F	4.1	3.0	0.31	0.47	0.65	1.54
38	61	F	3.9	3.0	0.30	0.47	0.68	1.65
39	45	F	5.0	2.4	0.11	0.54	0.66	1.09
43	45	F	4.2	2.2				
44	44	F	4.3	2.0	0.32	0.37	0.66	0.65
45	36	F	4.2	2.1	0.21	0.37	0.62	0.90
47	64	F	4.4	2.7	0.23	0.41	0.90	1.15
48	47	F	3.5	2.9	0.16	0.49	0.52	1.75
49	40	F	4.2	1.7				
50	62	F	3.8	1.8	0.28	0.37	0.47	0.68

Mean Age 50.1 years Age Range 28 - 66 years

Table III.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rate in Auto-immune Thyroiditis.

Case No.	Thymol Turbidity (Units)	Thymol Flocculation	Cephalin Cholesterol	Colloidal Gold (Units)	Zinc Sulphate Turbidity (Units)	E.S.R. (mm/hr.)
2	8	3	3	5		16
3	4	1	0	5		4
5	12	3	3	5	40	7
6	6	2		0	15	37
7	4	1		1	17	4
8	6	3	3	3		66
9	1	0		0	24	34
10	14	3	2	5		40
11	5	0	2	5		5
12	3	1	0	4	22	15
14	10	3	3	5		14
15	8	3	0	5		30
16	5	4	3	5	27	30
17	12	3	3	5		32
18	3	0	3	5	18	22
19	3	0	2	2	9	6
20	7	3	2	5		12
21	4	3	2	5		12
22	10	3		5	60	57
23	1	0	0	1	3	8
24	1	0	0	1	3	46
25	2	0		5	25	8
26	14	4	0	5		23
27	3	2	2	5		9
28	5	0		5	23	10
29	1	0		1	15	11
30	5	4	3	5		19
33	5	3	2	3	13	38
34	11	4		4	30	46
35	2	0		0	13	18
36	1	0		0	14	4
37	6	2		2	22	25
38	14	3		3	23	31
39	4	1		1	13	14
43	4	0		5	31	13
44	1	0		1	8	78
45	2	0		1	8	23
47	2	0		0	12	12
48	5	1		5	15	9
49	4	0			15	22
50	1	0	0	1		18

Mean Age 50.1 years Age Range 28 - 66 years.

TABLE IV.

Results of Serum Protein Investigations in Primary Hypothyroidism.

TABLE V.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rate in Primary Hypothyroidism.

Table IV.

Results of Serum Protein Investigations in Primary Hypothyroidism

Case No.	Age	Sex	Thyroid Auto-antibody Tests Prec.	CF	Serum Proteins (g./100ml.). Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin
1	52	M	+	++	4.4	2.0	0.25	0.25	0.53	0.98
2	61	C	+	++	3.7	2.1	0.23	0.28	0.55	1.04
3	60	F	+	++	5.6	3.0	0.27	0.35	1.23	1.15
4	56	F	+	++	4.3	2.2	0.22	0.24	1.95	0.88
7	67	F	+	-	3.9	2.8				
8	64	F	+	++	4.7	3.0	0.05	0.08	0.71	0.71
9	64	F	+	-	4.5	2.0	0.06	0.54	0.75	1.11
11	56	F	+	++	4.7	1.6				
12	57	F	-	++	4.3	2.2	0.29	0.69	0.55	0.66
15	55	M	-	++	4.2	2.1	0.29	0.39	0.58	0.84
16	49	M	-	++	4.6	1.6	0.14	0.41	0.43	0.62
18	56	F	-	++	4.1	1.9	0.29	0.42	0.50	0.69
19	56	F	-	++	3.7	2.0				
20	70	F	-	++	5.9	2.5	0.13	0.66	0.63	1.08
21	38	F	-	++	3.7	2.1				
22	39	F	-	++	4.5	2.0				
23	59	F	-	++	3.9	1.7				
24	64	F	-	++	3.9	1.6				
26	57	M	-	+	4.0	1.8	0.04	0.09	0.82	0.86
27	56	F	-	+	4.5	1.5	0.17	0.33	0.47	0.56
28	56	F	-	+	4.5	1.5	0.13	0.51	0.45	0.42
30	56	F	-	+	3.9	2.1	0.27	0.38	0.68	0.77
32	67	F	-	+	3.9					
37	56	M	-	-	4.5	1.8	0.13	0.27	0.59	0.81
38	36	M	-	-	4.3	2.2	0.15	0.43	0.53	1.10
39	50	F	-	-	4.9	1.8	0.17	0.45	0.58	0.61
41	56	F	-	-	4.0	1.5	0.12	0.29	0.41	0.68
42	42	F	-	-	4.0	2.7	0.20	0.42	0.83	1.09
44	64	F	-	-	4.9	1.7	0.16	0.35	0.62	0.57
45	73	F	-	-	4.2	2.1	0.25	0.55	0.48	0.89
46	55	F	-	-	4.5	1.4	0.21	0.29	0.45	0.55
48	57	F	-	-	3.8	1.4	0.22	0.28	0.41	0.62
49	52	M	-	-	4.2	2.2				
51	61	M	-	-	3.6	3.9	0.22	0.94	1.36	1.40
54	62	F	-	-	4.2	2.1				
63	37	F	-	-	4.0	2.3				
67	34	F	-	-	3.8	1.4				
68	49	F	-	-	4.5	1.5				
70	65	F	-	-	3.9	2.4				
71	52	F	-	-	4.3	2.6	0.14	0.63	0.96	0.88

Mean Age 55.4 years Age Range 34- 73 years

For further clinical details see appendices Chapter III Section 1.

T.64V. Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rate in Primary Hypothyroidism.

Case No.	Age	Sex	Thymol Turbidity (Units)	Thymol Flocculation	Cephalin Cholesterol	Colloidal Gold (Units)	Zinc Sulphate Turbidity (Units)	E.S.R. (mm/hr)
1	52	M	4	1		0	14	6
2	61	F	5	1		5	24	41
3	56	F	2	0			17	32
4	56	F	1	0		4	15	13
5	50	F	2	0			11	
6	47	F	2	0	0	0		
7	67	F	1	0			13	21
8	64	F	1	0		2	11	21
9	56	F	2	0	0	3		5
11	57	F	2	0	1	3		
12	57	F				0		18
13	36	F	2	0	0	3		
14	63	F	2	0	0	0		15
15	55	M	3	0	3			19
16	49	M	2	0	0	2		
17	60	F	3	0			18	5
18	56	F				0		
19	56	F	3	0	0			17
20	70	F	1	0	0	3		17
21	38	F	3	0	0	2		82
22	39	F	3	0	0	4		8
23	59	F	1	0	2	5		13
24	64	F	1	0	0	0		31
25	38	F	2	3	0	2		
26	57	M	1	0	0	4		18
27	56	F	1	1	1	2		25
28	60	F	2	0		0	10	12
29	53	F	1	0			7	31
30	56	M				0		31
31	65	F	1	0	0			
32	67	F	2	0	0	1		32
33	53	F	1	0	0	1		6
36	38	F	4	1		3	18	55
37	56	M	2	0	0	2		
38	36	M	4	0	2	1		17
39	50	F	1	0		1	11	23
40	66	F	3	3	0			
41	56	F	1	0	0			5
42	42	F	1	0			5	3
44	64	F	2	0	0	0		22
45	73	F	1	0	0	0		
46	55	F	1	0		0	14	
47	62	F	2	0	0	0		
48	51	F	1	0		1	14	
49	52	M	1	0		0	18	
51	61	M	1	0		0	7	
52	50	M						10
53	51	1	0				13	
54	62	F	1	0	0	2	9	
55	67	F	1	0				
56	58	F	1	0			8	
57	50	F	2	0	0		8	
61	51	M	3	0	0	5		
63	37	F						10
66	56	F	1	0			8	
67	34	F	2	0	0	2		8
68	49	F	2	0	0	2		20
69	40	F	2	0	1	5		
70	65	F	3 1				16	18
71	52	F	1	0	0	2		14

Mean Age 54.4 years. Age Range 24 - 70 years.

Table VI.

Results of Serum Protein Investigations in Simple Goitre.

Table VI.

Results of Serum Protein Investigations in Simple Goitre

Case No.	Age	Sex	Serum Proteins (g./100ml) Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin
1	44	F	5.6	1.9	0.15	0.34	0.54	0.87
2	28	F	5.0	1.5	0.08	0.27	0.41	0.74
3	31	F	4.9	2.0	0.22	0.43	0.47	0.89
4	42	F	4.2	2.1	0.26	0.49	0.58	0.78
5	21	F	5.5	1.5				
6	35	F	4.9	2.1	0.19	0.52	0.59	0.80
7	56	F	4.3	2.2	0.20	0.33	0.80	0.87
8	20	F	4.4	1.6	0.21	0.29	0.43	0.62
9	53	F	4.8	2.0	0.26	0.48	0.56	0.71
10	37	F	5.5	2.3	0.21	0.52	0.71	0.86
11	47	F	5.3	1.9	0.20	0.48	0.44	0.78
12	32	F	4.9	1.9	0.12	0.36	0.57	0.84
13	37	F	5.4	1.5	0.15	0.29	0.45	0.61
14	42	F	5.4	1.5	0.09	0.36	0.51	0.54
15	25	F	4.8	2.2	0.19	0.47	0.43	1.10
16	25	F	5.0	2.5	0.35	0.54	0.67	0.94
17	43	F	4.9	2.0	0.11	0.39	0.53	0.97
18	16	F	5.4	1.5	0.22	0.37	0.40	0.50
19	19	F	5.6	2.2	0.19	0.49	0.61	0.92
20	33	F	5.0	1.4	0.06	0.23	0.41	0.70
21	31	F	5.6	1.9	0.23	0.44	0.45	0.79
22	21	F	4.9	2.1	0.23	0.42	0.56	0.86
23	39	F	4.3	1.4				
24	25	F	5.9	1.7	0.16	0.39	0.44	0.71
25	32	F	4.2	1.9	0.19	0.38	0.32	1.01
26	47	M	3.9	1.7	0.21	0.29	0.46	0.75
27	32	F	4.5	1.9	0.17	0.49	0.43	0.81
28	33	F	4.4	1.9	0.35	0.25	0.47	0.84
29	67	F	4.2	1.6				
30	37	F	4.3	1.7				
31	46	F	4.5	1.7	0.29	0.39	0.41	0.60
32	50	F	4.3	2.1				
33	39	F	4.6	1.8				

Mean age 35.9 years Age Range 16 - 67 years.

Table VII.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rate in Simple Goitre.

Table VII. Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rate in Simple Goitre.

Case No.	Age	Sex	Thymol Turbidity (Units)	Thymol Flocculation	Cephalin Cholesterol	Colloidal Gold (Units)	Zinc Sulphate Turbidity (Units)	E.S.R. (mm/hr)
1	44	F	2	0		3		6
2	28	F	1	0		1		9
3	31	F	1	0		5		3
4	44	F	1	0		1		5
5	21	F	1	0		1		11
6	35	F	1	0		1		8
7	56	F	3	0		2		12
8	20	F	3	0		3		4
9	53	F	1	0		0		3
10	37	F	1	0		1		8
11	47	F	1	0		5		7
12	32	F	2	1		3		6
13	37	F	2	0		1		2
14	42	F	2	0		4		10
15	25	F	2	0		2		1
16	29	F	1	0		0		3
17	49	F	3	0		3		3
18	16	F	2	0		0		2
19	19	F	1	0		5		3
20	33	F	1	0		3		5
21	31	F	1	0		1		8
22	21	F	1	0		0	7	6
23	39	F	2	0		3		5
24	25	F	2	0		4	8	7
25	32	F	3	1		2	12	11
26	47	M	1	0		3	23	9
27	32	F	1	0		1		4
28	33	F	1	0		0	9	2
29	67	F	2	0		4	12	16
30	37	F	1	0			12	12
31	46	F						6
32	50	F	1	0		5		3
33	39	F	3	0		3	6	5
34	42	F	1	0	0	0		
35	26	F	1	0		3	12	9
36	33	F	2	0	1	5		11
37	47	F	1	0			8	11
38	21	F	1	0	0	1	8	2
39	36	F	1	0	0	1		7
40	55	F	1	0		0	15	8
41	19	F	2	0	0	4		7
42	54	F	1	0		5	19	4
43	36	F	9	0	1	3		10
44	48	F	1	0	0	2		7
45	32	F	1	0		0	7	4
46	37	F	2	0		1	8	3
47	40	F	1	0	0	1		2
48	27	F	1	0	0	1		6
49	27	F	0	0		0		
50	45	F	1	0	0			
51	43	F	1	0		1	12	7
52	16	F	1	0	0	1		4
53	20	F	1	0	0	0		13
54	34	F	1	0	0	4		
55	30	F	1	0	0	1		7
56	21	F	1	0	0	5		9
57	40	F	2	0	3	1		12
58	25	F	0	0	0	4		8
59	39	F	2	0	0	1		18
60	47	F	1	0	0	1		6
61	34	F	1	0		4	25	13
62	47	F	1	0	0	0		
63	33	F	1	0			13	2
64	32	F	1	0	0	2		1
6560	60	F	1	0	0	0		1
66	44	F	1	0	1	2		1
67	50	F	1	0	0	2		2
68	46	F	1	0		3	20	6
69	42	F	1	0		0	4	2
70	39	F	2	0	2	3		4
71	21	F	2	0	0	3		2
72	47	F	2	0	0	0		3
73	33	F	1	0	0			2
74	26	F	2	0			7	6
75	36	F	1	0			8	
76	54	F	1	0			5	
77	19	F	2	0			8	4
78	55	F	2	0	0	4		
79	36	F	1	0		1	9	5
80	27	F	1	0	2	3		
81	41	F	2	0		2	13	6
82	36	F	2	0		1	7	
83	31	F	1	0	4	5	8	
84	49	F	1	0			7	3
85	36	F	3	0	0	2		8
86	26	F	1	0	0	5		
87	28	F	1	0	0			
88	43	F	1	0	0	1		
89	45	F	1	0	0	1		
90	15	F	1	0	0	1		11
91	21	F	2	0		2	16	8
92	30	F	3	0	1	1		13
93	25	F	2	0	0	2		3
94	40	F	2	0		1	11	13
95	21	F	1	0		0	8	6
96	30	F	2	0		2	12	8
97	34	F	6	0		5	5	7
98	30	F	2	0	1	4	16	19
99	50	F	1	0		1	5	10
100	55	F	1	0		0	11	11
101	27	F	1	0		2	8	8
102	27	F	1	0	1	5		19
103	42	F	2	0	1	4		9
104	43	F	3	0	2	5		6
105	17	F	1	0	0	1		11
106	20	F	2	0	0	4		
107	31	F	1	0	0	1		13
108	30	F	1	0		2	0	7
109	23	F	2	0			8	5
110	26	F	1	0			7	8
111	24	F	1	0	0			4
112	23	F	2	0	0	4		8
113	40	F	1	0	0		9	6
114	42	F	1	0				8
115	41	F	1	0	0	5	11	
116	63	F	2	0	0	0		1
117	51	F	1	0	2	1		8
118	60	F	2	0	0			2
119	23	F	2	0	0	2		5
120	28	F	1	0	0	0		5
121	40	F	1	0	0	1		8
122	42	F	3	0	1	3		11
123	46	F	1	0	1			10
124	33	F	1	0	2	3	12	
125	35	F	1	0	2	3		
12651	31	F	2	0	0	2		
127	53	F	1	0	0	1		

Mean Age 35.5 years

Age average 15 - 60 years.

