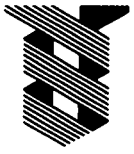
Open access • Journal Article • DOI:10.1056/NEJM198212093072407

Immunology of autoimmune thyroid diseases. — Source link

C. R. Strakosch, Björn E. Wenzel, Vas V. Row, Robert Volpé

Published on: 09 Dec 1982 - The New England Journal of Medicine (Massachusetts Medical Society)

SEMINARS IN MEDICINE
OF THE
BETH ISRAEL HOSPITAL, BOSTON



JEFFREY S. FLIER, M.D., *Editor*
MARY JEAN MOORE, *Assistant Editor*

IMMUNOLOGY OF AUTOIMMUNE THYROID DISEASES

CHRISTOPHER R. STRAKOSCH, M.D.,
BJÖRN E. WENZEL, PH.D.,
VAS V. ROW, M.SC., M.A.,
AND ROBERT VOLPÉ, M.D.

IN 1897 Ehrlich[1] coined the term "horror autotoxicus" to describe his view that the body seemed "unwilling" to mount an immune assault on its own tissues. In the early part of this century, with the hypothesis that the hyperplastic thymus gland might, in some obscure way, cause Graves' disease,[2] the field of thyroid autoimmunity was opened, and in the past two decades it has received particular impetus. The study of autoimmune thyroid disorders has provided valuable insights into the pathogenesis not only of specific thyroid disorders but also of autoimmune diseases in general.

THE B LYMPHOCYTE IN AUTOIMMUNE THYROID DISEASE

Many humoral and cellular mechanisms in autoimmune thyroid disease have been discovered in the past 25 years. In general, studies of the immune system have focused on humoral rather than cellular mechanisms because of the early recognition of the role of antibodies in immunity, the ease with which antibodies can be measured, and the special characteristics of some of these antibodies. The year 1956 was particularly important in the study of autoimmune thyroid disease. In that year Roitt et al.[3] detected high titers of antibodies to thyroglobulin in patients with Hashimoto's thyroiditis, Rose and Witebsky[4] first induced thyroiditis in rabbits immunized with thyroid-gland homogenate, and Adams and Purves[5] detected a substance in the serum of some patients with Graves' disease that caused prolonged stimulation of the thyroid gland. The substance was later called long-acting thyroid stimulator (LATS) and was found to be an antibody.[2] Since the term LATS is now usually applied to a particular mouse bioassay,[6] the term thyroid-stimulating antibody (TSAb) is considered more appropriate.

TSAb has received considerable attention because of its unique action and ultimate clinical expression as hyperthyroidism. An IgG,[7,8] it mimics the action of thyroid-stimulating hormone (TSH) by stimulating cyclic AMP production,[9] radioactive iodine uptake,[10] and colloid droplet formation.[11] Hence, the effects of TSAb and TSH on the intracellular metabolism of thyroid follicles are essentially the same.[12]

There is much evidence that the TSH receptor is the antigen to which TSAb is the antibody, but this point remains unproved. Fenzi et al.[13] have removed TSH receptors by affinity chromatography and found TSAb, but not TSH, still bound to thyroid membranes; these results suggest that the TSH receptor is not the binding site for TSAb. In addition, Solomon and Chopra,[14] using the LATS protector assay, have found that TSH does not prevent adsorption of LATS onto thyroid membranes.

In an attempt to resolve this point, TSH and TSAb were incubated together with solubilized thyroid membranes. TSH-receptor and TSAb-receptor complexes were found, but not TSH–TSAb-receptor complexes. These data suggest that TSH and TSAb compete with each other for the same binding site on the TSH-receptor molecule.[15,16] Endo et al.[17] have shown that the IgG specific to Graves' disease will bind to TSH receptors in tissues other than the thyroid — for example, fat cells. The observation that where there is TSH binding there is also TSAb binding further supports the notion that TSAb is an antibody to the TSH receptor. Finally, Wenzel et al.[18] discovered that the peripheral blood of patients with Graves' disease contained an increased number of the B lymphocytes that bind partially purified TSH-receptor protein.

