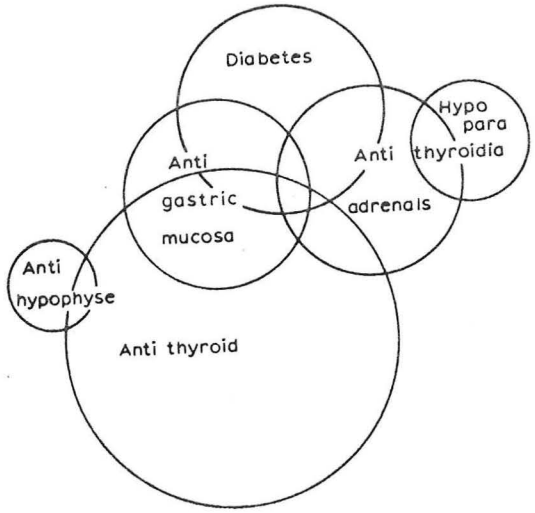
Endo

POLYGLANDULAR AUTOIMMUNE SYNDROMES



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POLYGLANDULAR AUTOIMMUNE SYNDROMES

The concept of polyglandular disease was initiated about 70 years ago by reports of patients with coexistent nontuberculous adrenal insufficiency and lymphocytic thyroiditis (1,2, reviewed in 3). Subsequent reports confirmed an association of Addison's disease with lymphocytic thyroiditis and emphasized the similarity in the lymphocytic infiltration that was found in the adrenal cortex and thyroid gland (4,5). The spectrum of polyglandular disease was also extended in later reports by the recognition of clinical myxedema (6), hyperthyroidism (7), diabetes mellitus (7), and hypoparathyroidism (8) in association with Addison's disease. The first suggestion that an immunologic mechanism might be of importance in these polyglandular disorders was made by Bloodworth, Kirkendall, and Carr in 1954 (9). In 1956 Roitt et al reported their demonstration of thyroid antibodies in the serum of patients with Hashimoto's thyroiditis (10), and over the ensuing 7 years circulating adrenal antibodies were demonstrated in patients with Addison's disease (11,12). It is now recognized that failure of virtually every endocrine gland may be accompanied by the presence of circulating organ-specific autoantibodies to that gland. The term polyglandular autoimmune (PGA) syndrome has been proposed to designate endocrine dysfunction involving two or more glands on the basis of an autoimmune mechanism (13). In most instances the effect of the autoimmune process is destruction of the target glands with consequent endocrine hypofunction. In the case of the thyroid gland, however, in addition to hypothyroidism due to thyroiditis, there may be stimulation of thyroid hormone secretion by circulating antibodies that bind to the TSH receptor. Moreover, some patients with polyglandular autoimmunity develop autoimmune disorders involving nonendocrine systems. Although the pathogenesis of target organ dysfunction in the PGA syndromes has begun to be elucidated, the etiology of the initiation of the immune response is still highly speculative.

Table I summarizes the prevalences of association between some of the principal endocrine and nonendocrine components of PGA disease. Concealed within these data are several patterns of disease association that have emerged from analyses of families with polyglandular autoimmunity (14,15). On the basis of age of onset, associations of specific endocrine disorders in an affected individual, as well as on maintenance of these specific associations within families, 2 categories of PGA disease have been delineated. These have been termed PGA syndrome types I and II, the principal manifestations of which are described in Table II (13). PGA type I is also referred to as the candidiasis-endocrinopathy syndrome or as juvenile autoimmune polyendocrinopathy. The features of Schmidt's syndrome are encompassed by the type II disorder. There are other associations of autoimmune endocrine and nonendocrine disease--for example, the coexistence of autoimmune thyroid disease with insulin-dependent diabetes mellitus and/or pernicious anemia. Some of these cases represent incomplete forms of the type II syndrome; others however (in particular those associated with pernicious anemia) most likely represent different clinical syndromes.

TABLE I

PREVALENCES OF DISEASE ASSOCIATION IN POLYGLANDULAR AUTOIMMUNITY

Population Studied	Addison's Disease	Insulin-Dependent Diabetes Mellitus	Autoimmune Thyroid Disease	Pernicious Anemia+
Addison's Disease	--	14%	18%*	2%
Insulin-Dependent Diabetes Mellitus	rare	--	4-8%/12%**	3-5%
Autoimmune Thyroid Disease	rare	7%	--	2-11%
Pernicious Anemia	rare	8%	20%/13%**	--
General Population	.003%	0.3%	2%/3%**	0.1%

*clinical

**clinical/subclinical

+includes latent PA

TABLE II

PRINCIPAL MANIFESTATIONS OF THE POLYGLANDULAR AUTOIMMUNE SYNDROMES

Syndromes Associated with Addison's Disease

PGA Type I
- Hypoparathyroidism
- Chronic Mucocutaneous Candidiasis
- Adrenal Insufficiency

PGA Type II
- Adrenal Insufficiency
- Autoimmune Thyroid Disease
- Insulin-Dependent Diabetes Mellitus

Syndromes Without Addison's Disease

Autoimmune Thyroid Disease - Insulin-Dependent Diabetes Mellitus - Pernicious Anemia

Autoimmune Thyroid Disease - Pernicious Anemia with
- Lymphocytic Hypophysitis
- Myasthenia Gravis
- Primary Biliary Cirrhosis
- Connective Tissue Diseases

It should be noted that before a diagnosis of one of these syndromes is made, the possibility of a nonautoimmune disorder resulting in failure of multiple endocrine glands should be entertained. In addition to hypopituitarism, various infiltrative disorders such as hemochromatosis and

amyloidosis may be responsible for polyglandular failure. Also, a syndrome has been recently described in which hypofunction of multiple endocrine organs occurs in connection with a plasma cell dyscrasia. This has been termed the POEMS syndrome to designate its principal features --polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (16).

POLYGLANDULAR AUTOIMMUNITY ASSOCIATED WITH ADDISON'S DISEASE

PGA Syndrome Type I

This syndrome is characterized by the triad of hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis. The presence of any two of the three conditions is sufficient to make the diagnosis. A patient with only a single element of the syndrome should be considered as affected if other family members are known to have one or more of the other components. Hypoparathyroidism and chronic mucocutaneous candidiasis are the most frequent manifestations of PGA type I (Table III), and occur together in more than 70% of cases (15). Neither of these conditions occurs in the other forms of polyglandular autoimmunity. The complete triad with adrenal insufficiency occurs in approximately a third of patients (15).

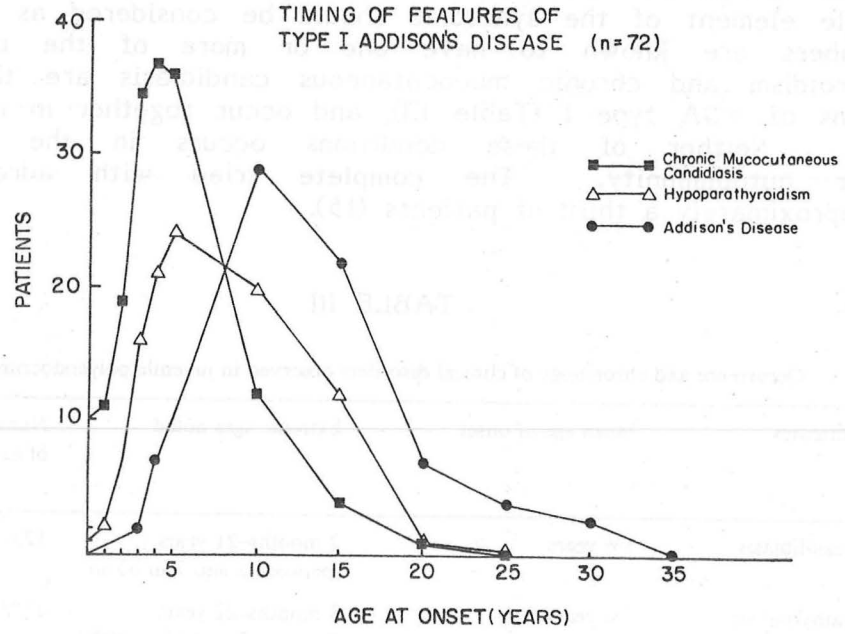
TABLE III

Occurrence and chronology of clinical disorders observed in juvenile polyendocrinopathies

Clinical diseases	Mean age of onset	Extreme ages noted	Number of cases	Frequency %
Chronic candidiasis	5 ½ years	2 months–21 years (between 2 and 7 in 80%)	125/166	75
Hypoparathyroidism	7 ½ years	3 months–22 years (between 2 and 10 in 80%)	147/166	88.5
Hypothyroidism	9 ½ years	3–15 years	11/166	6.6
Adrenal insufficiency	13 years	1 ½–34 years (between 5 and 16 in 80%)	100/166	60
Gonadal insufficiency	diagnosis at puberty	4–21 years	19/42	45
Thyroiditis	17 years	15–18 years	9/166	5.4
Chronic diarrhea and/or malabsorption	8 years	1 ½–30 years	41/166	25
Alopecia	8 years	1–21 years	33/166	20
Pernicious anemia	16 years	7–21 years	27/166	16
Cirrhosis and/or active hepatitis	17 years	5–21 years	14/166	8.5
Vitiligo	–	3–28 years	6/166	3.6
Diabetes mellitus NID ID	–	6–24 years	2/166 2/166	2.5

Onset of the disorder is during childhood, with the first manifestations always developing before the age of 15 years. Hypoparathyroidism and/or candidiasis are usually present by the age of 5, and typically precede by several years the appearance of adrenal insufficiency (Fig. 1) (13-15). Occasionally a simultaneous onset of hypoparathyroidism and adrenal insufficiency is observed, but only rarely does Addison's disease precede hypoparathyroidism. The mean age of onset of Addison's disease in PGA type I is 12-13 years. With the appearance of adrenal insufficiency, transient hypercalcemia may develop even in patients with antecedent hypoparathyroidism (13,17,18).

Figure 1



Ref. 13

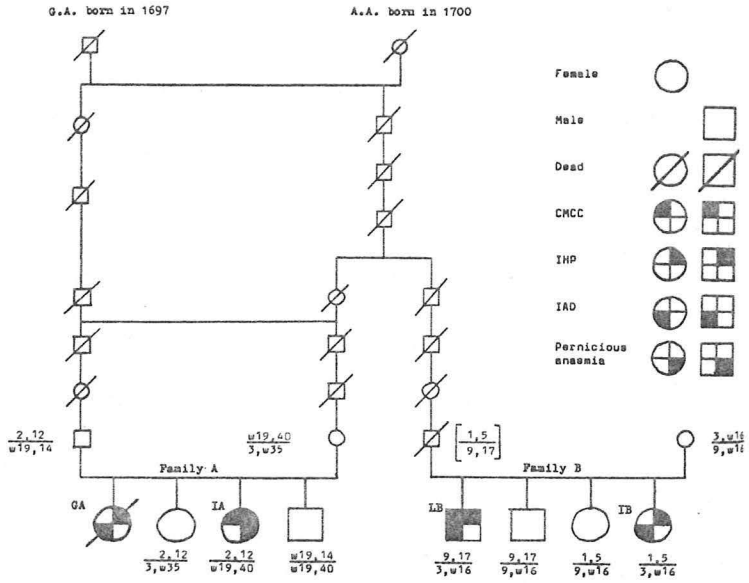
The ages of onset for candidiasis, hypoparathyroidism and Addison's disease are compared. Candidiasis occurs early and Addison's disease, when present in Type I PGA, occurs late. In only 3 of 41 patients was Addison's disease diagnosed before hypoparathyroidism.

Other endocrine disorders that occur in association with PGA type I are primary gonadal failure and autoimmune thyroid disease (13,15,19-21). Insulin-dependent (type I) diabetes mellitus is only rarely observed (15). Two patients with evidence of anterior pituitary insufficiency (22,23) and two with diabetes insipidus (24,25) have been reported. Primary gonadal failure was present in 19 (3 male, 16 female) of 42 patients with PGA I who had reached the age of 16 years at the time of case review (15). Thus 45% of patients beyond the age of expected puberty have gonadal insufficiency. Concomitant adrenal insufficiency was present in 16 of these 19 patients. Autoimmune thyroid disease is less frequent, occurring in approximately 12% of patients with PGA I; cases are about equally divided between primary myxedema (atrophic thyroiditis) and Hashimoto's thyroiditis (Table III). No case of Graves' disease has been reported in association with this syndrome.

Nonendocrine components of PGA I, in addition to mucocutaneous candidiasis, include pernicious anemia in 16%, chronic diarrhea and/or malabsorption in 25%, alopecia in 20%, and chronic liver disease in 8.5% of patients. Vitiligo is found in approximately 4% (15).

PGA type I is rare, probably comprising 10-20% of all cases of primary idiopathic hypoparathyroidism (itself a rare disorder) (26). Familial aggregation occurs in at least 50% of cases. The pattern of aggregation within PGA I families, the increased prevalence of consanguinity, and frequency analyses of affected family members all suggest an autosomal recessive mode of inheritance (Fig. 2) (14,15,27). Females are affected more frequently than males (female to male ratio of 1.7 to 1) (15). There is no evidence to date of disease linkage to the HLA system among affected family members (27).