TABLE VIII.

Results of Serum Protein Investigations in Thyrotoxicosis.

TABLE IX.

Results of Serum Flocculation tests and Erythrocyte Sedimentation Rates in Thyrotoxicosis.

Table VIII.

Results of Serum Protein Investigations in Thyrotoxicosis

Case No.	Age	Sex	Thyroid Antibody Prec.	Auto-tests CF	Serum Proteins (g/100ml). Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin
1	43	F	-	+	4.3	2.1				
2	31	F	-	-	4.1	1.9	0.13	0.28	0.50	0.99
3	48	F	-	+	4.6	1.5	0.17	0.34	0.39	0.60
4	26	F	-	++	4.7	1.8				
5	21	F	-	++	3.8	1.5	0.17	0.38	0.34	0.61
6	65	F	-	-	3.6	1.9	0.21	0.49	0.42	0.78
7	66	F	+	++	4.0	1.8	0.17	0.34	0.68	0.62
8	48	F	+	++	4.2	1.3	0.17	0.28	0.36	0.49
9	21	F	+	++	4.4	1.9				
10	48	F	-	+	3.9	2.0	0.23	0.43	0.63	0.71
11	37	F	-	-	4.4	1.8	0.19	0.43	0.47	0.71
12	54	F	-	+	4.3	1.7	0.14	0.37	0.52	0.67
13	48	F	-	++	3.6	2.0				
14	50	F	-	+	4.3	2.2	0.20	0.39	0.58	1.03
15	37	M	-	++	4.0	1.9	0.13	0.38	0.41	0.97
16	41	M	-	++	4.5	2.5	0.20	0.52	0.80	0.98
17	55	F	-	-	4.0	2.6	0.28	0.62	0.63	1.08
18	28	F	-	++	3.7	1.9	0.20	0.29	0.49	0.92
19	29	F	-	++	4.0	1.6	0.18	0.35	0.43	0.63
20	41	F	-	-	4.8	1.6	0.19	0.19	0.52	0.69
21	25	M	-	-	4.0	2.1	0.19	0.43	0.57	0.91
22	37	F	-	-	3.3	1.3				
23	43	M	-	-	4.0	2.4	0.23	0.53	0.67	0.97
24	43	F	-	-	4.7	2.5	0.25	0.48	0.78	0.99
25	40	F	-	++	4.1	2.6	0.23	0.60	0.59	1.18
26	51	M	-	-	3.9	2.4	0.10	0.41	0.77	1.12
27	47	M	-	++	3.6	1.9	0.24	0.34	0.50	0.81
28	44	M	-	++	4.0	2.0	0.16	0.53	0.62	0.69
29	33	F	-	-	5.0	1.4				
30	25	F	-	-	3.6	1.9				
31	59	F	-	++	3.8	1.4	0.12	0.29	0.39	0.60
32	38	F	-	-	4.0	1.8	0.16	0.37	0.47	0.83
33	59	F	-	-	4.2	1.6	0.17	0.33	0.27	0.84
34	49	F	-	-	3.9	1.6	0.19	0.29	0.38	0.73
35	51	F	-	-	4.7	1.5				
36	20	F	-	++	4.8	1.5	0.11	0.44	0.40	0.56
37	43	M	-	+	4.0	1.9	0.13	0.28	0.50	0.99

Mean age 41.8 years Age range 20 - 66 years.

Table IX. Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rates in Thyrotoxicosis.

Case No.	Thymol Turbidity (Units)	Thymol Flocculation	Cephalin Cholesterol	Colloidal Gold (Units)	Zinc Sulphate Turbidity (Units)	B.S.R. (mm/hr)	Age	Sex	Thyroid Auto-antibody Tests Prec	CF
1	2	0	0	4		16	43	F	-	+
2	3	0	3	4		5	31	F		
3	1	0		1	9	12	46	F		
4	1	0		2	13	8	26	F	-	+
5	2		2	4		2	21	F		
6	1	0	4	3			55	F		
7	2	0	0	2	10	5	66	F	-	+
8	1	0		1	15	6	49	F		
9	1			3	18	4	21	F		
10	2	0	2	4		9	48	F		
11	1	0	0	3		6	37	F		
12	1	0	0	5		13	34	F	-	+
13	1	0	0	1		5	48	F		
14	1	0	1	5		2	30	F		
15	1	0	2	5		3	37	M		
16	1	0	3	1		1	41	M		
17	1	0	3	0			55	F		
18	1	0	0	1			57	F		
19	1	0	0	3		11	57	F		
20	2	0	0	1		8	57	F		
21	2	0	0	2		19	44	M		
22	2	0	0	2		9	39	F		
23	1	0	0	0		4	57	F		
24	1	0	0	0			43	F		
25	1	0	0	5		2	43	M		
26	1	0	0	3		1	40	F		
27	1	0	0	3		11	51	M		
28	1	0	0	1		7	47	M		
29	1	0	0	1		6	44	M		
30	1	0	0	2		5	33	F		
31	1	0	0	2	14	7	29	F		
32	1	0	0	1		8	29	F		
33	4	1	0	3		4	38	F		
34	1	1	0	2		2	59	F		
35	1	0	0	3		3	49	F		
36	1	0	0	1		3	51	F		
37	2	0	0	3	9	4	20	F		
38	1	0	0	3		11	20	M		
39	3	0	0	4		12	47	M		
40	1	0	4	3		17	34	F		
41	2	0	0	4		8	49	F		
42	2	0	0	2	5	11	49	F		
43	1	0	0	2	5		48	F		
44	1	0	0	2	1	4	28	F		
45	1	0	0	2	1	7	30	F		
46	1	1	0	0	0		51	M		
47	2	0	0	2	3	3	38	M		
48	1	1	0	0	3	14	55	M		
49	1	0	0	0	1	8	68	F		
50	1	0	0	0	1		55	F		
51	1	1	0	0	1	6	35	F		
52	1	1	0	0	0		52	F		
53	1	1	0	0	0		56	F		
54	1	1	0	0	0	6	57	F		
55	1	1	0	0	1	17	38	F		
56	1	1	0	0	1	15	46	F		
57	1	1	0	0	0		46	F		
58	1	1	0	0	0	7	55	F		
59	1	1	0	0	0	10	50	F		
60	2	1	0	0	0	13	44	F	-	+
61	1	1	0	0	0	7	33	F		
62	1	1	0	0	0	11	38	M		
63	1	1	0	0	1	8	45	F		
64	1	1	0	0	2	7	40	F		
65	1	1	0	0	2	3	38	F		
66	1	1	0	0	2	10	40	F		
67	1	1	0	0	2	2	39	F		
68	2	1	0	0	2	2	19	F		
69	2	1	0	0	2	11	35	M		
70	1	1	0	0	3	2	38	M		
71	1	1	0	0	3	4	54	M		
72	1	1	0	0	3	3	30	M		
73	1	1	0	0	3	2	52	M		
74	1	1	0	0	3	11	43	M		
75	1	1	0	0	3	1	37	M		
76	1	1	1	0	3	2	29	M		
77	1	1	0	0	3	10	46	M		
78	1	1	0	0	3	7	57	M		
79	1	1	0	0	3		50	M		
80	1	1	1	0	3	10	49	M		
81	2	1	1	0	3	12	46	M		
82	1	1	1	0	3	4	78	M		
83	1	1	0	0	3		59	M		
84	1	1	0	0	3	13	59	M		
85	2	1	0	0	3	4	57	M		
86	2	1	0	0	3	7	36	M		
87	2	1	2	0	3	2	32	M		
88	1	1	0	0	3		59	M		
89	1	1	0	0	3	14	36	M		
90	1	1	0	0	3	7	47	M		
91	1	1	0	0	3		53	M		
92	1	1	0	0	3	7	19	M		
93	1	1	0	0	3		36	M		
94	1	1	0	0	3	6	71	M		
95	1	1	0	0	3	7	36	M		
96	1	1	0	0	3	3	55	M		
97	1	1	0	0	3	8	44	M		
98	1	1	0	0	3	7	51	M		
99	1	1	0	0	3		26	M		
100	2	1	0	0	3	8	49	M		
101	1	1	0	0	3	4	35	M		
102	1	1	0	0	3		51	M		
103	1	2	0	0	3		49	M		
104	2	1	0	0	3	16	56	M		
105	1	1	0	0	3	15	62	M	-	+
106	1	1	0	0	3	9	79	M		
107	1	1	0	0	3	8	54	M		
108	2	1	0	0	3		64	M		
109	1	1	0	0	3	5	72	M		
110	1	1	0	0	3	7	52	M		
111	1	1	0	0	3	11	61	M		
112	1	1	0	0	3	6	29	M		
113	1	1	0	0	3	2	55	M		
114	2	1	0	0	3		40	M		
115	1	1	0	0	3		21	M		
116	1	1	0	0	3		17	M		
117	1	1	0	0	3		25	M		
118	1	1	0	0	3		47	M		
119	1	1	0	0	3	11	47	M		
120	1	1	0	0	3	8	38	M		
121	2	1	0	0	3	10	38	M		
122	2	1	0	0	3	12	49	M		
123	2	1	0	0	3	9	46	M		
124	2	1	0	0	3	2	49	M		
125	1	1	0	0	3	2	41	M		
126	1	1	0	0	3	10	60	M		
127	1	1	0	0	3	15	48	M		
128	1	1	0	0	3	8	48	M		
129	1	1	0	0	3	10	50	M		
130	1	1	0	0	3	6	50	M		
131	1	2	0	0	3	7	50	M		
132	2	2	0	0	3	9	41	M		
133	2	2	0	0	3	13	30	M		
134	2	2	0	0	3	5	28	M		
135	2	2	0	0	3	2	28	M		
136	2	2	0	0	3	15	64	M		
137	2	2	0	0	3	7	55	M		
138	2	2	0	0	3	6	55	M		
139	2	2	0	0	3	5	20	M		
140	2	2	0	0	3	8	59	M		
141	1	1	0	0	3	7	7	M		
142	1	1	0	0	3	9	7	M		
143	1	1	0	0	3	14	0	M		
144	1	1	0	0	3	19	11	M		
145	4	1	0	0	3	19	51	M		
146	1	1	0	0	3	9	12	M		
147	1	1	0	0	3	4	6	M		
148	1	1	0	0	3	7	20	M		
149	1	1	0	0	3	8	50	M		
150	1	1	0	0	3	10	69	M		
151	1	1	0	0	3	10	35	M		
152	1	1	0	0	3	2	35	M		
153	2	1	0	0	3	3	36	M		
154	2	1	0	0	3	9	24	M		
155	2	1	0	0	3	9	46	M		
156	1	1	0	0	3	11	57	M		
157	1	1	0	0	3	11	40	M		
158	1	1	0	0	3	9	38	M		
159	1	1	0	0	3	12	43	M		
160	1	1	0	0	3	5	38	M		
161	1	1	0	0	3	13	36	M		
162	1	1	0	0	3	5	59	M		
163	1	1	0	0	3	11	8	M		
164	1	1	0	0	3	8	14	M		
165	1	1	0	0	3	4	37	M		
166	1	1	0	0	3	7	29	M		
167	1	1	0	0	3	8	36	M		
168	1	1	0	0	3	11	32	M		
169	1	1	0	0	3	7	38	M		
170	1	1	0	0	3	15	48	M		
171	1	1	0	0	3	16	32	M		
172	1	1	0	0	3	11	21	M		
173	1	1	0	0	3		21	M		
174	1	1	0	0	3	7	11	M		
175	1	1	0	0	3	8	40	M		
176	1	1	0	0	3	11	7	M		
177	1	1	0	0	3	15	49	M		
178	1	1	0	0	3	16	32	M		
179	1	1	0	0	3	11	21	M		
180	1	1	0	0	3		21	M		
181	1	1	0	0	3		21	M		
182	1	1	0	0	3		21	M		
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185	1	1	0	0	3		21	M		
186	1	1	0	0	3		21	M		
187	1	1	0	0	3		21	M		
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189	1	1	0	0	3		21	M		
190	1	1	0	0	3		21	M		
191	1	1	0	0	3		21	M		
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204	1	1	0	0	3		21	M		
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216	1	1	0	0	3		21	M		
217	1	1	0	0	3		21	M		
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220	1	1	0	0	3		21	M		
221	1	1	0	0	3		21	M		
222	1	1	0	0	3		21	M		
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227	1	1	0	0	3		21	M		
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229	1	1	0	0	3		21	M		
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231	1	1	0	0	3		21	M		
232	1	1	0	0	3		21	M		
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243	1	1	0	0	3		21	M		
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245	1	1	0	0	3		21	M		
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251	1	1	0	0	3		21	M		
252	1	1	0	0	3		21	M		
253	1	1	0	0	3		21	M		
254	1	1	0	0	3		21	M		
255	1	1	0	0	3		21	M		
256	1	1	0	0	3		21	M		
257	1	1	0	0	3		21	M		
258	1	1	0	0	3		21	M		
259	1	1	0	0	3		21	M		
260	1	1	0	0	3		21	M		
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262	1	1	0	0	3		21	M		
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268	1	1	0	0	3		21	M		
269	1	1	0	0	3		21	M		
270	1	1	0	0	3		21	M		
271	1	1	0	0	3		21	M		
272	1	1	0	0	3		21	M		
273	1	1	0	0	3		21	M		
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276	1	1	0	0	3		21	M		
277	1	1	0	0	3		21	M		
278	1	1	0	0	3		21	M		
279	1	1	0	0	3		21	M		
280	1	1	0	0	3		21	M		
281	1	1	0	0	3		21	M		
282	1	1	0	0	3		21	M		
283	1	1	0	0	3		21	M		
284	1	1	0	0	3		21	M		
285	1	1	0	0	3		21	M		
286	1	1	0	0	3		21	M		
287	1	1	0	0	3		21	M		
288	1	1	0	0	3		21	M		
289	1	1	0	0	3		21	M		
290	1	1	0	0	3		21	M		
291	1	1	0	0	3		21	M		
292	1	1	0	0	3		21	M		
293	1	1	0	0	3		21	M		
294	1	1	0	0	3		21	M		
295	1	1	0	0	3		21	M		
296	1	1	0	0	3		21	M		
297	1	1	0	0	3		21	M		
298	1	1	0	0	3		21	M		
299	1	1	0	0	3		21	M		
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302	1	1	0	0	3		21	M		
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304	1	1	0	0	3		21	M		
305	1	1	0	0	3		21	M		
306	1	1	0	0	3		21	M		
307	1	1	0	0	3		21	M		
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325	1	1	0	0	3		21	M		
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327	1	1	0	0	3		21	M		
328	1	1	0	0	3		21	M		
329	1	1	0	0	3		21	M		
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332	1	1	0	0	3		21	M		
333	1	1	0	0	3		21	M		
334	1	1	0	0	3		21	M		
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336	1	1	0	0	3		21	M		
337	1	1	0	0	3		21	M		
338	1	1	0	0	3		21	M		
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352	1	1	0	0	3		21	M		
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354	1	1	0	0	3		21	M		
355	1	1	0	0	3		21	M		
356	1	1	0	0	3		21	M		
357	1	1	0	0	3		21	M		
358	1	1	0	0	3		21	M		
359	1	1	0	0	3		21	M		
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368	1	1	0	0	3		21	M		
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376	1	1	0	0	3		21	M		
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382	1	1	0	0	3		21	M		
383	1	1	0	0	3		21	M		
384	1	1	0	0	3		21	M		
385	1	1	0	0	3		21	M		
386	1	1	0	0	3		21	M		
387	1	1	0	0	3		21	M		
388	1	1	0	0	3		21	M		
389	1	1	0	0	3		21	M		
390	1	1	0	0	3		21	M		
391	1	1	0	0	3		21	M		
392	1	1	0	0	3		21	M		
393	1	1	0	0	3		21	M		
394	1	1	0	0	3		21	M		
395	1	1	0	0	3		21	M		
396	1	1	0	0	3		21	M		
397	1	1	0	0	3		21	M		
398	1	1	0	0	3		21	M		
399	1	1	0	0	3		21	M		
400	1	1	0	0	3		21	M		

Mean Age: 42.3 years. Age range 19-79 years.

