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Immunohistological Findings in Hashimoto's Thyroiditis, Focal Lymphocytic Thyroiditis and Thyroiditis de Quervain

Comparative Study

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Summary. 65 cases of focal lymphocytic thyroiditis and Hashimoto's disease and five cases of thyroiditis de Quervain were studied with immunohistological methods. In both focal lymphocytic thyroiditis and Hashimoto's disease, lymph follicles with active germinal centers were found which contained germinal center cells that stained positively for intracytoplasmic immunoglobulins (heavy and/or light chains). Positively staining germinal center cells made up only a minor portion of overall immunoglobulin-positive cells; most of the positive infiltrating cells were plasmacytes arranged in small groups or clusters among thyroid follicles. Thus the number of immunoglobulin-containing cells differed greatly between focal lymphocytic thyroiditis, where sites of infiltration were represented by lymph follicles, and Hashimoto's disease. In the former, only a few cells outside lymph follicles stained positively for intracytoplasmic immunoglobulins, whereas in the latter numerous cells within areas of coherent infiltration did. Furthermore, in most cases of Hashimoto's disease macrophages and giant cells with positive staining for lysozyme were present in variable numbers, while in focal thyroiditis they were less frequent or absent. Between these two immunohistologically separable groups, i.e. focal lymphocytic thyroiditis and Hashimoto's disease, there were many cases with features of both. Considering the occurrence of such intermediate forms and some immunohistological similarities between Hashimoto's disease and focal lymphocytic thyroiditis (nearly identical ratio of the different immunoglobulin classes and similar distribution of immunoglobulin-positive germinal center cells), it is likely that these lesions represent different activities of a same immunological process.

Thyroiditis de Quervain was characterized immunologically by numerous macrophage clusters and giant cells that both stained positively for lysozyme. Compared with the giant cells seen in Hashimoto's disease (mainly of Langhans type), those of de Quervain's thyroiditis (mainly of foreign body type) were

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larger and more numerous. Lymph follicles (with or without active germinal centers) were not observed. Among infiltrating cells, numerous plasmacytes that stained positively for intracytoplasmic immunoglobulins were identified. Their number and the distribution pattern of the different classes of immunoglobulins contained within them was similar to those seen in Hashimoto's disease.

Key words: Hashimoto's thyroiditis – Focal thyroiditis – Granulomatous thyroiditis – Immunohistology

The first antigen detected in Hashimoto's disease was thyroglobulin (Roitt et al. 1956; Doniach and Roitt 1957); subsequently the microsomal fraction of thyroid epithelial cells (Trotter et al. 1957; Roitt and Doniach 1958; Holborow et al. 1959), a second component of colloid (other than thyroglobulin) (Balfour et al. 1961), and the epithelial surface antigen were also identified (Fagraeus and Jonsson 1970). Infiltrating lymphocytes and plasma cells were identified as sites of antibody production against thyroglobulin and microsomal antigen (Mellors et al. 1962; McLachlan et al. 1979). The serum concentrations of antibodies to thyroglobulin or microsomal antigen correlate only roughly with the extent of thyroid infiltrates (Roitt and Doniach 1958; Porter and Fennell 1961). Low titers of antibodies are therefore compatible with both diffuse and focal infiltration in the gland. Thyroid antibodies are present also in other inflammatory or neoplastic thyroid diseases (Stuart and Allan 1958; Blizzard et al. 1959; Cline et al. 1959).

Separation of Hashimoto's thyroiditis from focal thyroiditis by morphological methods is easy in cases of diffuse or slight focal infiltration, but becomes difficult or impossible when focal infiltrates are pronounced (Woolner et al. 1959). The overlapping of the histological features of Hashimoto's disease and focal lymphoplasmocytic thyroiditis is obvious; the question arises as to whether these are two distinct entities or only one pathologic process with Hashimoto's thyroiditis at the one end and focal thyroiditis at the other end of a broad spectrum. The present study was undertaken in order to answer this question.

Material and Methods

Thyroid tissue from 65 patients who had undergone partial or total thyroidectomy for goiter or suspected malignancy was investigated. 60 patients revealed slight to severe lymphoplasmocytic infiltration of the thyroid, and thyroiditis de Quervain was diagnosed in 5 patients. 6 μm thick sections from samples of each case were stained with HE, PAS, and Gomori. In all cases, detection of intracytoplasmic immunoglobulins was performed by a modified application of the method of Sternberger et al. (1970). Preincubation with trypsin was carried out with a solution of 0.01 % MERCK trypsyn (art. no 24579) for 1–2 min at room temperature. Dilutions of primary antisera were 1 : 2,400 for kappa, 1 : 2,400 for lambda, 1 : 200 for IgG, 1 : 400 for IgM, 1 : 800 for IgA and 1 : 100 for lysozyme. In each case, a positive reaction control was performed with slides of a lymph node showing features of follicular hyperplasia. Negative controls were performed by replacing the specific antiserum by normal rabbit serum or pure TRIS saline. All antisera used were obtained from DAKO Immunoglobulins Ltd., Copenhagen, Denmark.

Semiquantitative analysis was carried out with a MOP-AMO$_3$ instrument.

Degree of Infiltration of Thyroid Tissue was assessed by counting infiltrating cells, i.e. lymphocytes, plasma cells, monocytes and macrophages. The smallest units to be counted amounted to at least 10 mononuclear cells. On each slide, a focal point was marked with a pencil. 10 squares measuring

1 mm × 1 mm at intervals of 2 mm were investigated. Six of the squares were aligned on a first and four of the squares on a second cross line through the focal point. Integration of infiltrated areas was performed at a magnification of 10 × 8. The results obtained were divided into five groups with a different degree of infiltration. The five groups were: 1–10, 10–20, 20–40, 40–80, and 80–100% infiltration.

Number of Cells Containing Immunoglobulins Within Infiltrated Areas. Within 10 squares composed of infiltrating cells, the number of positive cells was evaluated. The squares measuring 0.1 × 0.1 mm were randomly chosen within a field of 1 cm^2, the focal point of which was identical with that of the slide. Counting for light chains (kappa/lambda) and heavy chains (g, m, and a) was performed at a magnification of 40 × 8.

The Absolute Number of Germinal Centers was determined by counting the germinal centers within a field of 1 cm^2 of which the focal point was identical with the focal point of the slide.

The Relative Number of Germinal Centers represents the absolute number of germinal centers in relation to the degree of infiltration. In each infiltration group, the arithmetic mean (5, 15, 30, 60, and 90% respectively) was taken.