Figure 2



Ref. 27

Fig. 2. Pedigree of families A and B. HLA antigens indicated. The brackets denote that the haplotype was deduced from those of the siblings.

Circulating organ-specific antibodies are frequently present in patients with PGA I (Table IV). In one study that included 63 patients with this syndrome, 48% had adrenal antibodies, 29% had thyroid antibodies, and 11% had antibodies directed against gastric parietal cells (28). Antibodies reacting with parathyroid chief and oxyphil cells were found in 13 of 32 patients in

TABLE IV

ORGAN SPECIFIC ANTIBODIES IN PGA TYPE I

Adrenal	48%
Thyroid	29%
Gastric	11%
Parathyroid	41%
Steroid Cell	86%*
Vasopressin Cell	
Prolactin Cell	

*of PGA I patients with Addison's disease

another series (all of whom had hypoparathyroidism) (29). In addition, antibodies that cross-react with steroid-producing cells of ovary, testis, and placenta ("steroid cell antibodies") are commonly detected in PGA I patients with clinical Addison's disease (30). One patient with diabetes insipidus associated with a circulating antibody to vasopressin-secreting cells of the hypothalamus (25), and two patients with antibodies to prolactin-secreting cells of the anterior pituitary (without evidence of pituitary insufficiency) (31) have also been reported. There are no systematic studies of cell-mediated immune responses directed against specific endocrine organ antigens in PGA type I. However migration inhibition factor production has been demonstrated by lymphocytes from patients with idiopathic hypoparathyroidism against parathyroid and adrenal antigens (32). Other parameters of cell-mediated immunity (delayed hypersensitivity, lymphocyte stimulation by mitogens and antigens, and evaluation of suppressor T-cell activity) have been normal or variably defective in patients with PGA I and in unaffected family members (27,33,34). Although the genetic defect underlying this syndrome is almost certainly one that involves diminished suppressor T cell regulation (see below), the clinical significance of abnormal responses in delayed hypersensitivity and in in vitro lymphocyte stimulation tests is not clear. For example, patients with mucocutaneous candidiasis who demonstrate defective T-cell mediated responses prior to specific treatment for the candidiasis have been shown to have normal or near-normal responses following treatment with the antifungal drug ketoconazole (35).

With early diagnosis and treatment of the hypoparathyroidism and adrenal insufficiency, prognosis is good. Deaths are most frequently related to delayed recognition and treatment of acute adrenal crisis, but may also be the consequence of complications of chronic liver disease (13). Autopsy findings are remarkable for parathyroid and adrenocortical atrophy with lymphocytic infiltration. Lymphocytic infiltration of the thyroid is observed in approximately one-third of cases, but gonadal infiltration is less frequent. Liver involvement is marked by findings of chronic active hepatitis and postnecrotic cirrhosis (15).

Frequent clinical and biochemical surveillance of patients at risk of developing Addison's disease is important to enable diagnosis and initiation of replacement therapy prior to development of acute adrenal crisis. Routine biochemical screening should be conducted at least annually, but with increased frequency if clinical symptoms or signs suggestive of adrenal insufficiency develop. Early alerting signals include complaints of weakness and easy fatigability with or without salt craving, and in children, a decrease in linear growth rate. In a child with primary hypoparathyroidism, an increase in serum calcium (unrelated to a change in the dose of calcium or vitamin D) may signal the development of adrenal insufficiency. Isolated hypoaldosteronism has also been reported as the initial manifestation of Addison's disease in 2 patients with PGA I (36,37). Progression of adrenal failure with a decrease in glucocorticoid secretion occurred over a several-year period in both patients (37). Biochemical monitoring of adrenal status is routinely accomplished by assessing adrenocortical secretory reserve in an ACTH stimulation test (38). Measurement of plasma ACTH levels may also be useful. If a normal cortisol response to exogenous ACTH is observed in the setting of clinical symptoms suggestive of adrenal insufficiency (particularly if intermittent or persistent hypercalcemia has been noted), aldosterone secretion should be evaluated. The role of adrenal antibody measurement in the prospective follow-up of PGA I patients at risk of developing Addison's disease has not been established. Small preliminary studies however suggest that circulating adrenal antibodies may be the first evidence of impending adrenal insufficiency in such individuals (38,39). Adrenal antibodies that are able to fix the membrane attack complex of complement (C5-C9) in vitro may in particular have a strong predictive value as to the future development of Addison's disease (39).

PGA Syndrome Type II

PGA type II (Schmidt's syndrome) is narrowly defined as the association of primary adrenal insufficiency with autoimmune thyroid disease and/or insulin-dependent diabetes mellitus (13). Only patients with autoimmune Addison's disease are included by this designation. However it may be more accurate to also consider as affected (1) those relatives of patients with the complete syndrome who themselves have one or more principal disease components but normal adrenal function; (2) patients with autoimmune thyroid disease and/or insulin-dependent diabetes mellitus (with or without type II relatives) who have circulating adrenal antibodies; and (3) patients with primary gonadal failure as the only other endocrine abnormality associated with Addison's disease. Regardless of definition the key element of the PGA II syndrome is adrenal insufficiency. The emphasis of adrenal insufficiency as the central component of PGA II is a reflection of the extraordinarily high frequency of associated organ-specific autoimmune disease observed among Addisonian patients. Of patients with Schmidt's syndrome (as defined by the more restrictive criteria), approximately 70% have autoimmune thyroid disease and 50% have insulin-dependent diabetes mellitus (Table V) (13). The autoimmune thyroid disease is about equally divided in frequency between Graves' disease and thyroiditis (Hashimoto's plus atrophic thyroiditis) (40). In addition silent thyrotoxic thyroiditis has also been reported (41). Hypoparathyroidism is not associated with PGA type II.

Components of the PGA type II disorder begin at a later age than in the type I syndrome. The onset of Addison's disease in PGA II is greater than 20 years

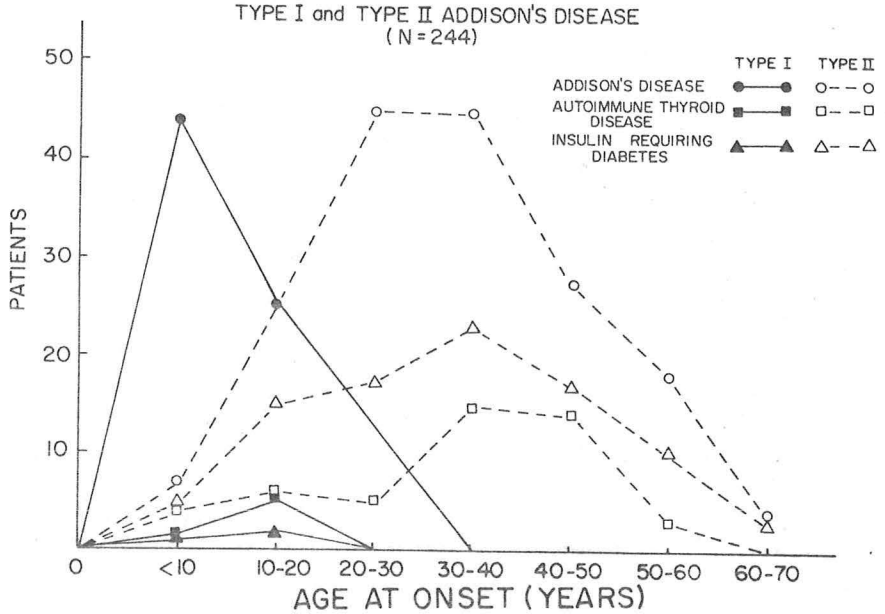
in more than 50% of patients and occurs over a much broader age range as compared to type I disease (Fig. 3) (13,14,42). Age-at-onset distribution of diabetes mellitus parallels that of Addison's disease, whereas autoimmune thyroid disease tends to develop at a slightly later age (13,42). Adrenal insufficiency is the initial manifestation of the syndrome in approximately 40-50% of cases in retrospective series (14,42), with subsequent components

TABLE V

PGA SYNDROME TYPE II (SCHMIDT SYNDROME)

Clinical Manifestations (Prevalence)	Adrenal Insufficiency	(100%)
	Autoimmune Thyroid Disease	(70%)
	Insulin-Dependent Diabetes Mellitus	(50%)
	Gonadal Failure	(5%-50%)
	Diabetes Insipidus	
Other Associated Disorders	Vitiligo	(4.5%)
	Alopecia	
	Pernicious Anemia	
	Myasthenia Gravis	
	Immune Thrombocytopenic Purpura	
	Sjogren's Syndrome	
	Rheumatoid Arthritis	

Figure 3



Ref. 13

The age of onset of Addison's disease in Type II PGA (dotted lines) is compared with the age of onset in Type I PGA syndrome (solid lines). The age of onset for autoimmune thyroid disease (ATD) and insulin-requiring diabetes (IRD) in both syndromes also are presented. Diabetes and ATD occur infrequently in Type I PGA. Although the data on this graph do not so indicate, ATD is more frequent than IRD in patients with the Type II PGA syndrome. The age of onset of ATD was infrequently known, in contrast to IRD, and, therefore, data for patients with IRD exceed that of patients with ATD in this graph.

appearing up to 20 years later (mean of 7 years) (14). In another 20% thyroid disease or diabetes mellitus develops simultaneously with adrenal insufficiency,

and in about 30-40% of cases Addison's disease follows the appearance of the other disorders (14,42).

Primary hypogonadism is reported in from 5% (13,30) to 20-50% (42,43) of patients with PGA II, and in some cases it is the first manifestation of the syndrome (43,44). In some patients, hypogonadism is the only extra-adrenal manifestation of the disorder (42,43). As in the type I disorder, ovarian failure is much more frequently detected than is testicular failure. Diabetes insipidus may be a fifth endocrine component of PGA II. One patient with the type II syndrome has been reported in whom diabetes insipidus developed in association with a circulating antibody to vasopressin-secreting cells of the hypothalamus (25). Another patient with a PGA II syndrome consisting of primary hypothyroidism, primary adrenal insufficiency, and ACTH deficiency has also been described (45).

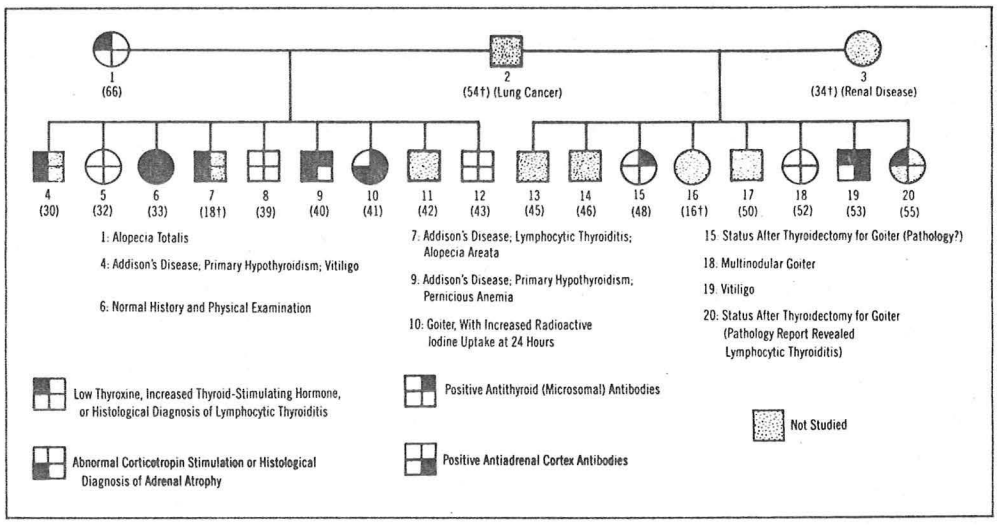
Nonendocrine disorders associated with PGA type II include pernicious anemia (42,46-50), vitiligo, (46-48,50-52) and alopecia (48,50,53). Pernicious anemia and alopecia occur much less frequently than in the type I syndrome. In one review of 224 cases of type II PGA, only 1 case each of pernicious anemia and alopecia was found (13). IgA deficiency (54,55) myasthenia gravis (48), and Sjogren's syndrome (56) have also been reported in isolated cases.

PGA type II occurs with a higher frequency than the type I disorder, but is still relatively rare. The prevalence of idiopathic Addison's disease in the general population is probably on the order of 40 to 50 per million (39). In approximately 40% of patients with idiopathic Addison's disease, a second or third endocrine disorder characteristic of the type II PGA syndrome is also present (40,42,43,57). Thus, an extrapolated prevalence of PGA II is about 15 to 20 per million. As in the type I syndrome, approximately 50% of cases of Schmidt's syndrome are familial (14), but the mode of disease transmission varies from family to family (Fig. 4, Fig. 5). A single gene mutation transmitted in an autosomal recessive pattern is suggested by the family studies of Spinner, Blizzard, and Childs (14), but in other pedigrees autosomal dominant transmission (52) or polygenic inheritance (50) is observed. The ratio of affected females to males is 1.8 to 1 (13), similar to that observed in the type I syndrome.