TABLE X.

Results of Serum Protein Investigations in Thyrotoxic Patients with Exophthalmic Ophthalmoplegia.

TABLE XI.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rates in Thyrotoxic Patients with Exophthalmic Ophthalmoplegia.

Table X.

Results of Serum Protein Investigations in Thyrotoxic Patients with Exophthalmic Ophthalmoplegia.

Case No.	Age	Sex	Serum Proteins (g.100ml)					
			Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin
1	33	F	3.5	1.3	0.09	0.30	0.42	0.49
2	58	F	4.0	2.5	0.29	0.64	0.56	1.01
3	42	M	4.6	2.6	0.22	0.46	0.64	1.30
4	53	M	4.0	2.5	0.28	0.65	0.55	1.02
5	47	F	3.7	1.8	0.21	0.46	0.40	0.73
6	47	M	4.0	1.5				
7	55	M	4.8	1.5	0.17	0.30	0.39	0.65
8	55	F	4.0	2.0				
10	39	F	3.9	2.0	0.25	0.27	0.60	0.88
11	45	M	4.4	1.8	0.21	0.46	0.40	0.73
12	73	F	3.6	1.9	0.23	0.26	0.57	0.84
13	37	M	4.0	1.8	0.14	0.43	0.48	0.74
14	65	M	3.7	1.9	0.15	0.45	0.53	0.76
15	25	F	4.9	1.5	0.19	0.21	0.44	0.67
16	56	M	3.9	2.1	0.13	0.79	0.47	0.72
17	69	M	4.0	2.0	0.24	0.28	0.60	0.88

Table XI.

Results of Serum Flocculation Tests and Erythrocyte Sedimentation Rates in Thyrotoxic Patients with Exophthalmic Ophthalmoplegia.

Case No.	Thymol Turbidity (Units).	Thymol Flocculation.	Cephalin Cholesterol.	Colloidal Gold (Units).	Zinc Sulphate Turbidity (Units).
1	2	0	0	4	23
2	2	0			
3	1	0		3	9
4	1	0		2	12
5	1	0		0	12
6	1	0		4	11
7	2	0		0	7
8	1	0	0	2	
9	1	0		0	13
10	2	1	1	1	
11	1	0		4	19
12	1	0		1	13
13				1	
14	1	0			10
15	1	0		0	11
16	1	0		2	10

Mean Range: 49.9 years. Age Range: 25 - 72 years.

TABLE XII.

Results of Serum Protein Determinations in Thyrotoxic Patients Euthyroid after treatment.

TABLE XIII.

Results of Serum Flocculation Tests in Thyrotoxic Patients Euthyroid after treatment.

Table XII.

Results of Serum Protein Determinations in Thyrotoxic Patients Euthyroid after Treatment

Case No.	Age	Sex	Serum Proteins (g./100ml.) Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin	Treatment and Remarks.
1	50	M	5.0	1.4	0.13	0.25	0.37	0.56	Methylthiouracil
2	70	F	5.0	1.5	0.11	0.26	0.46	0.67	I^{131} Therapy
3	41	F	4.8	2.0	0.16	0.42	0.64	0.80	Sub-total thyroidectomy I^{131} therapy
4	46	M	5.0	2.2	0.28	0.37	0.44	1.11	I^{131} Therapy
5	45	F	4.9	2.0	0.21	0.52	0.57	0.70	I^{131} Therapy
6	66	F	4.9	1.9	0.23	0.49	0.52	0.67	I^{131} Therapy
7	34	F	4.8	2.2	2.27	0.37	0.59	0.97	Sub-total Thyroidectomy
8	65	M	4.9	1.9	0.21	0.31	0.46	0.92	I^{131} Therapy
9	26	F	4.9	1.5	0.19	0.38	0.42	0.52	Pot. Iodide
10	37	M	4.8	2.0	0.14	0.30	0.52	1.03	Methylthiouracil
11	72	F	4.8	1.9	0.08	0.32	0.55	0.95	I^{131} Therapy
12	31	F	4.8	2.0	0.24	0.46	0.48	0.82	Carbimazole
13	20	F	3.7	1.7	0.22	0.31	0.46	0.71	Pot. Perchlorate
14	53	F	4.1	1.5	0.20	0.36	0.42	0.53	I^{131} Therapy
15	40	F	3.9	1.6	0.18	0.32	0.48	0.63	Pot. Perchlorate
16	47	F	4.2	1.9	0.17	0.43	0.59	0.71	I^{131} Therapy

Mean age 46.4 years Age Range 20 - 70 years.

Table XIII.

Results of Serum Flocculation Tests in Thyrotoxic Patients Euthyroid after Treatment.

Case No.	Thymol Turbidity (Units)	Thymol Flocculation	Cephalin Cholesterol	Colloidal Gold (Units)	Zinc Sulphate Turbidity (Units)
1	5	0	1	5	
2	2	0		2	8
3	2	0	0	1	
4	1	0	0	1	
5	1	0		1	5
6	2	0		0	11
7	1	0	0	0	
8	1	0		3	9
10	3	2	3	4	
11	1	0		4	6
12	2	0		2	11
13	3	0	2	3	
14	1	0	0	1	
15	1	0		2	13
16	1	0	0	2	
	Mean Age 46.4 years			Age Range 20 - 70 years	

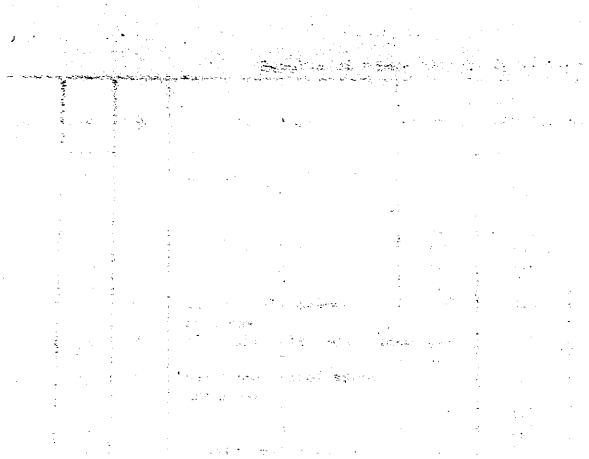


TABLE XIV.

Results of Serum Protein Investigations in Thyroid Neoplasm.

TABLE XV.

Results of Serum Flocculation Tests in Erythrocyte Sedimentation Rate in Thyroid Neoplasm.

Table XIV.

Results of Serum Protein Investigations in Thyroid Neoplasm

Case No.	Age	Sex	Histology	SERUM PROTEINS (g./100ml) Albumin	Globulin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin
1	20	F	Papillary adeno-carcinoma	3.9	2.0	0.18	0.60	0.48	0.73
2	47	F	"	4.3	1.8	0.18	0.40	0.40	0.83
3	73	F	"	3.4	2.1	0.24	0.50	0.45	0.91
4	31	M	"	5.0	1.8	0.19	0.52	0.45	0.64
5	32	M	"	4.2	1.7	0.17	0.37	0.39	0.76
6	60	M	"	4.1	1.8	0.15	0.52	0.41	0.72
7	75	M	"	5.1	1.8	0.16	0.55	0.37	0.73
8	19	M	Hurthle cell adeno-carcinoma	5.0	2.5	0.18	0.80	0.63	0.89
9	51	F	Follicular adeno-carcinoma	4.1	1.8	0.21	0.43	0.48	0.69
10	54	F	"	5.0	1.8	0.30	0.41	0.49	0.73
13	69	F	Undifferentiated adeno-carcinoma	3.8	1.9	0.20	0.47	0.43	0.80
14	69	F	"	5.4	1.9	0.18	0.49	0.44	0.79
15	72	F	"	4.9	1.9	0.34	0.41	0.54	0.61
16	72	M	Spindle cell carcinoma	5.0	2.1	0.19	0.48	0.44	0.98
17	57	F	Lymphosarcoma	3.7	2.0	0.21	0.50	0.45	0.85

Mean Age 52.3 years Age Range 19 - 75 years. For further Clinical details-see Appendices of Chapter II Section 5.

Table XV.

Results of Serum Flocculation Tests in Erythrocyte Sedimentation Rate in Thyroid Neoplasm.

Case No.	Thymol Turbidity (Units)	Thymol Flocculation	Cephalin Cholesterol	Colloidal Gold (Units)	Zinc Sulphate Turbidity (Units)	E.S.R. (mm/hr)
1	2	0	0			
2	1	0		2		36
3	1	0		2	13	41
4	1	0		1		25
5	1	0		1		10
6	1	0		1	8	7
7	1	0			8	31
8	1	0		0		5
9	2	0	0	4		35
10	1	0		2	6	5
11	1	0			5	10
13	3	1		5	16	36
14	1	0			7	
15	1	0		0	9	47
16	2	0		3	9	37
17	1	0		4	20	68

Mean Age 54.3 years Age Range 19 - 75 years

SECTION 4. Iodine Metabolism in Auto-immune Thyroiditis.

TABLE I. Results of Iodine Studies in Auto-immune Thyroiditis.

Table I.

Results of Iodine Studies in Auto-immune Thyroiditis

Case No.	Radioiodine uptake (% dose) 2½hr I^{132}	4hr I^{131}	48hr I^{131}	PBI^{131} at 48hrs (% dose/litre)	BII^{131} at 48 hrs (% PBI^{131})	PBI (µg.%)	Pot. Perchlorate Discharge	Thyroxine suppression	TSH Tests I^{132} uptake (%)	TSH Tests PBI^{132} discharge (% dose/Litre)
1		28.7	27.9	0.39	23	3.2				
2		39.9	44.3	0.26		0.6	+	Normal		
3		31.4	27.2	0.64		2.6	-	"		
4		14.0	18.0	0.14		0.5	+	"		
5		41.2	29.0	0.40		0.7	+	"		
6		27.8	37.5	0.22		3.2	-	"		
7	28.5	37.0	54.2	0.05	12	2.5	-	"		0.08
8		40.9	45.3	0.36		1.6	+	"		
9		40.0	34.8	0.28		2.1	-	"		
10		20.0	23.0	0.36		1.1	-	"		
11		46.6	54.5	0.49		3.6	-	"		
12		50.6	55.6	0.42		5.3	+	"		
13		77.1	66.1	2.74		3.1	-	"		
14		47.0	56.9	0.86		4.8	-	"		
15		24.3	17.3	0.18		0.7		"		0.01
16	29.1	52.0	49.8	0.32		2.8		"		
17		22.1	14.9	0.13		0.8		"		
18		53.7	61.2	1.38		3.3	-	"		
19		41.5	42.6	0.10		3.7		"		
20		16.5	16.6	0.05		2.5	-			
21	30.8	51.3	76.4	0.46		4.6	+			0.12
22		35.6	34.3	0.39		3.1	-	"		
23		28.0	17.0	0.23		2.1		"		
24		19.3	13.6	0.09				"		
25	46.6	44.9	54.2	0.24	95	4.1	+	"	+14	0.16
26	33.1	48.3	53.1	0.34		2.3	-	"		
27		40.0	31.0	0.47		4.1		"		
28		39.5	40.4	0.34		1.8	-	"		
29	14.7	17.2	19.2	0.61		2.9				0.12
30	36.5	34.8	39.6	0.28		1.2	-	"	+10	
31		45.6	59.7	0.41		3.3	-	"		
32		32.0	26.0	0.05		1.3	+	"		
33	30.7	39.0	48.1	0.21		2.1	-	"	-50	0.10
34	17.8	37.0	39.2	0.95	18.9	2.0	-	"		0.03
35	18.2	16.9	10.2	0.31		1.1	-	"		0
36	16.7	20.1	10.4	0.19		1.3	+	"	+18	
37	24.4	36.6	39.6	0.22	44.7	4.9				+0.23
38	19.7	46.0	54.5	0.29		2.4				
39	10.3	18.7	36.6	0.40	0	1.8				+0.19
40		61.4	79.8	0.05		2.1	-	Normal		
41		43.0	42.0	1.00		4.3	+	"		
42		60.3	74.6	0.24		3.0	+	"		
43		46.2	43.1	0.40		3.2	+	"		
44		7.5	10.3	0.35	5	1.5			+4	
45		13.9	13.7	0.06		2.2			-0.6	
46		30.0	47.5	0.40	42				-4.9	
47		28.6	26.4	1.32						
48	31.5	47.1	56.3	1.08	33	3.1			+2.3	
49		45.8	60.0	0.60						

TABLE II. Results of Stable Iodine Studies in Auto-immune Thyroiditis.

Table II.

Results of Stable Iodine Studies in Auto-immune Thyroiditis.

Case No.	Thyroid Clearance (ml./ min.)	Plasma Inorganic Iodine (ug./ 100 ml.)	Absolute Iodine Uptake (ug./ hr.)	Intrathyroidal Exchangeable Iodine (mg.)	Protein-bound Iodine (ug./100 ml.)	Renal Iodide Clearance (ml./min.)
7	21.2	[illegible]	4.1	0	2.5	28.0
16	15.9	0.24	2.2		2.8	28.9
21	16.7	0.58	5.9		4.6	22.1
25	52.9	0.06	1.8	1.3	4.1	24.1
26	46.5	0.02	0.7	1.2	2.3	38.2
29	2.9	0.32	0.6	0.1	2.9	26.9
30	34.8	0.10	2.1	0.05	1.2	43.5
33	23.0	0.08	1.12	0.84	2.1	27.6
34	19.3	0.09	1.0	1.0	2.0	30.3
35	3.6	0.33	0.7		1.1	20.3
36	5.7	0.24	0.82		1.3	16.5
37	19.1	0.35	4.0	3.8	4.9	25.8
38	6.7	0.09	0.4	1.1	2.4	40.4
39	17.7			0.4	1.8	27.5
48	32.8	0.11	2.1	0.4	3.1	

SECTION 5. The Differential Diagnosis of Auto-immune Thyroiditis.

TABLE I.

Clinical Findings in 79 Patients.

with Simple Goitre.