Results

Lymphoplasmocytic Thyroiditis

The subdivision of cases into five groups according to the degree of infiltration revealed the following distribution (Table 1): focal infiltrates were slight in 12 cases

Table 1. Subdivision of 60 cases of lymphoplasmocytic thyroiditis into groups of varying degrees of infiltration density

Histological group	I	II	III	IV	V
Degree of infiltration	1–10	10–20	20–40	40–80	80–100%
Number of cases	12	13	15	7	13

Table 2. Thyroid function in lymphoplasmocytic thyroiditis

Histological group	Thyroid function					
	revealed by interview and physical examination			revealed by I^{131} study or T_3/T_4 test		
	eu-	hypo-	hyperthyroid	eu-	hypo-	hyperthyroid
I	8	0	2	5	0	2
II	9	0	2	3	0	2
III	8	0	3	4	0	3
IV	5	1	0	0	1	0
V	8	3	0	2	6	0
I–V	38	4	7	14	7	7

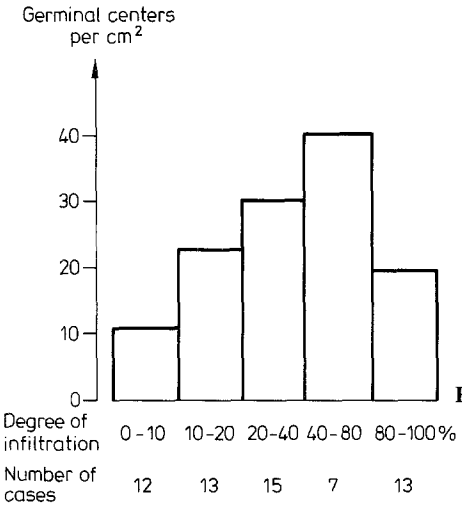

Fig. 1. Absolute number (mean) of germinal centers

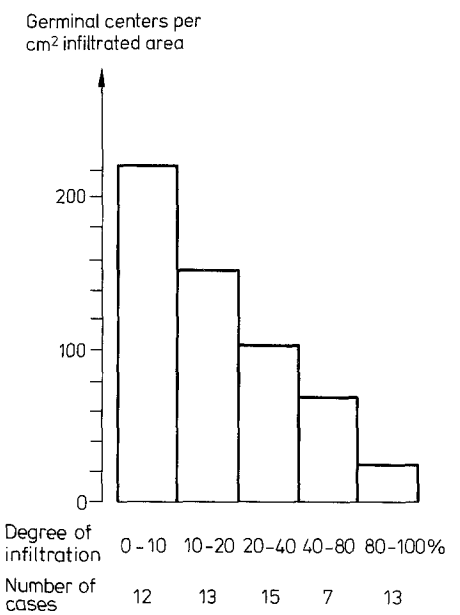

Fig. 2. Relative number (mean) of germinal centers

(1–10% infiltration) and pronounced in 13 cases (10–20% infiltration); 15 cases (20–40% infiltration) represented a borderline group between focal and coherent infiltration. In seven cases, coherent infiltration ranging from 40–80% was observed; in 13 cases (80–100% infiltration) nearly all thyroid tissue was interspersed with or even replaced by infiltrating cells.

Clinical Data. Of the 60 patients, 56 were female and 4 male. The median age was 49.1 ± 13.1 years. The time from onset of thyroid enlargement until operation ranged from 1 month to several years and bore no relation to the degree of

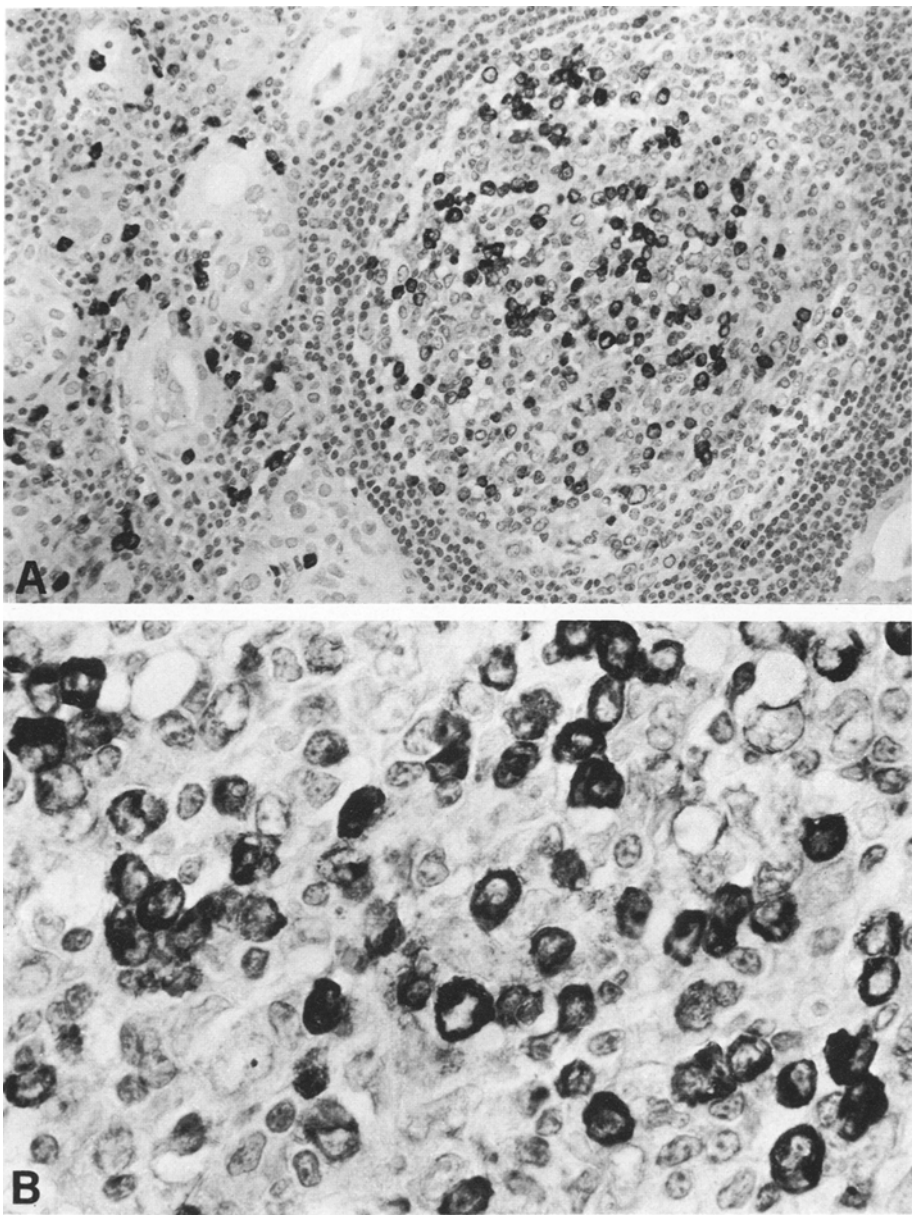

Fig. 3A, B. Hashimoto's disease. Morphology of germinal center. **A** Germinal center encompassed by a small cuff of lymphocytes comprises numerous cells staining positively for lambda light chain. Lambda-positive plasma cells are scattered throughout adjacent thyroid tissue. ×320. **B** Higher magnification. Large- and medium-sized germinal center cells are positive for lambda light chain. Positive cells resembling plasma cells are also present. ×800

