Internal Medicine Grand Rounds

T H Y R O I D I T I S

"A pain in the neck"

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Introduction

The term thyroiditis includes a group of disorders with differing etiologies. The terminology and the classification schemes are arbitrary and somewhat confusing. The following is a portion of the classification put forth by the American Thyroid Association (7):

Diseases Primarily Characterized by Euthyroidism

5. Acute Thyroiditis
   Suppurative (Specify organism if known).
   (Subacute) nonsuppurative (specify virus if known).

6. Chronic Thyroiditis
   Lymphocytic (Hashimoto)
   Nonspecific
   Invasive Fibrous (Riedel)
   Suppurative (specify organism).
   Nonsuppurative due to (specify tuberculosis, syphilis or other).

This classification is flawed in that Hashimoto's disease is a cause of hypothyroidism while nonsuppurative (Subacute) Acute thyroiditis may cause hyperthyroidism early and hypothyroidism late in the clinical course.

This review will briefly cover suppurative acute and chronic thyroiditis, Subacute thyroiditis, and Invasive fibrous thyroiditis. Chronic Lymphocytic Thyroiditis will be described in more detail since it is more common and its pathogenesis may have broad biological consequences applicable to a number of so-called autoimmune diseases.

Another form of thyroiditis is that caused by radiation (x-ray treatment or radioiodine therapy). This topic will not be described here but is discussed in reference 4.

General references for the topic of thyroiditis are given below:

1) Werner, S.C. and Ingbar, S.H. Editors. The Thyroid, Third Edition (Harper & Row, New York), 1971, pp 847-876, Section V (Chapters 50, 51 and 52) deal with thyroiditis.

2) DeGroot, L.J. and Stanbury, J.B. The Thyroid and Its Diseases. Fourth Edition. (John, Wiley & Son, New York), 1975, pp 572-636. Chapters 13 and 14 provide up-to-date discussion.

3) Bastenie, P.A. and Ermans, A.M. Editors. Thyroiditis and Thyroid Function: Clinical, Morphological and Physiopathological Studies. (Volume 36: Modern Trends in Physiological Sciences, Pergamon Press, Oxford) 1972. *"All you want to know about thyroiditis up to that time."*

4) Hazard, J. B. Thyroiditis: A Review. *Am. J. Clin. Path.* 25:289-298 and 399-426, 1955. *"A useful review despite its age."*

5) Surgery of the Thyroid Gland. C.E. Sedgwick, Editor. (Volume 15: Major Problems in Clinical Surgery edited by J. E. Dunphy, W.B. Saunders Co., Philadelphia) 1974.

6) Hermann, P. Pathophysiological Aspects in Surgical Treatment of Thyroid Disease. *Progr. Surg.* 7:1-55, 1969.

7) Werner, S.C. Classification of Thyroid Disease: Report of the Committee on Nomenclature, American Thyroid Association. *J. Clin. Endocrinol.* 29:860, 1969.

Infectious Thyroiditis (1, 4, 8-13)

Infections of the thyroid gland are very rare and may be suppurative or nonsuppurative, acute or chronic. The causative organism is seldom recovered unless abscess formation and drainage occur. Etiological agents are listed below:

Causes of Acute Suppurative Thyroiditis

*Strep hemolyticus
*Staph Aureus
*Pneumococcus
Salmonella typhosa
Hemophilus influenza
E. Coli
S. paratyphi

*most common

Causes of Chronic Infectious Thyroiditis

Syphilis
Tuberculosis
Actinomycosis
Echinococcosis

Acute nonsuppurative thyroiditis has been attributed to viral infection, particularly measles, mumps and chickenpox, and is often classified with subacute thyroiditis described later.

Acute thyroiditis usually follows infections of the pharynx or upper respiratory tract. Routes of infection include (1) the blood stream, (2) direct invasion from nearby structures, (3) lymphatic spread, (4) direct trauma, or (5) via a persistent thyroglossal duct.

Blood borne infections are considered most prevalent. A History of goiter is present in one-third of patients suggesting that previous pathology in the gland makes it more susceptible to infection.

Clinical Features of acute thyroiditis include the prompt onset of fever, chills, and malaise in association with signs of inflammation in the neck. Pain and marked tenderness are evident over the thyroid gland. Local swelling, induration and redness are noted but fluctuation is unusual. Regional lymph nodes are involved. Pain on swallowing, hoarseness, aphonia, and pressure symptoms may develop and the patient resists extension of the neck.

Differential diagnoses includes subacute thyroiditis, cellulitis, cervical adenitis, acute hemorrhage into an adenoma and fulminant malignancy.

Laboratory findings include leucocytosis and a mild increase in serum thyroxine levels. The patients usually remain euthyroid, and the RAI uptake is normal except for the region involved in the infection where the findings of a "cold nodule" may be simulated. Blood cultures may be positive.

The clinical course is progressive with rupture of the abscess either externally or into the trachea, esophagus or mediastinum. Thrombophlebitis may develop. Treatment includes rest, local heat, and a trial of antibiotics generally selected on the basis that Strep, Staph or Pneumococci are the most common agents involved. If an abscess forms, it may be surgically drained or excised. Tracheostomy may be needed if edema of the larynx occurs.

Prognosis is usually good and thyroid function remains intact in most cases.

Chronic Infectious Thyroiditis

The thyroid gland may be involved in disseminated tuberculosis but the true incidence is unknown because of the confusion with subacute thyroiditis. The gland is large and may be fixed. Caseous necrosis is present along with fibrosis. Treatment may require subtotal thyroidectomy in addition to chemotherapy.

Syphilis may product diffuse thyroiditis or a gumma which must be differentiated from malignant disease, tuberculosis or Riedel's struma. Consult reference (4) for details of this very rare lesion.

8) Volpe, R. Treatment of Thyroiditis. *Mod. Treat.* 6:474, 1969.

9) Strahan, R.W., et al. Thyroiditis. A Classification and Review. *Laryngoscope* 81:1388, 1971.

10) Rundle, F.F. Joll's Diseases of the Thyroid Gland. (Grune & Stralton, Inc., New York) 1951, Second Edition.

11) Leers, W.D., et al. Suppurative Thyroiditis: An unusual case caused by Actinomyces Naeslundi. *Canad. Med. Assoc. J.* 101:56, 1969.

12) Alsever, R.N. et al. Haemophilus influenzae Pericarditis and Empyema with Thyroiditis in an Adult. *J.A.M.A.* 230:1426, 1974.

13) Gaafar, H. and El-Garem, F. Acute Thyroiditis with Gas Formation. *J. Laryngol. and Otol.* 89:323, 1975.

Subacute Thyroiditis

Synonyms: de Quervain's thyroiditis, granulomatous thyroiditis, giant cell thyroiditis, creeping thyroiditis, struma granulomatosa, acute noninfectious thyroiditis, pseudotuberculous thyroiditis, acute nonsuppurative thyroiditis, viral thyroiditis.

Background: This disease was first described by de Quervain in 1904, and was initially considered a rare pathologic entity. More recent reports indicate that it is fairly common. It's onset may be acute, subacute or chronic and the thyroid gland is involved in a generalized, self-limited, nonbacterial inflammatory process. Current opinion favors a viral etiology.

Clinical Features (14-20): The onset of this disease is often abrupt, and is usually associated with painful swelling of the thyroid and general symptoms of weakness, malaise and fever. A sore throat is a common presenting complaint but patients may actually be referring to pain in the thyroid gland rather than to pharyngeal pain. Clinical signs and symptoms are summarized in Table 1 (14).

Table 1

Signs and Symptoms of Granulomatous Thyroiditis

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

Patients are affected between ages 21-50. Some authors report an equal sex ratio but others find that females are more often affected with a F/M ratio of 4.5 to 1. The thyroid gland is often moderately enlarged and firm. Asymmetrical enlargement may be seen and the disease may progressively involve other parts of the gland ("Creeping thyroiditis"). Some of these findings are summarized in Table 2 (14).

Table 2

Clinical and Pathological Characteristics of Chronic Granulomatous Thyroiditis[a]

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

A number of cases are now being reported in which a goiter is present without pain and the patients appear hyperthyroid. They are discovered because ^{131}I uptake is depressed rather than increased as is the case in classical hyperthyroidism (21).

Laboratory findings: The erythrocyte sedimentation rate is markedly increased. Leucocytosis is inconstant and transient. Variable findings have included increased plasma fibrinogen levels, increased serum globulins, and a low serum iron level with anemia. These latter findings have been attributed to the nonspecific effects of the presumed viral infection (14). Thyroid function studies are variable and depend upon the stage of the disease (Table 3) (14).

Table 3

PATHOLOGICAL STAGES

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

Early in the course, there is active destruction of the gland associated with the release of various iodinated materials into the plasma. Hyperthyroidism is seen at this time but the ^{131}I-uptake is low, and the scan is abnormal. TSH levels are normal and do not increase following injection of Thyrotropin Releasing Hormone (TRH) (22).

In the second stage, the thyroglobulin stores are depleted and glandular regeneration is beginning. TSH levels are high but T_3 and T_4 levels are low. ^{131}I-uptake may be normal despite inadequate hormonogenesis. As expected, clinical hypothyroidism occurs at this stage.

During the recovery phase, the TSH may still be elevated despite normal T_3 and T_4 levels until full recovery occurs. In a few instances, hypothyroidism has persisted but complete recovery is the rule.

Pathology: Grossly, the thyroid gland is moderately enlarged and the inflammatory process does not extend beyond the capsule of the gland

The microscopic picture (Figure 1) includes the following:

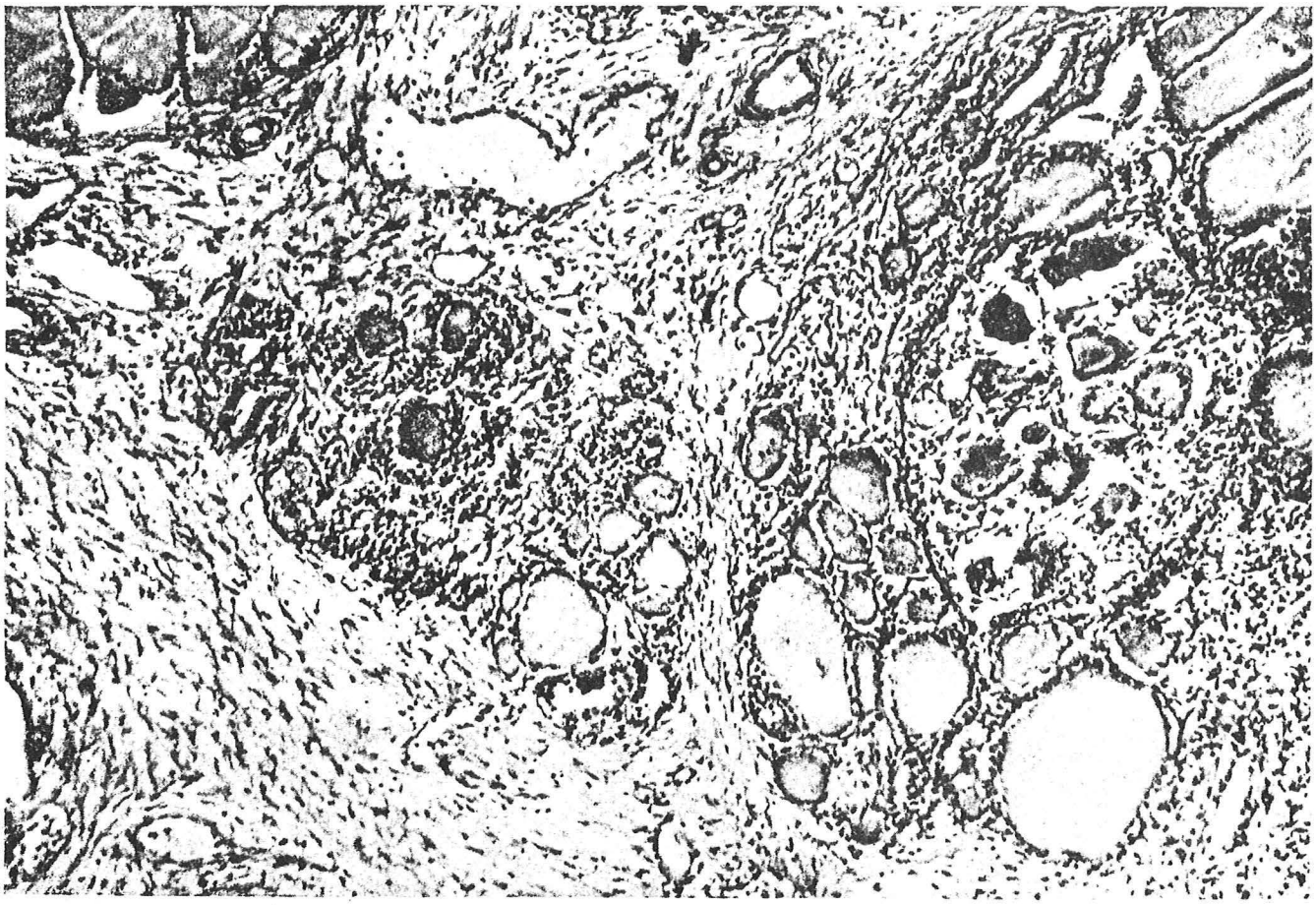
1) The epithelial lining of acini is necrotic and desquamated.

2) The colloid content is altered and much reduced.

3) Penetration of polys, round cells and large connective tissue cells into necrotic acini. A prominent feature is the presence of large multinucleated giant cells of the foreign body type that often contain fragments of colloid.

4) Inflammation is usually patchy.

Figure 1



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

There is little information about the structure of the thyroid gland during recovery.

Etiology: Several clinical aspects of the disease suggest a viral etiology (19).

1) Upper respiratory infection may precede the attack.

2) A prodromal phase of muscular pain, malaise and fatigue occurs.

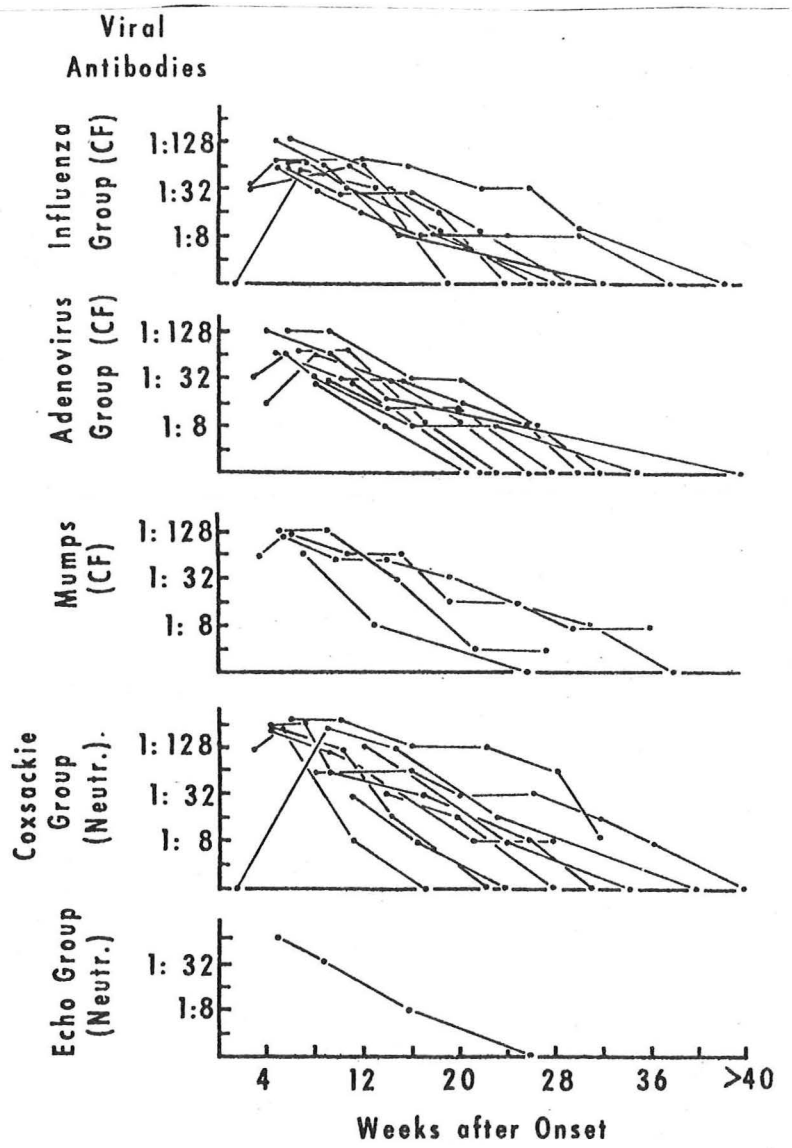
3) The disease may appear during outbreaks of specific viral diseases.

4) Complete recovery is usual.

5) Leucocytosis may be minimal and transient.

Viral antibody titers have risen in a number of patients with subacute thyroiditis at the onset of this disease (Figure 2), but this change may only represent an anamnestic response to inflammation of the thyroid (26).

Figure 2



Graph showing titers of serial viral antibodies in the 32 patients who had 4-fold changes in dilution of these antibodies. Only the single viral antibody showing the greatest change in dilution during the period of observation is depicted for each patient.

Attempts to isolate virus particles from affected glands have not been uniformly successful (2, 27). Inspection of Figure 2, indicates that a variety of viruses have been implicated.

An autoimmune process has been suggested but thyroid antibodies are not detected initially, increase only to low titers if at all, and disappear in a short time, (Table 4) (26).

Table 4

Antithyroid antibodies at time of initial examination: number of cases

Time of initial examination (weeks after onset)	No. of cases examined	Pos. TRCA	Pos. C.F.	Pos. both
1	2	0	0	0
2	2	0	0	0
2-4	13	1	0	0
4-6	25	6	3	3
6-8	18	5	1	1
8-12	8	4	2	2
12-16	3	2	1	1

A recent brief communication suggested that the HL-A antigen (W5) was present with an increased frequency in patients with subacute thyroiditis but more work is needed to substantiate this claim (28). If true, more emphasis must be given to the possibility that a problem exists in the immune system.

Diagnosis: The abrupt onset of systemic symptoms in association with painful swelling of the thyroid is highly suggestive. A low uptake of ^{131}I by the thyroid gland helps to differentiate this disease from classical hyperthyroidism when hypermetabolic symptoms are present. The complete differential diagnosis is listed in Table 5 (17).

Table 5

Differential Diagnosis of Subacute Thyroiditis
Acute suppurative thyroiditis
Cellulitis of the neck
Cervical adenitis
Earache
Esophagitis
Fever of unknown origin
Hashimoto's thyroiditis
Myositis
Myxedema
Neuritis
Nodular goiter
Pharyngitis
Psychoneurosis
Riedel's struma
Sarcoidosis
Temperomandibular joint syndrome
Thyroid adenoma
Thyroid malignancy
Thyrotoxicosis
Tonsillitis
Tooth abscess

A technetium scan may be helpful in patients who ingested iodide just prior to evaluation. Exogenous iodide will markedly reduce the ^{131}I-uptake but will not influence the technetium uptake significantly. In contrast, the inflammed gland of subacute thyroiditis will not take up either agent to any significant extent (29).

Treatment (1, 2, 17, 18). The disease is usually self-limited and surgery is not needed unless cancer is considered a possibility.

Aspirin in doses of 4-5 gm per day is helpful in many cases.

Thyroid hormone in replacement doses is helpful if the gland remains enlarged and painful. Reduction in the size of the gland often occurs. Chronic thyroid hormone replacement is needed only if the patient becomes hypothyroid.

Patients with very tender glands and severe systemic symptoms will respond to prednisone in a dose of 20 mg per day. After one week at this dose, the dose is slowly tapered over one month's time. Symptoms promptly recur if steroids are withdrawn too quickly. The overall course of the disease does not appear shortened by steroid therapy.

X-ray therapy (500-1000 R) relieves the inflammation but is no longer used.

14) Bastenie, P.A., et al. Subacute and chronic granulomatous thyroiditis. Chapter 3 in Reference 3.

15) Woolner, L.B., et al. Granulomatous Thyroiditis. (de Quervain's Thyroiditis) *J. Clin. Endocrin. and Metab.* 17:1202, 1957.

16) Furszyfer, J., et al. Subacute (Granulomatous) Thyroiditis in Olmstead County, Minnesota. *Mayo Clin. Proc.* 45:396, 1970.

17) Greene, J.N. Subacute Thyroiditis. *Am. J. Med.* 51:97, 1971.

18) Hamburger, J.I. Subacute Thyroiditis: Diagnostic Difficulties and Simple Treatment. *J. Nuclear Med.* 15:81, 1974.

19) Volpe, R., et al. Subacute Thyroiditis: A Disease Commonly Mistaken for Pharyngitis. *J. Canad. Med. Assoc.* 77:297, 1957.

20) Saito, S., et al. Subacute Thyroiditis: Observations on 98 cases for the last 14 years. *Tohoku J. Exp. Med.* 113:141, 1974.

21) Papapetrous, P.D. and Jackson, I.M.D. Thyrotoxicosis due to "Silent Thyroiditis". *Lancet* 1:361, 1975.

22) Larsen, P.R. Serum Triiodothyronine, Thyroxine and Thyrotropin During Hyperthyroid, Hypothyroid and Recovery Phases of Subacute Nonsuppurative Thyroiditis. *Metab.* 23:467, 1974.

23) Ogihara, T., et al. Serum Thyrotropin and Thyroid Hormones in the Course of Subacute Thyroiditis. *J. Clin. Endocrinol. and Metab.* 37:602, 1973.

24) Volpe, R., et al. Thyroid Function in Subacute Thyroiditis. *J. Clin. Endocrinol. and Metab.* 22:65, 1958.

25) Glinoer, D., et al. Sequential Study of the impairment of Thyroid Function in the Early Stage of Subacute Thyroiditis. *Acta Endocrinologia* 77:26, 1974.

26) Volpe, R., et al. Circulating Viral and Thyroid Antibodies in Subacute Thyroiditis. *J. Clin. Endocrin.* 27:1275, 1967.

27) Stancek, D., et al. Isolation and some Serological and Epidemiological Data on the Viruses Recovered from Patients with Subacute Thyroiditis de Quervain. *Med. Microbiol. Immunol.* 161:133, 1975.