Table I. Clinical Findings in 79 Patients with Simple Goitre

Case No.	Age	Sex	Thyroid Auto-antibody Tests Preo.	CF	Duration (Yrs.)	Firm	Size (g)	Diffuse ±	Other
1	44	F	-	-	20	-	50	+	
2	28	F	-	-	5	+	75	+	
3	31	F	-	-	2	-	75	+	
4	44	F	-	-	15	-	100	+	
5	21	F	-	-	16	-	100	+	
6	35	F	-	-	3	+	75	-	"Discomfort" and choking
7	56	F	-	+	1	-	75	+	Dysphonia. Tracheal compression Fixation.
8	20	F	-	-	16	-	300	+	
9	53	F	-	-	1	-	50	+	
10	37	F	-	-	5	+	100	-	" Tightness"
11	47	F	-	-	3	-	75	+	"Tightness"
12	32	F	-	-	23	-	75	+	
13	37	F	-	-	30	+	300	-	"Choking on recumbency.
14	42	F	-	-	0.5	-	50	+	
15	25	F	-	-	4	-	75	+	
16	25	F	-	-	7	-	75	+	
17	43	F	-	-	2	-	100	-	"Choking"
18	16	F	-	-	5	-	50	+	
19	19	F	-	-	1	-	50	+	
20	33	F	-	-	20	-	50	+	
21	31	F	-	-	3	+	75	-	Bruit present
22	21	F	-	-	10	+	75	-	"Choking"
23	39	F	-	-	20	-	75	-	
24	25	F	-	-	2 weeks	-	75	+	
25	32	F	-	-	1	+	300	-	Bruit. Discomfort on swallowing.
26	47	F	-	-	10	-	75	+	
27	32	F	-	-	3	+	100	-	
28	33	F	-	-	Unaware	-	75	+	
29	67	F	-	-	0.75	+	50	+	
30	37	F	-	-	0.75	-	50	+	
31	46	F	-	-	1.5	-	50	-	
32	50	F	-	-	Unaware	+	50	+	
33	39	F	-	-	5	+	75	+	
34	42	F	-	-	0.5	-	75	+	
35	26	F	-	-	3	-	50	+	
36	33	F	-	-	5	+	50	-	Painful
37	47	F	-	-	8	-	75	+	
38	21	F	-	-	6	-	100	+	
39	36	F	-	-	4	-	75	+	Choking
40	55	F	-	-	13	+	125	-	
41	19	F	-	-	4	-	175	+	Choking
42	54	F	-	-	10	-	200	-	
43	36	F	-	+	20	+	300	+	Choking, hoarseness.
44	48	F	-	-	7 months	+	100	+	
45	32	F	-	-	Unaware	+	75	+	
46	37	F	-	-	37	+	75	-	Painful
47	40	F	-	-	11	+	100	+	
48	27	F	-	-	6	-	75	+	
49	27	F	-	-	16	-	75	+	Occasionally painful
50	45	F	-	-	1	-	100	-	
51	43	F	-	-	0.5	+	50	-	
52	16	F	-	-	11 months	+	75	+	
53	20	F	-	-	5	-	125	-	Bruit present. Choking
54	34	F	-	-	15	-	150	-	
55	30	F	-	-	Unaware	-	150	+	
56	21	F	-	-	4	-	125	+	
57	40	F	-	-	Unaware	-	50	+	
58	25	F	-	-	3	+	50	+	
59	30	F	-	-	4	+	75	+	
60	47	F	-	-	2	+	100	+	
61	34	F	-	-	5 weeks	-	200	+	
62	47	F	-	-	1 month	-	75	+	
63	33	F	-	-	3	-	150	-	
64	32	F	-	-	2	-	75	+	
65	60	F	-	-	6	+	100	+	
66	44	F	-	-	3 weeks	+	50	-	
67	50	F	-	-	2.5	-	150	-	Choking
68	46	F	-	-	1	-	150	+	
69	42	F	-	-	0.25	-	75	+	Painful
70	38	F	-	-	0.5	-	75	+	
71	21	F	-	-	20	+	175	-	Choking
72	47	F	-	-	10	-	125	+	
73	33	F	-	-	6	-	250	+	
74	26	F	-	-	0.5	-	100	+	
75	36	F	-	-	2	-	125	+	
76	54	F	-	-	1	-	75	+	
77	19	F	-	-	20	-	75	-	
78	55	F	-	-	Unaware	-	75	-	
79	36	F	-	-	14	-	75	+	

(± Diffuse, + Nodular, -)

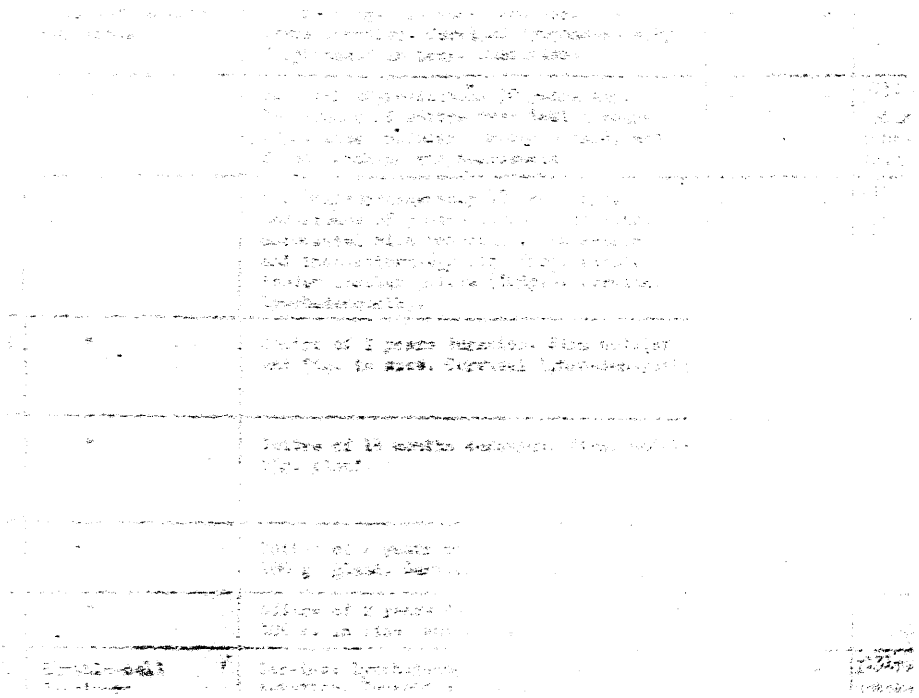


TABLE II.

Clinical data on 18 Patients with Thyroid Neoplasm.

Table II. Clinical data on 18 Patients with Thyroid Neoplasm

Case No.	Age	Sex	Histology	Clinical Features	Thyroid-auto antibody Tests Prec.	CF	Comments
1	19	F	Papillary adeno-carcinoma	Goitre (75g., diffuse, and firm) of 3 years duration. Cervical lymphadenopathy "Tightness" in neck. Huskiness.	-	-	
2	47	F	"	Subtotal thyroidectomy 30 years ago. Recurrence of goitre over last 5 years. 125g. size, nodular, stony - hard, and fixed. Choking and hoarseness.	-	-	I^{131} Tests; 4hr uptake 46.5% dose, 48hr. PBI^{131} 0.2% dose/l.
3	73	F	"	Subtotalthyroidectomy 11 years ago. Recurrence of goitre during past year, associated with "choking", hoarseness, and inspiratory Stridor. Hard, fixed, tender nodular goitre (105g.). Cervical lymphadenopathy.	+	+	I^{131}Tests: 4 hr uptake 14.3% dose, 48hr PBI^{131} 0.09% dose/l. Focal Hashimoto's thyroditis present in biopsy
4	31	M	"	Goitre of 2 years duration. Firm nodular, and 75g. in size. Cervical lymphadenopathy.	-	-	I^{131}Tests; 4 hr uptake 24.1% dose, 48 hr PBI^{131} 0.05% dose/l.
5	32	M	"	Goitre of 18 months duration. Firm, nodular 75g. gland.	-	-	I^{131}Tests: 4 hr uptake 28% dose, 48hr PBI^{131} 0.05% dose/l.
6	60	M	"	Goitre of 1 years duration. Firm, nodular 100 g. gland. Cervical lymphadenopathy.	-	-	I^{131} Tests; 4 hr uptake 23.1% dose.
7	75	M	"	Goitre of 2 years duration. Firm, nodular 100 g. in size, and fixed	-	-	
8	19	M	Hürthle-cell Carcinoma	Cervical lymphadenopathy of 2 years duration. Thyroid not palpable	-	-	I^{131}Tests: 4 hr uptake 39.0% dose, 48 hr PBI^{131} 0.05% dose/l
9	51	F	Follicular-cell Carcinoma	Goitre for 30 years. Removed 8 years previously. Presented with Metastases in ilium, ribs, and skull.	-	-	I^{131}Tests: 24 hr uptake 24.2% dose 48 hr PBI^{131} 0.05% dose/l
10	54	G	"	Goitre 1 year. Hard, Tender 150 g. in size.	-	-	I^{131}Tests: 4hr 88% dose, 48hr PBI^{131} 0.05% dose/l.
11	69	F	"	Goitre removed 7 years ago. Metastases in spine	-	-	
12	55	F	"	Firm, nodular goitre, 150 g. in size. 6 months duration. Hoarseness.	-	-	I^{131}Tests: 4hr uptake 19.6% dose, 48hr PBI^{131} 0.29% dose/l.
13	69	F	Undifferentiated adeno-carcinoma	Goitre of 3 months duration 75g, nodular hard, fixed. Cervical lymphadenopathy laryngeal palsy. Dysphonia. Stridor.	-	+	I^{131}Tests: 4 hr uptake 26.8% dose. Focal Hashimoto's thyroditis present in biopsy.
14	69	F	"	Goitre of 6 month's duration. Removed 3 years ago. Presented with Metastases in Humerus.	-	-	
15	72	F	"	Goitre of 6 month's duration. Hard, nodular, fixed. 75g. in size. Tender. Hoarseness and choking.	-	-	I^{131}Tests: 4 hr uptake 18.1% dose, 48 hr 0.47 % dose/l
16	72	M	Spindle-cell Carcinoma	Goitre of 2 years duration. Painful, hard, fixed, and nodular. 75g. in size. Cervical lymphadenopathy. Hoarseness, Paralysis of vocal cord.	-	-	I^{131}Tests: 4 hr uptake 38.0% dose, 48hr 0.05% dose/l
17	57	F	Lymphosarcoma	Goitre of 2 years duration, with recent increase in size. Tender, painful, hard nodular, and fixed goitre. 100 g. in size Dyspnoea. Dysphagia.	-	-	I^{131}Tests: 4 hr uptake 18.6% dose, 48hr PBI^{131} 0.14% dose /l.
18	78	F	Struma Reticulosa	Goitre of 5 months duration. Firm, nodular, 150g. Hoarseness.	-	-	I^{131}Tests 4 hr uptake 19.6% dose, 48hr PBI^{131} 0.29% dose/l.

SECTION 6. The treatment of Auto-immune Thyroiditis.

TABLE I.

Effect of treatment with Thyroxine Sodium in 19 Patients with Auto-immune Thyroiditis.

Table I. Effect of Treatment with Thyroxine Sodium in 19 Patients with Auto-immune Thyroditis.

Case No.	Mean Neck Diameter (inches)	Thyroid Auto-antibody tests Prec.	CF.	Serum Protein (g./100ml.) Alb.	Glob.	% Glob.	Thymol Turbidity (units)	Thymol Flocculation (units)	E.S.R. (mm./hr)	Duration of Treatment (months)
3	14.5	+	+	4.7	2.3	1.34	4	1	16	6
	13.5	+	+	4.8	1.9					
6	14.0	-	++	3.9	2.1	0.79	6	2	37	
	13.0	-	++				3	0	23	12
7	13.5	+	++	4.3	2.2	1.08	4	1	4	
	12.5	+	++	4.9	3.6	1.12	5	2	6	13
10	14.5	+	++	4.6	2.3	0.98	14	3	40	
	13.5	+	++	5.1	2.1		5	2	6	4.5
12	13.75	+	++	4.7	2.1	0.96	3	1	15	
	12.75	+	++	4.5	2.2	0.74	2	0	10	25
14	14.0	+	++	3.9	3.0	0.58	10	3	14	
	13.0	-	++	4.1	2.1	0.42	4	2	7	28
16	15.5	-	++	4.2	2.2	1.60	4	4	30	
	14.0	-	++	4.4	2.2	0.82	2	2	11	15
	13.5	-	++						10	36
18	14.0	-	++	4.0	2.4	0.83	4	0	22	
	13.0	-	++	4.3	2.4	0.75	2	0		12
19	12.75	+	++	4.3	3.5	1.66	3	0	6	
	12.0	-	++	4.6	1.9	0.79	2	0	3	19
21	15.5	+	++	3.7	2.3	1.18	4	0	20	
	14.5	+	++	4.3	2.2	1.02	1	0	9	3
22	15.25	+	++	3.5	3.5	2.53	12	3	57	
	14.0	+	++	5.2	2.7	1.19	4	0	21	16
23	13.75	+	++	4.7	1.8		1	1	8	
	12.5	+	++	4.8	1.8		0	0	9	14
25	15.74	+	++	4.3	2.5	1.42	2	0	8	
	15.0	+	++	5.1	1.7	0.90	3	0		2
26	15.0	+	++	4.2	2.2	1.09	14	4	23	
	13.5	+	++	5.1	2.0	0.95	6	2		18
30	14.75	+	++	3.8	2.3	0.90	5	4	19	
	14.0	+	++						25	4
	14.0	+	++							5
	13.75	+	++							6
	13.5	+	++	4.5	1.9	0.75			24	8
33	15.25	+	++	4.2	2.2	1.15	5	3	38	
	14.25	-	++						14	36
34	18.0	+	++	5.0	4.6	2.68	11	4	46	
	17.75						10	3	60	0.25
	17.75	+	++				10	4	76	0.5
	17.75						10	4	59	0.75
	16.75	+	++				10	4		2
	17.0	+	++				10	4	31	3
	17.0	+	++						39	4
	16.5	+	++	3.9	4.1	2.16	9	3	34	6
37	14.5	+	++	4.1	3.0	1.54	6	2	25	
	14.0						5	2	20	1
	13.75	+	++				4	2	44	2
	13.5	+	++	3.9	2.6	1.31	8	4		3
	13.25						6	3	34	4
	13.5						5	3	22	6
	15.5	+	++	4.2	2.5	1.32	4	2	24	10
38	16.5	+	++	3.9	3.0	1.65	14	3	31	
	15.75	+	++	3.9	3.0		12	4	30	0.5
	15.5	+	++				10	4		2
	15	+	++							5
	15.5	+	++							6
	15	+	++	4.2	2.5	1.02	10	4	30	9

TABLE II. Effect of Surgery in 6 Patients with Auto-immune Thyroiditis.

TABLE II.

Effect of Surgery in 6 Patients with Auto-immune Thyroditis.

Case No.	Thyroid Auto-Antibody Tests Prec.	CF	Serum Proteins (g./100ml) Albumin	Globulin	Gamma-Globulin	Thymol Turbidity (Units)	Thymol Flocculation (units)	E.S.R. (mm./hr)	Duration of Treatment (months)
5	+	++	3.8	3.0	1.66	12	3	7	
	+	++	4.0	3.1	1.42	10	2	10	0.5
	-	++	4.5	2.7	1.33	7	2	12	1.5
	-	++	4.3	2.4	1.08	5	1	4	2
11	-	++	4.5	2.0	0.90	5	0	5	
	-	++	4.6	1.9	0.95	4	0	18	1.5
20	-	-	3.5	2.9	2.06	7	3	12	
	-	-	3.8	2.5	1.99	4	2	8	3
	-	-	4.2	2.1	1.16	2	1	7	12
24	+	++	3.8	2.0	0.74	1	0	46	
	+	++				2	0		3
	-	++				2	0		6
	-	++				1	0		12
	-	++	4.1	2.1	0.82	0	0	16	18
28	+	++	4.3	2.2	1.10	5	0	10	
	-	++	4.6	1.6	0.59	2	0	7	18
50	-	+	3.8	1.8	0.66	1	0	18	
	-	+	3.9	1.7	0.57	1	0	16	1.5
	-	+				1	0	8	3
	-	-	4.2	1.9	0.74	0	0	7	4

APPENDICES - Chapter III.

