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Recent Progress in Diagnosis and Treatment of Hypothyroid Conditions

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Theme 1

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Foreword

In September 1979 the XVth International Congress of Therapeutics was held in Brussels under the patronage of Her Majesty the Queen of the Belgians and under the auspices of the International Union of Therapeutics. These Congresses, which take place every second year, aim at the assessment of our present knowledge in the therapeutics of various fields of medicine.

Three themes were chosen for the Brussels Congress because of their importance and present interest:

1. Recent progress in the diagnosis and treatment of hypothyroid conditions;
2. Prevention and treatment of coronary heart disease and its complications;
3. New advances in the diagnosis and treatment of depressive illness.

Invitations were issued to experts from different European countries and the United States, who well know the problems of these various topics.

The Organizing Committee of the Congress decided to publish these symposia in the form of three separate monographs. The book, which is presented today to the medical public has been edited by Professor P.A. Bastenie and his associates, Professor L. Vanhaelst and Dr M. Bonnyns. It concerns 'Recent Progress in Diagnosis and Treatment of Hypothyroid Conditions'. This book also contains the proceedings of a Round Table meeting dedicated to a matter of special interest: 'Hypothyroidism and the Heart'.

The book forms a coherent entity and I feel certain that it will be useful to its readers, whether they are endocrinologists, internists or cardiologists.

Professor Jean Lequime
President of the XVth International
Congress of Therapeutics

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1. SYMPOSIUM: HYPOTHYROID CONDITIONS

2. ROUND TABLE: HYPOTHYROIDISM AND THE HEART

1. Symposium on Hypothyroid Conditions

Chairmen

L. BASCHIERI (Pisa)
A.M. ERMANS (Brussels)

Hypothyroid conditions

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Myxoedema remained unknown till 1874, when 5 cases were described by W.W. Gull. In 1888, a Commission appointed by the Clinical Society of London under the chairmanship of W.M. Ord gave as its conclusions: 'That a general review of symptoms and pathology leads to the belief that the disease described under the name of myxoedema, as observed in adults, is practically the same disease as that named sporadic cretinism when affecting children; that myxoedema is probably identical with cachexia strumipriva and that a very close affinity exists between myxoedema and endemic cretinism. That while these several conditions appear, in the main, to depend on, or to be associated with destruction or loss of the function of the thyroid gland, the ultimate cause of such destruction or loss is at present not evident.' Three years later, Dr Murray showed that treatment with thyroid extracts wiped out all signs and symptoms of the disease.

Although the existence of lesser degrees of the disease had been hinted at by the Clinical Society report and some had even been reported by Hertoghe (1914), up to the present time, most classical textbooks still teach myxoedema as described in the Victorian period. Thus: 'myxoedema is the clinical manifestation of complete loss of thyroid function due to total atrophy of the gland and is characterized by a low basal metabolism, increase of weight, thickening of the skin and mental disturbance' (Textbook of Medicine by Sir John Conybeare, 10th edition, 1952).

Abbreviations: T4: thyroxine; T3: triiodothyronine; TSH: thyroid stimulating hormone or thyrotrophin; TRH: thyrotrophin releasing hormone; AAT: autoimmune asymptomatic thyroiditis; $PB^{127}I$: protein bound iodine; $PB^{131}I$ and $PB^{125}I$: protein bound radioactive iodine; BEI: butanol extractable iodine; N-BEI: non-BEI.

This static concept of a disease said to be rare, severe and assimilated to the total and sudden glandular insufficiency induced by surgical or experimental thyroidectomy, should presently give place to that of a dynamic process leading to the gradual loss of thyroid function. This concept is based on pathological, immunological, biological and clinical findings and opens up prospects of earlier diagnosis and therapy.

Pathological studies

That the thyroid atrophy, the underlying lesion of severe hypothyroidism, may result from advanced chronic atrophic thyroiditis was first suggested by Simmonds (1923) and confirmed by later studies