Most of the principal components of PGA type II - Addison's disease, insulin-dependent diabetes mellitus, Graves' disease and atrophic thyroiditis - are individually associated with an increased prevalence of the HLA antigens B8 and DR3 in Caucasian patients (58). [Patients with Hashimoto's (goitrous) thyroiditis alone, however, do not have a significant increase in the frequency of B8/DR3, although a significant increase in DR5 has been observed (58). Similarly, no association of isolated premature primary gonadal failure and HLA B8/DR3 has been reported.] In type II PGA there is also an increased prevalence of HLA B8/DR3 in affected members of many but not all pedigrees (Fig. 5) (48-50,51,52,58). HLA studies of several PGA II families with multiple affected members suggest that disease susceptibility for all components of the syndrome is transmitted by a gene or genes on the same parental chromosome, but that the HLA haplotype involved in disease transmission is frequently B8/DR3 negative. Nevertheless, many such patients do receive the B8/DR3 haplotype from the parent

not implicated in tranmission of the disorder (51,58,59). Such data suggest that even when B8/DR3 is not directly linked to the disease-associated allele, its presence is necessary for disease expression.

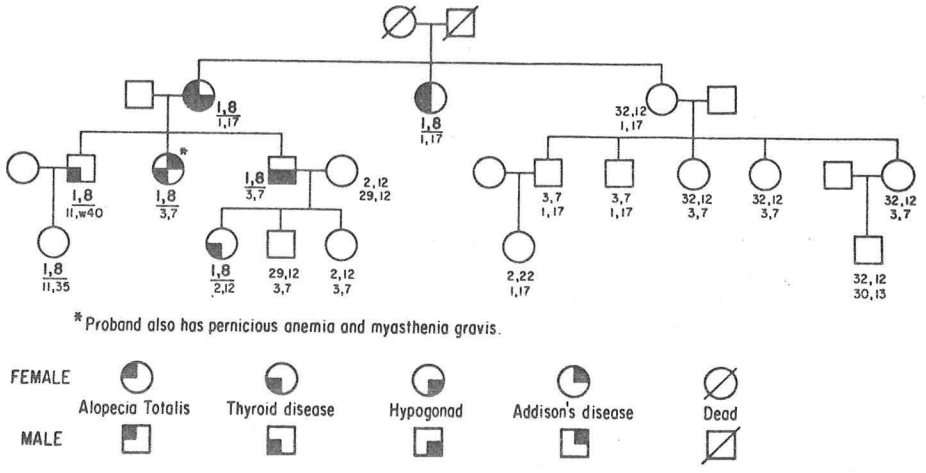
Figure 4



Ref. 50

Family pedigree. Numbers in parentheses indicate age in years; daggers, deceased.

Figure 5



Ref. 48

Results of HLA Typing and Clinical Evaluation of the Kindred.
The proband is indicated by the asterisk. Haplotypes, depicted one above the other, were deduced from the HLA typing and the pattern of inheritance. The HLA-A1,B8 haplotype is underlined. Occurrence of disease is as noted.

Circulating organ-specific antibodies are detected in a high proportion of patients with PGA II (Table VI). Between 60% and 95% have antibodies directed against adrenal cytoplasmic (microsomal) antigens (28,30,57,60). Thyroid

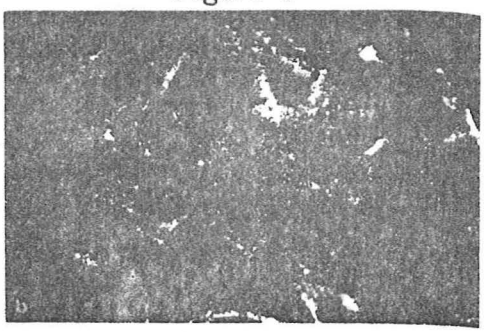
TABLE VI

ORGAN-SPECIFIC ANTIBODIES IN PGA TYPE II

Adrenal	60% - 95%
Thyroid	70%
Gastric	40%
Islet cell	25%
Steroid cell	13%
Prolactin cell	

microsomal and/or thyroglobulin antibodies occur in approximately 70%, and gastric antibodies (antiparietal cell and/or anti-intrinsic factor) are reported in about 40% of patients (28). Islet cell antibodies are present in 25% of type II PGA patients [in 16% of those who do not have diabetes mellitus, and in 50% of patients with insulin-treated diabetes (irrespective of duration of the diabetes)] (61). In fact the first reports of the presence of islet cell antibodies in patients with diabetes mellitus involved patients with PGA disease (62,63). Steroid cell antibodies are detected in 13% of patients with the type II syndrome (30). Six patients with classical Schmidt's syndrome and prolactin cell antibodies associated with normal pituitary function have also been described (31). A pathogenetic role for organ-specific antibodies in the development of endocrine gland dysfunction is strengthened by the observation that the microsomal antigens against which these antibodies are directed are also expressed on the cell surface of isolated adrenal (64), thyroid (Fig. 6) (65), pancreatic β (66), and ovarian granulosa cells (67). In vitro

Figure 6

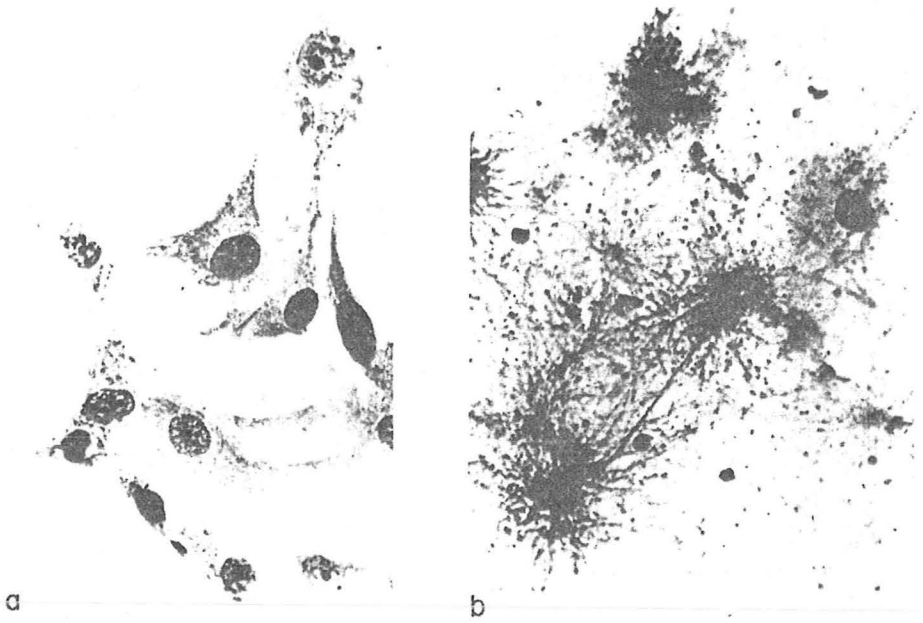


Ref. 65

Cell surface "microsomal" staining on monolayers of cultured thyroid cells - indirect immunfluorescent staining using serum containing microsomal antibodies from a patient with thyrotoxicosis.

cytotoxicity of these cell-surface reactive antibodies due to complement activation and/or to antibody-dependent cell mediated cytotoxicity has been demonstrated for thyroid microsomal (65), islet cell (68-70) and gonadal (Fig. 7) (67) antibodies. Furthermore, a prospective study of nondiabetic patients

Figure 7

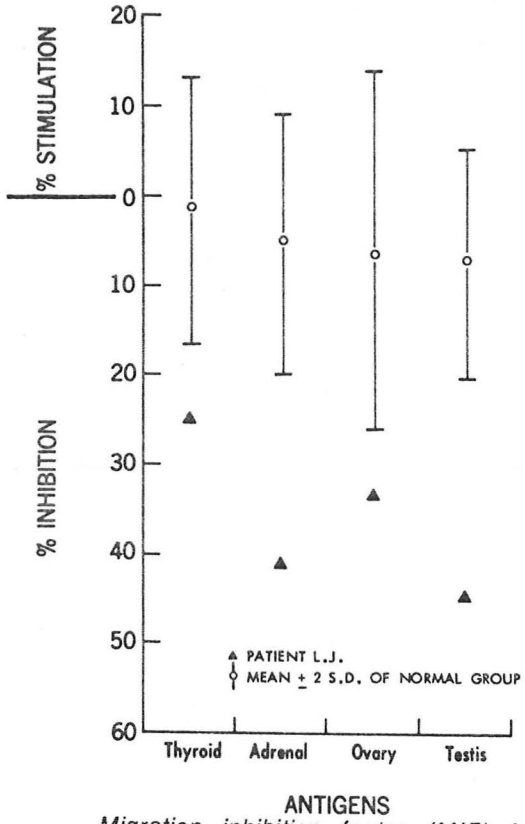


Ref. 67

Morphological appearance of human granulosa cells after 3 days in culture. (a) With serum giving a "confluent" staining pattern in the indirect immunofluorescence test with sections of human corpus luteum. No complement was present. (b) With the same serum in the presence of complement. × 640. From McNatty *et al.* (1975).

with polyendocrine disease (including patients with type II PGA) has shown that the risk of developing diabetes is greatest among those with complement-fixing antibodies (71,72). A similar predictive value of circulating adrenal antibodies for the development of Addison's disease has also been reported (39,73). In patients with autoimmune thyroid disease, antibodies that interact with or perturb the TSH receptor may result in hyperthyroidism (74,75), goitrous thyroiditis (76,77) or primary (atrophic) myxedema (78-81). Altered cellular immunity can also be demonstrated in patients with each of the disease components of PGA II, including (1) a decrease in cutaneous delayed hypersensitivity (82), (2) migration inhibition factor production in response to tissue specific antigens (Fig. 8) (83-86), (3) decreased suppressor T cell numbers and function (87-91), (4) increased antibody-dependent cell mediated cytotoxicity (92-95), and (5) increases in circulating Ia-positive T lymphocytes (96-98).

Figure 8



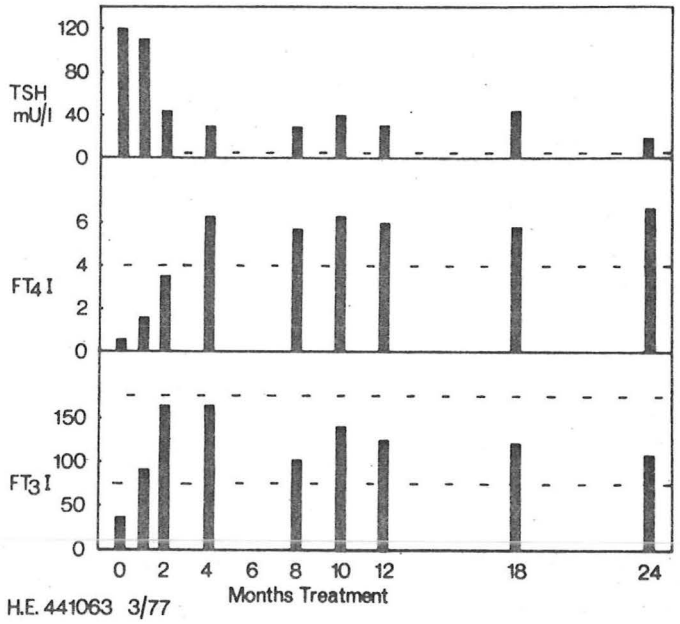
Ref. 84

Migration inhibition factor (MIF) in response to crude human thyroid, adrenal, ovarian and testicular antigens. Using these test antigens, lymphocytes from this patient released significant migration inhibition factor with each antigen, when compared to the normal control group. However, when tested against human liver and stomach antigen, this patient produced no migration inhibition factor (not depicted on figure).

The criteria for diagnosis and the management of PGA II are those of the individual endocrinopathies. However 2 points should be considered in the evaluation of certain patients with PGA. First, in hypothyroid patients with suspected coexistent adrenal insufficiency, plasma cortisol measurements rather than urinary 17-hydroxysteroids must be utilized for the evaluation since steroid metabolites are reduced in the presence of hypothyroidism regardless of adrenal status. Second, evaluation for hypothyroidism in a clinically euthyroid patient with Addison's disease should be deferred until cortisol replacement has been given for several months. Elevated TSH levels are commonly observed in patients with glucocorticoid deficiency [whether due to primary (autoimmune or nonautoimmune) (99,100) or secondary (100,101) adrenal failure], but return to normal following cortisol treatment. Furthermore, in some Addisonian patients, clearly subnormal thyroid hormone levels associated with an elevated TSH may return to normal or near-normal following cortisol replacement (Fig. 9) (99,100,

102-105). Most of these latter patients have clinical features of Hashimoto's thyroiditis with elevated levels of microsomal antibodies, and it is postulated that physiological steroid replacement results in suppression of the autoimmune thyroiditis (99). Thus, evaluation of thyroid function in patients with untreated adrenal insufficiency does not reliably detect either diminished thyroid reserve or permanent primary hypothyroidism.

Figure 9



Ref. 99

Serial changes in TSH, FT_4I, and FT_3I in a 33-yr-old woman with Addison's disease (case 1) before and during 24 months of adrenal replacement therapy. Thyroid cytoplasmic autoantibodies were positive, but clinical features of thyroid deficiency were absent. - - -, Limits of normal ranges.