SECTION 1. The Relationship of Auto-immune Thyroiditis to Primary Hypothyroidism.

TABLE I

Clinical Findings in Primary Hypothyroidism.

TABLE I. Clinical Findings in Primary Hypothyroidism

Case No.	Age	Sex	Hypothyroid Diagnostic Index	History of Goitre and/or Thyrotoxicosis	Family History of Thyroid Disease	Serum Cholesterol (mg./100ml)	BMR (%)	E.C.G.	Thyroid Auto-Antibody Tests Preo	CFT	Comments
1	52	M	+22	-	Sister with Goitre	295	-20	+	+	+	
2	61	F	+27	-	Daughter with thyrotoxicosis	245	+3	-	+	++	
3	60	F	+14	-	-	370	+6	+	+	++	Described in Text
4	56	F	+13	-	Sister with Goitre	200	+17	+	+	++	Rheumatoid Arthritis
5	50	F	+19	-	-	685	-22	+	+	++	
6	47	F	+2	-	-	220		-	+	-	Euthyroid
7	67	F	+4	-	Maternal Aunt with Goitre	308		+	+	-	
8	64	F	+20	-	-	375	-6	+	+	++	Rheumatoid Arthritis
9	64	F	+27	15 yrs previously ? Thyrotoxicosis	Brother's daughter with hypothyroidism	390	-25	+	+	-	
10	76	F	+32	-	-	400		+	+	++	
11	56	F	+30	Goitre 6 yrs previously	-	390		+	+	++	
12	57	F	+23	Goitre 20 yrs previously.	-	365	-1	+	-	++	
13	36	F	+27	-	-	225		+	-	++	
14	63	F	+34	-	-	440		+	-	++	
15	55	M	+31	-	-	310	-20	+	-	++	
16	49	M	+2	-	-	225		-	-	++	Euthyroid
17	60	F	+28	? Thyrotoxicosis 16 yrs previously.	-	295		+	-	++	
18	56	F		-	-	232	0	+	-	++	
19	70	F		-	-	425		+	-	++	
20	38	F	+3	-	-	485		+	-	++	
21	39	F	+29	-	-	435	-26	+	-	++	
22	59	F	-6	-	-			-	-	++	Euthyroid
23	64	F	-1	-	-	160		-	-	++	Euthyroid
24	38	F	+34	-	-		-2	+	-	++	
25	56	F	+31	Goitre ? Thyrotoxic 11 yrs previously.	-	425	0	+	-	++	
26	57	M		-	-	355		+	-	+	
27	56	F	+2			201	+3	-	-	+	
28	56	F	+24	-	-	470	-21	+	-	+	
29	53	F	+40	-	Brother with Goitre	512	-33	+	-	+	
30	56	M	+11	-	-			+	-	+	
31	65	F	+23	-	-	300	-6	+	-	+	
32	67	F	+35	-	-	225	-34	+	-	+	
33	53	F	+33	Goitre 25 yrs previously.	-	330	-18		-	+	
34	69	M	+39	-	-	390		+	-	+	
35	49	F	+1	-	-	140		-	-	+	Euthyroid
36	38	F	+14	Goitre 2 yrs previously	-	150	-26	+	-	+	
37	56	M	+18	-	-	290		+	-	-	
38	36	M	+11	-	-	292		+	-	-	
39	50	F	+13	Goitre 30 yrs previously	-	285	+18	+	-	-	
40	66	F	+23	-	-	303	-27	+	-	-	
41	56	F	+17	-	-	250		+	-	-	
42	42	F	+23	-	-	330	-20	+	-	-	
43	43	F	+3	-	-	170		-	-	-	Euthyroid
44	64	F	+35	-	-	325	-7	+	-	-	
45	73	F	+21	-	-	125	+15	-	-	-	
46	55	F	+32	? Thyrotoxic 20 yrs previously	Brothers daughter with Goitre	355	-10	+	-	-	
47	62	F	+24	-	-	385		+	-	-	
48	51	F	+18	-	-	265	+48	-	-	-	
49	52	M	+33	-	-	305		+	-	-	
50	37	F	+2	-	-	160		-	-	-	Euthyroid
51	61	M	+30	-	-	365		+	-	-	
52	50	M	+21	-	-	205		-	-	-	
53	51	F	+13	-	-	225		-	-	-	
54	62	F	+23	? Thyrotoxic 16 yrs previously	-			+	-	-	
55	67	F	-2	-	-	265	+12	+	-	-	
56	58	F	+8	-	-	285	+17	+	-	-	
57	50	F	+35	-	-	401		+	-	-	
58	73	F	+2	-	Paternal female cousin with Thyrotoxicosis			-	-	-	Euthyroid
59	67	F	-6	-	-			-	-	-	Euthyroid
60	40	F	-4	-	-			-	-	-	Euthyroid
61	51	M	+27	-	-	321	+5	+	-	-	
62	59	M	+3	-	-			-	-	-	Euthyroid
63	37	F	+29	-	-	290		+	-	-	
64	65	F	+4	-	-			-	-	-	Euthyroid
65	52	F	-2	-	-			-	-	-	Euthyroid
66	56	F	+36	-	-	391		+	-	-	
67	34	F	+31	-	-	335	-5	+	-	-	
68	49	F	+32	-	-	270	+34	+	-	-	
69	40	F	+35	-	-		-20	+	-	-	
70	65	F	+24	-	-			+	-	-	
71	52	F	+26	-	-	205	-6	+	-	-	

TABLE II. Results of Radioiodine tests in Primary Hypothyroidism.

TABLE II.

Results of Radioiodine Tests in Primary Hypothyroidism

Case No.	4 hr uptake (% dose)	48 hr uptake (% dose)	48 hr PBI^{131} (% dose/l)	48 hr BII^{131} (% PBI^{131})	Pot. Perchlorate Discharge Test	TSH Test	PBI (µg%)
1	15.2	18.7	0.15		-		1.0
2	16.9	10.7	0.24		-		1.6
3	18.8	35.1	0.58	35	+		3.0
4	17.1	13.3	0.05		-		1.5
5		3.9	0.12				
6	6.1		0.05				
7	12.0	24.0	0.87	40			1.5
8						-	1.3
9		15.0	0.33				
10						-	
11	12.1	13.2					
12		11.4	0.11				
13	12.8	27.4	0.05				
15	16.1	17.9	0.10				
16						-	
18	18.0	8.2	0.05				
19							2.1
20	10.5	8.1	0.10				
21	15.0	15.5	0.12				
24	9.6	4.3	0.05				
25							
26	3.8	1.3	0.05				
27	9.9		0.05				
28	9.6	18.8	0.10				1.7
29		0.5	0.05				0.6
30	10.0	7.3	0.05				
31		3.0	0.05				
33	12.1	2.5	0.05				
34						-	
35						-	
36	11.6	25.1	0.16		-		2.2
37						-	
38						-	
39						-	
40		15.0					
41	7.2	0.6	0.05				
42	13.4	54.8	0.24				5.1
43						-	
44						-	
45	10.9	1.2	0.05				
46	11.8	16.9	0.14				
47	12.6	30.3	0.12				3.5
48	15.0	29.2	1.10		+	-	4.6
49						-	
51						-	
52							2.2
55						-	
56	10.5	36.7	0.05		-		
62	13.2	24.1	0.18				
66	11.3	49.6	0.45				
67							
68	13.4	21.2	0.11				
69	1.5	9.0	0.05				
70	13.8		0.05				

SECTION 2. The Relationship of Auto-immune Thyroiditis to Thyrotoxicosis.

SECTION 2(b). The Clinical Significance of the Complement-Fixation Test in Thyrotoxicosis.

TABLE II.

Relation between the Complement-Fixation Test and Clinical Features of Thyrotoxicosis.

Table II.

Relation between the Complement Fixation Test and Clinical Features of Thyrotoxicosis.

Clinical Features		Number of Cases "Untreated" -	+	++	Total	Results of CF test "Treated" -	+	++	Total
Age in years	10-19	3	1	0	4	1	0	0	1
	20-29	27	6	7	40	7	3	6	16
	30-39	35	17	18	70	27	11	12	50
	40-49	32	16	20	68	28	15	22	65
	50-59	26	8	14	48	25	16	26	67
	60-69	9	1	2	12	6	2	5	13
	70 and over	9	2	0	11	2	1	0	3
Goitre Type	Diffuse	83	32	40	155	64	29	35	128
	Nodular	45	17	17	79	26	17	32	75
	Absent	13	2	4	19	6	3	4	13
Goitre Size (g.)	50	48	20	11	79	34	18	16	68
	75	45	18	24	87	33	14	17	64
	100 and more	35	11	22	68	23	13	34	70
Goitre Duration (months)	0-11	40	18	33	91	17	12	7	36
	12-59	34	8	14	56	32	12	21	65
	60 and over	10	3	2	15	25	12	29	66
Duration of Symptoms (months)	0-11	67	31	30	128	27	9	9	45
	12-59	65	20	28	113	42	26	29	97
	60 and over	9	0	3	12	27	13	33	73
Severity of Symptoms (Clinical Diagnostic Index)	Under 10	3	0	1	4	0	0	1	1
	11-19	11	1	3	15	0	3	1	4
	20-25	36	17	13	66	41	17	27	85
	26-30	41	18	23	82	29	18	22	69
	31 and over	50	15	21	86	26	10	20	56
Eye Signs	Exophthalmos	85	35	36	156	68	33	49	150
	Severe Exophthalmos	13	5	6	24	10	6	2	18
Drug Reactions		12	1	5	18	10	2	8	20
Family History of Thyroid Disease		36	17	22	75	25	10	29	64
TOTAL		141	51	61	253	96	48	71	215

The data in this table was compiled from an analysis of punch cards using the Hollerith system.

TABLE VII.

Correlation between the Complement-Fixation Test and the Response to Antithyroid Drugs in 103 "Untreated" Cases.

Table VII.

Correlation between the Complement-Fixation Test and the Response to Antithyroid Drugs in 103 "Untreated" cases.

Complement-Fixation Test	Outcome of Treatment					
	Control satisfactory		Hypothyroid*		Relapse+	
	No.	%	No.	%	No.	%
(-)	49	92.4	2	3.8	2	3.8
(+)	27	93.1	1	3.4	1	3.4
(++)	19	90.4	1	4.8	1	4.8

* i.e. during course of treatment.

\+ i.e. following course of treatment lasting 18 months.

TABLE IX

Comparison between the "Untreated" and "Treated" Thyrotoxic Patients.

Table IX.

Comparison between the "Untreated" and "Treated" Thyrotoxic Patients.

Clinical Feature	"Untreated"	"Treated"
Total No. of cases	253	215
Mean Age	42 years	46 years
Goitre — Nodular	31%	35%
Goitre — Size (mean)	70g.	74g.
Goitre — Duration (mean)	21 months	45 months
Symptoms — Intensity*	28	27+
Symptoms — Duration (mean)	22 months	38 months

* The intensity of the illness as judged by the 'Clinical diagnostic index'

+ 'Clinical diagnostic index' before treatment given.

APPENDICES - CHAPTER IV.

SECTION 1. The Association of Auto-immune Thyroiditis and the Connective Tissue Diseases, with particular reference to Rheumatoid Arthritis.

TABLE I.

Clinical and Laboratory Details in Auto-immune Thyroiditis.

(Group 1A)

Table I.

Clinical and Laboratory Details in Auto-immune Thyroiditis (Group 1A)

Case No.	Age	Sex	Thyroid Auto-Antibody tests Prec.	CF	Clinical Evidence of Arthritis	X-ray of Hands	Rose-Waaler Test	LE cell Test	Comments
1	70	F	-	AC	None	-	-	-	
2	56	F	+	++	Suggestive	Suggestive	-	-	Not rheumatoid arthritis
3	52	F	+	+	None	-	-	-	
4	63	M	+	++	Present	+	+	+	See text for Clinical details
5	41	F	+	++	None	-	-	-	
6	63	F	-	++	None	-	-	-	
7	62	F	+	++	None	-	-	-	
8	49	F	+	++	None	-	+	-	Not rheumatoid arthritis
9	63	F	+	-	None	-	-	-	
10	52	F	+	++	None	-	-		
11	37	F	-	++	None	-	-	-	
12	48	F	+	++	None		-		
13	67	F	+	++	Present	+	+	-	See Text for clinical details
14	28	F	+	++	None	-	-		
15	57	F	+	++	None	-	-		
16	40	F	-	++	None	-	-	-	
17	45	F	+	++	None	-	-	-	
18	52	F	-	++	None	-	-		
19	66	F	+	++	None	-	+	-	Not rheumatoid arthritis
20	48	F	-	-	None	-	-	-	
21	63	M	+	++	None	-	-		
22	56	F	+	++	None	-	-	-	
23	44	F	+	++	None	-	-		
24	53	F	+	++	None	-	-	-	
25	50	F	+	++	None	-	+	-	Not rheumatoid arthritis
26	43	F	+	++	None	-	-	-	
27	54	F	+	++	None	-	-		
28	50	F	+	++	None	-	-	-	
29	59	M	-	++	None	-	-	-	
30	45	F	+	++	None	-	-	-	
31	61	F	+	++	Present	+	+	-	See text for clinical details
32	65	F	+	+	Present	+	+	-	See text for clinical details
33	55	F	+	++	None	-	-	-	
34	51	M	+	++	None	-	-	-	
35	46	F	-	++	None	-	-	-	
36	50	F	+	++	None	-	-	-	
37	44	F	+	++	None	-	-	-	
38	61	F	+	++	None	-	-	-	
39	45	F	+	++	None	-	-		
40	52	F	-	++	Present	+	+	-	See text for clinical details
41	66	F	+	AC	Present	+	+	-	See text for clinical details
42	57	F	+	++	None	-	-	-	
43	45	F	+	++	None	-	-	-	
44	44	F	+	++	None	-	-	-	
45	36	F	+	++	None	-	-		
46	57	F	+	++	Present	+	-	-	See text for clinical details
47	64	F	-	++	None	-	-		
48	47	F	-	++	None	-	-	-	
49	40	F	+	++	None	-	-		
50	62	F	-	+	None	-	-		

TABLE II.