Originally, TSAb was measured by an assay that determined the amount of radioactive iodine released from primed thyroid glands of guinea pigs after injection of serum from patients with Graves' disease; the assay was subsequently modified for mice.[6] Since its introduction, many other assays for the IgG specific to Graves' disease have been described. Some measure the inhibition of TSH binding to receptor sites,[19] whereas others measure the stimulation of cyclic AMP or thyroid-hormone production in human thyroid slices or thyroid cells in culture.[11,20,21]

A plethora of terms have been used to denote this IgG; the particular one chosen depends on the activities measured and the laboratory where the experiment is performed. The term "thyrotropin-receptor antibody" is probably the most general, since most of the evidence cited above suggests that the TSH receptor is the related antigen. The term "TSAb" should be employed to refer to the antibodies that cause stimulation in a functional assay, but this term is inappropri-

From the Endocrine Research Laboratory, Department of Medicine, Wellesley Hospital, University of Toronto, Ontario. Address reprint requests to Dr. Volpé at the Department of Medicine, Wellesley Hospital, 160 Wellesley St. East, Toronto, ON M4Y 1J3, Canada.

Supported in part by a grant (MT 859) from the Medical Research Council of Canada.

ate for some forms of IgG that inhibit TSH binding because they do not stimulate the thyroid.[22,23] Certain antibodies may even contribute to hypothyroidism by binding to the thyrotropin receptor and blocking the action of TSH.[24]

Thyrotropin-receptor antibody is detectable in some but not all patients who have been diagnosed as having Graves' hyperthyroidism. One problem is that the disease is difficult to diagnose. European studies have shown that Graves' disease is not the only cause of hyperthyroidism associated with diffuse uptake on scintiscan. Studer et al.[25] and Schleusener et al.[26] have described a diffuse micronodular goiter (a variant of Plummer's disease) that is not associated with ophthalmopathy or other immune disturbances and is associated with HLA genotypes that are different from those in Graves' disease. Besides the difficulty in diagnosis, there may be technical problems with the assays, or an assay may not be sensitive enough to detect the antibody. One extremely sensitive but difficult cytochemical assay permitted detection of a stimulating factor in the serum of all patients with Graves' disease who were studied.[27] The results, however, were inconclusive, since the factor was also detected in most patients with toxic multinodular goiter and even euthyroid goiter.

Although measurement of thyrotropin-receptor antibody is important for an understanding of the cause of Graves' disease, it has been of little assistance to the clinician in diagnosis and management, and the assays are time-consuming, technically difficult, and expensive. Some investigators[28-30] claim that the persistence of thyrotropin-receptor antibody after a course of treatment can be used to predict a relapse, but others disagree.[31,32]

Recently, Drexhage et al.[33] described another family of antibodies that may be directed against the TSH receptor. Like TSH, these antibodies appear to induce goiter, but unlike TSH, they do not induce the release of hormones. Patients with goitrous Graves' disease or goitrous Hashimoto's thyroiditis appear to have antibodies that promote thyroid growth, whereas patients with atrophic thyroiditis have antibodies that inhibit thyroid growth. It is unclear how these antibodies block the growth-promoting effect of TSH but remain undetected in assays that measure inhibition of TSH binding to the TSH receptor.

It is also unclear why, within the family of glycoprotein hormones, receptors for TSH are commonly a target for autoimmune attack, but receptors for luteinizing hormone, follicle-stimulating hormone, and human chorionic gonadotropin apparently are not. Other receptors to which autoantibodies have been found include the insulin receptors in certain patients with insulin resistance, the acetylcholine receptor in patients with myasthenia gravis,[34] and probably the beta-adrenergic receptor in some patients with allergic rhinitis and asthma.[35]

Thyrotropin-receptor antibody is not the only thyroid antibody present in autoimmune thyroid disorders. The most common antibodies that are also important clinically are thyroglobulin and thyroid microsomal antibodies. A high titer of thyroglobulin antibody, a non-complement-fixing antibody, is found in about 55 per cent of patients with Hashimoto's thyroiditis and 25 per cent of patients with Graves' disease. It occurs less often in patients with thyroid cancer and other autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis, and a low titer is found in about 10 to 20 per cent of normal subjects (particularly elderly women).[34] Thyroglobulin antibody also appears transiently in some patients with subacute thyroiditis. The usual method of measurement is by the hemagglutination technique. Recently, a new radioassay with greater sensitivity has been developed. As compared with the hemagglutination technique, it detects a higher prevalence of thyroglobulin antibody in patients with Graves' or Hashimoto's disease, but tests of more normal subjects are also positive. In addition, this radioassay gives falsely high titers in the presence of high concentrations of plasma thyroglobulin.[36]