It should not be considered mandatory to formally evaluate all patients with primary hypothyroidism or other forms of autoimmune thyroid disease for clinically latent adrenal insufficiency. The prevalence of autoimmune adrenal insufficiency among patients with autoimmune thyroid disease is very low. Only if other factors recognized to be associated with an increased risk of developing adrenal insufficiency are present--for example, insulin-dependent diabetes mellitus or a positive family history of PGA type II -- should a patient with primary hypothyroidism, Hashimoto's thyroiditis, or Graves' disease be evaluated more thoroughly for latent adrenal insufficiency. Similarly, a patient with PGA type II manifested by adrenal insufficiency and Hashimoto's thyroiditis should not be considered at high risk of developing pernicious anemia, and attempts to detect subclinical disease are not warranted. Maintaining a high index of suspicion in patients at increased risk of developing other endocrinopathies and evaluating for specific disorders at periodic intervals of followup is probably the most efficient approach.

At the present time adrenal and steroid cell antibody measurements are not routinely available, and their value as predictors of eventual endocrine gland failure have not been established. Adrenal antibodies however may be of use in delineating patients with type II (as well as type I) PGA (Table VII) (39,73).

Table VII

CLINICAL, IMMUNOLOGICAL, AND METABOLIC FOLLOW UP IN 9 SUBJECTS WITH ADRENAL AUTOANTIBODIES

		At entry to study:			Adrenal antibodies†							Steroid-cell antibodies			Period of AA-positivity before onset Addison's	Other antibodies
Pt	Sex	Age (yr)	Autoimmune diseases	Test date*	IgG	IgA	IgM	C3	C4	C5	C9	IgG	C3	ACTH test		
1	F	45	Graves, IDDM	Dec 81	32	–	–	32	+	+	+	–	–	Normal	..	..
				Dec 82	32	–	–	32	+	+	+	–	–	Normal	..	..
2	M	8	Hypoparathyroidism, candidiasis, and vitiligo	Mar 80	16	–	–	16	+	+	+	+	+	Normal	..	MPCA
				Mar 81	16	–	–	16	+	+	+	+	+	Normal	..	MPCA, ICA
				Feb 82	16	–	–	16	+	+	+	+	+	No response‡	24 mo	MPCA, ICA
				Jul 82	16	–	–	16	+	+	+	+	+			MPCA, ICA
3	F	36	Hashimoto	Dec 79	128	–	–	64	+	+	+	–	–	Normal	..	TMA, TGHA
				Dec 82	64	–	–	64	+	+	+	–	–	Normal	..	TMA, TGHA
4	F	6	Hypoparathyroidism, candidiasis	Dec 79	128	–	–	64	+	+	+	+	+	Normal	..	ICA
				Mar 81	64	–	–	32	+	+	+	+	+	Normal	..	ICA
				Jun 82	32	–	–	8	+	+	+	+	+	No response‡	31 mo	ICA, TMA, TGHA
				Dec 82	16	–	–	8	+	+	+	+	+			ICA, TMA, TGHA
5	M	64	Graves	Jun 79	8	–	–	8	+	–	–	–	–	Normal	..	TMA, TGHA
				Dec 82	8	–	–	4	+	–	–	–	–	Normal	..	TMA, TGHA
6	F	19	IDDM	Jan 81	256	4	1	256	+	+	+	–	–	Impaired	..	TGHA, ICA
				Dec 82	256	2	–	256	+	+	+	–	–	Impaired	..	TGHA, ICA, TMA
7	M	32	..	Jun 82	32	1	–	16	+	+	+	–	–	Impaired	..	TMA
				Jul 82	32	1	–	16	+	+	+	–	–	No response‡	1 mo	TMA
8	M	11	IDDM	Dec 79	128	–	–	64	+	+	+	–	–	Impaired	..	ICA
				Dec 80	128	–	–	64	+	+	+	–	–	Impaired	..	ICA, PCA
				Dec 81	16	–	–	8	+	+	+	–	–	No response‡	25 mo	ICA, PCA
				Dec 82	8	–	–	8	+	+	+	–	–			ICA, PCA
9	F	49	Hashimoto	Dec 80	8	–	2	8	+	–	–	–	–	Normal	..	TMA, TGHA
				Dec 82	16	–	2	16	+	–	–	–	–	Normal	..	TMA, TGHA

†Reciprocal titre. C3, C4, C5, C9 = complement fixing. IDDM = insulin-dependent diabetes mellitus. MPCA = melanin-producing cell autoantibodies. ICA = complement-fixing islet-cell autoantibodies. TMA = thyroid microsomal autoantibodies. TGHA = thyroglobulin autoantibodies. PCA = parietal-cell autoantibodies. *Date of entry to study. ‡Addison's disease.

Ref. 39

Longitudinal studies of additional patients should clarify their clinical utility. In the case of islet cell antibodies (which can be measured commercially), fluctuating levels have been demonstrated in nondiabetic first-degree relatives of insulin-dependent diabetics. Although measurable at some point during the period of surveillance, the antibodies disappeared in 12 of 20 subjects in one study and normal glucose tolerance was maintained (106). Thus, islet cell antibodies as currently measured, although of interest in attempting to define the pathogenesis of insulin-dependent diabetes, do not appear to be useful in predicting either the inevitability of appearance or time of onset of disease (106, 107). The predictive value of the 2-hour oral glucose tolerance test for the development of diabetes in siblings of insulin-dependent diabetics is similar to that for positive islet cell antibodies (108, 109), even though the first documentable abnormality may be the presence of antibodies (110). First-degree relatives of patients with type II PGA should be informed of the early symptoms of the major disorders for which they are at risk, and screened if suggestive symptoms appear. Routine HLA typing is not recommended.

POLYGLANDULAR AUTOIMMUNITY WITHOUT ADDISON'S DISEASE

Associations of autoimmune endocrine diseases without the occurrence of primary adrenal insufficiency are well recognized. In most such cases, autoimmune thyroid disease coexists with a second autoimmune disorder. The second disorder may involve an endocrine gland - the pancreatic islets or less commonly, the anterior pituitary - or a nonendocrine structure. Pernicious anemia is the most frequent nonendocrine disorder occurring in association with autoimmune thyroid disease, but myasthenia gravis, primary biliary cirrhosis, vitiligo, alopecia, Sjogren's syndrome, and other connective tissue diseases are also included in the disease spectrum.

Autoimmune Thyroid Disease - Insulin-Dependent Diabetes Mellitus - Pernicious Anemia

A small fraction of patients with autoimmune thyroid disease (73) and insulin-dependent diabetes mellitus (111) have circulating adrenal antibodies. Since a significant number of these patients have biochemical and/or clinical evidence of early adrenal insufficiency, they should be considered as having the type II PGA syndrome. The association of autoimmune thyroid disease, insulin-dependent diabetes mellitus, and pernicious anemia without adrenal insufficiency occurs much more frequently.

Autoimmune thyroid disease and atrophic gastritis/pernicious anemia. The frequency of frank or latent pernicious anemia (PA) is increased among patients with autoimmune thyroid disease who are older than 40 years of age (Table VIII)

TABLE VIII

PREVALENCE OF PERNICIOUS ANEMIA IN PATIENTS WITH AUTOIMMUNE THYROID DISEASE

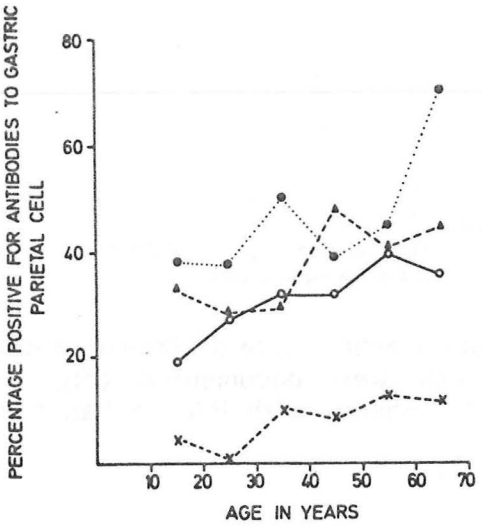
	Number Studied	Pernicious anemia	
		Number	Percentage
Thyrotoxicosis			
> 40 Years	1332	28	2.1
< 40 Years	291	0	0
Total	1623	28	1.7
Hashimoto's Thyroiditis			
> 40 Years	100	5	5.0
< 40 Years	20	0	0
Total	120	5	4.2
Primary Hypothyroidism			
> 40 Years	260	34	13.1
< 40 Years	37	0	0
Total	297	34	11.4

Ref. 112

(112). Particularly striking is the 13% incidence of PA in patients with primary hypothyroidism, but the incidence of PA associated with Hashimoto's thyroiditis (5%) and with Graves' disease (2%) is also significantly increased relative to that found in age-matched controls [(0.35%) (113)]. Atrophic gastritis with achlorhydria or hypochlorhydria but normal B_{12} absorption is also

frequent in patients with autoimmune thyroid disease (112). Complement-fixing antibodies to gastric parietal cells are more prevalent in patients with all forms of autoimmune thyroid disease than in age and sex-matched controls (Fig. 10) (112). Overall, between 20% to 30% of patients with autoimmune thyroid disease have circulating parietal cell antibodies (as compared to a frequency of 60% - 90% in patients with PA). The cytoplasmic microsomal antigen(s) against which the parietal cell antibody is directed is also expressed on the surface of the parietal cell, and complement-mediated cytotoxicity has been demonstrated in vitro by incubating serum positive for parietal cell antibody with a suspension of gastric parietal cells (114).

Figure 10



Ref. 112

The incidence of parietal cell antibodies in each decade in 753 female thyrotoxic patients (O———O), 117 female euthyroid Hashimoto thyroiditis patients (●· · · ·●), and 255 spontaneous primary hypothyroid patients (▲---▲) compared to that in 443 control subjects (×---×). From Irvine (1975b).

There is also an increased prevalence of autoimmune thyroid disease among patients with PA. In a recent study of 143 patients with PA, well-documented thyroid disease was present in one-third (115). Approximately 9% were clinically hyperthyroid, 12% were hypothyroid, and at least an additional 13% had an elevated TSH level consistent with subclinical primary hypothyroidism. In the patients with clinical hypothyroidism, the diagnosis of PA was usually made concomitant with or within 1 to 2 years following the diagnosis of thyroid disease. Hyperthyroidism on the other hand typically preceded the PA. This observation most likely reflects the younger age at diagnosis of patients with hyperthyroidism as compared to those with primary hypothyroidism. Between 30% and 50% of patients with PA have elevated titers of thyroid microsomal antibodies (Table IX) (115-117), which is similar to the overall frequency of clinical and subclinical thyroid disease in this group.

Table IX

Frequency of autoantibodies and circulating immune complexes in patients with pernicious anaemia (n = 82) and Hashimoto's thyroiditis (n = 41).

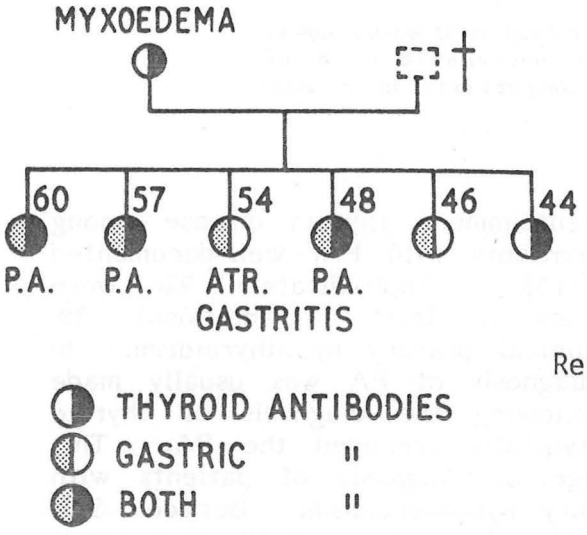
	Pernicious anaemia %	Hashimoto's thyroiditis %
Parietal cell antibodies (PCA)	87.9**	42.3[1)]
Intrinsic factor antibodies (IFA)	38.2**	0
Thyroglobulin antibodies (TgAb)	34.6**	100
Microsomal antibodies (MAb)	52.5**	97.8
Immune complexes (IC)	2.5**	63

Ref. 117

1) only 26 patients investigated.
** $P < 0.01$ when testing difference between frequency of Ab in pernicious anaemia and Hashimoto's thyroiditis. (Fisher's Exact test and Chi-square test).

The coexistence of autoimmune thyroid disease and/or PA in multiple members of individual families is also well documented (Fig. 11, Fig. 12) (118,119). In one study of 71 relatives of probands with PA, 15 had findings consistent with

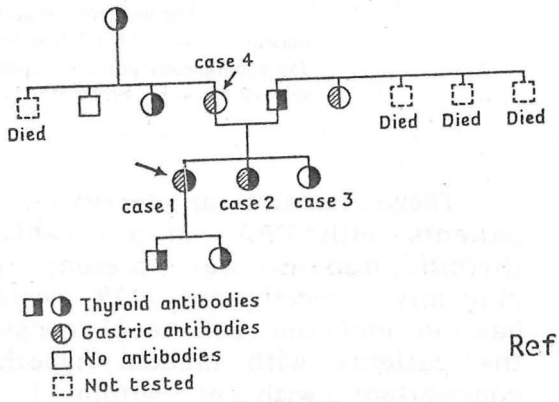
Figure 11



Ref. 118

Autoantibodies in family with pernicious anemia.