Clinical and Laboratory Details in

Rheumatoid Arthritis

(Group 2A)

Table II. Clinical and Laboratory Details in Rheumatoid Arthritis (Group 2A)

Case No.	Age	Sex	Dur. of Arthritis (Yrs.)	Treatment*	Rose-Waaler	X-ray Hands	L.E.Cell Test	Thyroid Antibody tests Prec.	Thyroid Antibody tests CFT	Comment
1	55	F	3	S.	+	+	+	-	++ (non-specific)	No Goitre
2	57	F	6	S. P B.	+	+		-	-	"
3	56	F	2	S.	+	+		-	-	"
4	67	F	8	S. P B.	-	+		-	-	"
5	35	F	2	S.	-	+		-	+	"
6	59	F	6	S. P B.C.	+	+	-	-	-	No Goitre. Rheumatic Heart Disease.
7	51	F	7	S.P B. C.	-	+		-	-	No Goitre
8	21	F	1	S	-	+		-	-	Simple Goitre. I^{131} tests: 4-hr uptake 59% dose, 48hr P.B.I. 0.059%/dose/litre
9	59	F	4	S. P B.	+	-		-	-	No Goitre
10	53	F	6	S. P B. C.	+	+		-	-	"
11	63	F	4	S. P B.	-	+		-	-	"
12	55	F	7	S. P B. C.	-	+		-	-	"
13	53	F	5	S. C.	+	+		-	-	"
14	64	F	2	S.	-	+	-	+	++	Primary hypothyroidism
15	59	F	3	S.	-	+		-	-	No Goitre
17	48	F	5	S. C.	-	+	-	-	-	Felty's syndrome
18	63	F	6	S. C.	+	+	+	-	Anticomplementary	Diabetes Mellitus Pulmonary Tuberculosis
19	56	F	1		+	+	-	+	++	Primary hypothyroidism
20	46	F	7	S. P B. C.	+	-	-	-	-	No goitre,but 48 hr.P.B.I. 0.33%dose/litre. Potassium perchlorate discharge test negative.
21	51	F	25	S. P B. C.G.	+	+	-	-	++ (non-specific)	Cirrhosis of Liver. No Goitre
22	49	F	11	S. P B. C.	+	-	-	-	++	No Goitre. I^{131} tests normal
23	62	F	10	S.C.	-	+	-	-	-	No Goitre
24	45	F	6	S.	+	-		-	-	"
25	56	F	7	S.	+	-	-	-	++	No Goitre. I^{131} tests normal
26	64	F	18	S. P B. C.	+	+	+	-	+	No Goitre I^{131} tests normal
27	62	F	10	S.C.	+	+	+	-	++	No Goitre I^{131} tests normal
28	41	F	6	S.C.	-	+	-	-	-	Simple Goitre. I^{131} tests 4 hr uptake 35%/dose, 48 hr P.B.I. 0.05%/dose/litre.
29	56	F	11	S.C.	+	-	-	-	++	No Goitre I^{131} tests normal
30	55	F	16	S. P B. C.	-	+		-	++	No Goitre I^{131} tests normal
31	51	F	2	S.	+	+	-	-	+	No Goitre I^{131} tests normal. Carcinoma of breast
32	46	F	11	S. P B.	-	+		-	-	No Goitre
33	51	F	8	S.	-	+		-	-	"
34	51	F	15	S. P B. C. G.	+	+	-	-	-	"
35	59	F	7	S. C.	-	+		-	-	"
37	56	F	4	S.	+	-		-	-	"
38	39	F	11	S. C.	+	+		-	+	No Goitre I^{131} tests normal
40	56	F	3	S.	+	-		-	-	No Goitre
41	55	F	2	S.	-	+		-	-	"
42	66	F	6	S. P B.	-	+		-	-	"
43	57	F	8	S. C.	+	+		-	-	"
44	55	F	10	S. P B.	+	+		-	-	"
45	57	F	6	S. P B. C.	-	+	-	-	+	I^{131} tests normal
46	62	F	13	S. P B. C.	+	+	-	-	-	Felty's syndrome. No Goitre
47	44	F	3	S.	+	-	-	-	-	No Goitre
48	39	F	2	S.		+		-	-	Simple Goitre. I^{131} tests; 4hr uptake 63% dose;48 hr P.B.I. 0.1% dose/litre
49	60	F	4	S.		+		-	-	No Goitre
50	62	M	8	S. C.	+	+	-	-	-	"
51	65	M	13	S. P B. C.	+			-	-	"
52	74	M	10	S.	-	+		-	-	"
53	54	M	14	S. P B. C.	+	+		-	-	"
54	66	M	7	S.	+			-	-	"
55	63	M	3	S.		+		-	-	"
56	54	M	2			+		-	-	"
57	68	M	7	S.		+		-	-	"
58	64	M	11	S. P B. C.	+	+		-	-	"
59	74	M	4	S.		+		-	-	"
60	38	M	7	S. P B.		+		-	-	"
61	40	M	21	S. P B. C.	-	+		-	-	"
62	56	M	13	S. C.	-	+		-	-	"
63	34	M	11	S.	-	+		-	-	"
64	18	M	2	S.	-	+		-	-	"
65	56	M	10	S. P B.	+	+		-	-	"
66	32	M	14	S. P B. C.	+	+		-	-	"
67	17	M	1		+	+	-	-	-	"
68	57	M	5	S.	+	-	-	-	-	"
69	48	M	2	S.	+	-	-	-	-	"
70	65	M	8	S. P B. C.	+	+		-	-	"
71	57	M	5	S. P B.	+	+	-	-	-	"
72	56	M	3	S	-	+		-	-	"
73	35	M	1		+	-	-	-	-	"

* Treatment; S= salicylates. P B. = phenylbutazone. C = steroids. G.= Gold.

TABLE III.

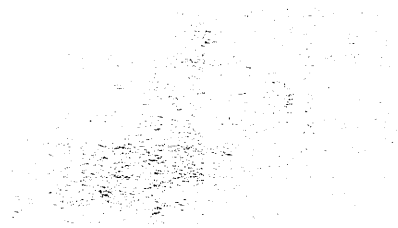
Clinical and Laboratory Data in Miscellaneous Connective Tissue Diseases, including Sjögren's Disease. (Group 3)

Table III.

Clinical and Laboratory Data in Miscellaneous Connective Tissue Diseases, including Sjögren's disease.....(Group 3).

Case No.	Clinical Condition	Age	Sex	Steroid therapy	L.E. Cell test	Bass Shaker test	Thymol turbidity (units)	gamma-globulin (mg.%)	E.S.R. (mm/first hr.)	W.B.C. (cells/c.mm.)	goitre	Thyroid Investigation ^{131}I Tests: Clin. status	4-hr. ^{131}I uptake (% dose)	48-hr. PBI ^{131}I (µdose/l.)	Pot. Perchlorate discharge test	Thyroid auto-antibody tests: Prec.	Thyroid auto-antibody tests: CFF	
1	systemic lupus erythematosis	53	F	-	+	-	1	1.10	84	2,400	-	Eu.	38	0.07		-	-	
2	"	36	F	+	+	-	2	1.12	95	1,900	-	Eu.	87	0.05		-	-	
3	"	32	F	-	+	-	5	2.10	68	5,400	-	Eu.				-	-	
4	"	60	F	-	+	+	1	0.76	75	8,050	-	Eu.	33	0.16	-	-	++	
5	"	38	F	+	+	-	6	1.28	50		-	Eu.	41	0.10	+	-	AO	
6	"	36	F	+	+		5	1.81	48	4,100	-	Eu.	87	0.05		-	++	(N-S)
7	"	38	F	+	+	-			22	3,100	-	Eu.	17	0.12			++	(N-S)
8	"	22	F	+	+	-	3	0.92	113	1,100	+ (soft, 75 g.)	Eu.	63	0.12	-	-	++	(N-S)
9	"	64	F	-	+	+	3	0.87	83	700	-	Eu.	87	0.10		-	++	(N-S)
10	Scleroderma	64	F	-	-	-	7	1.65	43	3,400	-	Eu.	35	0.07	-	-	-	
11	"	50	F	+	-	-	1	1.25	35	3,100	-	Eu.	87	0.08	-	-	++	
12	"	43	M	+	-	-	1	0.56	8	7,400	-	Eu.	87	0.08	-	-	-	
13	"	27	M	+	-	-	2		15	5,700	-	Eu.	33	0.07	+	-	-	
14	"	31	F	+	-	-	3		39	7,400	-	Eu.	83	0.08	-	-	++	(N-S)
15	"	49	F	-	-	-	4	1.12	38	5,400	-	Hypo.	7	0.05	-	-	++	
16	Dermatomyositis	49	F	+	-	-	1	1.00	85	6,100	-	Eu.	49	0.24		-	-	
17	"	64	F	-	-	-	3	1.30	19	8,700	-	Hypo.	15	1.60	+	-	++	
18	Periarteritis Nodosa	31	F	+	-	-	1	0.95	7		-	Eu.				-	-	
19	"	52	M	+	-	-	2		13		-	Eu.				-	-	
20	Sjögren's disease	67	F	+	-	+	4	1.20	25	2,100	-	Eu.	40	0.11		-	-	
21	" Rheumatoid arthritis	60	F	+	+	+	8	2.70	45	9,500	+ * (firm, 150g)	Eu.				+	++	

* Histology of the thyroid gland showed diffuse Askanazy-cell change, but no thyroiditis.



SECTION 2. The Association of Auto-immune Thyroiditis and Acquired Haemolytic Anaemia.

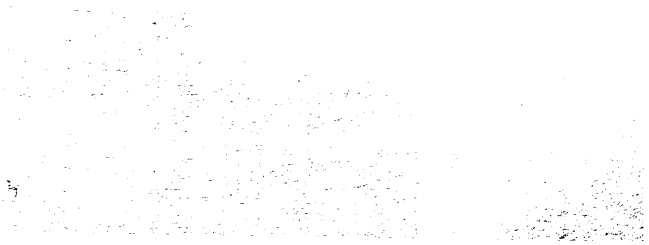


TABLE I.

Results of Haematological Investigations in Auto-immune Thyroiditis.

Table I. Results of Haematological Investigations in Auto-immune Thyroiditis

Case No.	Hb (%)	PCV (%)	MCHC (%)	WBC (cells/c.mm)	Differential Count	Reticulocyte Count (%)	Coombs Test	Cr^{51} Half-life* (days)	Marrow	Comments
1	69	34	30	4,200	Normal	2	Negative	25	Normoblastic	Hepato-splenomegaly. Liver biopsy normal. Gastrectomy for gastric neoplasm 3 years previously.
2	90	44	30	4,900		2	Negative			
3	97	34	31			2	Negative			
4	100	46.5	31.75	8,000		2	Negative	26	Normoblastic	
5	86	43	30	5,700	Normal	2	Negative			
6	75	36.75	30.5	7,200	Normal	2	Negative			
7	96	44.5	31.75	4,800	Normal	2	Negative			
8	64	34	28	7,000		2	Negative			Iron deficiency anaemia secondary to menorrhagia.
9	94	44.5	31.25	5,300	Normal	2	Negative			
10	104	49	315	7,400	Normal	2	Negative			
11	95	42	33	7,200		2	Negative			
12	97	45	32			2	Negative			
13	74		29.75	7,900	Normal	2	Negative			
14	80	39.5	30	8,500	Normal	2	Negative			
15	78	38	30.5	4,300	Normal	2	Negative			
16	84	40	31	8,400	Normal	2	Negative			
17	80	37.75	31.5	6,800	Normal	2	Negative			
18	96	43.5	33	4,900		2	Negative			
19	84	39	32	4,600		2	Negative			
20	93	44	31	8,700		2	Negative			
21	104		32	6,800	Normal	2	Negative			
22	68	35	29	6,100		2	Negative		Normoblastic	Iron Deficiency anaemia.
23	80	36.5	32.5	7,000	Normal	2	Negative			
24	96	44.5	32	6,100		2	Negative			
25	80	37	32	6,000	Normal	2	Negative			
26	104	46	33	5,200	Normal	2	Negative			
27	109	48.5	33	4,000		2	Negative			
28	90	42.5	31.5	7,700		2	Negative			
29	98	45.75	32	5,700		2	Negative			
30	85	42	30	5,400	Normal	2	Negative			
31	97	35.5	32	4,900	Normal	0.5	Negative	27		
32	74	41	26	5,800	Normal	2	Negative			
33	88	41	31.75	4,600		2	Negative			
34	94	49	28.5	6,700	Normal	2	Negative	25.5		
35	80	37.75	31.75			2	Negative			
36	95	43	33	6,400	Normal	2	Negative			
37	94	44.5	31.5	6,400	Normal	2	Negative			
38	80	39.5	30	7,100	Normal	2	Negative			
39	98	46	31.5	10,000	Normal	2	Negative			
40	81	40	30	6,400	Normal	2	Negative			
41	85		28.5	5,600	Normal	2	Negative			
42	84	40	31.5	5,100						
6 months	68	31.5	32	4,000	Normal	5		12	Normoblastic	
2 years	71	33	31	6,500	Normal	2.5				See text for clinical details.
43	92	42.5	32.25	8,100		2	Negative			
44	76	38	30	8,400	Normal	4.5			Normoblastic	Iron Deficiency anaemia associated with recurrent haemoptysis due to mitral stenosis and pulmonary haemosiderosis.
45	88	40	32			2	Negative			
46	86	40.5	31.5	4,500	Normal	2	Negative			
47	97	35.5	32			2	Negative			
48	90	42.5	31.25	5,200	Normal	2	Negative			
49	86	42	31			2	Negative			
50	81	38	31			2	Negative			

* Normal value 25-30 days.

TABLE II.

Results of Thyroid Investigations in 22 Patients with Acquired Auto-immune Haemolytic Anaemia.

Table II. Results of Thyroid Investigations in 22 Patients with Acquired Auto-immune Haemolytic Anaemia

Case No.	Clinical Diagnosis	Clinical Status	Goitre	Thyroid Auto-Antibody Tests				4 hr I^{131} Uptake (% dose)	48 hr I^{131} Uptake (% dose/l)	Pot. Perchlorate Discharge	Serum PBI (µg.%)	Comments
				Prec.	Complement-Fixation spec.	Complement-Fixation non spec.	AC					
1	Reticulo Sarcoma	Euthyroid	None	-			+	30	0.07		5.2	
2	Hodgkin's Disease	"	"	-				25	0.05		4.7	
3	Acquired Idiopathic Haemolytic Anaemia	"	"	-								
4	Rheumatoid Arthritis. Hypo-gamma-globulinaemia	"	"	-		+						
5	Acquired Idiopathic Haemolytic Anaemia	"	"	-								
6	"	"	"	-				35	0.10		3.9	
7	"	"	"	-								
8	Rheumatic Heart Disease	Thyrotoxic	Soft Diffuse 50g	-				47	1.35		10.6	Subtotal thyroidectomy 25 years previously.
9	Staphylococcal pneumonia	Euthyroid	None	-		+						
10	Acquired Idiopathic Haemolytic Anaemia	"	"	-								
11	"	"	"	-								
12	"	"	"	-								
13	"	"	"	-				75	0.47	+	3.7	
14	"	"	"	-								
15	"	"	"	-	++			42	0.10	-	4.1	
16	"	"	"	-	+			49	0.56	-	5.2	
17	"	"	"	-		+						
18	Reticulo Sarcoma	"	"	-		+						
19	Acquired Idiopathic Haemolytic Anaemia	"	"	-	+							
20	Hodgkin's Disease	"	"	-								
21	Acquired Idiopathic Haemolytic Anaemia	"	"	+	++							Auto-immune Thyroiditis. Confirmed at autopsy.
22	"	"	"	-	++			30	0.21		6.3	

TABLE III.

Clinical and Laboratory Findings in 22 Patients with Acquired Auto-immune Haemolytic Anaemia.

Table III.

Clinical and Laboratory Findings in 22 Patients with Acquired Auto-immune Haemolytic Anaemia.