Thyroid microsomal antibody is a complement-fixing antibody that is detected, usually by the hemagglutination technique, in 95 per cent of patients with Hashimoto's thyroiditis, 90 per cent of patients with idiopathic myxedema, and 80 per cent of patients with Graves' disease.[34] It appears to correlate better with histopathologic lesions in Hashimoto's thyroiditis than does thyroglobulin antibody, and it is detected less often in normal subjects. The antigen to this antibody has a cell surface and an intracellular component, but its exact nature is unknown.

Antinuclear antibodies are also found in autoimmune thyroid disease, as are antibodies to cell membranes, to a colloid component other than thyroglobulin, and to the thyroid hormones themselves.[34]

Figure 1 summarizes the immune effector mechanisms that may operate in Graves' disease and Hashimoto's thyroiditis.

The T Lymphocyte in Autoimmune Thyroid Disease

B lymphocytes, which are precursors of the plasma cells that produce the antibodies, are controlled by subsets of the T-lymphocyte population. Helper T lymphocytes cause B lymphocytes to differentiate into plasma cells, and suppressor T lymphocytes limit the immune reaction to "nonself" and probably suppress immunity to "self." Suppressor T cells act through helper T cells to suppress the B-cell response — that is, specific suppressor cells normally suppress specific helper cells. Effector T cells, which are responsible for direct cytotoxicity, are also controlled by suppressor T lymphocytes.

Although it is more difficult to measure T-lymphocyte response (cell-mediated immunity) than B-lymphocyte response (humoral immunity), techniques have been developed to study abnormalities of cell-mediated immunity in autoimmune thyroid disease.

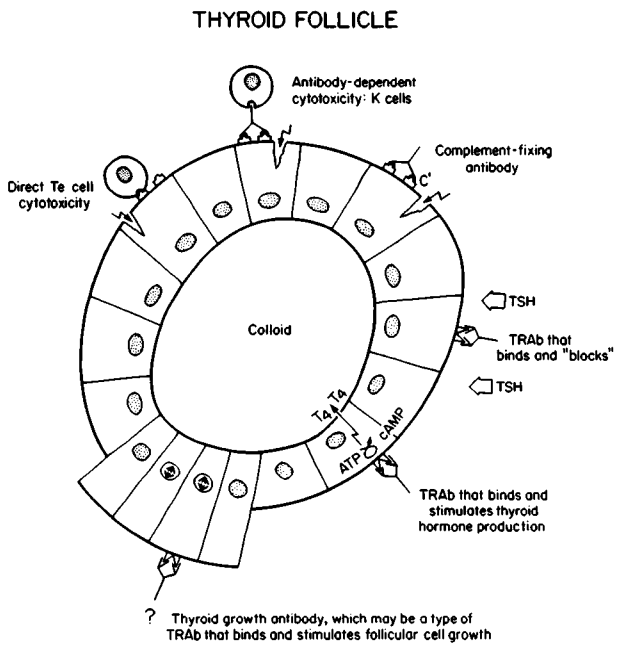


Figure 1. Composite Diagram of the Possible Immune Effector Mechanisms in Graves' Disease and Hashimoto's Thyroiditis.

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.

Antigens stimulate sensitized T lymphocytes to produce a family of small proteins known as lymphokines, which have potent effects on other lymphocytes. One lymphokine causes nonspecific inhibition of lymphocyte migration and is known as migration-inhibition factor. Measurement of migration-inhibition factor in response to specific antigens is the least difficult method for determining T-cell sensitization.

One index of cell-mediated immunity in patients with Graves' or Hashimoto's disease is the production of migration-inhibition factor by lymphocytes after exposure to thyroid antigen in vitro.[37] However, early studies, which used macrophages, mononuclear cells, and whole leukocyte preparations as the migrating cells, were criticized because elements other than T lymphocytes were involved in the procedure. A further problem was the inability to detect migration-inhibition factor in the cultured supernatants of antigen-stimulated lymphocytes from patients with Graves' or Hashimoto's disease, when normal lymphocytes were used as the indicator cells.