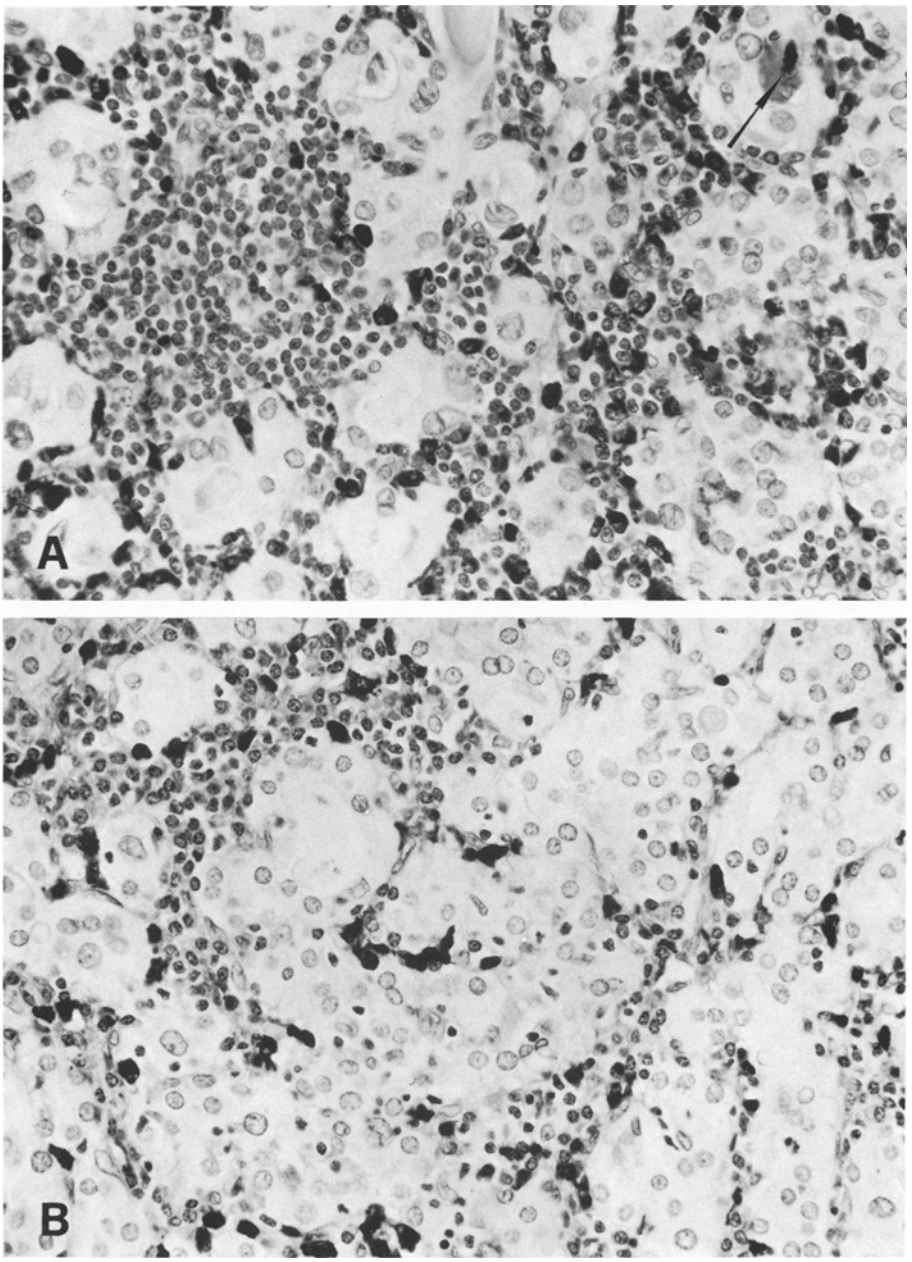

Fig. 4A, B. Hashimoto's disease. Ratio of kappa: lambda-positive plasma cells. **A** More than half the infiltrating plasma cells are positive for kappa light chain. Note an intrafollicular plasma cell (*arrow*). A cluster of small lymphocytes is at the upper left. ×320. **B** Same case as in A. Between oncocytically transformed epithelial cells, numerous lambda-positive plasma cells were identified, but about 2/3 of all plasma cells present do not stain for lambda light chain. ×320

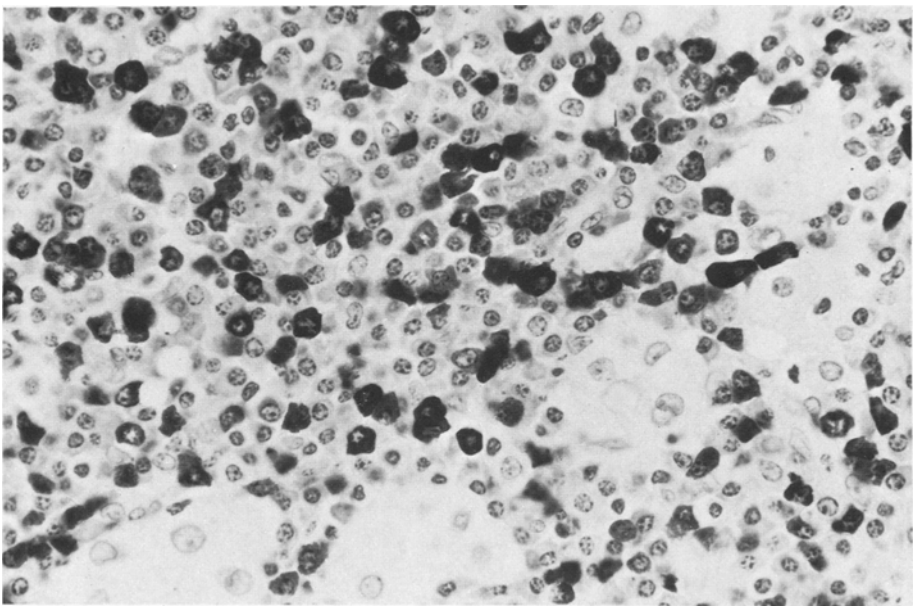

Fig. 5. Hashimoto's disease. Field of plasmocytoma-like appearance. Reaction for light chains (lambda) is positive in about 40 % of plasma cells. The remaining plasma cells were positive for kappa light chain. × 400

infiltration. There were six patients operated for suspected malignancy in group V (infiltration 80–100 %). In these patients, the thyroid had enlarged within a few months.

In three additional cases (two from group III and one from group II), suspected malignancy was confirmed by surgery (one papillary carcinoma of the thyroid, one anaplastic carcinoma of the thyroid and one highly malignant lymphoma of centroblastic type). In all other cases, the indication for operation was benign enlargement of the thyroid (struma nodosa and struma diffusa). In two cases, thyroid enlargement was preceded by pregnancy. The clinical data of thyroid function are listed in Table 2. Cases with hyperthyroidism occurred mainly in the groups with focal infiltration, hyperthyroidism was severe in two patients, one of whom manifested exophthalmos (case of group II). Hypothyroidism was diagnosed only in cases with severe infiltration (groups IV and V). In three patients of group V, hypothyroidism was detected by clinical tests only.