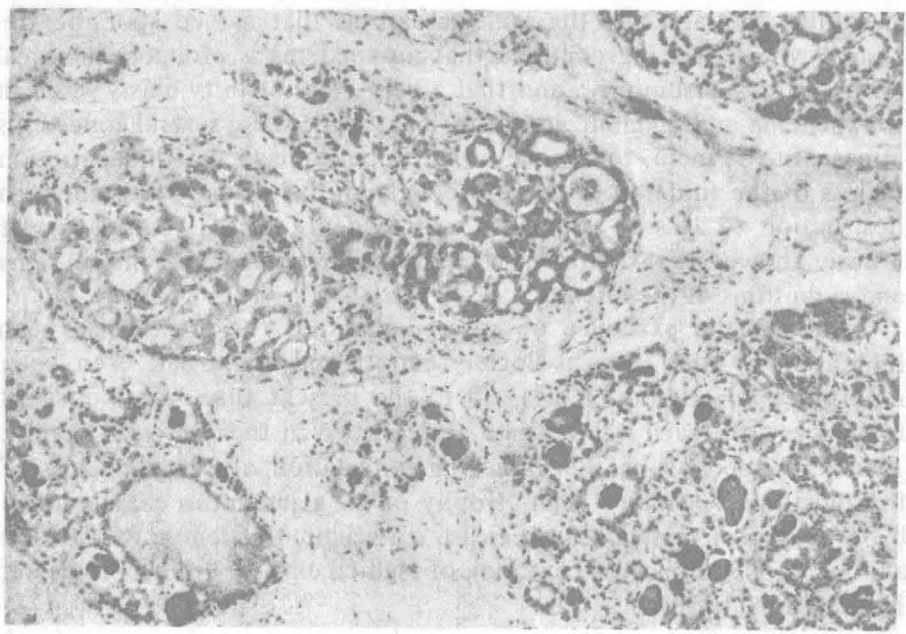

Fig. 1. Thyroid autoradiography from a 68-year-old patient admitted with Adams-Stokes syndrome, thrombophlebitis and multiple pulmonary infarcts who died from a cerebral infarct. High titres of thyroid antibodies (thyroglobulin and cell-fluorescent) had been detected. Twenty-seven days before death she had received a dose of ^{125}Iodine. Radio-iodine can be seen in the colloid and inside the thyroid cells in the right and lower part of the picture. In the left upper part, clusters of typical oncocytes devoid of colloid are free from radio-iodine. In this part of the gland, infiltrates are strikingly absent. The morphological and biochemical anomalies appear as primary thyroid-cell lesions.

(Bastenie, 1937, 1944; Douglass and Jacobson, 1957; Sclare, 1963). The systematic post-mortem investigation of the thyroid in hospitalized subjects who had died from various non-thyroidal diseases showed in nearly 20% of the cases (more especially in those of elderly women), lympho-plasmatocytic infiltrates, varying from small focal to large diffuse inflammatory lesions. In close connection with these infiltrates, serial sections revealed the presence of peculiar, swollen, eosinophilic thyroid cells, called Hürthle cells or oncocytes. At the time, the whole process was viewed as a lympho-plasmatocytic reaction against products of cellular proteolysis (Bastenie, 1937). Later studies were to show that the thyroid oncocytes were filled with mitochondria but devoid of lysosomic material and unable to take up radioactive iodine (Fig. 1): the question remains open whether they represent victims of the inflammatory process or sites of immunogen production.

In the most severely affected glands, the amount of thyroid parenchyme was greatly reduced and sclerotic tissue developed, completing a continuous spectrum of thyroid alterations from focal asymptomatic stages to those underlying severe myxoedema (Figs. 2 and 4).