28) Nyulassy, S., et al. The HL-A System and Subacute Thyroiditis. A Preliminary Report. *Tissue Antigens* 6:105, 1975.

29) Spindel, A. and Diengott, D. Use of Technetium in the Differential Diagnosis between Subacute Thyroiditis and other Thyroid diseases. *Israel Med. J.* 10:1410, 1974.

Invasive Fibrous Thyroiditis (Riedel)

Synonyms: Riedel's Struma, Riedel's Thyroiditis, ligneous thyroiditis, woody thyroiditis, eisenharte strumitis, chronic productive thyroiditis, struma fibrosa, strumitis chronica.

Background: This is a rare disease now reasonably well separated from the other forms of thyroiditis as a distinct entity. The condition was first described in two patients by Riedel in 1896. Case reports appeared frequently until 1912 when Hashimoto described chronic lymphocytic thyroiditis as a possible separate disease (30). In 1931, Graham and McCullagh (31) established Riedel's Struma and Hashimoto's Thyroiditis as distinct clinical entities. Woolner, et al. (32) reviewed the incidence of this disease at the Mayo Clinic from 1920 through 1956, and found only 20 cases in some 42,000 thyroidectomies (0.06%). These workers also established firm histological guidelines for its pathologic diagnosis.

Table 6

CLINICAL FEATURES

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

Clinical Features: (30, 32, 34, 42). (Table 6) (42) More recent reports indicate that the disease is usually seen in patients between 20 and 40 years of age. Females are more often affected with a female/male ratio of 2 - 4/1. Onset of symptoms may be sudden or gradual. Patients may have an antecedent history of goiter but often no previous thyroid disorder is present. Thyroid enlargement occurs and is unilateral in 30% of the cases. The involved portion of the gland is described as being "stony hard" or "iron hard" in virtually every case. Another distinctive features of this disease is the fact that the fibrosis extends beyond the capsule of the thyroid gland to involve the carotid sheath, trachea, strap muscles, internal jugular, and the esophagus. This diffuse process produces pressure symptoms resulting in stridor, dyspnea, paralysis of the recurrent laryngeal nerve, esophageal obstruction or frank suffocation. Regional lymph nodes are rarely, if ever, enlarged. The gland is usually neither painful nor tender to palpation. Pain referred to the ear, throat or occiput is also unusual. Myxedema is very unusual except where fibrosis has involved practically the entire gland. Systemic signs and symptoms, such as fever and malaise, are rare.

Laboratory findings are minimal. Mild leucocytosis may occur, and the erythrocyte sedimentation rate may be mildly elevated. Antithyroglobulin antibody or microsomal antibodies are either completely absent or are present only in low titer. The thyroid scan is normal except in affected areas where no uptake occurs. Other thyroid function studies are normal unless the gland is completely destroyed.

Pathology: Salient features distinguishing this disease from other forms of thyroiditis are:

1) Destruction of the capsule and invasion of perithyroidal tissue -- often visible by inspection at surgery.

2) Lack of oxyphilic cells (oncocytes or Hurthle cells) which are rich in mitochondria -- significance unclear but a help to the pathologist.

3) Absence of significant lympocytic infiltrates or giant cells.

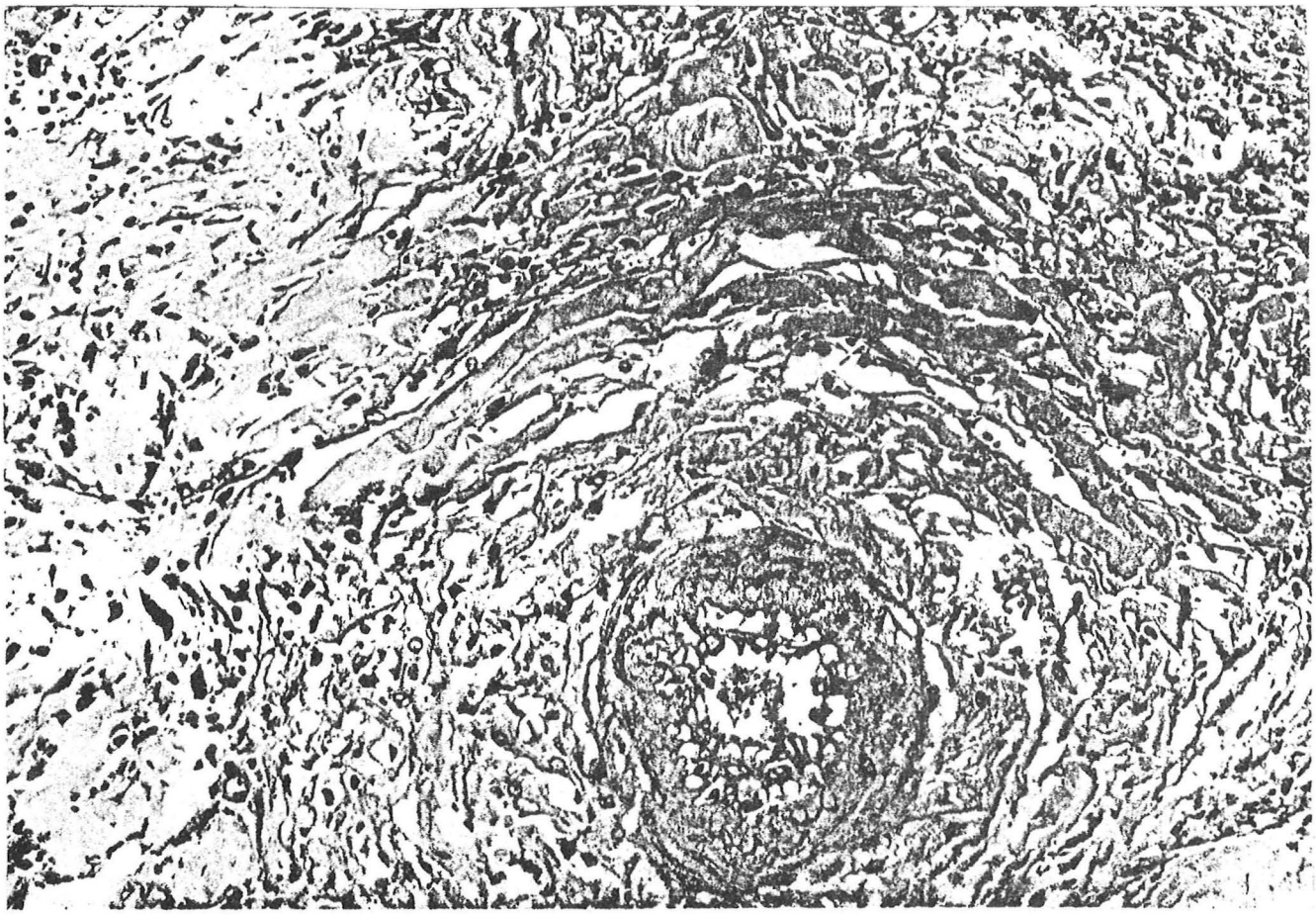
4) Tendency to neutrophilic infiltration with occasional microabscess formation.

5) Involvement of large areas of the thyroid with dense fibrous tissue. resulting in loss of lobular structure.

Occasionally, an adenoma may be present in the fibrotic tissue.

Many cases show the presence of a lymphocytic periarteritis and arteritis marked by medial destruction and intimal proliferation (Figure 3) (42) Veins may also be involved.

Figure 3



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

Etiology: The etiology of this disease is unknown and two main theories have been proposed:

1) The process represents the end-result of a chronic inflammatory process triggered by subacute or Hashimoto's thyroiditis. Usually no history of antecedent thyroid disease is present, however, and patients with Hashimoto's thyroiditis or subacute thyroiditis do not progress to develop Invasive Fibrous Thyroiditis.

2) The disease may result from a general process leading to abnormal fibroblastic proliferation. This suggestion was made because a number of cases have been reported in which Invasive Fibrous Thyroiditis is associated with one or more of the following: Retroperitoneal fibrosis, mediastinal fibrosis sclerosing cholangitis, and pseudotumor of the orbit (36, 37, 38, 39, 40, 41).

Diagnosis: The major consideration is some form of malignancy, and this must be proved or disproved by operation and adequate biopsy. Rarely, syphilis (gumma), tuberculosis or actinomycosis must be considered. The clinical and laboratory findings of absence of pain or systemic symptoms, low or absent anti-thyroid antibodies, normal thyroid function, and a very hard mass in the thyroid usually serve to differentiate this form of thyroiditis from acute, subacute or Hashimoto's thyroiditis.

Treatment and course: Surgery is indicated to rule out malignancy, and to relieve pressure symptoms on the trachea or esophagus. Due to the fibrotic invasion, the gland cannot be freely removed from its capsule and considerable bleeding may be encountered. In cases of unilateral involvement, the involved lobe may be partly removed. Often the other lobe becomes involved later. Usually, the simpliest procedure is wedge resection or bisection at the isthmus to split the thyroid and relieve the constriction on the trachea.

Treatment with thyroid hormone does not influence the fibrotic process and is indicated only if myxedema results from diffuse destruction of the gland. Adrenal steroids have not been beneficial except in a few cases of multifocal fibrosis where they were used either alone (36) or in conjunction with cyclophosphamide (Cytoxan) (37).

30) Hazard, J.B. Thyroiditis: A Review. *Am. J. Clin. Path.* 25:289, 399, 1955.

31) Graham, A. and McCullagh, E.P. Atrophy and Fibrous associated with lymphoid tissue in the thyroid. *Arch. Surg.* 22:548, 1931.

32) Woolner, L.B., et al. Invasive Fibrous Thyroiditis (Riedel's Struma). *J. Clin. Endocrinol.* 17:201, 1957.

33) Woolner, L.B., et al. The Surgical Aspects of Thyroiditis. *Am. J. Surg.* 104:666, 1962.

34) Goodman, H.I. Riedel's Thyroiditis: A Review and Report of Two Cases. *Am. J. Surg.* 54:472, 1941.

35) Drury, M.I., et al. Invasive Fibrous (Riedel's Thyroiditis). *J. Irish Med. Assoc.* 67:388, 1974.

36) Bartholomew, L.G., et al. Sclerosing Cholangitis: Its Possible Association with Riedel's Struma and Fibrous Retroperitonitis - Report of 2 Cases. *New Eng. J. Med.* 269:8, 1963.

37) Amorosa, L.F., et al. Multifocal Fibrosis Involving the Thyroid, Face, and Orbits. *Arch. Int. Med.* 136:221, 1976.

38) Kiltredge, R.D. and Nash, A.D. The Many Faces of Sclerosing Fibrosis. *Am. J. Roentgenol. Radium Thero. Nucl. Med.* 122:288, 1974.

39) Schneider, R.J. Orbital Involvement in Riedel's Struma *Canad. J. Ophthal.* 11:87, 1976.

40) Raphael, H.A., et al. Riedel's Struma Associated with Fibrous Mediastinitis: Report of a Case. *Mayo Clin. Proc.* 41:375, 1966.

41) Comings, D.E., et al. Familial Multifocal Fibrosclerosis. *Ann. Int. Med.* 66:884, 1967.