A modified test for migration-inhibition factor, based on the method of Kowalczyk and Zembala,[38] has now been developed; it uses a purified preparation of T lymphocytes as the migrating cells. Because this test uses a largely homogeneous population of T lymphocytes both as the cells that produce the migration-inhibition factor and as the cells that indicate the presence of migration-inhibition factor, it is more specific and less variable than previous tests. Using this method, Okita et al.[39] found migration-inhibition factor and, by implication, T-lymphocyte sensitization in the majority of patients with Graves' disease or Hashimoto's thyroiditis who were studied. Moreover, addition of cultured supernatants of mononuclear cells from patients with these diseases to preparations of normal T lymphocytes inhibited migration of the normal lymphocytes; this result confirmed the presence of migration-inhibition factor.[40]

The thyroid antigen to which the T-cell response is directed has been more difficult to define. Mäkinen et al.[41] found that TSH blocked the proliferation of lymphocytes that ordinarily occurs after administration of thyroid-membrane preparations, suggesting that the TSH receptor is the target in cell-mediated immunity as well as in humoral immunity. The investigators hypothesized that TSH masked the TSH receptor and prevented antigenic recognition. However, this hypothesis could not be confirmed by Wall et al.[42] and has been disputed by other investigators,[43] who found that high concentrations of TSH had a nonspecific immunosuppressive action.

Since there are demonstrable abnormalities in both the cell-mediated and humoral mechanisms in the immune system of patients with Graves' disease or Hashimoto's thyroiditis and since both are controlled by subsets of T lymphocytes, it is logical to suspect that a defect in T-lymphocyte control is the cause of the disorders.

Animal models have been particularly helpful in determining how self-tolerance is maintained or lost. (Volpé[34] and Rose et al.[44] have provided detailed reviews of this subject.) Three theories attempt to explain self-tolerance. The first is clonal deletion, which was first described by Burnet.[45] It states that autoreactive T lymphocytes are either eliminated or permanently blocked during fetal life. An autoreactive clone develops by mutation.

The second theory is based on dynamic control. Suppressor T lymphocytes regulate the immune response and thus prevent each nonself challenge from resulting in a lymphoproliferative disorder; in addition, these cells suppress the response to self. This theory requires a "clonal balance"[44] between helper and suppressor T lymphocytes. Suppressor T lymphocytes also control effector T lymphocytes. The fact that immunization induces an antibody response to thyroglobulin in normal mice suggests that the clonal balance is being manipulated. Preliminary observations of the induction of thyroglobulin antibody in normal lymphocytes in vitro also favor the second theory.[46] Hence, it is likely that the development of an immune response to self is due to a deficiency in specific suppressor T lymphocytes, with the