In most cases subtotal strumectomy was performed. In nearly all cases of group V and in several cases of the other groups, postoperative substitution of thyroid hormone proved to be necessary.

Histology. The most prominent areas of infiltration were lymph follicles with active germinal centers. The *absolute* number of germinal centers increased with the degree of infiltration (Fig. 1), except in the last group, where a reduction of absolute number of germinal centers was noted. A reliable measure of the actual share of infiltrates contributed by active germinal centers is given by the *relative* number of germinal centers (Fig. 2). In focal lymphoplasmocytic thyroiditis (groups I and II),

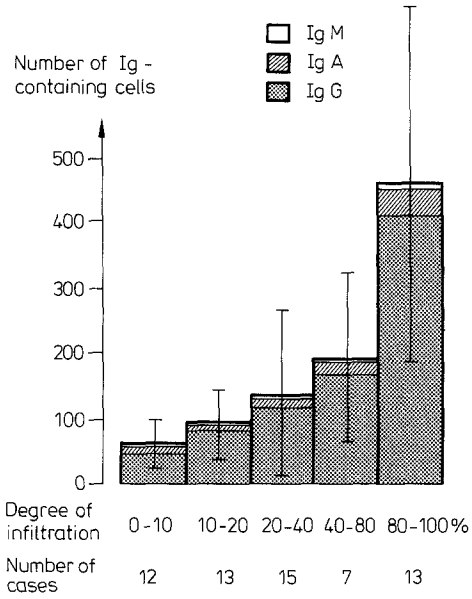

Fig. 6. Number of cells containing intracytoplasmatic immunoglobulins

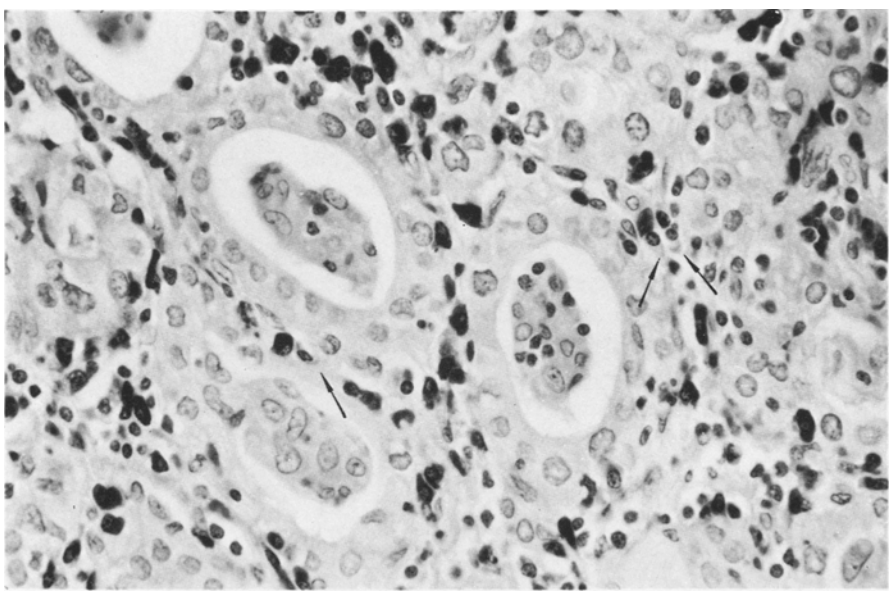

Fig. 7. Hashimoto's disease. Most infiltrating cells are plasmacytes, which stain positively for IgG. Only a few IgG-negative plasma cells are detectable (*arrows*). × 400

most of the infiltrating sites consisted of lymph follicles, whereas in cases with severe infiltration (groups IV and V) most of the infiltrate was formed by lymphocytes, plasma cells, and macrophages, arranged in small and large groups. This is shown by a continuous decrease of the relative number of germinal centers in combination with progressive degree of infiltration.