Figure 12



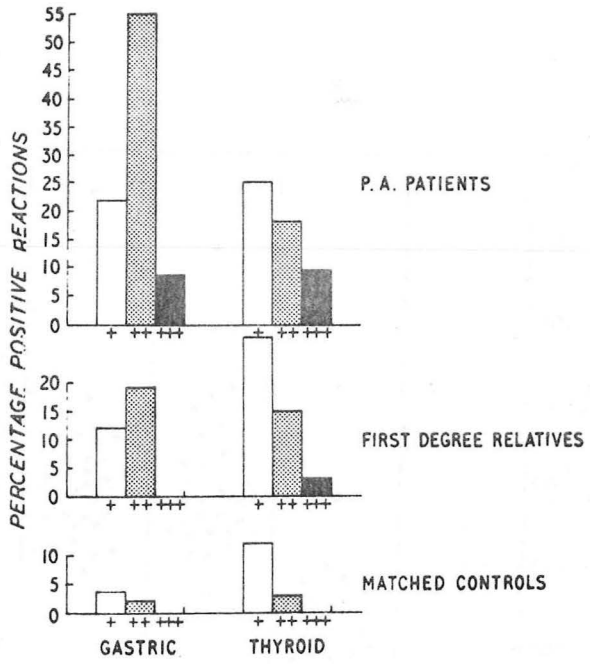
Ref. 119

Family tree.
An arrow points to the presenting patient with both thyrotoxicosis and pernicious anæmia. One sister also had both diseases. Another sister was found to have a subclinical thyroid defect, and their mother had latent pernicious anæmia. Thyroid antibodies are traced through four generations.

goitrous thyroiditis, 4 had thyrotoxicosis, and 5 had primary hypothyroidism (118). TSH levels were not measured, such that the prevalence of subclinical

primary hypothyroidism was not assessed. In this same study thyroid and gastric parietal cell antibodies were examined in a total of 113 first- and second-degree relatives: thyroid antibodies (microsomal plus thyroglobulin) were found in 50% (comparable to the frequency in the PA probands themselves) (Fig. 13), and both thyroid and gastric antibodies were present in 23% (116,118).

Figure 13



Ref. 116

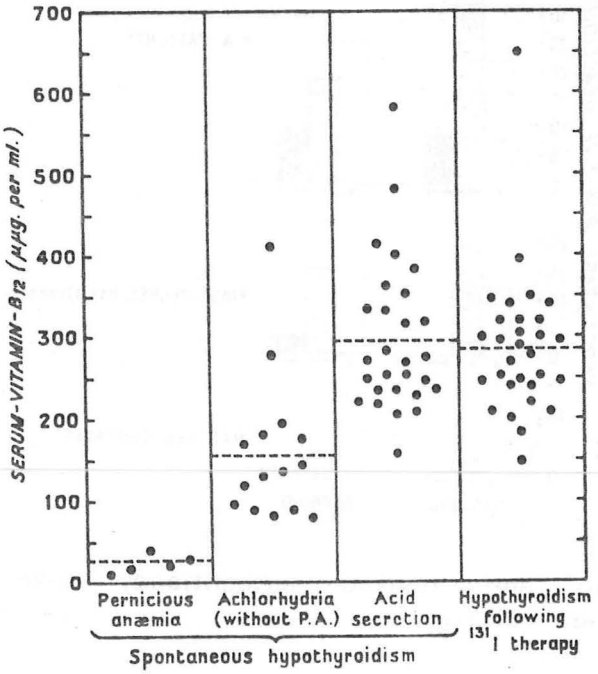
Comparison of gastric and thyroid autoantibody levels in patients with pernicious anemia and their relatives.

HLA typing of patients with PA (unselected for the presence of other organ-specific autoimmune diseases) reveals an increased prevalence of the DR5 antigen (117,120). Patients with Hashimoto's thyroiditis also have an increased prevalence of DR5 (121,122), a factor that may be of importance in the frequency of association of these two disorders. The frequency of HLA DR3 is not increased in patients with Hashimoto's disease and/or pernicious anemia. When PA occurs in association with organ-specific autoimmune diseases other than Hashimoto's thyroiditis (eg., Graves' disease or primary atrophic thyroiditis), there is an increased prevalence of HLA B8 (and therefore of DR3, which is in linkage disequlibrium with B8) (123).

As a result of the high prevalence of autoimmune thyroid disease among patients with PA, routine evaluation of all patients should include a serum T_4, T_3 resin uptake and TSH. In addition, evaluation of thyroid microsomal antibody status may provide a parameter to assess risk of future development of thyroid disease. In patients with autoimmune thyroid disease, routine

assessment of B_{12} status should be reserved for those over the age of 40 years. Latent PA (that is, a low serum B_{12} level associated with evidence of B_{12} malabsorption in a patient who is not anemic and who has a normoblastic bone marrow) as well as achlorhydria with and without B_{12} deficiency are particularly prevalent among patients with primary hypothyroidism (Fig. 14) (124). Furthermore, a progressive impairment of B_{12} absorption in hypothyroid patients has been demonstrated despite adequate treatment of the hypothyroidism (124).

Figure 14

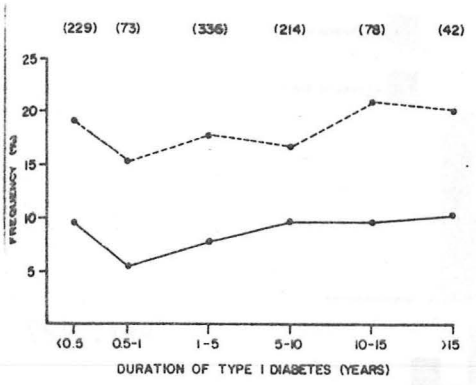


Ref. 124

Serum vitamin B_{12} values in patients with hypothyroidism. The horizontal lines indicate the mean value of each group. Reproduced from Tudhope and Wilson (1962) with kind permission of the authors and the Editor of *Lancet*.

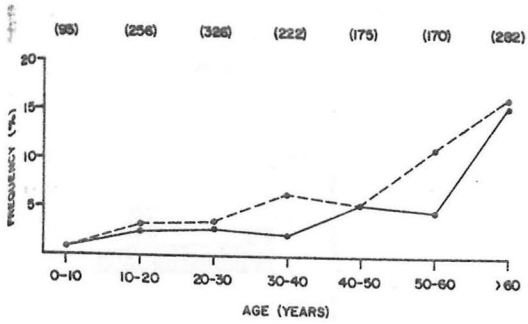
Insulin-dependent diabetes mellitus and autoimmune thyroid disease-pernicious anemia. Clinical and subclinical autoimmune thyroid disease, as well as the frequency of circulating thyroid microsomal antibodies, are increased in patients with insulin-dependent diabetes mellitus (125-129). Microsomal antibodies are reported in 17% to 28% of insulin-dependent diabetics (125,126,128), an incidence that is significantly higher than in age-, sex-, and race-matched controls, but similar to that found in control individuals older than 60 years of age (130). In young diabetics (diagnosis of insulin-dependent diabetes made at less than 30 years of age), the frequency of thyroid microsomal antibodies is constant and unrelated to the duration of diabetes (Fig. 15) (130). Thus, in this group of patients microsomal antibody status at any point

Figure 15a



Frequency of thyroid microsomal (broken line) and gastric parietal cell autoantibodies (solid line) in patients with Type 1 diabetes grouped by duration of disease. Figures in parentheses represent the number of patients in each duration group

Figure 15b



Frequency of thyroid microsomal (broken line) and gastric parietal cell autoantibodies (solid line) per decade of age in 1524 control patients. The figures in parentheses represent the number of people in each decade of age

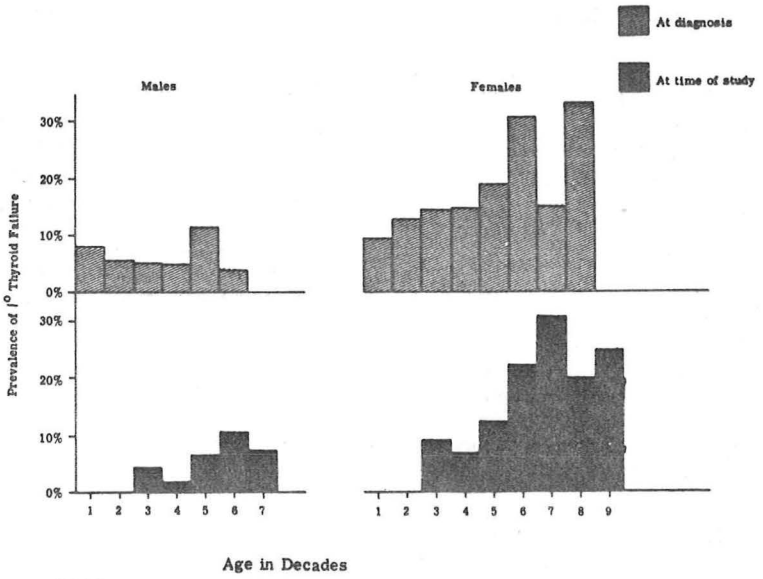
Ref. 130

following the diagnosis of diabetes correlates positively with antibody status at any future time. However, transient expression of thyroid microsomal antibodies has been reported in older diabetics with normal TSH levels (131). Subclinical primary hypothyroidism, as manifested by an elevated TSH with or without a low serum T_4, is reported in approximately 12% of insulin-dependent diabetic patients (127), and clinically overt hypothyrodism occurs in approximately 2.5% to 3% (127,129,132). Of the patients with subclinical disease, 88% have positive microsomal antibodies (126). Progression to biochemical hypothyroidism in diabetic patients with positive antibodies and an elevated TSH occurs at a rate of about 5% per year (131), similar to the rate of progression in a comparable group of nondiabetics (133). The incidence of subclinical and overt hypothyroidism is greater in women than in men (Fig. 16) (127,128) and greater in whites than in blacks (128). Hyperthyroidism is reported in between 1-5% of insulin-dependent diabetics (128,129,132,134) so that as many as 20% of patients with type I diabetes have some form of autoimmune thyroid disease.

The presence of microsomal antibodies in insulin-dependent diabetics is associated with an even greater incidence of thyroid disease. In one series of 117 young diabetics (age at diagnosis less than 30 years) who had positive microsomal antibodies, 45% had either primary hypothyroidism (38% of patients) or hyperthyroidism (7% of patients) (128).

The prevalence of autoimmune thyroid disease is also increased relative to controls in first-degree relatives of insulin-dependent diabetics (129). Furthermore, of diabetics with microsomal antibodies, a positive history of thyroid disease and/or presence of antibodies occurs in at least one first-degree relative in 70% of families (128).

Figure 16



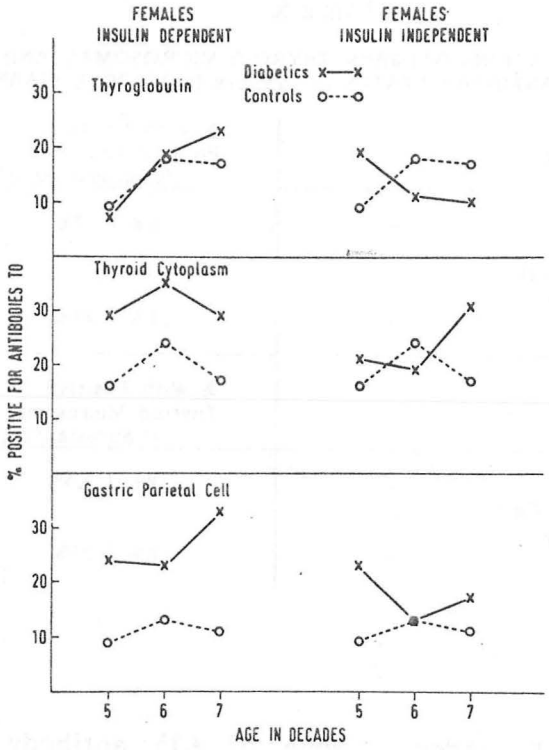
Ref. 127

Prevalence of an elevated serum TSH concentration in IDD according to sex, age at diagnosis of diabetes, and age at time of study.

The epidemiologic characteristics of the group of patients with diabetes mellitus who have coexistent autoimmune thyroid disease differ from those with diabetes alone. First, in the group with both diabetes and thyroid disease, the frequency of diabetics who are insulin-dependent (60%) is approximately twice that observed in a general diabetic population (33%) (135). Second, the median age at diagnosis of the patients with insulin-dependent diabetes and thyroid disease (36 years) is older than that observed in the majority of insulin-dependent diabetics (median age less than 25 years). Finally, in the group with thyroid disease the female to male ratio (6.4:1) is substantially greater than that observed among all diabetics (1.3:1).