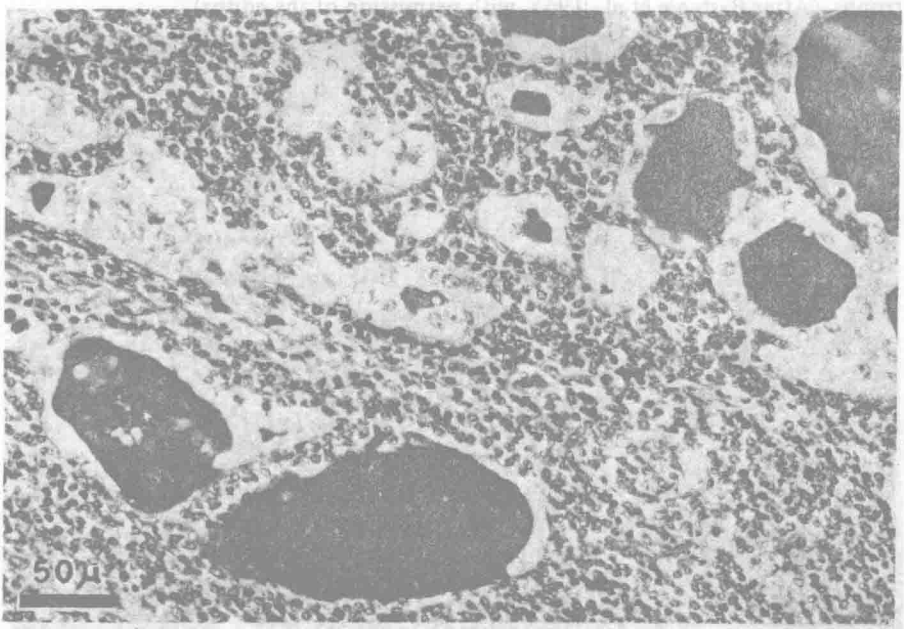

Fig. 2. Thyroid parenchyma remnants, mostly distorted, amongst lympho- and plasmatocyte infiltrates. (Female patient, 75 years old; severe untreated myxoedema).

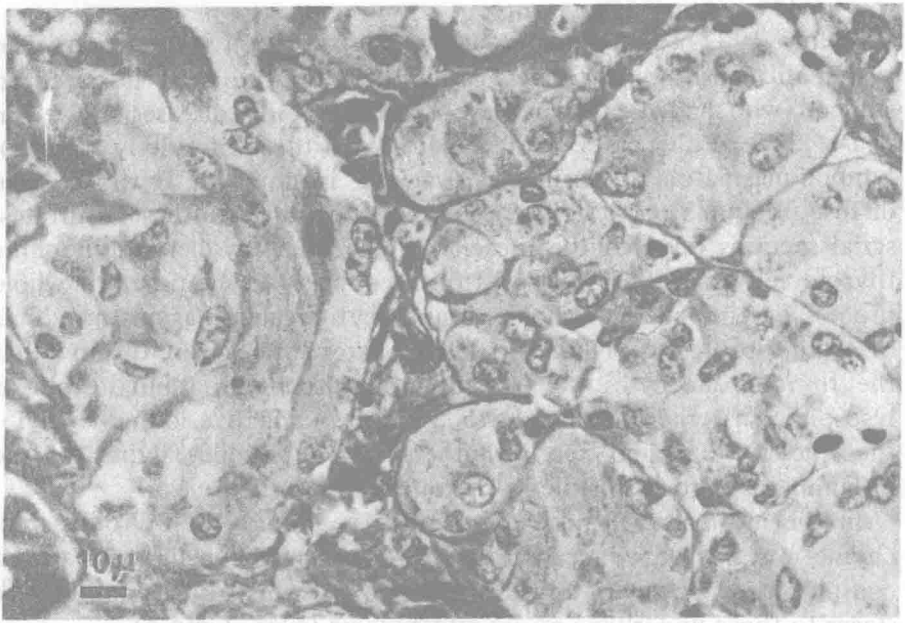

Fig. 3. Pituitary of same patient. Marked hypertrophy and hyperplasia of thyrotrophs. (After Bastenie et al., 1965, with permission of the editor).