Germinal center cells, which stained positively for immunoglobulins, made up

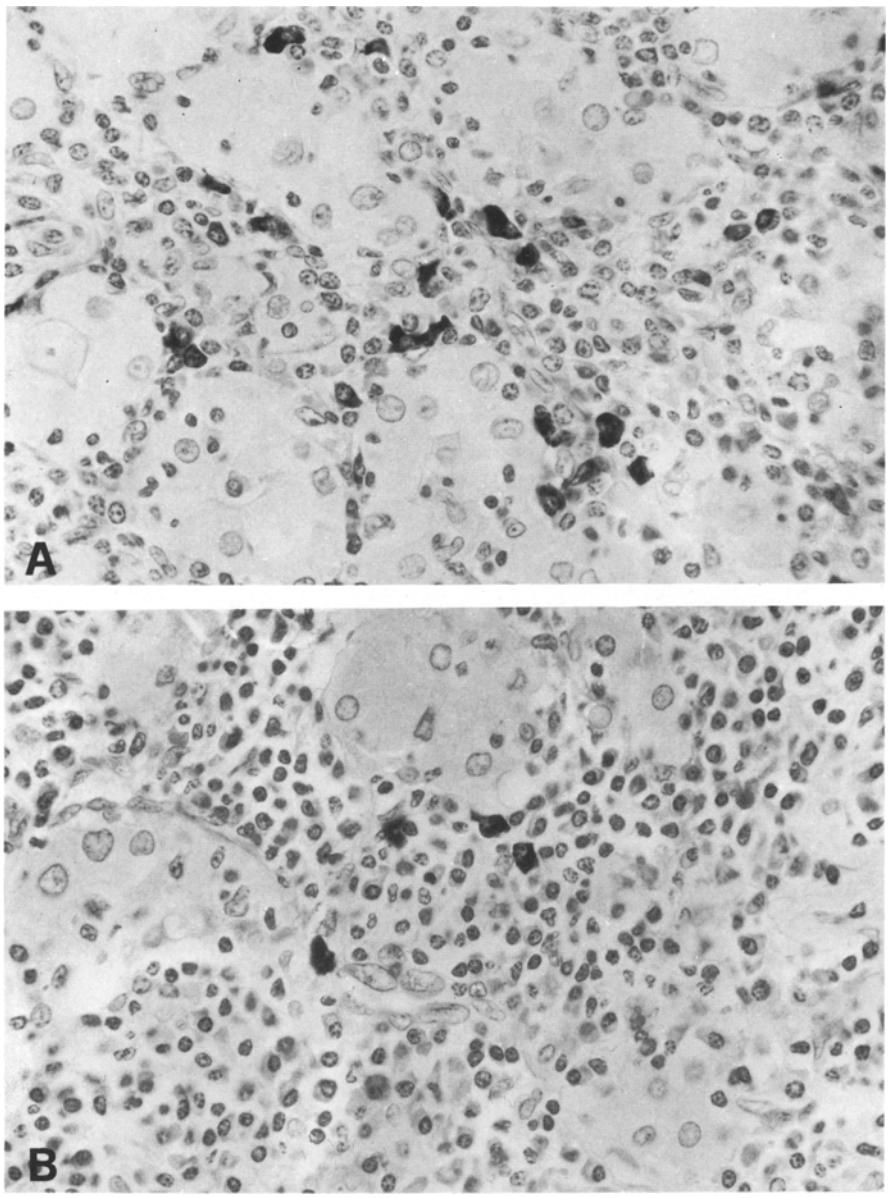

Fig. 8A, B. Hashimoto's thyroiditis. Presence of IgA- and IgM-positive plasma cells. **A** Several plasma cells positive for IgA are scattered among numerous plasma cells without positive staining. (Most of these cells are positive for IgG). ×400. **B** Same case as A. Only four plasma cells show positive staining for IgM. ×400

only a minor proportion of Ig-positive infiltrating cells. Within germinal centers of 30 cases from all five groups, positive cells for kappa or lambda chains were detectable (Fig. 3). Kappa- and lambda-positive cells both occurred in the same germinal centers; in seven of these cases germinal center cells were also positive for IgG. In seven cases germinal centers contained IgG- and IgM-positive cells. In

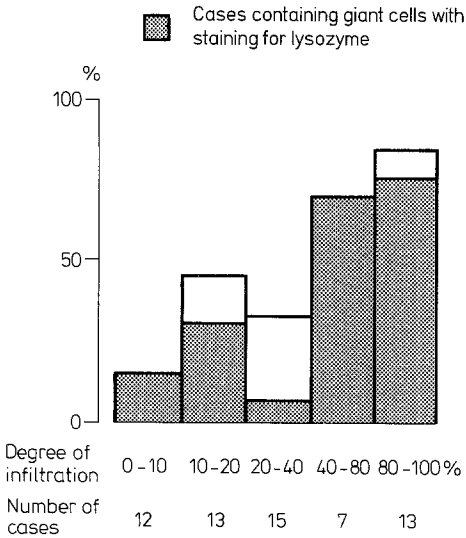

Fig. 9. Percentage of cases with giant cells

one case, germinal centers showed IgG-, IgM- and IgA-positive cells. Tingible body macrophages which reacted positively for lysozyme were only detected within huge germinal centers.

The major part of the Ig-positive infiltrating cells consisted of extrafollicular plasmocytes. In the cases with marked infiltration, plasma cells were abundant; they were arranged in small clusters or islets among thyroid epithelia (Fig. 4). In a few cases, they even formed fields of plasmocytoma-like appearance; the reactive nature of such fields was shown by immunohistological staining (Fig. 5). In all cases, these infiltrates consisted of a mixture of plasma cells positive for lambda light chains and plasma cells positive for kappa light chains. In more than 30 cases, the ratio of kappa- to lambda-positive plasma cells ranged between 1,2 : 1 and 3 : 1 (Fig. 4); in 16 cases the ratio was 1 : 1 and in five cases lambda-positive cells were slightly more numerous. The distribution of heavy chains was as follows (Fig. 6): most of plasma cells were of the type IgG/kappa or IgG/lambda (Fig. 7). IgA-positive cells were less frequent (Fig. 8A) but regularly detectable. IgM-positive cells were rare (Fig. 8B) or even absent. The approximate ratio of IgG : IgA : IgM-positive cells was 80 : 10 : 1. In two cases of group V where pronounced fibrosis was present, many IgA-positive plasma cells were localized within connective tissue septa.

In focal lymphocytic thyroiditis (groups I and II), plasma cells were less frequent; they occurred preferentially between thyroid follicles or around lymph follicles.

Giant cells of mainly intrafollicular localization were present in most cases of Hashimoto's thyroiditis (groups IV and V); in some they were numerous, in others less frequent. In focal thyroiditis, a small number of giant cells were identified in a few cases of group I and in more than a third of the cases of group II. In all groups there were cases with giant cells which gave a positive reaction for lysozyme (Fig. 9). The greatest number of positively staining macrophages, epithelioid cells and giant