42) Bastenie, P.A. Invasive Fibrous Thyroiditis (Riedel), Chapter 4 in reference (3).

Lymphocytic Thyroiditis (Hashimoto)

Synonyms: Lymphadenoid goiter, chronic lymphocytic thyroiditis, Hashimoto's disease, Hashimoto's goiter, autoimmune thyroiditis, struma lymphomatosa.

Background: In 1912, Hashimoto made a detailed description of this disorder in 4 patients, all women over 40 (43). He referred to the disorder as struma lymphomatosa. Subsequently, the pathology of this disease was well described but there was no clue to its etiology until Rose and Witebsky produced thyroid lesions in animals immunized with homologous thyroid extract in Freund's adjuvant (44). At about the same time, Roitt, et al. demonstrated the presence of antithyroglobulin antibodies in the serum of patients with this disease (45). These observations resulted in many reports concerning the autoimmune nature of Hashimoto's thyroiditis but the exact cause is still unknown.

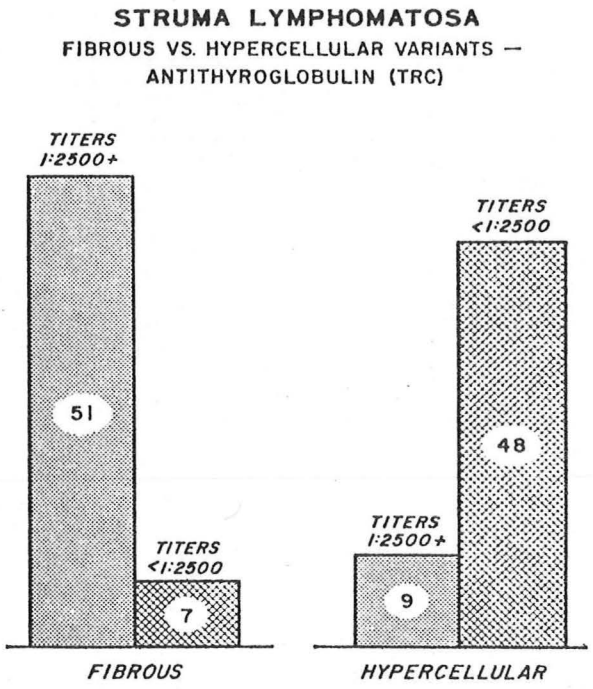
Clinical Features: (1, 2, 3, 4) The disease occurs far more frequently in females with a female/male ratio ranging for 4/1 to 9/1. For a time, the incidence of this disease was thought to be increasing (46, 47) but this apparent change has been attributed to a greater awareness of the disease and to broadening criteria for its definition (48). It most commonly occurs between the ages 40 and 60, but there is a wide range (14-89 years).

Onset is insidious with diffuse swelling of the thyroid. Pain is rare but tenderness is occasionally observed. The thyroid may enlarge in a few weeks or grow gradually over several years. Usually the gland is 2-5 times its normal size, firm and rubbery, but not rock hard. Asymmetry occurs in about one-third of cases, and the surface of the gland may be smoothly lobular or nodular. Cervical lymph nodes are rarely enlarged. Generalized complaints are few (fatigue, nervousness) but occasionally pressure symptoms (dysphagia, hoarseness, choking) develop.

Several variants occur.

1) A Fibrous Variant (49): This variant may occur in up to 12% of cases. There is marked fibrous replacement of from one-third to most of the parenchyma with typical changes of Hashimoto's disease in other parts of the gland. Fibrosis does not extend beyond the capsule. Clinically, the goiter is firm and may have enlarged recently. Pressure symptoms are common. There is confusion with malignant disease both clinically and pathologically. The antithyroglobulin antibody titers are especially high in this variant (Figure 4) (50).

Figure 4



Distribution of antithyroglobulin titers in the 115 cases of struma lymphomatosa

2) Exophthalmic Form (51, 52): Exophthalmos may occur with histologically proven Hashimoto's disease in patients without any evidence for prior or present hyperthyroidism. This variant is uncommon. Exophthalmos-producing substance (EPS) has been implicated but proof is lacking.

3) Hyperplastic Variant of Adolescence (53-58): There is not universal agreement that this is a variant of Hashimoto's thyroiditis but antibodies to Thyroglobulin are often demonstrated. The age range is 4 to 17 years. In a recent paper (58), the disease had a prevalence of 1.2%. Thyroid were enlarged in 85%, being firm in 60%, and lobulated in 75%. Thyroglobulin antibodies were demonstrable in 76% using the tanned red cell technique and in 93% by the radioimmunoassay. TSH levels were increased in 7 of 15 subjects but most patients were clinically euthyroid. Spontaneous resolution of thyroiditis occurred in 15 of 32 untreated patients and in 14 of 30 treated with thyroid hormone.

Association with other diseases: The association of Hashimoto's disease has been reported with a number of disorders (Table 7). Many of these reports describe isolated cases, utilize poor controls or suffer from inadequate statistical analysis, and consequently, true associations remain vague. See reference 76 for a critique.

Table 7

Hepatic cirrhosis (59)
Nephropathy (60)
Paget's Disease of Bone (61)
Addison's Disease (62)
Sjogren's Syndrome (63)
Systemic Lupus Erythematosis (64, 65)
Diabetes Mellitus (66)
Rheumatoid Arthritis (67)
Pernicious Anemia (68, 69, 93, 94)
False Positive test for Syphilis (70)
Gonadal Dysgenesis (71)
Downs Syndrome (72)
Breast Cancer (73)
Sarcoidosis (74)
Ocular Myesthenia Gravis (75)

Adrenal Function in Autoimmune Thyroiditis is normal (77).

Of the associations suggested, that of atrophic gastritis and pernicions anemia with Hashimoto's thyroiditis seems best supported (93, 94) but not all observers agree (95).

Laboratory Findings: (78-81) Thyroid function tests vary depending on the state of the disease. Early in the disease, PBI and ^{131}I-uptake are slightly elevated but the T_4 concentration and BMR are normal. The PBI-T_4I difference is large because the secretion of abnormal iodoprotein elevates the PBI without influencing the T_4 level. Later in the clinical course, the PBI, ^{131}I-uptake and T_4 become subnormal but T_3 may increase along with TSH. Eventually, full-blown myxedema may occur if thyroid replacement therapy is withheld.

Humoral antibodies toward several antigens have been described in Hashimoto's thyroiditis (3, 82, 83, 91). These are summarized in Table 8.

Table 8

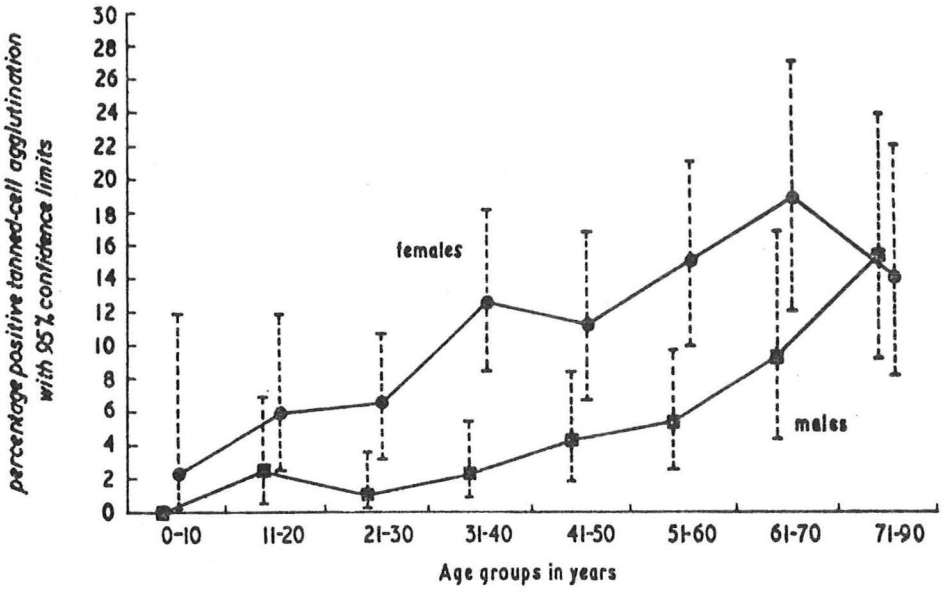
Autoantigens Present in Hashimoto's Disease and Techniques for Detection

Antigen	Test used to identify antibody
Thyroglobulin	Precipitin
	Tanned red cell hemagglutination (TGHA)
	Antigen-binding capacity
	Coons' technique on fixed sections of thyroid tissue: colloid localization
	Passive cutaneous anaphylaxis
	Solid-phase radioimmune assay
Colloid component other than thyroglobulin	Coons' technique on fixed sections: colloid localization
Microsomal antigen	Complement fixation
	Coons' technique on unfixed sections of thyroid tissue: cell localization
	Cytotoxic effect on cultured thyroid cells
	Tanned red cell hemagglutination (MCHA)
	Solid-phase radioimmune assay
Nuclear component	Coons' technique on unfixed sections of tissue: nuclear localization

The colloid component other than thyroglobulin was thought to be iodoalbumin but there is not universal agreement regarding its identity. The possible significance of these antibodies in the pathogenesis of Hashimoto's thyroiditis will be discussed below. Two points should be made here:

1. The thyroid antibodies increase with age in the general population (Figure 5), (92) and comparative studies must therefore be done with great care.

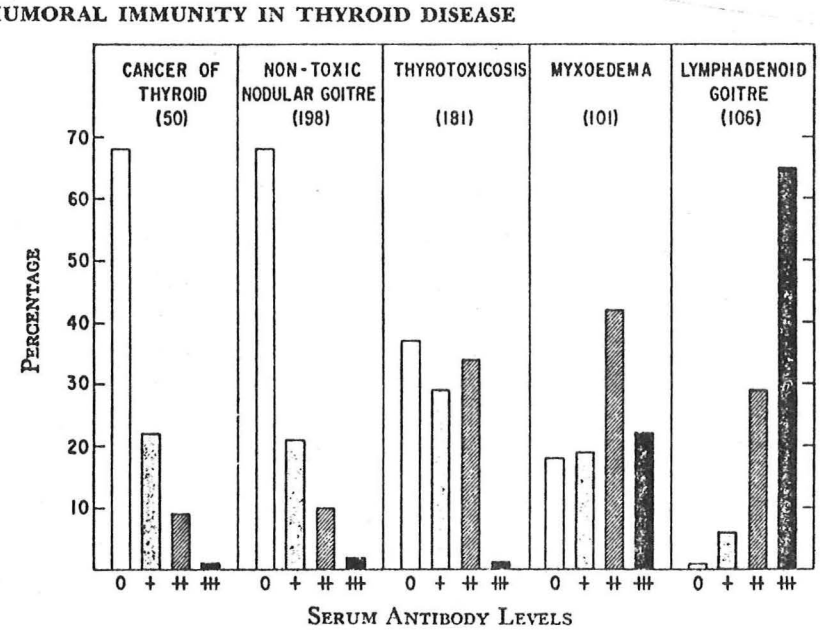
Figure 5



—Incidence of thyroglobulin antibodies in relation to age and sex in 2,252 normal subjects. Ninety-five per cent confidence limits are shown .