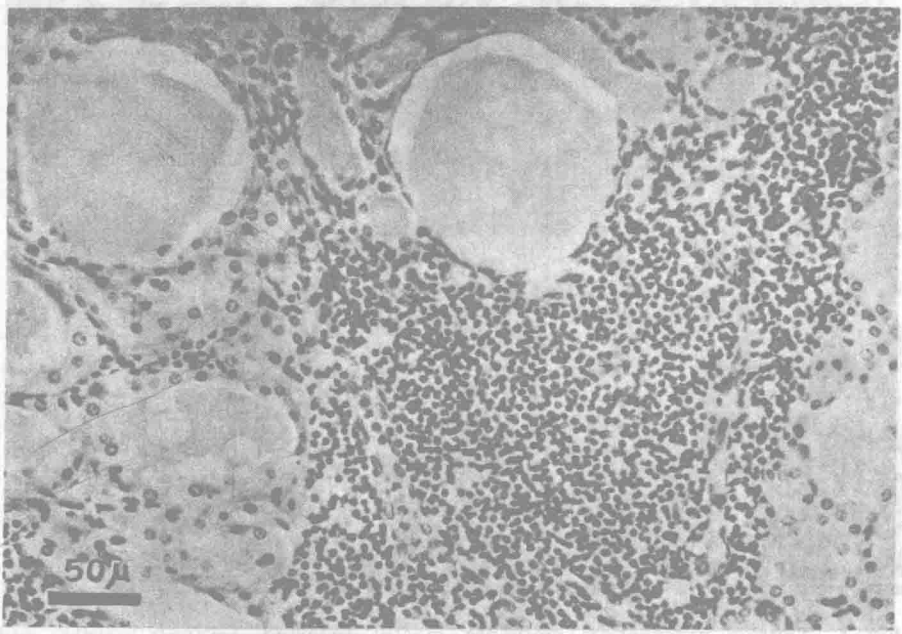

Fig. 4. Focal thyroiditis, with localized oncocytes. (Female patient, 49 years old; with asymptomatic thyroiditis).

In the pituitary of the subjects so affected, various degrees of hyperplasia and hypertrophy of a certain class of pituitary cell were observed giving them the appearance of the experimental 'thyroidectomy-cells' (Figs. 3 and 5). Similar pituitary changes had indeed been described in thyroidectomized animals and in a few cases of human subjects with thyroid atrophy (Wegelin, 1924; Berblinger, 1932). Recent studies, using elective affinity stains have shown that the 'thyreoprive' cells arise from changes in specific basophil cells: they may be considered as the 'morphological outcome of a negative feed-back process' in the absence of normal quantities of thyroid hormones (Herlant and Pasteels, 1966, 1972). In myxoedematous subjects who died without adequate treatment, the large vacuolized, partially degranulated pituitary cells are hyperactive cells synthetizing and secreting large amounts of thyrotrophin (Fig. 3). They contain increased reserves of TSH, as measured in the pituitary itself (Bonnyns et al., 1972). After a few days of adequate treatment with thyroid hormones, the size of the thyrotrophs shrinks and the retracted cytoplasm is filled with lysosomal material, reabsorbing the secretory TSH granules

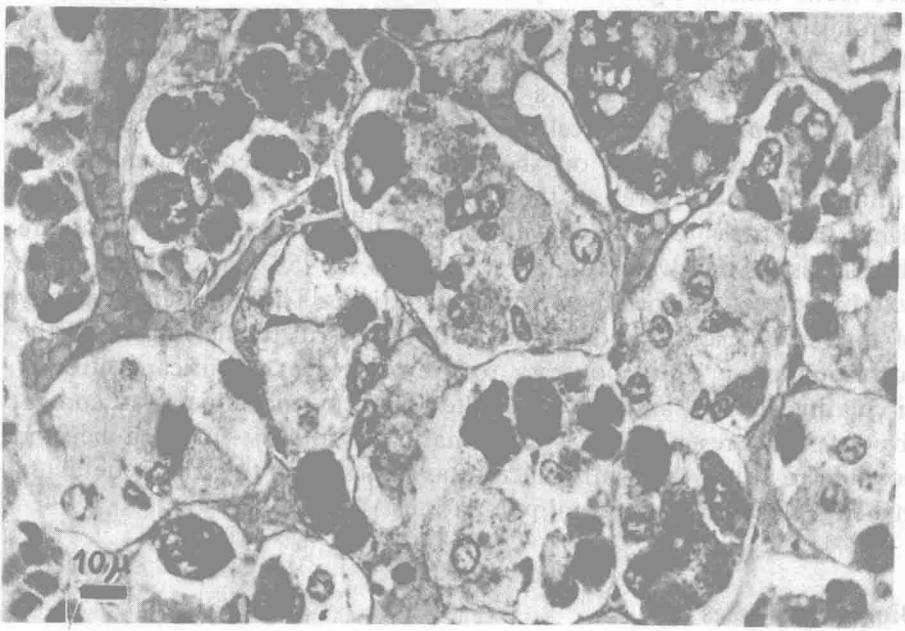

Fig. 5. Pituitary of same patient. Hypertrophy and hyperplasia of thyrotrophs. Vacuolization of basophilic cells. Same magnification as Fig. 3. (After Bastenie et al., 1965, with permission of the editor).

(Herlant and Pasteels, 1972). In asymptomatic thyroiditis, the cytological reactions only differ in degree from those observed in clinical hypothyroidism (Fig. 5): here too, increased amounts of thyrotrophic hormones have been detected in the pituitary tissue (Bonnyns et al., 1972) overflowing into the blood stream in the most serious cases (Bonnyns and Bastenie, 1966, 1967; Gordin et al., 1972). These morphological changes explain the older (Niepce, 1851) and recent (Guinet et al., 1976; Aizawa et al., 1978) observations of the increased volume of the pituitary gland in hypothyroid subjects, strictly in relation to the degree of hypothyroidism.