Case No.	Age	Sex	Hb. (%)	W.B.C. (cells/c.mm.)	Platelets (cells/c.mm.)	Reticulocyte Count (%)	Coombs Test	Cold Antibodies	Red-cell Fragility (%)	Cr.51 Half-life (days)	LE cell test	Clinical Diagnosis
1	53	F	60	2,400	30,000	2	+	-		22	-	Reticulosarcoma.
2	22	F	47	3,500	360,000	29	+	-		6	-	Hodgkin's disease.
3	26	F	46	5,800		12	+	+	0.45	12		Acquired idiopathic haemolytic anaemia.
4	47	F	60	2,500	140,000	14	+	+	0.46	9	-	Rheumatoid arthritis, hypogammaglobulinaemia.
5	18	F	64	8,200	360,000	13	+	-		7		Acquired idiopathic haemolytic anaemia.
6	69	F	58	1,200	65,000	2.5	+	+	0.46	16	-	" " " "
7	63	F	40	1,800	55,000	6	+	-	0.46	14	-	" " " "
8	45	M	56	5,800	270,000	15	+	+	..43	8	-	" " " "
9	70	F	72	7,200		7	+		..43	13	-	Staphylococcal pneumonia.
10	71	F	68	12,400	350,000	8	+	+	..46		-	Acquired idiopathic haemolytic anaemia.
11	51	F	64	8,300		9	+	-	..46		-	" " " "
12	55	M	48	4,100	220,000	20	+	-		4.4		" " " "
13	60	F	66	6,400	95,000	10	+	+		17.5	-	" " " "
14	80	F	42	2,360		27	+	+	..66	6.2		" " " "
15	55	F	35	8,700	430,000	28	+	+	..46	2.4		" " " "
16	59	F	29	7,800	190,000	33	+	+		5.8	+	" " " "
17	20	F	45	3,400	95,000	8	+	+		6.3	-	" " " "
18	17	F	27	4,600	150,000	30	+	-		20	-	Reticulosarcoma.
19	67	F	75	12,600	205,000	11	+	-	0.46	8	-	Acquired idiopathic haemolytic anaemia.
20	68	M	59	5,500	140,000	6	+	+		13	-	Hodgkin's disease.
21	49	F	43	2,100		18	+	-			-	Acquired idiopathic haemolytic anaemia.
22	39	F	58	4,200	190,000	7	+	-		8	-	" " " "

SECTION 3. The Association of Auto-immune Thyroiditis and Cirrhosis of the Liver.

TABLE I.

Results of Investigations of Liver Function in 50 Patients with Auto-immune Thyroiditis.

Table I. Results of Investigations of Liver Function in 50 Patients with Auto-immune Thyroiditis

Case No.	Age	Sex	Thyroid antibody Tests Prec	Thyroid antibody Tests CF	Hepato-megaly	Spleno-megaly	EMPIRICAL LIVER - FUNCTION TESTS Serum Bilirubin+ (mg.%)	Alkaline Phosphatase+ (King Units)	Thymol Turbidity+ (Units)	Thymol Floc+ (Units)	Zinc Sulphate Turbidity (Units)+	BSP Tests+ (%)	Liver Biopsy	Comments
1	70	F	-	AC*	Present	Present	0.7	12	7	4	31	6.0	Normal	Castrectomy 3 yrs previously for gastric neoplasm
2	56	F	+	++	Absent	Absent	1.1	8	8	3		4.2		
3	52	F	+	+	"	"	0.6	8	4	1		0.2		
4	63	M	+	++	"	"	1.0	7	3	3	18	6.0	Normal	
5	41	F	+	++	"	"	1.3	6	12	3	40	3.1		
6	63	F	-	++	"	"	0.7	5	6	2	15	2.1		
7	62	F	+	++	"	"	1.2	9	4	1	17	14.0	Normal	
8	49	F	+	++	"	"	1.0	8	6	3		2.3		
9	63	F	+	-	"	"	0.9	10	1	0	24	4.1		
10	52	F	+	++	"	"	0.8	6	14	3				
11	37	F	-	++	"	"	1.0	8	5	0		3.0		
12	48	F	+	++	"	"	0.8	6	3	1	22	3.0		
13	67	F	+	++	"	"	0.5	14	4	1	16	3.0		
14	28	F	+	++	"	"	0.5	12	10	3		0		
15	57	F	+	++	"	"	0.9	8	8	3		4.0		
16	40	F	-	++	"	"	0.6	8	5	4	27	3.0		
18	52	F	-	++	"	"	1.2	9	12	3				
19	66	F	+	++	"	"	1.1	9	3	0	18	2.3		
20	48	F	-	-	"	"	0.5	8	3	0	9	3.0		
21	63	M	+	++	"	"	1.0	8	7	3		4.0		
22	56	F	+	++	"	"	0.6	11	4	0	25	0		
23	44	F	+	++	"	"	1.0	7	4	3	60	2.0		
24	53	F	+	++	"	"	0.6	9	10	0	14			
25	50	F	+	++	"	"	0.8	9	1	0	3	3.0		
26	43	F	+	++	"	"	0.6	4	1	0	25	4.2		
27	54	F	+	++	"	"	0.5	12	2	4		4.0		
28	50	F	+	++	"	"	0.8	9	14	2				
29	59	M	-	++	"	"	0.6	8	3	0	23			
30	45	F	+	++	"	"	0.5	10	5	0	15	6.0	Normal	
31	61	F	+	++	"	"	1.5	8	1	4		0		
32	65	F	+	+	"	"	0.5	10	5	4	25	2.3		
33	55	F	+	++	"	"	0.9	9	7	0	13	3.0		
34	51	M	+	++	"	"	0.9	7	2	3	13	0		
35	46	F	-	++	"	"	0.9	7	5	4	30	13.0	Normal	
36	50	F	+	++	"	"	1.4	4	11	0	13	0.2		
37	44	F	+	++	"	"	0.9	9	2	0	14			
38	61	F	+	++	"	"	0.7	6	1	2	22	2.1		
39	45	F	+	++	"	"	0.5	11	6	3	23	3.0		
40	52	F	-	++	"	"	1.2	7	14	1	13	4.5		
41	66	F	+	AC	"	"	0.7	8	3	1	25	1.2		
42	57	F	+	++	"	Present	2.6	6	5	3	34	0	Normal	Acquired idiopathic haemolytic anaemia
43	45	F	+	++	"	Absent	0.8	11	4	0	31	0		
44	44	F	+	++	"	"	1.2	5	1	0	8	2		
45	36	F	+	++	"	"	1.0	8	2	0	8	4		
46	57	F	+	++	"	"	0.5	7	8	4	18			
47	64	F	-	++	"	"	0.6	8	2	0	12			
48	47	F	-	++	"	"	1.0	7	5	1	15	3		
49	40	F	+	++	"	"	1.4	10	4	0	15	4.6		
50	62	F	-	+	"	"	1.0	11	1	0		0.4		

* AC = Anticomplementary

+ normal values: serum bilirubin 0.2 - 1.2mg. per 100 ml; alkaline phosphatase 4 - 12 King units per 100 ml; Thymol turbidity 1 - 2 units, thymol flocculation negative, zinc sulphate turbidity 5 - 13 units, and BSP retention not exceeding 6% retention at 45 minutes.

TABLE II.

Clinical Data in Female Cirrhotic Patients

TABLE III.

Clinical Data in Male Cirrhotic Patients

Table II.

Clinical data in female cirrhotic Patients.

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age, (years).	58	79	63	45	59	57	62	58	64	61	54	39	61	67	57	54
Aetiology.	Idiopathic	Idiopathic	Idiopathic	Hepatitis	Alcoholic	Alcoholic	Idiopathic	Idiopathic	Idiopathic	Idiopathic	Idiopathic	Hepatitis	Hepatitis	Idiopathic	Idiopathic	Idiopathic
Duration of Illness, (months).	2	3	36	12	12	24	12	24	36	24	36	36	84	18	6	12
Liver } Enlargement, (inches).	2	4	4.5	2.5	4	7.5	-	7.5	3.75	3.75	1.5	-	2.5	2	3.75	2
Spleen }	-	2.5	2	-	1	.	-	2.5	2	2.5	-	1.75	1.5	-	-	1.5
Ascites.	-	+	+	+	+	+	+	-	-	+	-	-	+	-	+	-
Oedema.	-	+	+	-	-	+	+	-	-	-	+	-	+	-	+	-
Oesophageal Varices.	-	-	-	-	+	-	+	-	+	-	+	-	+	-	-	-
Liver Palms.	+	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+
Spider Naevi.	+	+	+	+	+	-	-	-	-	+	-	-	-	+	-	+
Facial Telangiectasia.	+	+	+	+	-	+	-	-	-	+	+	-	-	+	-	-
Jaundice.	-	+	+	-	-	+	+	+	-	+	+	-	-	-	+	-
History and/or Evidence of Hepatic Coma.	-	+	+	-	-	+	+	-	+	-	-	-	+	-	-	-
Age at Menopause, (years).	42	40	53		51	46	45	45	40	43	51		38	44	49	43
Cervical Smear Test.	+	-	+		+	-	-	-	-		-?		-	-	-	-
Progress.	Well	Died	Died	Died	Died	Poorly	Died	Died	well	well	well	Well	Died	Well	Died	Well
Duration of Follow-up, (months).	18	3	9	30	6	28	24	12	18	24	24	24	18	24	18	12

Table III.

Clinical Data in Male Cirrhotic Patients.

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age, (years).	58	71	56	55	62	49	46	51	46	52	63	50	58	37
Aetiology.	Haemochromotosis	Alcoholic	Alcoholic	Idiopathic	Alcoholic	Hepatitis	Alcoholic	Alcoholic	Alcoholic	Hepatitis	Idiopathic	Idiopathic	Alcoholic	Alcoholic
Duration of Illness, (months).	168	36	36	36	36	24	36	-	36	12	7	24	7	156
Liver Enlargement, (inches).	2.5	2	2.75	3.75	1.5	2	-	3.75	1.5	-	2.25	-	1.5	-
Splenic " (").	-	-	2	-	1.5	-	-	-	0.75	2	0.5	-	-	-
Ascites.	-	-	-	-	+	-	-	+	-	+	+	-	+	-
Oedema.	-	-	-	+	-	-	-	+	-	+	+	-	+	-
Oesophageal Varices.	+	-	-	-	+	-	-	+	-	-	-	-	+	+
Liver Palms.	-	-	-	-	-	-	+	+	-	-	-	-	-	+
Spider Naevi.	-	-	+	-	+	+	+	+	-	+	-	+	+	-
Facial Telangiectasis.	-	+	+	-	-	-	+	-	-	-	-	+	+	-
Gynaecomastia.	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Testicular Atrophy.	+	+	-	+	-	+	+	-	+	-	-	-	-	+
Jaundice.	+	-	-	-	-	-	-	-	+	-	-	-	+	-
History and/or Evidence of Hepatic Coma.	-	-	-	-	-	+	+	-	-	-	-	-	+	-
Progress.	Well	Well	Well	Well	Poorly	Died	Died	Died	Well	Died	Poorly	Died	Died	Well
Duration of Follow-up, (months).	24	18	24	18	24	6	11	24	36	8	11	9	6	9

TABLE IV.

Laboratory Findings in Female Cirrhotic Patients

TABLE V.

Laboratory Findings in Male Cirrhotic Patients

Table IV.

Laboratory Findings in Female Cirrhotic Patients.

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Serum Bilirubin. (mg.%)	0.5	32	20.6	1.3	1.3	6.6	10.0	13	1.1	1.4	1.7	2.0	1.0	1.3	1.2	0.6
Alkaline Phosphatase. (K.A. units)	48.2	77	30	15	23.3	31	20	69	20	16	7	25	5	15.8	57	70.8
Thymol Turbidity. (units)	8	4	4	6	12	5	5	2	5	6	3	4	8	12	11	8
Thymol Flocculation. (units)	1	0	4	3	4	3	4	0	3	2	2	2	3	0	0	4
Serum Albumin. (g.%)	3.3	3.3	3.2	3.3	4.0	2.5	2.7	2.2	4.4	2.7	3.3	3.7	3.8	5.0	3.9	4.0
Serum Globulin. (g.%)	4.9	2.9	3.2	2.1	4.4	2.3	3.2	3.1	2.9	2.1	2.0	2.2	3.1	2.5	2.3	4.7
Gamma Globulin. (g.%)	2.7	1.3	1.7	1.3	2.6	1.0	1.5	1.3	1.6	1.9	1.1	0.9	1.8	1.1	1.4	1.8
B.S.P. (%)	17	71	60	18	54	35	75	25	13	25	22	14	19	47	28	36
Serum Transaminase. (units)	104	166	212	296	142	114	88	104	251	147	83	36	55	31	114	
Serum Iron. (ug.%)	80	35	35	110	145	35	150	35	133	28	115	50	173	50	10	35
Serum Vitamin B_{12}. (total). (uug./ml.)	568	1433			617	1600			810	1215	705		420	550	490	150
Prothrombin Time/Control. (Sec.)	19/16	19/17	32/15	19/16	18/13	21/15		22/15		21/15	18/16	18/15		20/12	18/15	17/15
Serum Cholesterol. (mg.%)	233	320	335	157	180	200	300	213	120	137	90	205	132	120	125	335
Hb. (%)	84	96	71	91	85	86	90	70	78	74	79	66	85	70	43	105
W.B.C. (cells/c.mm.)	7,400	5,400	7,800	10,500	5,000	4,300	5,800	2,900	1,450	3,800	7,800	3,100	2,700	3,200	5,400	5,800
E.S.R. (mm./first hr.)	55	88	57	10	18	34	30	56	10	8	15	24	43	48	84	39
F.O.B.	+	-	+	-	-	+	+	-	+	-	-	-	-	-	-	+

Table V.

Laboratory Findings in Male Cirrhotic Patients.

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Serum Bilirubin. (mg.%)	0.8	1.0	2.3	1.6	1.2	0.7	1.5	3.9	5.4	1	0.2	0.6	1.9	0.9
Alkaline Phosphatase. (K.A. units)	10	19	9	19	10	9.2	18.8	14	62	15.6	25.1	10	28.2	12
Thymol Turbidity. (units)	2	16	9	1	10	15	6	5	2	8	8	2	18	3
Thymol Flocculation. (units)	1		4	0	4	3	3	0	0	3	0	2	4	0
Serum Albumin. (g.%)	3.6	3.2	2.3	3.7	4.2	4.2	3.0	4.2	4.8	2.8	2.3	2.6	3.8	4.0
Serum Globulin. (g.%)	2.4	6.8	3.7	2.4	2.8	4.4	4.0	2.2	4.0	3.7	3.8	4.9	4.9	2.7
Gamma Globulin. (g.%)	1.53	4.04	1.79	1.02	1.48	2.47	2.14	0.97	1.46	2.46	2.15	3.31	2.72	1.36
B.S.P. Test. (%)	0	41	25	17	24	70.5	20	19	26	37.5	12	38.5	15	0
Serum Transaminase. (units)	90	100	75	83	60	213	61	50	35	103	32	151	250	34
Serum Iron. (ug.%)	200	10	150	40	205	180	74	75	180	35	45	155	80	155
Serum Vitamin B_{12}. (total) (uug./ml.)	447	583	458	353	1022	647	1670	620	131	675	763	707	1860	640
Prothrombin Time/Control. (secs.)	24/16	19/13		21/15	19/16		18/14	20/15	19/16	18/14	16/13	21/15		19/16
Serum Cholesterol. (mg.%)	100	120	140	140	130	170	98	280	205	155	390	103	180	125
Hb. (%)	102	90	105	86	92	110	115	85	75	70	91	93	106	67
W.B.C. (cells/c.mm.)	6,200	5,600	8,400	7,000	4,600	8,000	6,400	7,200	5,200	2,400	3,750	4,600	9,000	3,500
E.S.R. (mm./first hr.)	10	102	45	45	40	4	5	90	88	3	64	115	4	24
F.O.B.	-	-	-	-	-	-	+	+	-	+	-	-	-	+

TABLE VI.

Liver Histology in Female Cirrhotic Patients

TABLE VII.

Liver Histology in Male Cirrhotic Patients

Table VI.

Liver Histology in Female Cirrhotic Patients.