2. The highest titers of antibody are usually found in Hashimoto's thyroiditis but significant levels can also be observed in myxedema and thyrotoxicosis (Figure 6) (85).

Figure 6



Incidence of circulating autoantibodies in various thyroid disorders. + Tanned red cell agglutination of 5 to 50 and low complement fixation titers; ++ tanned red cell agglutination titers of 2500 to 25,000 or strong complement fixation titers, or both; +++ positive precipitins, tanned red cell agglutination above 25,000, and usually a positive complement fixation test.

Using both tanned-red-cell and complement fixation tests, the percent positive responses for antibody are listed below:

Hashimoto's Thyroiditis	97%
Myxedema	83%
Thyrotoxicosis	63%
Non-toxic Goiter	33%
Thyroid Carcinoma	32%

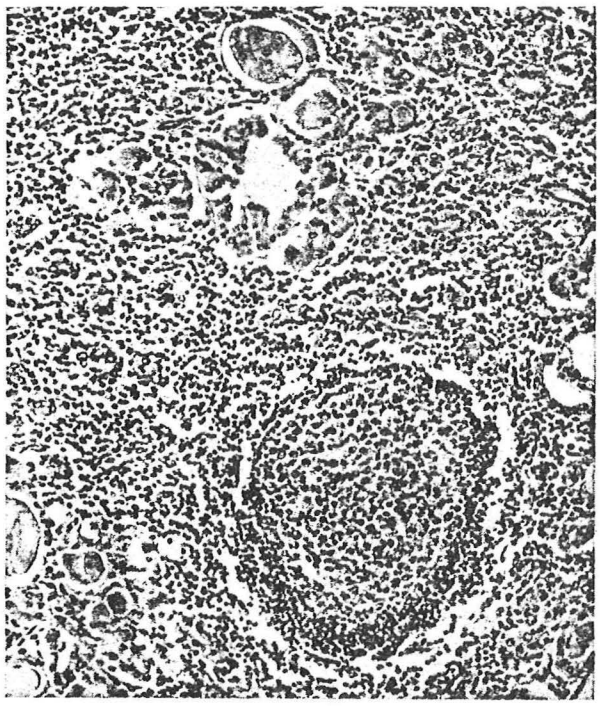
Twenty percent of the myxedema patients have very high titers comparable to those seen in Hashimoto's Thyroiditis, suggesting that the myxedema in these patients may have resulted from subclinical Hashimoto's thyroiditis.

Affinity constants and binding capacities of the anti-thyroglobulin antibodies have been compared in Graves Disease and Hashimoto's Thyroiditis and were found to be similar (86).

With regard to other tests, the erythrocyte sedimentation rate is sometimes elevated but routine hemograms are usually normal.

Pathology: The gland is firm, rubbery, and enlarged from 2-5 times normal. The capsule is intact. The parenchyma is infiltrated with large numbers of lymphoid cells interspersed with plasma cells (Figure 7) (49). Lymphoid follicles may be seen and much of the glandular architecture is destroyed. Nests of thyroid acini may persist and contain either atrophic cells or large, granular pink cells (variously called oncocytes, Hurthle cells or Askanazy cells) packed with mitochondria. The significance of these oncocytes is not really known but their appearance suggests they are undergoing intense metabolism.

Figure 7



Histologic Picture of Hashimoto's Thyroiditis at the Time of the Original Diagnosis (Hematoxylin and Eosin Stain X135).

A summary of the predominant cellular types is given in Table 9.

Table 9

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

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

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

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

Several detailed untrastructural studies have stressed the presence of phagocytic activity, the presence of transformed lymphocytes, and frequent signs of fusion between cells of the infiltrate and thyroid epithelia cells as evidence supporting the postulate of autoimmunity as the pathogenic mechanism in this disease (87-90).

In one study, distinct electron-dense deposits were noted in the follicular basement membrane of some thyroid follicles in every case of Hashimoto's Thyroiditis examined (90). These deposits were often in close association with plasma cells and were said to resemble the antigen-antibody deposits of immune-complex nephropathies. Their exact significance is unclear since immunofluorescent staining for antibody was positive in only one of 8 cases and that patient had SLE as well. Thus the proof that these deposits resemble antigen-antibody complexes is tenuous.

Etiology and Pathogenesis: (50, 82, 91, 92, 96, 101, 102) The etiology and pathogenesis of Hashimoto's thyroiditis remain unknown but the prevailing opinion is that it represents an autoimmune disease. In animal experiments, thyroiditis has been produced passively by injection of antibodies to thyroglobulin in only the rabbit and mouse. Injection of sensitized lymphocytes produces the disease in guinea pigs, rabbits and rats (96), and there is a tendency to favor cell-mediated immunity as the major process in the pathogenesis of the experimental disease.

Several observations in humans tend to support this opinion. Roitt and Doniach infused Hashimoto's serum containing high antibody titers into Rhesus monkeys but failed to produce lesions in the monkey glands despite the fact that human thyroid antibody cross-reacted with monkey thyroid gland (97). Parker and Beierwaltes followed 8 women with high plasma levels of antithyroglobulin antibody through pregnancy and found no evidence of clinical thyroid disease in their children although antibodies were detected in cord blood (98). One could argue that the actual offending antibody had been already absorbed by the patient or maternal thyroid gland and this may be possible since Nakamura and Weigle (99) were able to create thyroiditis in recipient rabbits if the antibody-containing plasma was taken from thyroidectomized donors.

Evidence for cell-mediated immunity in Hashimoto's disease is supported by the following evidence:

1) Lymphocytes taken from patients with Hashimoto's disease are cytotoxic to thyroid cells in tissue cultures (103).

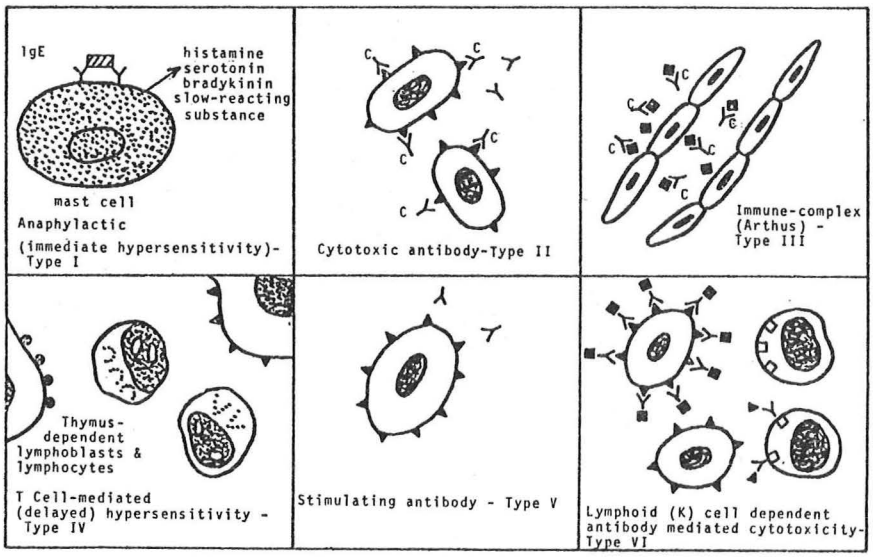
2) Lympocytes from patients with Hashimoto's thyroiditis are cytotoxic to heterologous cells coated with thyroid antigens (104).

3) Migration Inhibitory Factor is elaborated when cells from patients with Hashimoto's Disease come in contact with thyroid antigen (106).

Before summarizing recent in vitro experiments relating to Hashimoto's Disease it will help to review the different types of immunity.

There are six types of immune reactions that may cause harm in tissues (Figure 8) (106).

Figure 8



The main types of immune reactions that may be harmful to the tissues

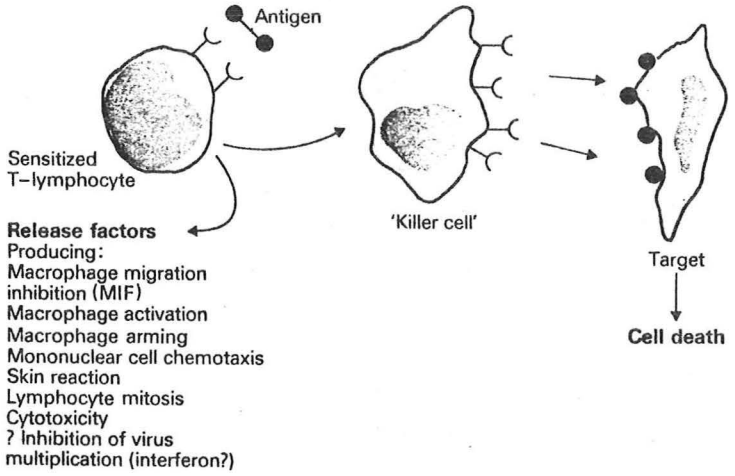
Type I: Antigen (Ag) reacts with a specific class of Antibody (Ab) bound to mast cells or basophils leading to degranulation of mast cells with release of vasoactive amines (eg. Anaphylaxis).

Type II: Ab binds to Ag on cell surface to result in a) phagocytosis, b) cytotoxicity by K cells or c) lysis by interaction with complement.

Type III: Interaction of Ag with humoral Ab activate complement which results in a number of events including platelet aggregation and release of vasoactive amines. (Arthus Reaction)

Type IV: Thymus dependent Lymphocytes with specific receptors for antigen release a series of factors that mediate delayed hypersensitivity (eg. Tuberculin Skin Test) (Figure 9) (84).

Figure 9

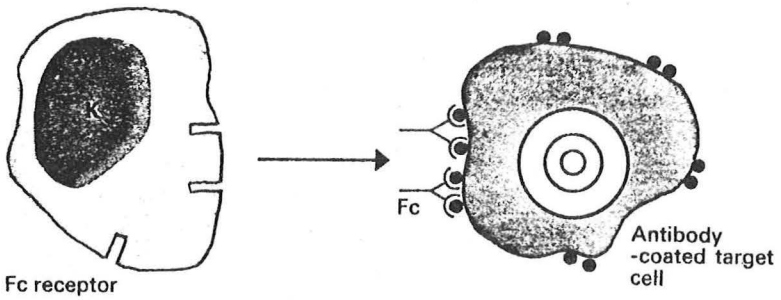


Type IV—Cell-mediated (delayed-type) hypersensitivity.

Type V: Non-complement fixing antibody interacts with the cell-surface Ag to stimulate the cell. Long-acting thyroid stimulator (LATS) is such a substance.

Type IV: K cells are stimulated to attack antibody-coated target cells by some extracellular mechanism. (Figure 10) (84).