Immunological studies

Soon after the discovery of thyroid antibodies in the serum of patients affected with Hashimoto's struma lymphomatosa (Roitt et al., 1956), the same circulating antibodies were demonstrated in patients with myxoedema (Owen and Smart, 1958) and also in a number of subjects free from clinical signs of thyroid disease but in whom lymphocytic thyroiditis was often found in biopsy or necropsy specimens (Goudie et al., 1959; Bastenie et al., 1967). Post-mortem examinations were performed on 247 cases from a population of over 2,000 hospitalized patients, admitted for miscellaneous diseases and screened for thyroid antibodies. Either none or an insignificant number of lymphocyte infiltrates were observed in the great majority of the subjects without significant titres of thyroid antibodies, whereas definite or severe thyroiditis lesions were found respectively in 75% and 96% of those who had presented with high or very high titres. The simultaneous assay of microsomal and thyroglobulin antibodies still further increased the correspondence. Thus, contrary to previous ideas, significant titres of circulating thyroid antibodies detected in euthyroid subjects are indicative of the presence of asymptomatic thyroiditis. It then became possible to study the significance of asymptomatic thyroiditis detected in a large hospital and general populations.

Biological studies

Iodine metabolism in hypothyroidism is characterized by lowering of both circulating thyroxine and triiodothyronine. The level of serum

$PB^{131}I$ is usually impossible to calculate (Litt. in Bastenie et al., 1972) owing to low radio-iodine uptake, barely increased by the administration of TSH. However in a few cases high values of $PB^{131}I$ have been reported reflecting the very small exchangeable iodine pool in the functioning tissue. The study of iodine metabolism in AAT by Buchanan et al. (1965) and by Camus et al. (1966, 1968) has disclosed similar, although less marked alterations (Table 1). As in Hashimoto's thyroiditis, the hypertrophic variant of autoimmune thyroiditis, plasma PBI and BEI are significantly decreased, while T4 levels remain in the lower normal range and T3 values are unchanged. The radioactive iodine uptake is usually normal, although high rates may occasionally be observed, easily reduced by the administration of potassium iodide (Buchanan et al., 1965). Moreover the radioactive iodine is rapidly discharged and after 24 hours, $PB^{131}I$ is significantly higher than in normal subjects. After TSH stimulation, plasma $PB^{127}I$ increases only moderately but $PB^{125}I$ rises sharply. The exchangeable organic iodine pool is reduced to less than half its normal value.

In 2 cases of AAT, histological specimens obtained after ^{125}I administration showed selective absence of radio-iodine uptake in isolated groups of oncocytes (Fig. 1). Increased levels of serum TSH present in 1/3 to 1/4 of AAT-affected subjects have already been mentioned. Exaggerated TRH responses have been described by Gordin and Lamberg (1972, 1974) and Tunbridge et al. (1977). In a number of subjects, this sign of increased pituitary TSH reserve has been found in

TABLE 1

Iodine metabolism in AAT

	Units	Patients without TGA	Patients with TGA
^{131}I uptake 24 hr	% dose	45 ± 11	44 ± 16
Plasma $PB^{127}I$	μg/dl	6.1 ± 1.6	5.4 ± 1.9
Plasma $PB^{125}I$ (24 hr)	% dose/l	0.02 ± 0.01	0.10 ± 0.10
Apparent release rate of thyroidal ^{131}I	% 24 hr	0.46 ± 0.25	1.12 ± 0.93
Specific activity of PBI discharged 24 hr after TSH	0.10^{-3} % dose/μg	6.5 ± 4.5	26.6 ± 21.4
Exchangeable thyroid organic pool	mg	8.1 ± 4.6	3.3 ± 3.5

TGA = thyroglobulin antibodies.
After Camus et al., 1968

the absence of elevated levels of serum TSH. In a recent study (Bastenie et al., 1980) 1/6 of 60 non-selected female subjects with circulating thyroid antibodies, presented with a markedly increased basal TSH level. However, in 1/3 of the subjects a normal level of basal TSH coincided with an excessive response to the administration of TRH, indicating the presence of increased intrapituitary TSH reserve. Needless to say, these signs of pituitary overactivity fall short of the tremendous reactions that characterize florid hypothyroidism. However, whereas the latter occur in states of very reduced serum levels of T3 and T4, in asymptomatic thyroiditis they are correlated with barely significant changes of T4, still within the normal range, in the absence of any change in the serum T3 levels.