Case No.	Nature of Specimen	Portal Cellularity				Necrosis	Fatty Change	Hypertrophy	Fibrosis	Bile Thrombi	Bile Duct Proliferation
		Lymphocytes	Lymphoid Follicles.	Polymorpho-nuclear Leucocytes.	Plasma Cells.						
1	Wedge	++	-	-	+	-	+	++	++	-	-
2	Autopsy	++	-	-	++	-	+	++	+	+	+
3	Autopsy	+	-	+	+	-	-	+	++	-	+
4	Autopsy	++	-	+	++	+	-	++	++	+	+
5	Needle	++	-	+	-	++	+	+	+++	+++	+
7	Autopsy	+	-	+	+	-	-	+	+	+	+
8	Autopsy	+	-	+	++	+	+	++	+	-	+
9	Needle	+	-	-	-	-	-	+	-	-	-
11	Wedge	+	-	+	++	+	-	+	++	+	+
12	Wedge	+	-	+	++	+	+	+	++	-	-
13	Autopsy	+	-	+	++	+	-	+	++	+	+
14	Needle	+	-	+	+	-	+	++	++	-	-
15	Autopsy	++	-	+	+	+	+	+	+++	+	+++
16	Needle	++++	+	-	+	-	-	+	+	-	+

Table VII.

Liver Histology in Male Cirrhotic Patients.

Case No.	Nature of Specimen	Portal Cellularity				Necrosis	Fatty Change	Hypertrophy	Fibrosis	Bile Thrombi	Bile Duct Proliferation
		Lymphocytes	Lymphoid Follicles	Polymorpho-nuclear Leucocytes.	Plasma Cells						
1	Needle	+	-	-	+	-	-	+	+++	-	-
3	Needle	++	-	-	++	-	+	+	++	-	+
8	Autopsy	+	-	+	+	+	++	+	+	-	+
9	Wedge	+	-	+	++	+	+	+	+	-	-
10	Autopsy	++	-	+	++	-	-	+	+	+	+
11	Needle	+	-	-	+	-	+	++	+	+	+
13	Autopsy	+	-	-	+	-	+	++	+++	+	+
14	Needle	+	-	-	+	+	+	+	+	+	+

TABLE VIII.

Results of Investigations of Thyroid Function in Female Cirrhotic Patients

TABLE IX

Results of Investigations of Thyroid Function in Male Cirrhotic Patients

Table VIII.

Results of Investigations of Thyroid Function in Female Cirrhotic Patients.

Case	Age.	Clinical Status	Goitre	Thyroid Auto-antibody Tests.		Radioiodine Tests			PBI (µg./100 ml.)	Thyroid Histology
				Precipitin	Complement-Fixation	4 hour uptake (% dose)	PBI^{131} (% dose/l.)	Perchlorate Discharge		
1	58	Euthyroid	None	+	++	10.2	0.22	+	3.5	
2	71	"	"	-	+	27.8	0.13	-	3.0	No post-mortem examination of thyroid performed.
3	63	"	"	-	++	24.5	0.54	+	3.6	Focal thyroiditis present.
4	45	"	"	-	++	20.2	0.21	-	4.4	Focal thyroiditis present.
5	59	"	"	-	++	43.1	0.05	-	5.5	
6	57	Euthyroid	None	-	-	19.3	0.23	-	4.3	
7	62	"	"	-	AC	32.0	0.05	-	7.0	Focal thyroiditis present.
8	58	"	"	-	-	20.1	0.28	-	4.9	Focal thyroiditis present.
9	64	"	"	-	-	15.9	0.1	-	7.5	
10	61	"	"	-	-	31.6	0.12	-	4.6	
11	54	"	"	-	AC	22.0	0.05	-	3.7	
12	39	"	"	-	-	24.5	0.05	+	5.5	
13	61	"	"	-	-	21.4	0.1	-	5.8	Focal thyroiditis present.
14	67	"	"	-	-	36.7	0.05	-	8.0	
15	51	"	"	-	++ (non-specific)	49.4	0.15	-	5.3	Focal thyroiditis present.
16	54	"	"	-	-	26.6	0.05		4.0	

Table IX.

Results of Investigations of Thyroid Function in Male Cirrhotic Patients.

Case	Age.	Clinical Status	Goitre	Thyroid Auto-antibody Tests.		Radioiodine Tests			PBI (µg./100 ml.)	Thyroid Histology
				Precipitin	Complement-Fixation	4 hour uptake (% dose)	PBI^{131} (% dose/l.)	Perchlorate Discharge		
1	58	Euthyroid	None	-	-	29.0	0.23	-	4.2	
2	71	"	"	-	-	37.2	0.05	-	5.2	
3	56	"	"	-	-	18.8	0.23	-	3.2	
4	55	"	"	-	+ (non-specific)	41.2	0.25	-	5.0	
5	62	"	"	-	-	26.8	0.05	-	6.2	
6	49	"	"	-	-	17.8	0.05	-	5.9	
7	46	"	"	-	-	24.2	0.05	-	5.6	
8	51	"	"	-	-	45.2	0.17	-	4.2	
9	46	"	"	-	++	33.2	0.05	-	4.8	
10	52	"	"	-	-	21.0	0.05	+	4.7	Thyroid not examined.
11	63	Hypothyroid	"	-	-	7.2	0.00	-	1.0	
12	50	Euthyroid	"	-	AC	27.3	0.05	-	5.7	Thyroid not examined.
13	58	"	"	-	+ (non-specific)	14.1	0.05	-	5.4	
14	37	"	"	-	-	13.6	0.05	-	4.8	

SECTION 4. The Antibody-forming Potential in Auto-immune Disease.

Table I.

TABLE I.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Auto-immune Thyroiditis.

Table I.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Auto-immune Thyroiditis

Thesis No.	Age	Sex	Clinical Status	Thyroid Auto-Antibody Tests Prec.	CF	Gamma-globulin (mg.%)	Tetanus Antitoxin Titres (Units/ml)	Comments.
2	56	F	Hypothyroid	+	++	1.42	>0.1<0.2	
3	52	F	Euthyroid	+	+	1.34	>0.5<1.0	
4	63	M	Hypothyroid	+	++	1.30	>0.1<0.2	Rheumatoid Arthritis. L.E.cell test positive Latent syphilis
5	41	F	Hypothyroid	+	++	1.66	0.01	
8	49	F	Hypothyroid	+	++	0.54	>5<10	
10	52	F	Hypothyroid	+	++	0.98	0.1	
12	48	F	Euthyroid	+	++	0.96	>0.01<0.02	
16	40	F	Euthyroid	-	++	1.60	>0.01-0.02	
17	45	F	Hypothyroid	+	++	1.22	>2. <5	
18	52	F	Euthyroid	-	++	0.83	0.01	
21	63	M	Euthyroid	+	++	1.18	>0.5<1.0	
25	50	F	Equivocally* Hypothyroid	+	++	1.42	>0.5<1.0	
26	43	F	Euthyroid	+	++	1.09	>0.5<1.0	
27	54	F	Hypothyroid	+	++	0.57	>0.1<0.2	
30	45	F	Hypothyroid	+	++	0.90	>0.05<0.1	
31	61	F	Euthyroid	+	++	0.68	>0.01<0.02	
33	55	F	Euthyroid	+	++	1.15	>0.05<0.1	
36	50	F	Equivocally* Hypothyroid	+	++	1.34	0.01	
42	57	F	Euthyroid	+	++	1.09	>0.01<0.02	Acquired idiopathic Coombs negative haemolytic anaemia
50	62	F	Hypothyroid	-	+	0.68	0.01	

* These patients have been classified as euthyroid in Figure1.

TABLE II.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Primary Hypothyroidism.

Table II.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Primary Hypothyroidism

Case No.	Age	Sex	Clinical Status	Thyroid Auto-antibody Tests Prec.	CF	Gamma-globulin (mg.%)	Tetanus Antitoxin titres (units/ml)	Comments
1	52	M	Hypothyroid	+	++	0.97	≥01 <02	
4	56	F	Hypothyroid	+	++	0.84	>0.05<0.1	Rheumatoid Arthritis
9	64	F	Hypothyroid	+	-	0.68	0.01	
19	56	F	Euthyroid	-	++	0.78	0.01	
22	39	F	Euthyroid	-	++	1.14	>1 < 2	
23	59	F	Euthyroid	-	++	0.89	>1 < 2	
24	59	F	Hypothyroid	-	++	0.56	> 0.1<0.2	
25	38	F	Euthyroid	-	++	1.25	>0.1 < 0.2	
27	56	F	Hypothyroid	-	+	0.56	0.2	
31	65	F	Euthyroid	-	+	0.65	>0.2 < 0.5	
32	67	F	Hypothyroid	-	+	0.94	>0.01	
33	53	F	Euthyroid	-	+	0.41	>0.5 < 1.0	
41	56	F	Hypothyroid	-	-	0.68	>0.5 < 1.0	
44	44	F	Euthyroid	-	-	1.00	0.01	
51	61	M	Hypothyroid	-	-	1.40	>0.01<0.02	
69	40	F	Euthyroid	-	-	1.15	>0.05 < 0.1	
70	65	F	Euthyroid	-	-	1.25	>0.2 <0.5	

TABLE III.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Cirrhosis of Liver.

Table III.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Female Patients with Cirrhosis of the Liver.

Case No.	Age (Yrs)	Sex	Aetiology of Cirrhosis	Thyroid Auto-Antibody Tests		Gamma-globulin (Units/ml)	Tetanus Anti-Toxin tetnes (Units/ml)	Comments
				Prec	CFT			
1	58	F	Idiopathic	+	++	2.67	<0.01	
2	71	F	Idiopathic	-	+	1.25	$>0.2 < 0.5$	
3	63	F	Idiopathic	-	++	1.69	$>0.2 < 0.5$	
4	45	F	Chronic Hepatitis	-	++	1.29	$>1 < 2$	
5	59	F	Alcoholic	-	++	2.58	$>0.5 < 1.0$	
6	57	F	Alcoholic	-	-	1.04	$>0.5 < 1.0$	
7	62	F	Idiopathic	-	Anticomplementary	1.48	$>0.2 < 0.5$	
8	58	F	Idiopathic	-	-	1.26	< 0.01	
9	64	F	Idiopathic	-	-	1.58	< 0.01	
10	61	F	Idiopathic	-	-	1.94	0.01	
11	54	F	Idiopathic	-	Anticomplementary	1.07	$>1 < 2$	
12	39	F	Chronic Hepatitis	-	-	0.92	0.01	
13	61	F	Chronic Hepatitis	-	-	1.78	$>0.1 < 0.2$	
14	67	F	Idiopathic	-	-	1.06	$>0.1 < 0.2$	
15	51	F	Idiopathic	-	++ (non specific)	1.37	$>0.05 < 0.1$	Rheumatoid Arthritis
16	54	F	Chronic Hepatitis	-	-	1.84	< 0.01	

TABLE IV.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Connective Tissue Disease.

Table IV.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Connective Tissue Disease.

Thesis No.	Clinical Condition	Age	Sex	Thyroid antibody Tests Prec.	Thyroid antibody Tests CF.	Gamma Globulin (g.%)	Tetanus Antitoxin Tetres (Units/ml.)	Comments
1	Systemic lupus erythematosis	53	F	-	-	1.10	>1.0 <2.0	
2	"	56	F	-	-	1.12	>0.01<0.02	On steroid therapy
3	"	32	F	-	-	2.10	>0.01<0.02	
6	"	36	F	-	++ (non specific)	1.81	>0.01<0.02	On steroid therapy
8	"	22	F	-	++ (non specific)	0.92	>0.2 <0.5	On steroid therapy
12	Scleroderma	43	M	-	-	0.56	>0.2 <0.5	On steroid therapy
15	"	49	F	-	++	1.12	>0.2 <0.5	
16	Dermatomyositis Primary Hypothyroidism	64	F	-	++	1.30	<0.01	
1	Rheumatoid arthritis	55	F	-	++ (non specific)	1.00	>0.01<0.02	
3	Rheumatoid arthritis	56	F	-	-	0.96	>0.05<0.1	
43	Rheumatoid arthritis	57	F	-	-	0.84	>0.1 <0.2	

TABLE V.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Controls.

Table V.

Clinical Details and Results of Primary Immunisation to Tetanus Toxoid in Controls

Case No.	Age	Sex	E.S.R. (mm/first hr.)	Gamma-Globulin (mg..%)	Tetanus Toxoid (Units/ml.)
1	59	F	4	0.79	> 0.05 < 0.1
2	56	F	7	0.62	> 0.02 < 0.05
3	63	F	9	0.56	> 2.0 < 5.0
4	69	F	11	0.62	> 0.1 < 0.2
5	40	F	7	0.61	> 0.05 < 0.1
6	38	F	10	0.82	> 0.1 < 0.2
7	57	F	3	0.42	> 0.05 < 0.1
8	58	F	2	0.53	> 0.05 < 0.1
9	35	F	5	0.74	> 0.05 < 0.1
10	58	F	3	0.96	> 0.1 < 0.2
11	38	F	8	0.83	> 0.1 < 0.2
12	68	F	11	0.86	> 0.1 < 0.2
13	58	F	2	0.65	> 2.0 < 5.0

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This thesis deals with a clinical study of auto-immune thyroiditis.

Chapter I is concerned with the background of the present study. The historical aspects, morbid anatomy, and past views regarding aetiology, are reviewed, and an account of the recent immunological developments is also given.

Chapter II deals with my observations in 50 patients with the disease and advantage has been taken of modern methods of investigation to study the clinical features. The role of the circulating thyroid auto-antibodies in the pathogenesis of the disease has been investigated in a study of the nature of skin reactions following the intradermal injection of sterile extracts of human thyroid tissue in patients with auto-immune thyroiditis. The biochemical changes in this condition also form part of the contents of this chapter and include observations of the serum proteins, serum flocculation tests, and erythrocyte sedimentation rate. The mechanism of these changes is discussed and their diagnostic significance evaluated. A detailed investigation of iodine metabolism has been undertaken and the abnormalities in the handling of both stable iodine and radioiodine is discussed. Finally, the differential diagnosis and treatment of the disease are considered in the light of these investigations.

Chapter III of the thesis is concerned with the relationship of auto-immune thyroiditis to primary hypothyroidism and to thyrotoxicosis. Evidence is presented that primary hypothyroidism is a pathological variant of auto-immune thyroiditis. Thyroid auto-antibodies have been studied in thyrotoxicosis in relation to the clinical features, to the outcome of antithyroid therapy, and to the focal lesions of auto-immune thyroiditis in the thyroid gland after operation. The results of these investigations help to elucidate the nature of the auto-immune reaction in thyrotoxicosis, and also have important practical implications in the management of the thyrotoxic patient.

Chapter IV deals with the wider implications of auto-immune disease resulting from a study of the clinical associations of auto-immune thyroiditis with the connective tissue disorders, in particular rheumatoid arthritis, the haemolytic anaemias, and cirrhosis of the liver. An experiment designed to measure the antibody-forming potential in patients with auto-immune disease is also reported in this chapter. Finally, the implications of these studies are discussed in relation to the clonal selection theory of antibody formation and to the concept of acquired immunological tolerance.

The thesis is presented in three volumes. Chapters I and II are presented in Volume I, Chapters III and IV in Volume II, and the Appendices and References in Volume III. Separate summaries are presented at the conclusion of each section and have been indexed in the table of contents. In order to facilitate the reading of the thesis I have enclosed a separate table of contents for each of Volumes I and II.