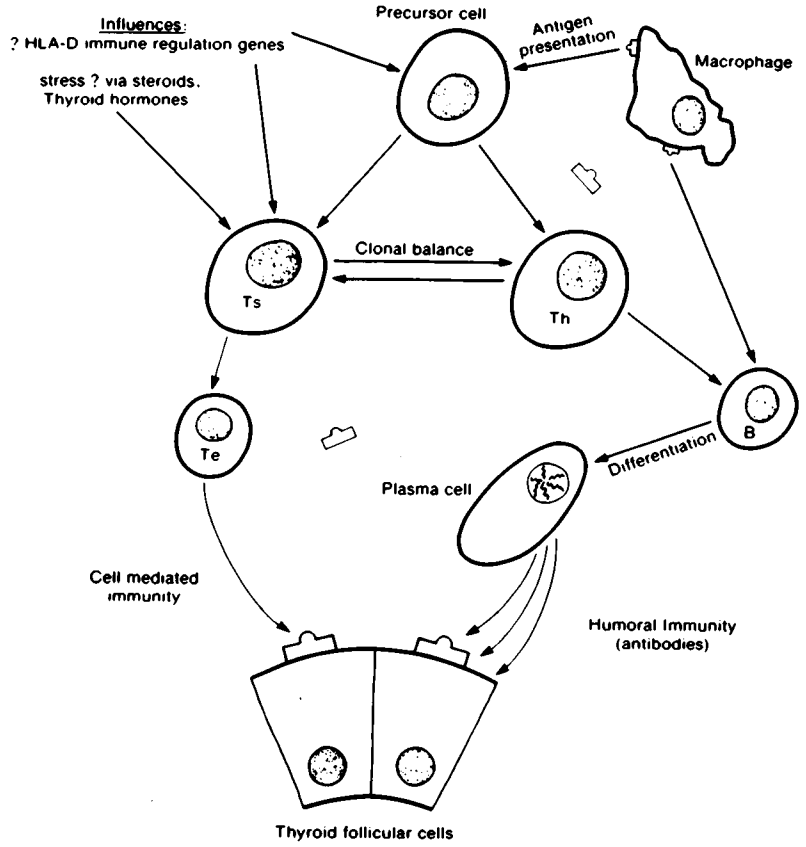


Figure 2. Postulated Mechanisms Whereby Control of the Immune Response Is Maintained or Lost.

Macrophages present thyroid antigen to precursor T lymphocytes, which differentiate into antigen-specific suppressor T lymphocytes (Ts) and helper T lymphocytes (Th). In Graves' disease and Hashimoto's thyroiditis, a genetically determined, antigen-specific deficiency may tip the balance between suppressor and helper T cells in favor of helper T cells. An alternative theory, which more easily explains the random appearance of the disease in a genetically predisposed population, proposes that helper T cells arise by random mutation. Other influences — for example, stress or abnormal thyroid-hormone levels — may depress suppressor-cell function and thereby alter the balance. The result is that the antigen-specific helper T clone expands and interacts with B cells, which also expand and differentiate into plasma cells, which in turn produce antibodies. The effector T clone (Te) may also expand and assault thyroid follicular cells, especially in Hashimoto's thyroiditis.

consequent imbalance in the ratios of helper to suppressor lymphocytes and suppressor to effector lymphocytes.[44]

A third theory incorporates the other two.[44] Thus, the random appearance of autoimmune thyroid disorders in genetically predisposed persons (who presumably have a defect in immune control) may be due to the random appearance (by normal random mutation) of the appropriate clone of autoreactive helper T lymphocytes for which immune control is inadequate — again because of a defect in antigen-specific suppressor T lymphocytes. Figure 2 shows the postulated mechanisms whereby control of the immune response is maintained or lost.

Considerable research has been devoted to determining the status of suppressor T lymphocytes in patients with autoimmune thyroid disorders. Evidence indicates that there is an organ-specific defect in suppressor T lymphocytes in both Graves' disease and Hashimoto's thyroiditis. When normal T lymphocytes are added to T lymphocytes from patients with either disorder and the combination is exposed to thyroid antigen, no migration-inhibition factor is produced.[47] The normal suppressor T lymphocytes appear to compensate for the postulated deficiency in the patient's suppressor lymphocytes. This effect is not due to dilution, since the suppressor effect is lost if the normal lymphocytes are first irradiated or treated with mitomycin C.[47,48] Both treatments preferentially inhibit suppressor cells, presumably interfering with the function of normal suppressor T cells and preventing compensation for the deficient lymphocytes.

There is further evidence that the suppressor effect is at least organ-specific, if not antigen-specific. In a study by Topliss et al.[49] T lymphocytes from patients with insulin-requiring diabetes mellitus of recent onset produced migration-inhibition factor when incubated with beta-cell antigen from the pancreatic islets of a patient with insulinoma. Presumably, these diabetic patients also had a suppressor-cell defect, although in this instance the defect involved the beta-cell antigen. However, when T lymphocytes from diabetic patients were added to T lymphocytes from patients with Graves' or Hashimoto's disease, in most instances the former abolished the ability of the latter to produce migration-inhibition factor in response to thyroid antigen. In these circumstances the T lymphocytes from the diabetic patients acted like normal T lymphocytes. The converse was also true: lymphocytes from patients with Graves' or Hashimoto's disease acted like normal T lymphocytes by abolishing the ability of T lymphocytes from patients with insulin-requiring diabetes mellitus to produce migration-inhibition factor in response to islet-cell antigen. These results indicate that the defect in suppressor cells is organ-specific rather than general.