The frequency of gastric parietal cell antibodies and of latent PA is increased in patients with insulin-dependent diabetes mellitus (130,136-138). In young diabetics, parietal cell antibodies are present in 7 to 9% (130,138,139) to 23% (137) (vs. 2% to 7% in matched nondiabetic controls) (Fig. 15), whereas in older patients, the prevalence increases to approximately 25% - 40% [vs. 15% - 20% in noninsulin-dependent diabetics (136,137) and 5% - 20% in older nondiabetic controls (130,136,137)] (Fig. 17). Young diabetic patients who also have thyroid microsomal antibodies have a frequency of parietal cell antibodies that is comparable to the frequency found in older patients--approximately 16% (128). Conversely, the frequency of thyroid microsomal antibodies is significantly increased in young diabetics who are parietal cell antibody-positive as compared to that observed in parietal cell antibody-negative patients (46% vs. 18% in Caucasians, 25% vs. 2.5% in blacks) (Table X). Approximately 26% of young insulin-dependent diabetics have both thyroid microsomal and parietal cell antibodies (138).

Figure 17



The percentage incidence of autoantibodies specific for thyroglobulin, thyroid cytoplasm, and gastric parietal-cell cytoplasm in a series of 1032 diabetics and of 871 controls according to sex and age in decades. When the diabetics were subdivided into insulin-dependent and insulin-independent groups, the increased incidence of thyroid and gastric antibodies compared to controls was confined to the insulin-dependent diabetics. From Irvine *et al.* (1970).

Ref. 137

Latent PA is estimated to occur in approximately 5% of older insulin-dependent diabetic women (137), and atrophic gastritis with achlorhydria has been found in about 50% of parietal cell antibody-positive young insulin-dependent diabetics (138). Furthermore, a family history of PA and/or parietal cell antibodies occurs in 60% of families of the diabetic probands who have antibodies. Studies of thyrogastric autoimmunity in families of insulin-dependent diabetics have revealed a lack of association with specific HLA alleles (140). Thus insulin-dependent diabetes and autoimmune thyroid disease/PA appear to segregate independently of one another.

Routine screening for subclinical hypothyroidism and/or latent pernicious anemia is appropriate for select groups of insulin-dependent diabetic patients. Riley, Maclaren, and Rosenbloom advocate screening all diabetic children for thyroid microsomal antibodies (128,141). In their studies, microsomal antibodies, if they are going to develop, are present by the time of diagnosis of insulin-dependent diabetes in almost all patients (130), and therefore need to be measured only once. Antibody-positive patients are then screened annually

TABLE X

CORRELATIONS BETWEEN THYROID MICROSOMAL AND PARIETAL CELL ANTIBODY STATUS IN INSULIN-DEPENDENT DIABETICS

Population Studied		% With Positive Parietal Cell Antibodies (Caucasian/Black)
Thyroid Microsomal Antibody	-	6% / 7%
	+	16% / 43%
		% With Positive Thyroid Microsomal Antibodies (Caucasian/Black)
Parietal Cell Antibody	-	18% / 2.5%
	+	46% / 25%

with a TSH and a free T_4 index. None of 635 antibody-negative patients has developed thyroid disease at the end of the most recent follow-up period (100% negative predictive value) whereas 43% of antibody-positive patients have clinical or subclinical hypothyroidism (141). Thyroxine therapy should be initiated in children with an elevated TSH. Although primary hypothyroidism that is biochemically manifested only by an elevation in TSH has not been associated with any detectable clinical abnormality in adult patients (142), it is probably unwise to withhold replacement thyroxine therapy from children during their period of active growth (141). Screening of adult insulin-dependent diabetics for subclinical hypothyroidism requires periodic assessment of serum T_4 and T_3 resin uptake, since TSH levels and microsomal antibody status may fluctuate during the period of follow-up (131). Thyroxine replacement should be initiated in all patients with a low free T_4 index associated with an elevated TSH, but the issue of treating adult patients with a persistent but isolated elevation of TSH is not resolved (133,142). Diabetic children who have thyroid microsomal antibodies, with or without evidence of primary hypothyroidism, should also be screened for the possibility of concomitant latent PA, particularly if parietal cell antibodies have been detected. Periodic screening for latent PA is also important in insulin-dependent diabetic adults, particularly in women older than 40 years.

Other Autoimmune Disorders Associated with Autoimmune Thyroid Disease-Pernicious Anemia

Lymphocytic hypophysitis. Over the past 20 years, at least 15 women with lymphocytic hypophysitis have been reported (see below), 3 of whom had coexistent Hashimoto's or silent thyroiditis (143-145). Another 2 patients with a granulomatous-lymphocytic hypophysitis, one in association with a similar

lesion in the thyroid (146) and another with primary hypothyroidism (147), have been described. Also 5 patients with partial hypopituitarism (including deficiency of ACTH in each case) and either primary hypothyroidism (45, 148-150) or silent thyroiditis (151) have been reported in whom the hypopituitarism has been postulated to be secondary to hypophysitis. PA has occurred in 2 patients with documented hypophysitis (144,152), 1 of whom also had Hashimoto's thyroiditis (144). In addition, focal lymphocytic infiltration of the adrenals has been found in some of these patients at autopsy (145,146). Antibodies to anterior pituitary cells have not been examined in any of the patients with documented or presumed hypophysitis occurring as a component of a PGA syndrome. However, such an antibody has been found in one patient with hypophysitis unassociated with other autoimmune disorders (153) as well as in a group of 19 patients with single or multiple autoimmune endocrine disease who had no evidence of pituitary dysfunction (31). In this latter group, the antibody was specifically directed against the pituitary prolactin cells.

Myasthenia gravis. Approximately 20% of patients with generalized myasthenia gravis have clinical autoimmune thyroid disease, and additional patients have organ-specific autoantibodies to thyroid, adrenal cortex, and islet cells (154). Pernicious anemia, usually in association with autoimmune thyroid disease, is also described (154,155). Autoimmune endocrine disease is much less common in patients with ocular myasthenia (154). Among patients with the generalized form of the disorder, those older than 40 years at the time of onset of myasthenia have a higher incidence of clinical autoimmune endocrine disease (35%) than do patients who are less than 40 years at onset (17%). The frequency of HLA B8/DR3 among the latter group however is greater than among older patients (154).

Primary biliary cirrhosis. Autoimmune thyroid disease in the form of primary hypothyroidism or Hashimoto's thyroiditis is reported in up to 20% of patients with primary biliary cirrhosis (PBC) (156-158), and thyroid microsomal antibodies are present in 20-35% (156,158). No increase in frequency of HLA DR3 or DR5 has been observed among patients with PBC, including those with concomitant thyroid disease (158).

Connective tissue diseases. An increased incidence of autoimmune thyroid disease, in particular of Graves' disease, has been reported among women with the polymyalgia rheumatica-giant cell arteritis (PR-GCA) syndrome (159). Of 101 patients with PR-GCA, 5 had thyrotoxicosis. All 5 were women, such that the prevalence of Graves' disease among the female patients in this series was 8.5%. Conversely, an increased incidence of PR-GCA - almost 3% - has been reported among patients with autoimmune thyroid disease (160,161). Other autoimmune connective tissue, hematologic, and dermatologic disorders - in particular, Sjogren's syndrome (56,162), rheumatoid arthritis (163), eosinophilic fasciitis (164,165), immune thrombocytopenic purpura (166,167), pemphigus (168), and bullous pemphigoid (169) - have been described in association with autoimmune thyroid disease and pernicious anemia.

CLINICAL AND AUTOIMMUNE FEATURES OF ENDOCRINE COMPONENTS OF THE PGA SYNDROMES

Adrenal Insufficiency

At least 40% of patients with autoimmune Addison's disease have one or more additional autoimmune disorders (Table XI) (40,42,43). Moreover, with continued

Table XI

A review of the literature concerning the prevalence of associated diseases in idiopathic Addison's disease

Paper published by	Number of patients	Diabetes mellitus	Thyrotoxicosis	Myxoedema and Hashimoto's goitre	Pernicious anaemia	Gonadal insufficiency	Hypoparathyroidism	Number of patients with one or more associated disease
Turkington and Lebovitz (1967)[a]	23	3 (13%)	1 (4%)	4 (17%)	1 (4%)	7 (30%)	–	9 (40%)
Maisey and Lessof (1969)[b]	40	4 (10%)	5 (12%)	4 (10%)	1 (3%)	2 (5%)	–	18 (45%)
Males, Spitler and Townsend 1971)[c]	18	1 (6%)	1 (6%)	2 (12%)	–	3 (18%)	3 (18%)	8 (44%)
Nerup (1974a)[d]	71	13 (18%)	7 (10%)	4 (5%)	2 (2%)	8 (11%)	–	28 (39%)
Total of the four series	152	21 (14%)	14 (9%)	14 (9%)	4 (3%)	20 (13%)	3 (2%)	63 (41%)

From Nerup (1974d) with kind permission of the author.
Materials collected during the years:
[a]Duke University School of Medicine, Durham, North Carolina, U.S.A., no information available.
[b]Guy's Hospital, London, 1948 to 1969.
[c]University of Oklahoma Medical Center, Oklahoma, U.S.A., 1950 to 1970.
[d]Denmark, 1950 to 1972.

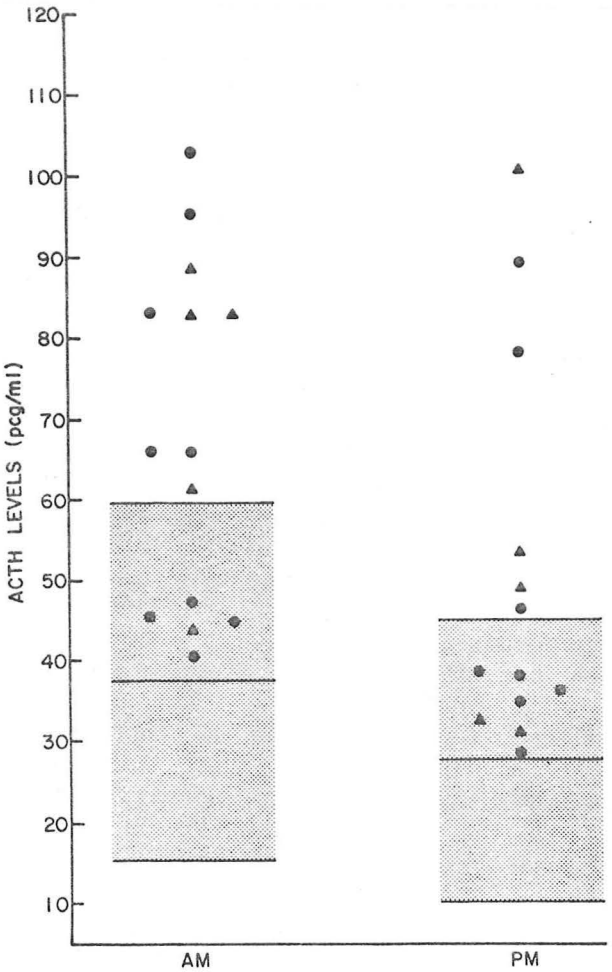
Ref. 40

followup it is possible that many patients with adrenal insufficiency alone will eventually fall into the PGA II syndrome category because of development of autoimmune thyroid disease and/or insulin-dependent diabetes mellitus. The prevalence of thyroid microsomal antibodies in clinically euthyroid patients with Addison's disease and no other overt endocrine disorder varies from 30% to 80% (28,170). In a recent study of 11 Addisonian patients with an elevated titer of microsomal antibodies (all of whom had normal cortisol levels on replacement therapy), a significant elevation in the mean TSH as compared to a control group was observed (170). Furthermore, a significant positive correlation was observed between the TSH level and antibody titer. The rate of progression of subclinical to clinical thyroid disease in patients with primary adrenal insufficiency is not known, but in non-Addisonian patients with an elevated TSH and positive microsomal antibodies, progression to hypothyroidism is reported to occur at a rate of about 5% per year (133). Approximately 18% of all patients with idiopathic Addison's disease have clinically apparent autoimmune thyroid disease (40). Islet cell antibodies have been observed in 4% of nondiabetic patients with Addison's disease who have no other autoimmune disorder (61). Frank diabetes mellitus occurs in approximately 14% of all patients with Addison's disease. Development of hypoparathyroidism and/or mucocutaneous candidiasis in a patient who has Addison's disease alone is unlikely since these conditions precede adrenal insufficiency in more than 90% of patients with PGA type I.

Circulating adrenocortical antibodies are present in approximately 50 to 70% of all patients with primary adrenal insufficiency (28,40,60) but occur

infrequently in patients with other autoimmune endocrine diseases [eg. in 1-4% of insulin-dependent diabetics (39,73,111) and in 2-5% of patients with autoimmune thyroid disease (39,73)]. However the occurrence of adrenal antibodies, in particular complement-fixing antibodies (39), in a patient without adrenal insufficiency is associated with an increased risk of future development of Addison's disease (39,73) as well as with biochemical evidence of decreased adrenal reserve (Fig. 18) (111). Evidence of cell-mediated adrenal autoimmunity is found in almost half of all patients with Addison's disease (83), and 90% have demonstrable humoral and/or cellular adrenal autoimmunity (83).