Figure 10



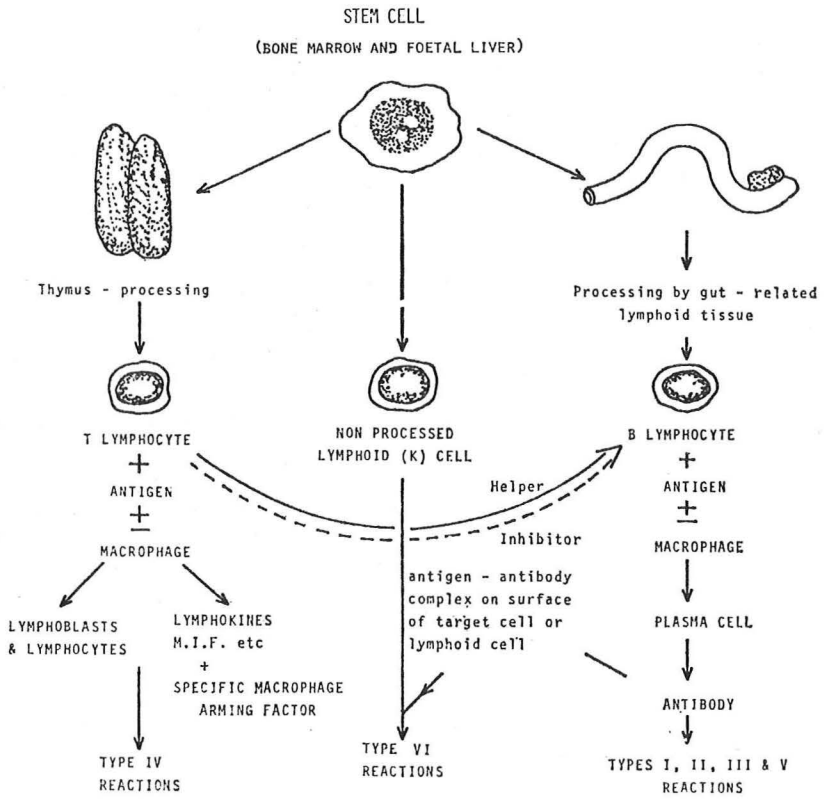
Killing of antibody-coated target by K-cell. The surface receptors for Ig Fc region bind the K-cell to the target which is then killed by an extracellular mechanism. Several different cell types may display K-cell activity.

These humoral and cell-mediated responses are carried out by the small lymphocyte. It is now clear that two populations of small lymphocytes occur (Figure 11) (106). Both are thought to arise from a stem cell in the bone marrow. One type, the T lymphocyte, is dependent upon the thymus to be immunocompetent. When it is exposed to antigen, it undergoes blast transformation and ultimately particpates in cell-mediated immunity (Type IV) (Figure 9). The B cell is dependent upon the Bursa of Fabricius, a lymphoid organ derived from the gut in chickens, (the human counterpart is not known) for its ability to produce antibody. When the B cell is exposed to antigen, it is transformed into antibody producing plasma cells which ultimately participate in Types I, II, III, V, and probably VI immune reactions.

Certain T cells are known to enhance B-cell activity and others appear to suppress B-cell activity. This type of T-cell/B-cell interaction may serve to regulate the antibody response. Since both humoral and cell-mediated immunity have been implicated in autoimmune thyroiditis, a number of experiments have been carried out to elucide the role of each process in the pathogenesis of Hashimoto's thyroiditis. The experiments of Calder and co-workers will be described to illustrate these points although the work of other authors could be cited.

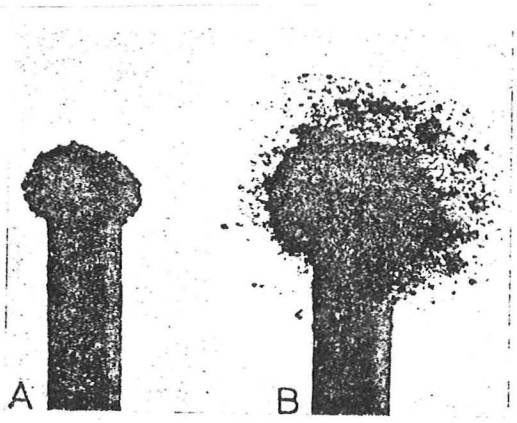
1) T lymphocytes sensitized to a specific antigen will produce a factor that inhibits migration of macrophages or leucocytes when that T-cell is exposed to that antigen. An example of the test is shown in Figure 12. The antigen was present in A and inhibited migration. In B, no antigen was present and migration was much greater than that observed in A.

Figure 11



. Role of T lymphocytes, B lymphocytes and nonprocessed lymphoid (K) cells in immunological responses. Many of these events involve cell proliferation, but for simplicity this has not been shown

Figure 12



Migration 'fans' in the leukocyte migration test. A, inhibition of migration in the presence of antigen compared with control area; B, in the absence of antigen

Calder and co-workers studied the effects of a series of antigens on the migration of leucocytes obtained from control subjects and from patients with Hashimoto's thyroiditis (Table 10). A high proportion (75%) of patients with Hashimoto's thyroiditis had circulating lymphocytes sensitized to constituents of the thyroid gland (107). Note that liver and kidney mitochondria produced inhibition, a finding waiting for significance.

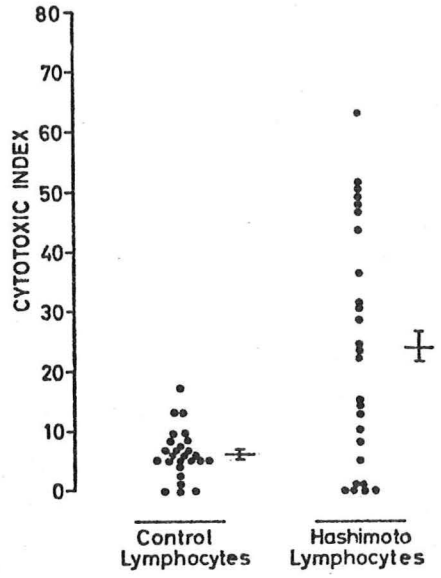
Table 10

The effect of antigens on the migration of leukocytes from control subjects and patients with Hashimoto thyroiditis. (Reproduced from Calder *et al.* 1972 by kind permission)

	Patients giving inhibition of migration			
	Hashimoto		*Control*	
Antigen	*No.*	*%*	*No.*	*%*
Crude thyroid extract	38/51	75	2/53	4
Thyroglobulin	14/32	44	2/36	6
Thyroid mitochondria	28/52	54	3/53	6
Thyroid microsomes	14/40	35	2/35	6
Liver mitochondria	8/17	47	0/16	0
Kidney mitochondria	5/11	45	0/13	0

2) Another test of cell-mediated immunity is the cytotoxicity of lymphocytes to target cells. In this case, chicken red cells were labeled with ^{51}Chromium and then coated with thyroglobulin. When the cells are lysed, the ^{51}Cr. is released and the amount of ^{51}Cr released is a measure of cytotoxicity. In this test Hashimoto lymphocytes had a cytotoxic index of 25.5 ± 3.8, while the control cell index was 6.3 ± 0.8. (Figure 13). No correlation was found between the cytotoxic index and the level of circulating antibody in each patient (108).

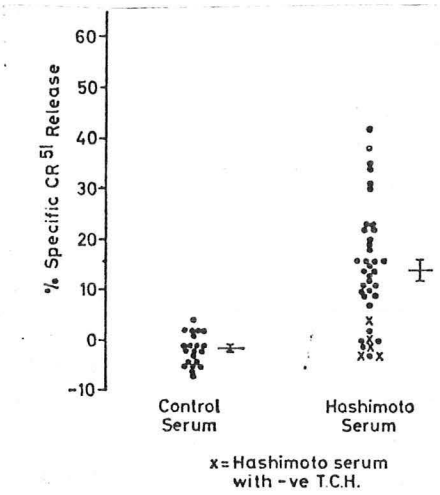
Figure 13



The effect of lymphocytes from control subjects and patients with Hashimoto thyroiditis on the release of ^{51}Cr from thyroglobulin-coated chicken red blood cells. (Reproduced from Calder et al. *1973 by kind permission)*

3) In another series of experiments serum from patients with Hashimoto's thyroiditis was incubated with non-immune lymphocytes. These incubated lymphocytes were then exposed to thyroglobulin-coated chicken RBC's and the cytotoxic index was measured (Figure 14). Those Hashimoto sera marked with an X did not contain antithyroglobulin antibody. The mean cytotoxic index for the Hashimoto sera was 14.1 ± 1.9 while that for the control sera was essentially zero (109).

Figure 14

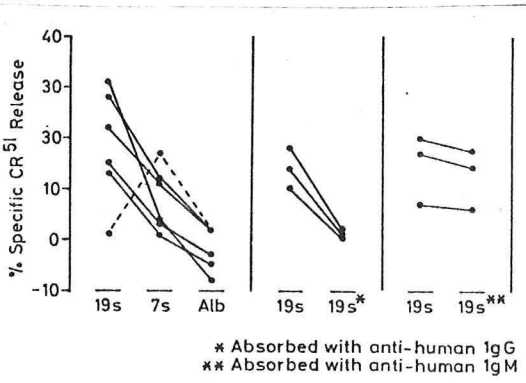


The effect of lymphoid cells from control subjects on the release of ^{51}Cr from thyroglobulin-coated target cells preincubated with control serum or serum from patients with Hashimoto thyroiditis. (Reproduced from Calder et al. *1973b by kind permission)*

The cytotoxicity was directly related to the level of thyroglobulin antibody in the serum. Serum samples from several subjects were separately fractionated and the 19s fraction was directly related to the cytotoxic activity in all but one patient (Figure 15). However activity of the 19s fraction could be absorbed out by anti-human IgG suggesting that the 19s material was an IgG antibody-antigen complex rather than a 19s IgM molecule.

These results indicated that Hashimoto serum contained complexes capable of stimulating non-immune lymphocytes to become killer cells.

Figure 15



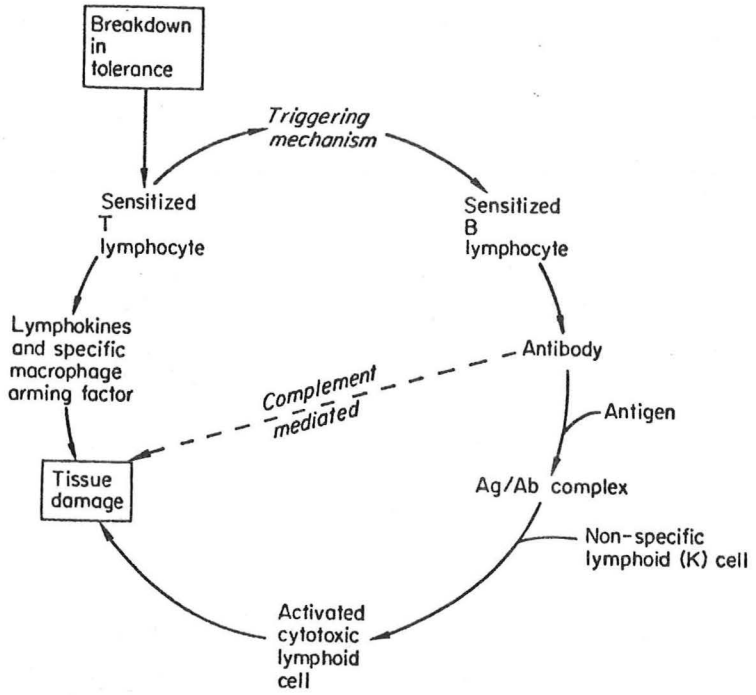
The effect of lymphoid cells from control subjects on the release of ^{51}Cr from thyroglobulin-coated target cells preincubated with Hashimoto serum fractions. (Reproduced from Calder et al. *1973b by kind permission)*

Thus, Calder and coworkers suggest that thyroid damage can be produced in one of two ways (110).