Other studies of the number and function of suppressor T cells in autoimmune thyroiditis have produced conflicting findings, probably because specific antigens or tests of antigen-specific clones of suppressor T lymphocytes were not employed. Using monoclonal antibodies that select particular subpopulations of T lymphocytes, Thielemans et al.[50] and Sridama et al.[51] found a decrease in the total number of suppres-

sor T lymphocytes in Graves' disease and Hashimoto's thyroiditis. Canonica et al.,[52] on the other hand, found the total number of suppressor cells to be normal.

In contrast to antigens, which act as specific stimulators, mitogens (plant-derived agents) act as nonspecific stimulators of certain subpopulations of lymphocytes. Studies of the effects of mitogens have also provided conflicting results. MacLean et al.[53] found that concanavalin A (which stimulates suppressor T cells) suppressed immunoglobulin synthesis by lymphocytes that were stimulated by pokeweed mitogen (which stimulates both T and B lymphocytes). Concanavalin A had no differential effect on lymphocytes from normal subjects or from patients with autoimmune thyroiditis. Aoki et al.,[54] on the other hand, found that concanavalin-A induced suppressor activity was reduced in patients with active Graves' disease but not in patients with Hashimoto's thyroiditis. Moreover, in patients with Graves' disease defective suppressor activity tended to return to normal after treatment. Similar results were obtained by Balázs et al.[55]

Beall[56] found that B lymphocytes from patients with autoimmune thyroiditis produced thyroglobulin antibody when stimulated with suboptimal amounts of pokeweed mitogen that had been combined with specific thyroglobulin antigen. Production continued even when the treated lymphocytes were cultured with normal T cells (which should have contained a subset of suppressor cells specific to thyroglobulin antigen). However, since even a suboptimal amount of pokeweed mitogen provides a substantial nonspecific stimulus, this response cannot be equated with a response to specific antigen alone. The conflict in the data from these studies probably reflects the difficulty of interpreting findings that are based on nonspecific stimulation with mitogens.

McLachlan et al.[57] also found that when B lymphocytes from patients with autoimmune thyroiditis were cultured with normal T cells in the absence of mitogen or antigen, thyroglobulin antibody continued to be produced. They concluded that activation of suppressor T lymphocytes may require stimulation by a specific antigen.

Together, these studies suggest that the general suppressor function in patients with autoimmune thyroid disease is normal. There is no evidence of generalized hypersensitivity,[58] and the number of suppressor T lymphocytes that are specifically responsible for suppressing the helper T lymphocytes specific for thyroid antigen probably represents only a small percentage of the total T-lymphocyte population. If so, one would not expect any reduction in the total number of suppressor T lymphocytes in the circulation.

In the studies of migration-inhibition factor and antibody production described above normal thyroid antigen was used as the specific stimulator. B and T lymphocytes in autoimmune thyroid disease are therefore sensitized to normal thyroid antigen. The evidence does not indicate that the antigen has been altered — for example, by viral infection. (One recent study suggested that autoimmune insulin-requiring diabetes mellitus is initiated by a virally induced lesion.[59]) When a viral infection does cause release of antigen, as in subacute thyroiditis, the suppressor-cell system appears to be overwhelmed, thyroid antibodies and thyrotropin-receptor antibody are temporarily produced,[60-62] and cell-mediated immunity to normal antigen occurs.[61,63] When the patient recovers from the infection, these abnormalities disappear; autoimmune disease develops only if there is a defect in immune surveillance.

Genetic Control of the Immune Response

It is interesting to attempt to understand why some people and not others have this apparent defect in the response of suppressor T cells to thyroid antigen, which renders them susceptible to autoimmune thyroid disease.

In mice, genes that map in the region that corresponds to the HLA-D locus in human beings are responsible for controlling the response of helper or suppressor T lymphocytes to a given antigen.[64] In white people Graves' hyperthyroidism is associated with HLA-DR3,[65] goitrous Hashimoto's thyroiditis with HLA-DR5, and atrophic thyroiditis apparently with HLA-DR3. Previous findings that linked Graves' disease with HLA-B8 probably reflected a linkage disequilibrium between HLA-DR3 and B8. These associations are not absolute; many patients with Graves' disease do not have the HLA-DR3 genotype, and most people with HLA-DR3 (20 per cent of the Canadian population) do not have Graves' disease. Thus, it appears that the gene associated with susceptibility to Graves' disease is not HLA-DR3 but may be very near it, also in linkage disequilibrium. It seems likely that patients with certain genotypes are predisposed to have a defect in the response of suppressor T cells to thyroid antigen. How this genotype causes an abnormality in a specific clone of suppressor T lymphocytes is unknown, as is the molecular nature of the abnormality.