Figure 18



Ref. 111

Plasma ACTH concentrations obtained at 0600 and 2000 h in IDD (▲) and non-IDD (●) subjects with AA. The *shaded area* represents the mean ± 2 SD of the values in the control (non-AA) group.

The prevalence of HLA B8 in patients with autoimmune Addison's disease is as high as 80% (168), with a relative risk conferred by this antigen of 8.3 to 8.8

(58). Extensive HLA DR typing has not been reported, but a close correlation between the presence of adrenal antibodies and DR3 in patients with Addison's disease has been found (171). A further enrichment in the prevalence of B8 among patients with Addison's disease who also have other autoimmune disorders has not been demonstrated. Inclusion of PGA I patients with Addison's disease may have precluded demonstration of such an enrichment, since an association with B8 in this group has not been found.

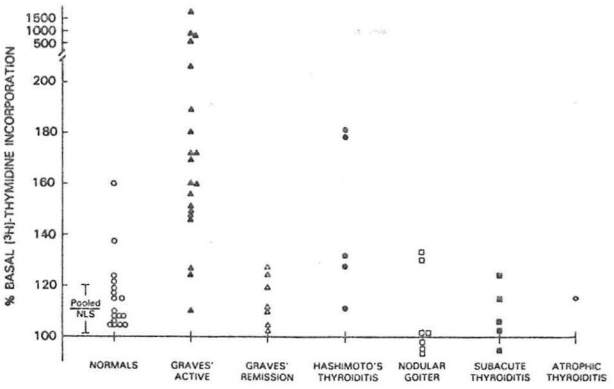
Autoimmune Thyroid Disease

The spectrum of thyroid disease found in patients with polyglandular autoimmunity encompasses atrophic thyroiditis (primary thyroprivic hypothyroidism), goitrous (chronic lymphocytic or Hashimoto's) thyroiditis, and diffuse toxic goiter (Graves' disease). In addition, silent postpartum thyroiditis with transient hyper- or hypothyroidism shares histopathologic and autoantibody features with Hashimoto's thyroiditis. In contrast to primary adrenal insufficiency, the prevalence of autoimmune thyroid disease in the general population is quite high. In one recent large community survey in England, 3% of the population (5% of the women and 1% of the men) had thyroid microsomal antibodies in association with an elevated TSH (172). Of women over 45 years of age, 10% had evidence of autoimmune thyroiditis with subclinical hypothyroidism. Clinically overt hypothyroidism was present in another 1% of the sample group (essentially all women), most of whom had elevated levels of microsomal antibodies. Hyperthyroidism was found in about 1.5%, but individuals were not classified as to the etiology of the thyrotoxicosis. Against this high background of thyroid disease in the general population, there is only a slight if any enrichment for primary adrenal insufficiency (39,73). The most frequently associated autoimmune disorder in patients with autoimmune thyroid disease is pernicious anemia (112). Myasthenia gravis is reported in up to 1% (173) and diabetes mellitus in up to 7% (174) of patients with thyrotoxicosis. However, the proportion of patients with Graves' disease vs. toxic multinodular goiter is not recorded in these series. A more recent analysis of the occurrence of insulin-dependent diabetes mellitus among patients with autoimmune thyroid disease reveals a prevalence of 5% among patients with Graves' disease and 8% among patients with thyroiditis (51). The prevalence of diabetes among all patients with autoimmune thryoid disease is approximately 7% (51). Among patients with autoimmune thyroid disease and diabetes mellitus there is an enrichment of insulin-dependent relative to noninsulin-dependent diabetes (ratio of 1.4 to 1) compared to the general diabetic population (ratio of 0.5 to 1) (135).

Circulating thyroid antibodies are found in most patients with autoimmune thyroid disease. Using an enzyme-linked immunosorbent assay, all patients with autoimmune thyroiditis in one study had IgG antibodies to thyroglobulin (175). Microsomal antibodies found in patients with autoimmune thyroiditis are directed against a lipoprotein bound to the intracellular vesicles that transport thyroglobulin from the Golgi apparatus to the follicular lumen. The microsomal antigen with which these antibodies react is also expressed on the thyroid cell surface (65). Unlike antibodies to thyroglobulin, microsomal antibodies fix complement and are cytotoxic to thyroid cells in vitro, and may therefore be important in the pathogenesis of the thyroiditis (65). Microsomal antibodies

are found in 95% of patients with Hashimoto's thyroiditis, 90% of patients with primary hypothyroidism, and 80% of patients with Graves' disease (176). Other antibodies described in patients with Hashimoto's thyroiditis include some that block TSH binding to its receptor (177) and others that directly stimulate thyroid growth. The latter antibody is also found in patients with active Graves' disease (Fig. 19) (76,77). Another group of antibodies described in

Figure 19



Ref. 77

Thyroid Growth as Measured by [^{3}H]Thymidine Uptake over 72 Hours in FRTL-5 Thyroid Cells.

IgGs from patients with the noted disease states were added during the incubation period. IgG-perturbed [^{3}H]thymidine uptake per microgram of cellular DNA was compared with basal [^{3}H]thymidine uptake and reported as a percentage of the basal level. The FRTL-5 cells had been deprived of thyrotropin for five days before the experiment. NLS denotes normal samples.

patients with primary atrophic hypothyroidism block the growth-stimulating effects of TSH (78). Patients with Graves' disease have circulating antibodies that bind to or perturb the TSH receptor and in so doing stimulate thyroid function (74,75). In addition, patients with Graves' disease as well as those with Hashimoto's thyroiditis have been found to have immune complexes, both circulating as well as in deposits within the thyroid (175). Disordered cell-mediated immunity, also well documented in patients with autoimmune thyroid disease, may have etiologic importance. The lymphokine migration inhibition factor (MIF) is produced by T lymphocytes obtained from many patients with autoimmune thyroiditis following exposure of the cells to thyroglobulin or to crude human thyroid antigen (85,89,175). Lymphocytes from Graves' disease patients also produce MIF in response to a crude thyroid antigen (85,89). In both cases, MIF production is prevented by inclusion of small numbers of normal T cells in the incubation (89).

Insulin-Dependent Diabetes Mellitus

The enrichment for insulin-dependent diabetes mellitus is most striking in the group of patients with PGA type II, but its prevalence is also increased among patients with autoimmune thyroid disease. As previously discussed, the prevalence of clinical and subclinical autoimmune thyroid disease, as well as

the occurrence of circulating antibodies to thyroid microsomes and gastric parietal cells, is also increased among patients with insulin-dependent (but not noninsulin-dependent) diabetes. In addition, approximately 2% of diabetics have adrenal antibodies (111,125), some of whom have evidence of decreased adrenal reserve (111). Among diabetics who have thyroid microsomal antibodies, with or without clinical thyroid disease, the prevalence of adrenal antibodies is even higher - approximately 4.5% (128).

Islet cell antibodies are found in from 60% to 85% of patients with newly-diagnosed insulin-dependent diabetes mellitus (171,178) but within several months of diagnosis the prevalence of antibodies is 50%. It remains at 50% for the first year but over the next several years it declines to 10%-20% (61,178). Islet cell antibodies are also reported in 20% of noninsulin-dependent diabetics requiring oral hypoglycemic therapy from the time of diagnosis; in 6% of nondiabetic patients with other organ-specific autoimmune diseases; and in 3% of first-degree nondiabetic relatives of islet cell antibody-positive individuals (171). These figures compare to a prevalence of islet cell antibodies in the general population of 0.5%. Longitudinal studies of antibody-positive subjects, including noninsulin-dependent diabetics (obese and nonobese) (61,179), first-degree relatives of insulin-dependent diabetics (71,107,110), as well as non-diabetic patients with other organ-specific autoimmune diseases (71,72), reveal that many go on to develop insulin-dependent diabetes. In addition, it has been shown that persistence of islet cell antibodies for a period greater than 3 to 5 years is more frequent in patients with PGA-associated diabetes (Table XII) (61,180,181). Cytotoxicity against islet cells mediated by these antibodies has been demonstrated in vitro (68-70). In addition there is evidence of disordered cell-mediated immunity directed against islet cells in patients with insulin-dependent diabetes mellitus (91,182).

Table XII

Prevalence of I.C.Ab. in insulin-treated diabetics with and without associated overt organ-specific autoimmune disease and according to the duration of the diabetes

	Duration from diagnosis of diabetes	
	<1 year	>5 years
With other autoimmune disease	8/13 = 62%	9/34 = 26%
Without other autoimmune disease	71/126 = 56%	22/318 = 7%
	N.S.	P <0.001

Ref. 61

Primary Gonadal Failure

Premature gonadal failure is a frequent accompaniment of PGA associated with Addison's disease, particularly in women with the type I form of the disorder (15,30). Although premature ovarian failure is also reported in association with the type II form of PGA, its frequency varies from one series to another (13,30,40). In the only report in which patients with type I and type II PGA were directly compared and the presence of steroid cell antibodies

was documented (30), 6/7 (86%) of patients with PGA I and 3/23 (13%) of patients with PGA II had steroid cell antibodies (Table XIII). Of these individuals, all of the former who had reached sexual maturity but only one of the latter had clinical symptoms of gonadal insufficiency.

Table XIII

SCA in type I and type II autoimmune polyglandular syndrome

Condition	No. of patients		
	Total	Adrenocortical Ab	SCA
Type I	7	7 (100%)	6 (85.7%)
Type II	23	22 (95.6%)	3 (13.0%)
Not classifiable[a]	17	8 (47.1%)	3 (17.6%)

Patients classified had either Addison's disease and/or adrenal autoantibodies. Ab, Antibodies.

[a] Insufficient patient history for classification or patients do not have adrenal autoimmunity, including control patient.

Ref. 30

In a different series of patients with idiopathic Addison's disease, as many as one-third of women had evidence of associated premature gonadal failure, and of these about two-thirds had steroid cell antibodies (40). In contrast, just slightly more than 1% of men with Addison's disease showed clinical evidence of testicular failure (40). Steroid cell antibodies have less frequently been detected in women with premature ovarian failure unassociated with Addison's disease (183-186), but all such patients have had demonstrable adrenal antibodies (185) and/or other autoimmune diseases (183-186). Indirect evidence of autoimmune oophoritis has also been adduced in 16 of 81 women with premature ovarian failure evaluated at the Mayo Clinic (186). In this study all women with the diagnosis of premature ovarian failure made during a 10-year period were evaluated for the presence of other endocrine disorders. Ten patients had Addison's disease (4 of whom had not been previously diagnosed, and 6 of whom had concomitant thyroid disease), 5 had evidence of thyroid disease, and 1 had myasthenia gravis.

Hypophysitis

Lymphocytic adenohypophysitis is a recently recognized disorder that has been described exclusively in women, usually during pregnancy or the postpartum period (187-190). The first 7 patients, reported between 1962 and 1980, all died of complications of hypopituitarism. More recently antemortem diagnosis has been made at the time of hypophysectomy performed because of the findings of a sellar mass during evaluation for visual field loss and/or hypopituitarism. In contrast to the finding of an enlarged pituitary in these latter patients, the pituitary glands in the autopsied patients initially reported were usually small in size. In both groups, however, histologic evaluation revealed

extensive lymphocytic infiltration of the anterior pituitary with varying numbers of plasma cells. Association of hypophysitis with other autoimmune endocrine disorders has been discussed above.

Circulating antibodies to anterior pituitary cells have been described in several groups of individuals. In one study of randomly selected postpartum women, antibodies were detected in 18% during the fifth to seventh postpartum days (191). Other groups in which pituitary antibodies have been described are patients with PGA disorders as described above (31, 192), and in patients with insulin-dependent diabetes mellitus and their first-degree relatives (31, 192). Most of the antibodies when examined have been to prolactin-secreting cells (31,192). However in neither of these latter groups has there been any evidence of hypopituitarism to date (31,192).

In evaluating patients with PGA the possibility of concomitant hypophysitis should be considered. Several patients with classical Schmidt's syndrome have been reported who had focal lymphocytic infiltration of the pituitary discovered at autopsy (3). Other patients with autoimmune thyroid disease and partial hypopituitarism have been described in whom the hypopituitarism has been postulated to be secondary to hypophysitis (148-151). The finding of an enlarged sella however in a patient with one or more primary endocrine deficiencies is probably more often due to secondary compensatory hyperplasia of specific pituitary trophic hormone-secreting cells (193) than to hypophysitis. Likewise, a finding of a modestly elevated serum prolactin (with or without galactorrhea) in a patient with evidence of autoimmune endocrine disease may be due to one of several possibilities (in addition to a coexistent prolactin-secreting pituitary tumor). These include autoimmune-mediated primary hypothyroidism, hypophysitis (187,188), and primary adrenal insufficiency (194). Specific pituitary-directed therapy should be reserved for patients who remain symptomatic from hyperprolactinemia and/or a pituitary mass following treatment of primary hypothyroidism and/or adrenal insufficiency.