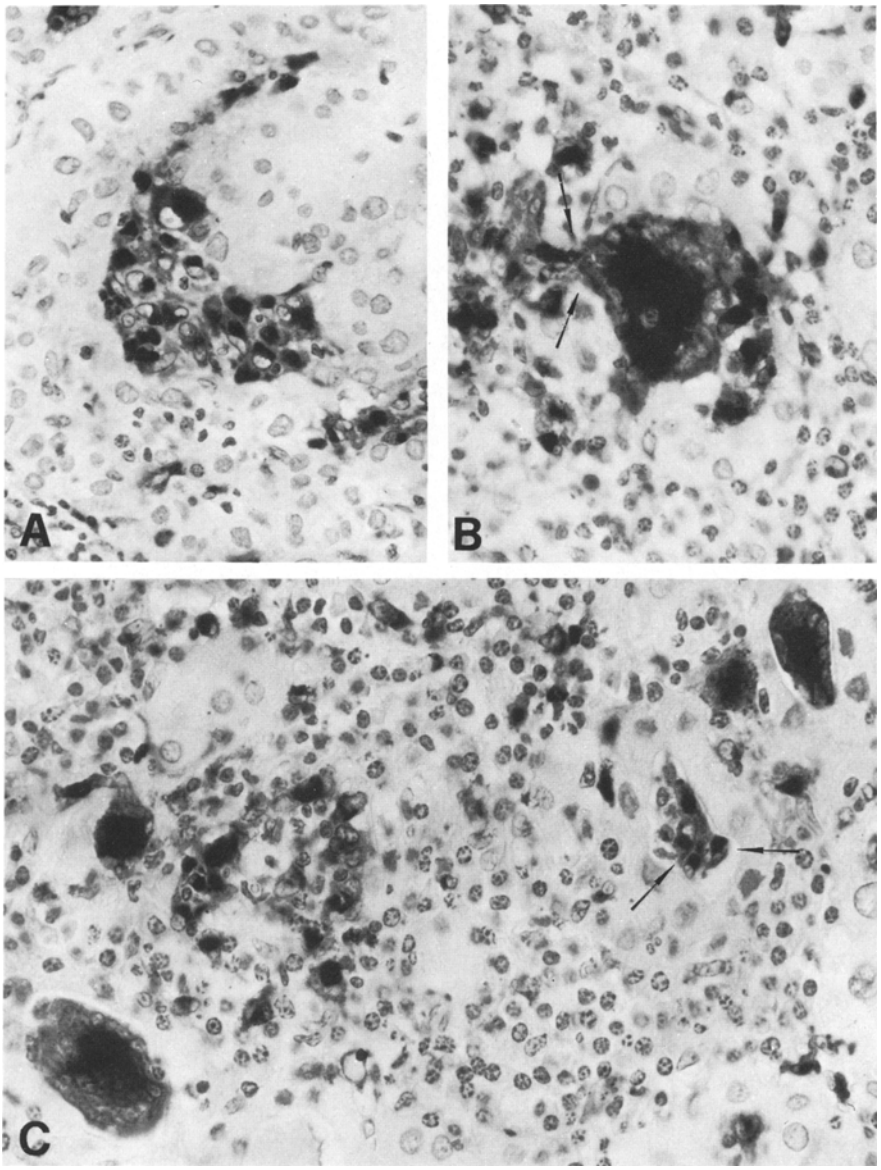

Fig. 10. Formation of giant cells that react positively for lysozyme. **A** Numerous lysozyme-positive macrophages and epithelioid cells are seen within a thyroid follicle. × 320. **B** Follicular lumen comprises lysozyme-positive macrophages in close contact with a giant cell also positive for lysozyme. Macrophages enter the follicular lumen through a gap in the epithelium (*arrows*) to join the giant cell. × 400. **C** Same case as B. Lysozyme-positive giant cells of intra- and extrafollicular localization are detectable. Macrophages and epithelioid cells are situated within the follicular lumina (*arrows*) or between infiltrating plasma cells. × 400

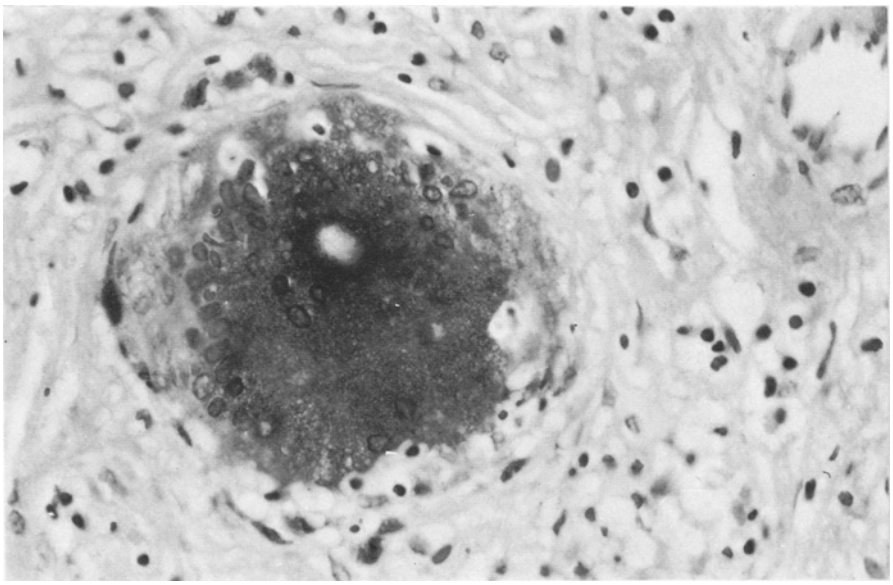

Fig. 11. Thyroiditis de Quervain. Giant cell of the foreign body type reacts strongly positive for lysozyme. ×400

cells was found in cases where infiltration was marked, the intensity of the reaction ranging from dark to light brown. Furthermore, muraminidase staining revealed some aspects of giant-cell formation (Fig. 10). Macrophages invading follicular lumina through gaps in the follicular epithelium could be detected. In addition, it was observed that within the same follicles macrophages or epithelioid cells, also strongly positive for lysozyme, were in close contact to lysozyme-positive giant cells and that these sites of contact of cellular borders were in the process of disintegration. In cases of groups IV and V, muraminidase-positive cells were often scattered throughout thyroid tissue and present also within small vessels.

Thyroiditis de Quervain

Clinical Data. All five patients were female and between 51 and 55 years of age. Four patients were operated for suspected malignancy. Thyroid enlargement occurred rapidly (1–3 months) and in three cases was preceded by upper respiratory tract infections. Four patients had pains radiating into the ears and neck.

Histology. Except for a few regions, thyroid tissue was altered by prominent clusters of macrophages and epithelioid cells within remnants of destroyed follicles. Numerous follicles were replaced by giant cells mainly of foreign-body type. In all cases fibrosis was prominent. Among the infiltrating cells, lymphocytes and plasma cells were numerous. Staining for intracytoplasmic light and heavy chains (lambda, kappa, IgG, IgA, IgM) revealed many positive plasma cells. The number of positive cells corresponded to the number of positive cells of group IV in Hashimoto's

thyroiditis, and the distribution of light and heavy chains was also similar. In all five cases giant cells proved to be strongly positive for lysozyme (Fig. 11). A few follicles of intact epithelium harboured lysozyme-positive giant cells and macrophages.

Discussion

Clinical Data

In all groups there were cases in which thyroid enlargement had been present for a few months only; mild focal or diffuse infiltrates had obviously formed within a short time. Similarly, infiltration in cases of thyroid enlargement over several months to years prior to surgery could also have developed within a short time during goiter formation. This interpretation is supported by the findings of Vickery and Hamlin (1961), that in most cases of Hashimoto's disease there is a steady state of infiltration over several years. Slowly progressive (time-dependent) infiltration, another way of achieving diffuse infiltration, was noted in a few cases only (Woolner et al. 1959; Vickery and Hamlin 1961).

Hypothyroidism is well known to occur in Hashimoto's disease (Lindsay et al. 1952; Furr and Crile 1954). In the cases in this series, it was always paralleled by diffuse infiltration and severe epithelial destruction; the loss of normal thyroid tissue is thus a very likely cause of the hypothyroidism. Hyperthyroidism preceding the development of Hashimoto's disease (Doniach and Roitt 1957), was diagnosed in a few cases (groups I to III), in one of which exophthalmos was an additional feature. The association of the clinical features of Graves' disease with the histology of Hashimoto's disease was mentioned by Eden and Trotter (1942) and later by Fatourechi et al. (1971). Further evidence of the close relationship of both disorders, which may well be attributed to closely related defects within the immunoregulatory system, derives from numerous immunological investigations (for references, see Kidd et al. 1980).

Histology

The morphological quantitation of infiltration revealed that the absolute number of germinal centers increased with the degree of infiltration, except for the group with total infiltration, where it was again reduced. The relative number of germinal centers was highest in the group with only mild focal infiltration and decreased with the degree of infiltration. Furthermore, it was evident that plasma cells were scarce in focal thyroiditis, yet constituted a major component in totally infiltrated thyroids. The morphology and immunohistology of germinal centers did not differ from that seen in stimulated lymph nodes. Large and medium-sized germinal center cells with positive staining for immunoglobulins, as in our cases, are formed during the primary and secondary immune response (Terashima et al. 1977). Plasma cells, which were identified also within germinal centers, may originate directly from the germinal center reaction (Lennert et al. 1967; Tsunoda et al. 1978).