Clinical studies

These have ascertained the progressive development of clinical hypothyroidism in subjects previously known to be affected with asymptomatic thyroiditis (Buchanan et al., 1965; Bastenie et al., 1967; Fowler and Swale, 1967). Gordin and Lamberg (1975) and Tunbridge and Clark (1978) have pointed out that those most prone to undergo such evolution are the subjects presenting with circulating thyroid antibodies and increased TSH and TRH reactions. However, as indicated by Tunbridge and Clark (1978) the prognosis of AAT remains unpre-

TABLE 2

Grades of premyxoedema (asymptomatic autoimmune thyroiditis) and clinical hypothyroidism

Pathological conditions	Degree	Thyroid autoimmunity	T3	T4	TRH	TSH
Asymptomatic thyroiditis	I	+	N	N	N	N
	II	++	N	N – low N	↑	N
	III	+ to +++	N	low N	↑	↑
Hypothyroidism subclinical or monosymptom.	I	+++	N	low N or ↓	↑↑	↑↑
overt	II	+++	↓	↓↓	↑↑	↑↑
severe	III	0 to +++	↓↓	↓↓	↑↑↑	↑↑↑

T3 = tri-iodothyronine; T4 = thyroxine; TRH = TSH releasing hormone; TSH = thyroid stimulating hormone

dictable: in most cases the process remains static, in some subjects it may even regress. On the other hand, far from always developing the classical polysymptomatic disease, clinical hypothyroidism may be restricted to the expression of one single clinical anomaly. Thus pleural effusion, paralytic ileus, periocular oedema, chemosis and hair loss may

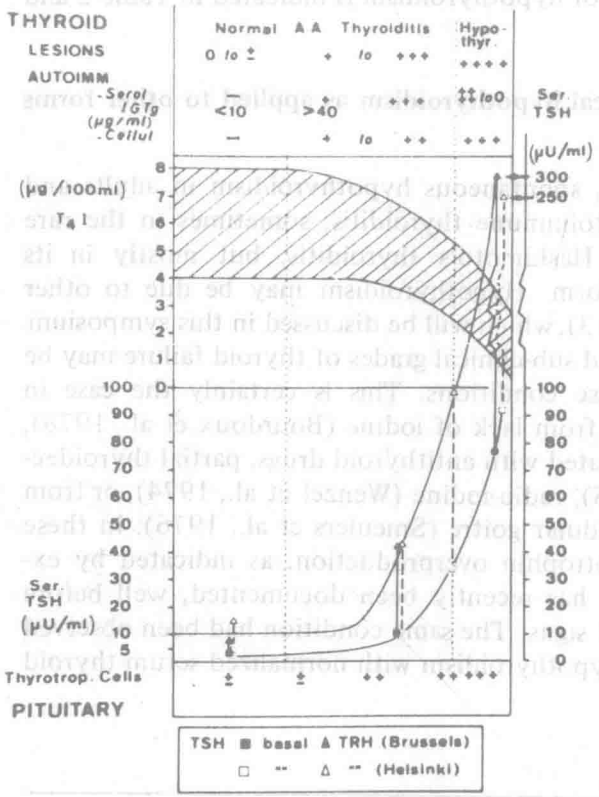

Fig. 6. Schematic development of autoimmune thyroiditis into clinical hypothyroidism (after Bastenie, 1977). This figure is made up by the apposition of cross-sectional observations of subclinical and clinical stages collected in Brussels by Bastenie et al. (1965); in Newcastle by Evered and co-workers (1973); in Helsinki by Lamberg (Gordin and Lamberg, 1975); in London by Fowler and his group (1967). The process starts as an autoimmune phenomenon, whether due to primary thyroid immunogen production (located in the oncocytes?) or to abnormal autoimmune reactions or to both of these factors. Initially the histological lesions are only detectable in vivo by serological and cellular immune reactions, later accompanied by the serological signs of increased intrapituitary thyrotrophin production and storage. While serum T3 levels remain unchanged, the T4 levels gradually decrease to the lower normal limits, inducing an increase in the pituitary reactions. Finally not only T4 but also T3 levels drop off and the clinical signs appear (cf. Table 2).