1. Autoantibody may coat target tissue and make the thyroid cells susceptible to K-cell attack.

2. Ag-Ab complexes may activate K-cells and give them specificity to destroy thyroid target cells.

Figure 16



Probable pathogenic mechanisms in organ-specific autoimmune disease.

A general scheme illustrating the probable pathogenesis of this (as well as other) organ specific disease is shown in Figure 16.

The cause or causes for the breakdown in tolerance and the triggering of antibody formation are unknown.

Searches have been made for common HL-A types in patients with Hashimoto's thyroiditis but in all but one report (111) no association was found (112-115). Interestingly, there is a correlation in the mouse (116) and in the chicken (117).

Possible factors initiating the immune response. A number of factors have been implicated in the cause of autoimmune thyroiditis (Table 11).

Table 11

Possible Predisposing Causes to Autoimmune Thyroiditis

1. Abnormal exposure to a normal antigen.
2. Development of an abnormal antigen.
3. Genetic Predisposition.
4. A basic "dyshormonogenesis" of the gland leading to autoimmunity.
5. Development of a "Mutant clone" against normal thyroid antigen.
6. Basement membrane defect.
7. End result of thyrotoxicosis.
8. Virus infection.
9. Abnormality of immune homeostasis.

Brief consideration will be given to each.

1) It was once assumed that thyroglobulin was a hidden antigen rarely entering the plasma. It is now clear that thyroglobulin frequently enters plasma under a variety of circumstances but most individuals do not develop thyroiditis.

2) An abnormal antigen has never been observed but minor differences in structure cannot be excluded. More importantly, thyroiditis can be produced by normal thyroid antigens experimentally.

3) There is convincing evidence to support a genetic predisposition but the mode of inheritance is not clear (122, 123). In several family studies, an increased occurrence of antithyroid antibodies has been found in apparently healthy relatives of patients with autoimmune thyroiditis (92, 118, 119) (Table 12).

Table 12

Incidence of Thyroid Antibodies in 201 Healthy Relatives of Adult Hashimoto Probands

Relatives of:	Proband Sole Member with Clinically Overt Disease			Probands from Families with More Than One Clinically Affected Member		
	Number Tested	Percentage with Thyroid Antibodies	Statistical Significance	Number Tested	Percentage with Thyroid Antibodies	Statistical Significance
Males	60	32	$0.01 < P < 0.02$	26	38	N.S.D.
Matched controls	60	12		26	15	
Females	76	45	$P < 0.001$	39	61	$P < 0.001$
Matched controls	76	14		39	18	

It is also of interest that there is family clustering of various types of thyroid disease such as Graves Disease and Hashimoto's thyroiditis (118, 119, 120). It is estimated that one-third of all adults with thyroid disease have family members affected with the same or a closely related disorder (121).

4) Dyshormonogenesis was proposed because iodinated proteins without hormonal activity have been found in the serum of patients with Hashimoto's Disease. One of these products is iodoalbumin. Antibodies to iodoalbumin have not been found and these iodinated proteins are thought to result secondarily from damage to the gland.

5) Evidence against a forbidden clone includes the finding that antithyroid antibodies are of several types and multiple immune responses such as LATS, antithyroblogulin and cell-mediated immunity may appear in the same patient. Also, patients with thyroid disease may also manifest antibodies directed toward other organs.

6) Evidence for a possible basement membrane defect has been presented earlier. Failure to find IgG in the particulate matter located at the Basement Membrane indicates these deposits are not Ag-Ab complexes. Basement Membrane damage is thought to represent a secondary change resulting from thyroid damage.

7) Patients with thyrotoxicosis may have anti-thyroid antibodies. Inspection of glands from thyrotoxic patients often reveals the presence of pathological changes of both thyrotoxicosis and thyroiditis. There is a clinical impression that this type of patient becomes hypothyroid rather quickly after surgery, ^{131}I therapy or spontaneously (82). It is now believed that Grave's Disease, Ideopathic Hypothyroidism and Hashimoto's Thyroiditis all represent manifestations of an autoimmune process where the antibody response differs for some unknown reason.

8) Virus Infections could release excessive thyroid antigen into plasma where Antibody formation would result. It might also produce mutant thyroid antigens. Long term observation of patients with subacute thyroiditis where a viral cause is strongly implicated has not revealed a striking increase in the incidence of Hashimoto's Disease.

9) An abnormality in immune homeostasis is the most popular theory used to explain several thyroid diseases at the present time. Some interplay of environmental and genetic factors is thought to result in a breakdown in immune tolerance. Suppressor T-cells may no longer function to control antibody production toward thyroid antigens. Alternatively, helper T-cells may become too helpful toward B cells in their ability to produce anti-thyroid antibodies. The kind of thyroid disease that results may simply relate to the type of antibody formed. If, for example, LATS is produced, it would bind to the TSH receptor on thyroid cells, stimulate them, and produce thyrotoxicosis. In other patients the thyroid antibodies would lead to thyroid inflammation and ultimate destruction. Depending on the clinical course, the patient may manifest ideopathic myxedema or Hashimoto's thyroiditis.

While this explanation may not ultimately prove true, there is little doubt that Hashimoto's Thyroiditis, Grave's Disease and Ideopathic Myxedema are all manifestations of an autoimmune process that links them closely together clinically.

Why do women suffer from thyroid disease so much more commonly than men? There is no good explanation or theory regarding this point except for the obvious proposals that ovarian secretions or some portion of the X-chromosome (or lack of the Y chromosome) allow the triggering of the autoimmune process to occur much more readily in the female.

Diagnosis, Treatment and Clinical Course: (1, 2) The finding of a firm goiter in a euthyroid or hypothyroid individual is suggestive. Pain and tenderness are unusual. Laboratory tests may not be very helpful depending on the stage of thyroid function encountered in the patient. TSH levels may be increased but are usually suppressible when T_3 is given. Antibodies to thyroglobulin are present in serum and titers greater than 1:2500 are diagnostic.

Surgery is indicated when cancer cannot be excluded and when pressure symptoms occur. It is not clear whether or not the incidence of thyroid cancer in Hashimoto's thyroiditis is increased. The diagnosis of non-toxic nodular goiter must be excluded -- in this disease the thyroid antibodies are very low. Riedel's struma is excluded from the fibrous variant of Hashimoto's on the same basis.

Hyperthyroidism may occur early in the course of Hashimoto's thyroiditis but it must be remembered that Grave's Disease and Hashimoto's Disease may co-exist in the same gland.

No treatment is needed in the asymptomatic patient with a small goiter. If the goiter is large, thyroid hormone therapy is indicated and the goiter will reduce in size in several months. Adrenocortical hormones have been used when the onset of the disease was fairly acute. Acute symptoms are ameliorated but the overall disease process continues and symptoms may recur when this treatment is stopped. Steroids are therefore not recommended.

The course of Hashimoto's Disease is variable. In many patients, the process remains static for many years while in others, hypothyroidism gradually develops (124-127). Regular follow-up of the asymptomatic patient is therefore necessary. With thyroid hormone treatment, there may be a gradual reduction in the thyroid antibody titers.

Pregnancy may influence the disease on rare occasion. Spontaneous remission of hypothyroidism occurred in one patient (128), and then reappeared 5 months post-partum. In another report 6 patients developed goiter, high titers of thyroid antibodies and hypothyroidism 1-3 months after delivery. In each case, there was spontaneous remission from 6-9 months after delivery (129). The significance of these findings is unclear.

43) Hashimoto, H. Zur Kenntnis der lymphomatosen Veranderung der Schilddruse (Struma Lymphomatosa), *Arch. Klin,. Chir.* 97:219, 1912.

44) Rose, N.R. and Witebsky, E. Studies on Organ Specificity: V. Changes in the thyroid glands of rabbits following active immunization with rabbit thyroid extracts. *J. Immun.* 76:417, 1956.

45) Roitt, I.M., Doniach, D., Campbell, P.N., and Hudson, R.V. Autoantibodies in Hashimoto 's Disease. *Lancet* 2:280, 1956.

46) Furszyfer, J., et al. Hashimoto's Thyroiditis in Olmstead County, Minnesota, 1935 though 1967. *Mayo Clin. Proc.* 45:586, 1970.

47) Furszyfer, J., et al. Epidemiologic Aspects of Hashimoto's Thyroiditis and Grave's Disease in Rochester, Minnesota (1935-1967), with special reference to Temporal Trends. *Metabolism* 21:197, 1972.

48) Neve, P., et al. Struma Lymphomatosa (Hashimoto). Chapter 5 in reference (3).

49) Katz, S.K. and Vickery, A.L. The Fibrous Variant of Hashimoto's Thyroiditis. *Human Pathology* 5:161, 1974.

50) Senhauser, D. Immunopathologic Correlations in Thyroiditis In The Thyroid, ed. Hazard, J.B. and Smith, D.E. (1964).

51) Eversman, J., et al. Hashimoto's Thyroiditis and Grave's Disease with exophthalmos without hyperthyroidism. *Cleveland Clin. Quart.* 33:179, 1966.

52) Wyse, E.P., et al. Ophthalmopathy without Hyperthyroidism in Patients with Histological Hashimoto's Thyroiditis. *J. Clin. Endocrin.* 28:1623, 1968.

53) Greenberg, A.H., et al. Juvenile Chronic Lymphocytic Thyroiditis: Clinical, Laboratory and Histological Correlations. *J. Clin. Endocrin.* 30:293, 1970.

54) Ling, S.M., et al. Euthyroid Goiters in Children: Correlation of Needle Biopsy with other Clinical and Laboratory Findings in Chronic Lymphocytic Thyroiditis and Simple Goiter.

55) Winter, J., et al. The Relationship of Juvenile Hypothyroidism to chronic Lymphocytic thyroiditis. *J. Pediat.* 69:709, 1966.

56) Monteleone, J.A., et al. Differentiation of Chronic Lymphocytic thyroiditis and simple goiter in pediatrics. *J. Pediat.* 83:381, 1973.

57) Ting, K.S.K., et al. Antithyroid Antibodies in Juvenile Lymphocytic Thyroiditis. *Am. J. Clin. Path.* 61:549, 1974.

58) Rallison, M.L., et al. Occurrence and natural history of chronic lymphocytic thyroiditis in childhood. *J. Pediat.* 86:675, 1975.

59) Luxton, R.W., et al. Hashimoto's struma lymphomatosa. Diagnostic Value of serum flocculation reactions. *Lancet* 2:105, 1956.

60) Luxton, R.W. Discussion of Hashimoto's disease, the clinical aspect. *Proc. Soc. Roy. Soc. Med.* 50:943 1957.

61) Luxton, R.W. Paget's Disease of bone associated with Hashimoto's struma lymphomatosa: A clue to the pathogenesis of Paget's Disease. *Lancet* 1:441, 1957.

62) Anderson, J.R., et al. Autoantibodies in Addison's Disease. *Lancet* 1:1123, 1957.

63) Block, K.J., et al. Sjogren's Syndrome. I. Serologic Reactions in patients with Sjogren's Syndrome with and without Rheumatoid Arthritis. *Arth. and Rheum.* 3:287, 1960.