The interfollicular infiltrates mainly consisted of lymphocytes and small plasma cells; in focal thyroiditis, lymphocytes predominated, whereas in Hashimoto's thyroiditis plasma cells were numerous. Most of the plasma cells were positive for

IgG; IgA-positive cells were less frequent and in two cases showed an affinity for fibrotic areas. Elevated serum concentrations of IgA were mentioned by Tomasi and Tisdale (1964) and Gleichmann and Deicher (1968) in advanced liver cirrhosis, and by Podleski (1971) in a case of Hashimoto's disease associated with diabetes. The ratio of IgG : IgM : IgA (standard deviations included) was similar to the serum levels of the series from Glynne and Thomson (1972). These authors also found a positive correlation between high IgG levels and antibody titers against thyroglobulin. Correspondence between thyroglobulin antibodies and the number of plasma cells was noted by Maagøe et al. (1977). In 1962 Mellors et al. had identified plasma cell infiltrates as the sites of thyroglobulin antibody production. Malignant lymphoma of the thyroid, mainly of B cell origin (Schwarze and Papadimitriou 1977), may be imitated by invasion of lymphocytes and plasma cells (Woolner et al. 1959). In such cases, immunoperoxidase staining is a helpful method of establishing the correct diagnosis.

Monocytes and macrophages constitute more than 10% of infiltrating cells in Hashimoto's disease (Tötterman et al. 1979). In this study, the presence of larger numbers of lysozyme-positive cells was restricted to the cases with prominent infiltration. In a few instances, lysozyme-positive macrophages were identified in immediate contact with degenerating epithelial cells, which also showed a weakly positive reaction for lysozyme. A possible function for lysozyme in the induction of cellular lesions is supported by the findings of Laryea et al. (1973); these authors showed a significant increase in lysozyme levels and cellular destruction in media incubated with Hashimoto leukocytes and thyroid cells when compared with media incubated with normal leukocytes and thyroid cells. Positive staining for lysozyme demonstrated the macrophage origin of most giant cells. These giant cells may possibly act as lysozyme-releasing endocrine "glands", similar to recently discussed lysozyme-producing giant cells of sarcoidosis (Lobo et al. 1978).

Thyroiditis de Quervain

The origin of the giant cells of thyroiditis de Quervain is still a matter of discussion; Batolo et al. (1967) and Satoh (1976) derive them from epithelial cells, whereas Nève (1970) and Reidbord and Fisher (1973) point to a macrophage origin. The strong positivity for lysozyme in all giant cells of the five cases investigated establishes their inflammatory (macrophage-derived) nature.

Comparison of Hashimoto's Disease, Focal Thyroiditis and Thyroiditis de Quervain

Based on the quantification of the degrees of infiltration, the histological and immunohistological findings were compared. The number of plasma cells increased in proportion to the degree of infiltration. The same was true for the number of germinal centers, except for the group of total infiltration, where the number of germinal centers was reduced. The ratios of kappa to lambda, and of IgG- to IgA- to IgM-positive plasma cells, however, were shown to be independent of the degree of infiltration.

Lysozyme-positive cells (macrophages as well as giant cells) were also more frequent in cases with diffuse infiltration. These findings are readily understandable if they are interpreted as the result of different activation of the B-dependent immune response. Low activation would result in focal germinal center formation only with a correspondingly low number of B lymphocytes and plasma cells, whereas high activation would give rise to multifocal germinal center formation and consequently to a high number of B lymphocytes and plasma cells. This interpretation is supported by several immunological findings: High numbers of mainly B lymphocytes, sensitized against thyroid antigens, were demonstrated within the blood (Perrudet-Badoux and Frei 1969; Roberts et al. 1973; Khalid et al. 1976; Richter et al. 1978; McGregor et al. 1979) and within the thyroid (Urbaniak et al. 1973; Tötterman 1978) of Hashimoto patients. Activated forms of B lymphocytes from Hashimoto thyroids are also capable of producing and releasing free thyroid antibodies (McLachlan et al. 1979). It is likely that these lymphocytes are derived from already primed (B_2) lymphocytes, which are known to originate from the germinal center reaction (Grobler et al. 1974). Thus the focal lymphoplasmocytic thyroiditis and the diffuse infiltration seen in Hashimoto's disease would represent different immunologic activities of the B cell system within *one* disorder.

The immunohistological findings in thyroiditis de Quervain do not diverge much from those of Hashimoto's disease. The number and ratio of Ig-positive cells was similar and giant cells, although much more frequent, were also positive for lysozyme. The only divergent feature was the absence of active lymph follicles. Consequently, the numerous plasma cells obviously did not originate from the germinal center reaction within the thyroid and thus their derivation from extrathyroid lymphocytes may be assumed. It should be mentioned that the exacerbated inflammatory changes occurring in thyroiditis de Quervain are probably induced by a viral infection (Eylan et al. 1957; Felix-Davies 1958).

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Literature

Balfour BM, Doniach D, Roitt IM, Couchman KG (1961) Fluorescent antibody studies in human thyroiditis: Auto-antibodies to an antigen of the thyroid colloid distinct from thyroglobulin. Br J Exp Pathol 42:307–16

Batolo D, Martines F, Carrozza G (1967) Morphogénèse, histochimie et signification des structures gigantocellulaires dans les thyroïdites idiopathiques. Pathol Eur 3:80–95

Blizzard RM, Hamwi GJ, Skillman TG, Wheeler WE (1959) Thyroglobulin antibodies in multiple thyroid diseases. N Engl J Med 260:112–6

Cline MJ, Selenkow HA, Brooke MS (1959) Autoimmunity in thyroid disease. N Engl J Med 260:117–21

Doniach D, Roitt IM (1957) Auto-immunity in Hashimoto's disease and its implications. J Clin Endorinol 17:1293–1304

Eden KC, Trotter WR (1941/42) A case of lymphadenoid goitre associated with the full clinical picture of Graves' disease. Br J Surg 29:320–2

Eylan E, Zmucky R (1957) Mumps virus and subacute thyroiditis. Evidence of a causal association. Lancet I:1062–3

Fagraeus A, Jonsson J (1970) Distribution of organ antigens over the surface of thyroid cells as examined by the immunofluorescence test. Immunology 18:413–6

Fatourechi V, McConahey WM, Woolner LB (1971) Hyperthyroidism associated with histologic Hashimoto's thyroiditis. Proc Mayo Clin 46:682–9

Felix-Davies D (1958) Autoimmunisation in subacute thyroiditis associated with evidence of infection by mumps virus. Lancet I:880–3

Furr WE, Crile G jr (1954) Struma lymphomatosa: clinical manifestations and response to therapy. J Clin Endocrinol 14:79–86

Gleichmann E, Deicher H (1968) Quantitative Immunglobulin-Bestimmungen im Serum bei entzündlichen Leberkrankheiten. II. Chronisch entzündliche Lebererkrankungen. Klin Wschr 46:801–2