Primary Hypoparathyroidism

Primary autoimmune hypoparathyroidism is a rare disorder usually beginning in childhood or adolescence. Pathologically it is characterized by parathyroid gland atrophy with lymphocytic infiltration. When primary hypoparathyroidism occurs in association with one or more other endocrine disorders it is essentially always in children as a component of a PGA I syndrome (195). [However, 1 Japanese patient has recently been reported with the constellation of isolated ACTH deficiency, Hashimoto's thyroiditis, diabetes mellitus (islet cell antibody negative), and primary hypoparathyroidism (196).] In one series of 74 patients with idiopathic hypoparathyroidism, 32 had an associated disorder characteristic of PGA I (195).

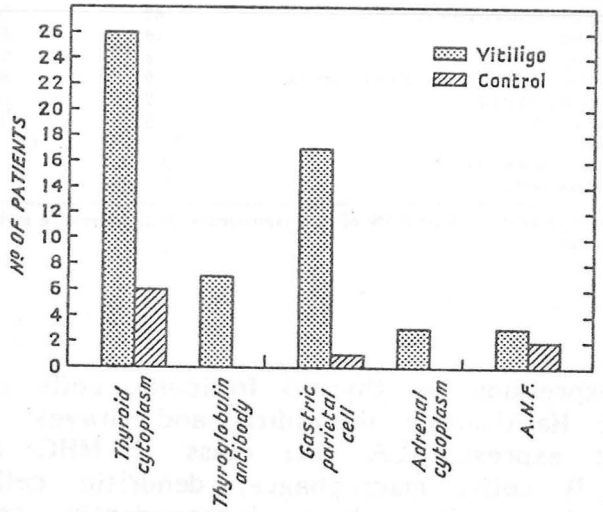
Approximately 40% of all patients with primary hypoparathyroidism have circulating antibodies to parathyroid cells (195). Parathyroid antibodies have also been reported in 25% of patients with Addison's disease (without hypoparathyroidism) as compared to 6% of a normal control group (195). Some of the Addisonian patients may however have been members of PGA I pedigrees. In addition, a high prevalence of antibodies to thyroid, adrenal, and gastric

parietal cells (195) as well as diminished antigen-specific suppressor T cell function (32) have been demonstrated.

VITILIGO AS A COMPONENT OF POLYGLANDULAR AUTOIMMUNE DISEASE

The prevalence of vitiligo is increased among patients with autoimmune endocrine disease as compared to the general population (8% to 15% vs. 1%) (197), whether occurring as an isolated disorder (198) or as part of a PGA syndrome (199). In addition, organ specific antibodies to thyroid, adrenal, gastric parietal and islet cells are more frequent in patients with vitiligo than in controls (Fig. 20) (200). Vitiligo is often familial, and an association with

Figure 20



Autoantibodies in 80 patients with vitiligo compared with controls matched for age and sex.

Ref. 200

HLA DR4 in Caucasian patients has been shown in one study (197). Although autoimmune destruction of melanocytes has long been postulated in the pathogenesis of vitiligo, it has not been until recently that antibodies to melanocytes have been detected in the majority (greater than 80%) of affected individuals (Table XIV) (201,202). Binding of antibody to a melanocyte cell surface antigen has also been demonstrated (201).

ETIOLOGY AND PATHOGENESIS OF POLYGLANDULAR AUTOIMMUNITY

Linkage of certain components of the PGA syndromes with the DR3 locus of the major histocompatibility complex has been clearly established. Because of the key role of HLA DR antigens in the processes of antigen presentation and subsequent T and B cell activation, it has been postulated that a mutation in a gene closely linked to the HLA DR locus and in linkage disequilibrium with the DR3 antigen is responsible for a primary immunoregulatory abnormality in HLA DR3 positive patients with polyglandular as well as other forms of autoimmune disease. Alternatively, the HLA DR3 haplotype itself may be directly involved in the initiation of autoimmunity by effecting enhanced antigen presentation.

For example, HLA DR status may be involved in determining the dose of antigen required to trigger helper or suppresser T cells. Evidence for direct participation of HLA-D region products in the imitation of autoimmune thyroid disease has been obtained by Bottazzo and co-workers (203). This group has

Table XIV

Antigen-binding Antibodies to Melanocytes in Vitiligo

Diagnosis	Number of patients	Percent with antibodies* to surface antigens
Vitiligo	61	82
Common vitiligo	14	100
Vitiligo and autoimmune diseases	42	74
Thyroiditis	18	89
Thyroiditis and diabetes	8	61
Hypoparathyroidism and alopecia areata	9	66
Pernicious anemia	2	50
Vitiligo and MCC	5	100
Melanoma	24	12
Nonpigmentary diseases	32	0
MCC without vitiligo	3	0

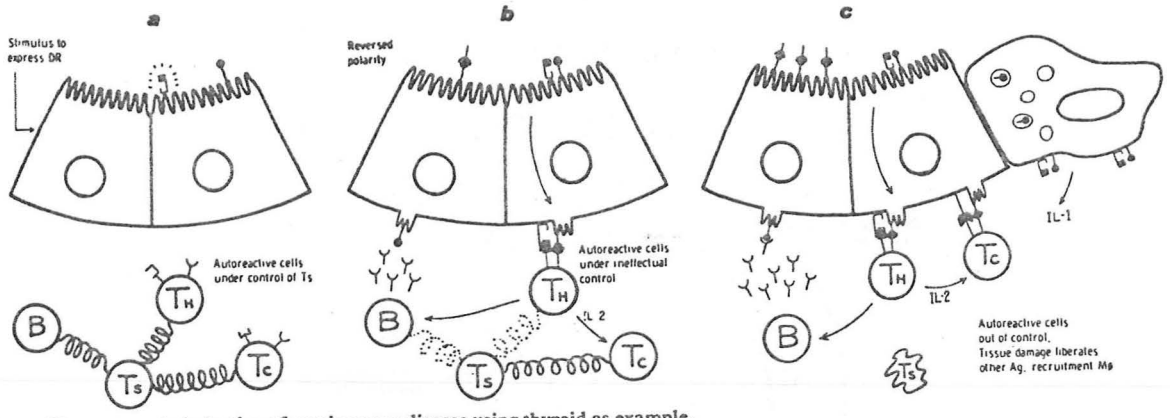
* Sera binding specifically at least 2.5% of cpm associated with acid-insoluble melanocyte macromolecules.

Ref. 201

demonstrated HLA-DR expression on thyroid follicular cells obtained from thyroid glands of patients with Hashimoto's thyroiditis and Graves' disease. Cells from normal thyroids do not express HLA DR; class II MHC antigen expression is normally restricted to B cells, macrophages, dendritic cells, and activated T cells. These results have since been independently confirmed (204). In addition, a spontaneous reversal of the polarity of antigen expression on the thyroid follicular cell surface has been demonstrated in thyroid glands from patients with Graves' disease (205). Thus, in autoimmune thyroid disease microsomal (and other) antigen is translocated from its normal location on the microvillous colloid edge of the thyroid follicular cells to the vascular pole. Bottazzo et al postulate that this reversed polarity of thyroid autoantigens together with inappropriately expressed DR molecules may enable antigen presentation to helper T cells, and thereby initiate the autoimmune process (Fig. 21) (206). Resultant autoantibody production coupled with an underlying defect in T suppressor function would be sufficient for the production of organ damage. It should be emphasized however that aberrant or ectopic expression of HLA DR and tissue antigens may be the consequence rather than the cause of the primary immune response (207).

Since correlations between HLA status and presence of disease are not absolute, other factors affecting immune response, including age, hormonal status, and environmental influences such as stress and infection, must also play a role in initiating and/or perpetuating autoimmunity in a genetically susceptible individual. For example, the relatively low concordance rate of autoimmune endocrinopathies in monozygotic twins suggests that environmental agents, such as viral infection in patients with insulin-dependent diabetes mellitus or infection with certain gram-negative bacteria in patients with autoimmune thyroid disease (208), are critical in induction of disease.

Figure 21



Ref. 206

Three stages in induction of autoimmune disease using thyroid as example.

(a) In genetically non-susceptible individuals, in absence of environmental stimuli there is normal polarity of antigens and a lack of DR expression, and consequently no autoimmunity. Environmental agents may induce DR ( ) as illustrated, but without reversion of polarity the antigen ( ) presentation cannot be efficient. Suppressor T cells (Ts) maintain other lymphocytes under control ( ).

(b) In genetically predisposed individuals, environmental agents induced DR expression DR polymorphism (eg, DR3) ( ) is of importance and reversed polarity of epithelial cell antigens permits antigen presentation of DR and autoantigen to T helper cells (T_H). T_H induce B lymphocytes to generate autoantibody ( ). During the long latency period, there is subclinical damage.

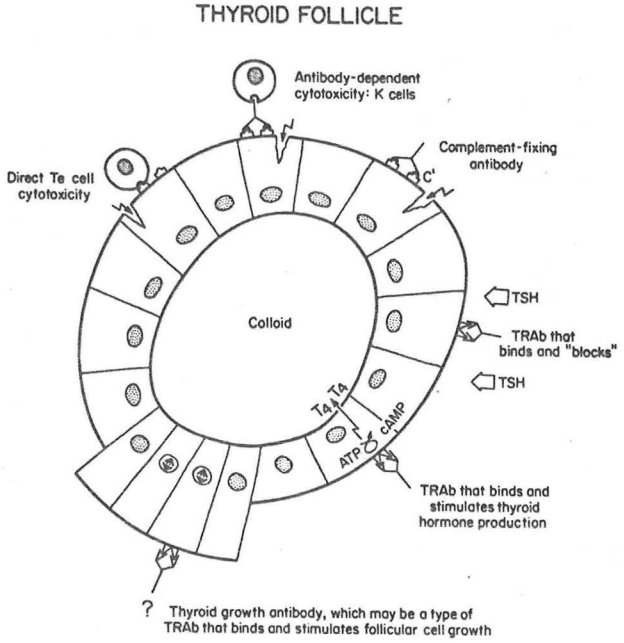
(c) With abnormality of T suppressor cell function (? organ specific) organ damage becomes clinically manifest, with infiltration of macrophages and release of many autoantigens and consequently other autoantibodies also generated, perpetuating the disease.

Along with elucidation of the genetic and other mechanisms involved in the induction of autoimmune disease, it is also important to understand by what means the abnormalities in immune regulation are effected. Much attention has focused on the possibility that the result of the primary genetic defect is an abnormality in suppressor T cell function. Deficient suppressor T-cell activity could explain unrestrained autoantibody production by B cells as well as unregulated lymphokine production by effector T cells.

Tissue damage and/or dysfunction occurring as a consequence of immune activation may develop through several different mechanisms. These are illustrated in Figure 22 utilizing the thyroid as the example target organ. Autoantibodies may participate directly in tissue damage by virtue of (1) complement fixation and activation following antigen binding, (2) in situ formation of immune complexes with complement activation, or (3) facilitation of natural killer (NK) cell binding to target cells. T cell-mediated damage may occur following cytotoxic T cell binding to specific target cell antigens or to class I and/or class II MHC antigens that may be expressed on the cell surface. Antibody-dependent cell mediated cytotoxicity, a function of NK cell number and activity, has also been implicated in the mechanism of tissue damage.

Why specific patterns of endocrine gland involvement occur in patients with PGA is not certain. It has been suggested that for each component disorder there is a specific genetic abnormality, possibly involving inherited defects in different clones of suppressor T lymphocytes (163). In support of this view, there is evidence that in families with insulin-dependent diabetes mellitus and autoimmune thyroid disease, the two disorders segregate independently of one

Figure 22



Ref. 176

Composite Diagram of the Possible Immune Effector Mechanisms in Graves' Disease and Hashimoto's Thyroiditis.

Cytotoxic mechanisms include direct cytotoxicity by sensitized effector (Te) cells, antibody-dependent cytotoxicity by killer (K) cells armed with antithyroid antibody, and cell lysis by complement-fixing thyroid antibody. The various types of thyrotropin-receptor antibody (TRAb) have different mechanisms of action. One type binds to the thyrotropin (TSH) receptor and blocks TSH from binding to the receptor. Another type — classic thyroid-stimulating antibody (TSAb) — binds to and stimulates the TSH receptor, which results in production of thyroid hormone by thyroid follicular cells. Thyroid growth antibody, which may be a type of TRAb, binds to the TSH receptor and causes growth of thyroid follicular cells but not production of thyroid hormone. A variant of this antibody binds and blocks growth.

another (140) (see above). There is also evidence that in some cases of PGA, autoantibodies are formed that cross-react with an antigen common to multiple endocrine target tissues (209). Notkins et al have produced monoclonal antibodies that cross-react with the thyroid follicle, anterior pituitary, gastric mucosa, and pancreatic islets by fusing peripheral blood lymphocytes from patients with insulin-dependent diabetes to either mouse or human myeloma cells (209, 210). An immunoaffinity column was synthesized utilizing the monoclonal antibody produced by one such fusion. When extracts of thyroid and stomach were passed over this column, and bound proteins were eluted, a single 35,000-molecular weight protein was identified (210). Several proteins, including one of 35,000 molecular weight, were also isolated from the pancreas utilizing the same technique, and two proteins were isolated from the pituitary (the 35,000 molecular weight protein plus growth hormone). Thus formation of an antibody directed against a common protein present in several endocrine tissues, perhaps one that has a role in the secretory process, could potentially explain the disease patterns observed in some patients with PGA.

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