64) White, R.G., et al. Lymphoid Goiter and the Syndrome of systemic Lupus erythematosis. *Lancet* 1:368, 1961.

65) Richards, G.E., et al. Symptomatic hypothyroidism in children with Collagen disease. *J. Pediat.* 87:82, 1975.

66) Pettit, M.D., et al. Antithyroid Antibody in juvenile diabetes. *J. Clin. Endocrin.* 21:209, 1961.

67) Buchanan, W.W., et al. Association of Hashimoto's thyroiditis and rheumatoid arthritis. *Lancet* 1:245, 1961.

68) Markson, J.L. and Moore, J.M. Autoimmunity in Pernicions Anemia and Iron deficiency anemia. *Lancet* 2:1240, 1962.

69) Rose, M.S., et al. Intrinsic-Factor Antibodies in absence of Pernicious Anemia. *Lancet* 2:9, 1970.

70) Shulman, L.E. and Harvey, A.M. Hashimoto's thyroiditis in false-positive reactors to the test for syphilis. *Am. J. Med.* 36:174, 1964.

71) Williams, E.D., et al. Thyroiditis and Gonadal Dysgenesis. *New Eng. J. Med.* 270:805, 1964.

72) Sylvester, P.E. Autoimmune Thyroiditis in Mental Handicap: Epidemiological Study based on Thyroid Histology. *J. Ment. Defic. Dis.* 17:18, 1973.

73) Itoh, K. and Maruchi, N. Breast Cancer in Patients with Hashimoto's Thyroiditis. *Lancet* 2:1119, 1975.

74) Lendy, M. and Dollberg L. Coincidence of Sarcoidosis and Hashimoto's thyroiditis. *Am. Rev. of Resp. Dis.* 112:113, 1975.

75) Osher, R.H. and Smith, J.L. Ocular Myasthenia Gravis and Hashimoto's Thyroiditis. *Am. J. Ophthal.* 79:1038, 1975.

76) Masi, A.T., et al. Hashimoto's Disease: An Epidemiological Critique. *J. Chron. Dis.* 18:1, 1965.

77) Finucane, J.F. and Kaiz, M. Adrenal Function in Autoimmune Thyroiditis. *Irish J. Med. Sci.* 145:338, 1974.

78) Camus, M., et al. Alterations of Iodine Metabolism in Asymptomatic Thyroiditis. *Metabolism* 17:1064, 1968.

79) Gray, H.W., et al. Intravenous Perchlorate Test in the diagnosis of Hashimoto's Disease. *Lancet* 1:335, 1974.

80) Paul, B.R., et al. Thyroid Imagining in Lymphocytic Thyroiditis. *Radiology* 115:139, 1975.

81) Gluck, F.B., et al. Chronic Lymphocytic Thyroiditis, Thyrotoxicosis, and Low Radioactive Iodine Uptake: Report of 4 cases. *New Eng. J. Med.* 293:624, 1975.

82) Hall, R. Immunological Aspects of Thyroid Function. *New Eng. J. Med.* 266:1204, 1962.

83) Beall, G.N. and Soloman, D.H. Immunologic Features of Thyroid Disease. *Postgrad. Med.* 54:181, 1973.

84) Roitt, I.M. Essential Immunology (Blackwell, Oxford) 1974, p 221.

85) Doniach, D., et al., Human Auto-immune Thyroiditis: Clinical Studies. *Brit. Med. J.* 1:365, 1960.

86) Dussault, J.H., et al. Qualitative aspects of thyroglobulin antibodies in Hashimoto's thyroiditis and Grave's Disease. *J. Canad. Med. Assoc.* 17:319, 1974.

87) Brandes, D., et al. Hashimoto's thyroiditis. Ultrastructive and Histochemistry of the cellular infiltrate. *Johns Hopkins Med. J.* 124:211, 1969.

88) Neve, P. The ultrastructure of thyroid in Chronic Autoimmune Thyroiditis. *Virchows Arch. Abt. A. Path. Anat.* 346:302, 1969.

89) Soderstrom, N., et al. Organization of the Invading Lymphoid Tissue in Human Lymphoid Thyroiditis. *Scan. J. Immunol.* 3:295, 1974.

90) Kalderon, A.E., et al. Ultrastructural Alterations of the Follicular Basement Membrane in Hashimoto's Thyroiditis. *Am. J. Med.* 55:485, 1973.

91) Doniach, D. and Roitt, I.M. Thyroid Autoallergic Disease. In Clinical Aspects of Immunology. eds. Gell, P.G.H., Coombs, R.R.A., and Lachmann, P.J. (Blackwell, Oxford) 3rd. edition, 1975, pp 1355-1386.

92) Doniach, D. and Roitt, I.M. Autoimmune Thyroid Disease. In Textbook of Immunopathology. eds. Miescher, P.A. and Muller-Eberhard, H.M. (Grune and Stratton, New York) 1969, pp 516-533.

93) Irvine, W.T., et al. The Immunopathy of Thyroid Disease. Current Topics in Thyroid Research. eds. Cassano, C., and Andreoli, M. (Academic Press, New York) 1965, p 773.

94) Ardeman, S., et al. Addisonian Pernicious Anemia and Intrinsic Factor Antibodies in Thyroid Disorders. *Quart. J. Med.* 35:421, 1966.

95) Mulhern, L.M., et al. Hashimoto's Disease: A search for Associated Disorders in 170 clinically detected cases. *Lancet* 2:508, 1966.

96) Bigazzi, P.E. and Rose, N.R. Spontaneous Autoimmune Thyroiditis in Animals as a Model of Human Disease. *Prog. Allergy* 19:245, 1975.

97) Roitt, I.M. and Donach, D. Human auto-immune thyroiditis: serological studies. *Lancet* 2:1027, 1958.

98) Parker, R.H. and Bererwaltes, W.H. Thyroid antibodies during pregnancy and in newborn. *J. Clin. Endocrinol.* 21:792, 1961.

99) Nakamura, R.M. and Weigle, W.O. Transfer of Experimental Autoimmune Thyroiditis by serum from Thyroidectomized Donors. *J. Exp. Med.* 130: 263, 1969.

100) Weigle, W.O. Experimental Autoimmune Thyroiditis Pathology Annual, 1973 series, ed. S.C. Sonmers. p 329.

101) Rose, N.R. and Witebsky, E. Experimental Thyroiditis. In Immunological Diseases. ed. M. Samter (Little, Brown, Boston) 2nd Edition, 1971, p 1179.

102) Beall, G.N. and Solomon, D.H. Hashimoto's Disease and Grave's Disease. In Immunological Diseases. ed. M. Samter (Little, Brown & Co., Boston) 2nd Edition, 1971, p 1198.

103) Laryea, E., et al. The effect of blood leucocytes from patients with Hashimoto's Disease on human thyroid cells in monolayer culture. *Clin. Endocrin.* 2:23, 1973.

104) Podleski, W.K. Cytotoxic Lymphocytes in Hashimoto's thyroiditis. *Clin. and Exp. Immunol.* 11:543, 1972.

105) Lamki, L., et al. Cell-mediated immunity in Grave's Disease and Hashimoto's Thyroiditis as shown by the demonstration of migration inhibition factor (MIF). *J. Clin. Endocrinol. and Metab.* 36:358, 1973.

106) Irvine, W.J. Autoimmune Mechanisms in Endocrine Disease. *Proc. Roy. Soc. Med.* 67:499, 1974.

107) Calder, E.A., et al. The effect of thyroid antigens on the in vitro migration of leucocytes from patients with Hashimoto's thyroiditis. *Clin. Exp. Immunol.* 12:429, 1972.

108) Calder, E.A., et al. Cytotoxic Lymphocytes in Hashimoto's Thyroiditis. *Clin. Exp. Immunol.* 14:19, 1973.

109) Calder, E.A., et al. Lymphocyte-dependent antibody-mediated cytotoxicity in Hashimoto Thyroiditis. *Clin. Exp. Immunol.* 14:153, 1973.

110) Calder, E.A., et al. Killer Cells and Immune Complexes in Thyroid Disease. *Proc. Roy. Soc. Med.* 68:10, 1975.

111) Farid, N.R., et al. HL-A Antigens in Grave's Disease and Hashimoto's Thyroiditis. *Int. Arch. Allergy Appl. Immun.* 49:837, 1975.

112) Bode, H.H., et al. Familial Lymphocytic Thyroiditis: Analysis of Linkage with Histocompatability and Blood Groups. *J. Clin. Endocrinol. and Metab.* 37:692, 1973.

113) Richiardi, P., et al. Absence of Linkage Between the HL-A System and Production of Anti-Thyroglobulin Antibodies. *Tissue Antigens* 5:213, 1975.

114) Dausset, J., et al. The Association of the HL-A Antigens with Diseases: A Review. *Clin. Immunol. and Immunopath.* 3:127, 1974.

115) Whittingham, S., et al. Thyrogastric AutoImmune Disease: Studies on the cell-mediated immune system and Histocompatability Antigens. *Clin. Exp. Immunol.* 19:289, 1975.

116) Rose, N.R., et al. Genetic Aspects of Autoimmune Thyroiditis. *Int. Arch. Allergy* 45:138, 1973.

117) Bacon, L.D., et al. Relation Between the Major Histocompatability (B) Locus and Autoimmune Thyroiditis in Obese Chickens. *Science* 186:274, 1974.

118) Fraser, G.R. The Genetics of Thyroid Disease. In Prog. in Med. Genetics eds. A.G. Steinberg and A. G. Bearn 6:89, 1969.

119) Fialkow, P.J. Genetic Aspects of Autoimmunity. In Prog. in Med. Genetics. ed. A.G. Steinberg and A.G. Bearn 6:117, 1969.

120) Buckanan, W.W., et al. Association of Thyrotoxicosis and Autoimmune thyroiditis. *Brit. Med. J.* 1:843, 1961.

121) Kline, E. *Deutsch. Med. Wschr.* 85:314, 1960.

122) Hall, R., et al. Thyroid Autoantibodies: A study of first degree relatives. *Clinical Genetics* 3:319, 1972.

123) Goldsmith, R.E. Familial Autoimmune Thyroiditis: Maternal - Fetal Relationship and the role of Generalized Autoimmunity. *J. Clin. Endocrinol. and Metab.* 37:265, 1973.

124) Vickery, A.L. and Hamlin, Jr. E. Struma Lymphomatosa (Hashimoto's Thyroiditis). Observations on Repeated biopsies in sixteen patients. *New Eng. J. Med.* 264:226, 1961.

125) Heimann, P. Treatment of Thyroiditis. *Acta Med. Scand.* 187:323, 1970.

126) Papapetron, P.D., et al. Long-term treatment of Hashimoto's Thyroiditis with Thyroxine. *Lancet* 2:1045, 1972.

127) Gordin, A and Lamberg, B.A. Natural Course of Symptomless Autoimmune Thyroiditis. *Lancet* 2:1234, 1975.

128) Nelson, J.C. and Palmer, F.J. A Remission of Goitrous Hypothyroidism During Pregnancy. *J. Clin. Endocrinol. and Metab.* 40:383, 1975.

129) Amino, N., et al. Transient Hypothyroidism after Delivery in Autoimmune Thyroiditis. *J. Clin. Endocrinol. and Metab.* 42:296, 1976.