Glynne A, Thomson JA (1972) Serum immunoglobulin levels in thyroid disease. Clin Exp Immunol 12:71–8

Grobler P, Buerki H, Cottier H, Hess MW, Stoner RD (1974) Cellular bases for relative radioresistance of the antibody-forming system at advanced stages of the secondary response to tetanus toxoid in mice. J Immunol 112:2154–65

Holborow EJ, Brown PC, Roitt IM, Doniach D (1959) Cytoplasmic localization of "complement-fixing" auto-antigen in human thyroid epithelium. Br J Exp Pathol 40:583–9

Khalid BAK, Hamilton NT, Cauchi MN (1976) Binding of thyroid microsomes by lymphocytes from patients with thyroid disease and normal subjects. Clin Exp Immunol 23:28–32

Kidd A, Okita N, Row VV, Volpé R (1980) Immunologic aspects of Graves' and Hashimoto's diseases. Metabolism 29:80–99

Laryea E, Row VV, Volpé R (1973) The effect of blood leucocytes from patients with Hashimoto's disease on human thyroid cells in monolayer culture. Clin Endocrinol 2:23–35

Lennert K, Caesar R, Müller HK (1967) Electron microscopic studies of germinal centers in man. In: Cottier H, Odartchenko N, Schindler R (ed) Germinal Centers in Immune Response. Springer, Berlin Heidelberg New York, pp 49–59

Lindsay S, Dailey ME, Friedlander J, Yee G, Soley MH (1952) Chronic thyroiditis: A clinical and pathologic study of 354 patients. J Clin Endocrinol 12:1578–1600

Lobo A, Carr I, Malcolm D (1978) The EM immunocytochemical demonstration of lysozyme in macrophage giant cells in sarcoidosis. Experientia 34:1088–9

Maagøe H, Reintoft I, Christensen HE, Simonsen J, Mogensen EF (1977) Lymphocytic thyroiditis. I. Correlation between morphological, immunological and clinical findings. Acta Med Scand 201:299–302

McGregor A, McLachlan S, Clark F, Rees Smith B, Hall R (1979) Thyroglobulin and microsomal autoantibody production by cultures of Hashimoto peripheral blood lymphocytes. Immunology 36:81–5

McLachlan SM, McGregor A, Rees Smith B, Hall R (1979) Thyroid autoantibody synthesis by Hashimoto thyroid lymphocytes. Lancet I:162–3

Mellors RC, Brzosko WJ, Sonkin LS (1962) Immunopathology of chronic nonspecific thyroiditis (autoimmune thyroiditis). Am J Pathol 41:425–36

Nève P (1970) Ultrastructure of the thyroid in de Quervain's subacute granulomatous thyroiditis. Virchows Arch [Pathol Anat] 351:87–98

Perrudet-Badoux A, Frei PC (1969) On the mechanism of "rosette" formation in human and experimental thyroiditis. Clin Exp Immunol 5:117–27

Podleski WK (1971) Quantitative distribution of IgG, IgM and IgA immunoglobulins in lymphocytic thyroiditis of the Hashimoto type. Arch Immunol Ter dosw 19:431–8

Porter DD, Fennell RH (1961) Serologic and immunohistochemical study of human and experimental thyroiditis. N Engl J Med 265:830–4

Reidbord HE, Fisher ER (1973) Ultrastructural features of subacute granulomatous thyroiditis and Hashimoto's disease. Am J Clin Pathol 59:327–37

Richter E, Wick G, Zambelis N, Ludwig H, Schernthaner G (1978) Demonstration and characterization of thyroglobulin-binding peripheral blood cells in Hashimoto patients by fluoroimmunocytoadherence. Clin Immunol Immunopathol 11:178–89

Roberts IM, Whittingham S, Mackay IR (1973) Tolerance to an autoantigen-thyroglobulin. Antigen-binding lymphocytes in thymus and blood in health and autoimmune disease. Lancet II:936–40

Roitt IM, Doniach D (1958) Human auto-immune thyroiditis: serological studies. Lancet II:1027–33

Roitt IM, Doniach D, Campbell PN, Vaughan Hudson R (1956) Auto-antibodies in Hashimoto's disease (lymphadenoid goitre). Lancet II:820–1

Satoh M (1976) Ultrastructure of the giant cell in de Quervain's subacute thyroiditis. Acta Pathol Jap 26:133–7

Schwarze EW, Papadimitriou C (1977) Maligne Lymphome der Schilddrüse. Verh Dtsch Ges Pathol 61:328–35

Sternberger LA, Hardy PH, Cuculis JJ, Meyer HG (1970) The unlabeled antibody enzyme method of immunohistochemistry. Preparation and properties of soluble antigen-antibody complex (horseradish peroxidase-antihorseradish peroxidase) and its use in identification of spirochetes. J Histochem Cytochem 18:315–33

Stuart AE, Allan WSA (1958) Auto-antibodies in thyroid carcinoma. Lancet II:47

Terashima K, Imai Y, Kasajima T, Tsunoda R, Takahashi K, Kojima M (1977) An ultrastructural study on antibody production of the lymph nodes of rats with special reference to the role of germinal centers. Acta Pathol Jpn 27:1–24

Tomasi TB, Tisdale WA (1964) Serum gamma-globulins in acute and chronic liver diseases. Nature 201:834–5

Tötterman TH (1978) Distribution of T-, B-, and thyroglobulin-binding lymphocytes infiltrating the gland in Graves' disease, Hashimoto's thyroiditis, and de Quervain's thyroiditis. Clin Immunol Immunopathol 10:270–7

Tötterman TH, Andersson LC, Häyry P (1979) Evidence for thyroid antigen-reactive T lymphocytes infiltrating the thyroid gland in Graves' disease. Clin Endocrinol 11:59–68

Trotter WR, Belyavin G, Waddams A (1957) Precipitating and complement-fixing antibodies in Hashimoto's disease. Proc Roy Soc Med 50:961–2

Tsunoda R, Terashima K, Takahashi K, Kojima M (1978) An ultrastructural study with enzyme-labeled antibody technique on immunoglobulin-containing cells in human tonsils, especially in germinal centers. Acta Pathol Jpn 28:53–75

Urbaniak SJ, Penhale WJ, Irvine WJ (1973) Circulating lymphocyte subpopulations in Hashimoto thyroiditis. Clin Exp Immunol 15:345–54

Vickery AL, Hamlin E (1961) Struma lymphomatosa (Hashimoto's thyroiditis). Observations on repeated biopsies in sixteen patients. N Engl J Med 264:226–9

Wick G, Richter E, Zambelis N, Ludwig H, Schernthaner G (1977) Demonstration of thyroglobulin-binding cells in Hashimoto patients by fluoroimmunocytoadherence. Lancet II:1180

Woolner LB, McConahey WM, Beahrs OH (1959) Struma lymphomatosa (Hashimoto's thyroiditis) and related thyroidal disorders. J Clin Endocinrol 19:53–83

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