Precipitation of the Disease

Given that there is a genetically determined defect in suppressor T lymphocytes in autoimmune thyroid disease, the next problem is understanding what factors result in initiation of the disorder. Most studies of this problem have investigated Graves' disease, because its symptoms are more dramatic than those of other autoimmune thyroid disorders and both remissions and relapses are common. It has been demonstrated that Graves' disease appears at random in the genetically predisposed population.[66] More than one mechanism may initiate the disorder. One such mechanism could be the random appearance of the appropriate autoreactive helper T lymphocyte for which control is inadequate. This event would be sufficient to initiate the disease. In other instances suppressor-cell function may be only partially defective. An age-related decline in the function of suppressor T cells

in a person who already has an abnormality in a clone of suppressor cells may also be sufficient.

The first report of Graves' disease, in the 19th century, pointed out an association between onset of the disorder and stress.[34] Although early reports were anecdotal, substantial indirect evidence now links stress and the onset of autoimmune disease. Bereavement depresses the lymphocyte response to mitogens in human beings,[67] and stress diminishes the lymphocyte response in animals.[68] The diminution in response may be due to steroid elevation during stress, but the work on this possibility is inconclusive.[69] Moreover, the large differences among species in lymphocyte sensitivity to steroids make extrapolation from animals to human beings difficult. Whatever the initiating mechanisms are, stress may cause decompensation of a genetically compromised population of suppressor T lymphocytes, thus allowing production of antibodies and cytotoxic effects by lymphocytes.[34] In this context stress could be emotional or biologic (for example, a viral infection).

In Graves' disease thyrotropin-receptor antibody induces elevated levels of thyroid hormone. Preliminary experiments in animals suggest that thyrotoxicosis also depresses the function of suppressor T lymphocytes.[70] The tendency in Graves' disease for abnormal suppressor function to become normal after treatment[70,71] indicates that the hyperthyroid state itself affects the immune system. This effect, although not related to the pathogenesis of the disease, may be important in the self-perpetuation of hyperthyroidism.

Administration of antithyroid agents, such as propylthiouracil, lowers thyroid-hormone levels and thus could lead to recovery of suppressor-cell function. Propylthiouracil and methimazole may also act as mild antimetabolites. Propylthiouracil has been shown to decrease both the uptake of tritiated thymidine by normal lymphocytes stimulated by mitogen[72] and the secretion of immunoglobulin by normal mononuclear cells stimulated by pokeweed mitogen (as measured by the plaque-forming assay).[73] Methimazole also decreases the amount of thyroglobulin antibody produced in culture by lymphocytes from patients with Hashimoto's disease.[74] On the other hand, Wenzel et al.[75] have shown that in Graves' disease the level of thyrotropin-receptor antibody falls at the same rate whether patients are treated with propylthiouracil or perchlorate. This finding suggests that the decline in thyroid-hormone levels, rather than any immunosuppressive effect of the thionamides, is responsible for normalizing immune control and stopping production of thyrotropin-receptor antibody.

In any event, remissions are probably possible only when the defect in suppressor T lymphocytes is not severe. The severity of this defect may be genetically related; patients with HLA-DR3 are unlikely to have a remission, whereas those without it are more likely to have a remission.[76]

Summary

The basic underlying defect in autoimmune thyroid disease appears to be a deficiency in antigen-specific suppressor T lymphocytes. This specific deficiency allows effector T lymphocytes to attack the thyroid cells and allows helper T lymphocytes (which may have arisen by spontaneous mutation) to induce plasma cells derived from expanded B-lymphocyte clones to produce antibodies. The defect in suppressor T lymphocytes seems to be genetically linked, since autoimmune thyroid disease is more common in patients with certain HLA types. By extrapolation from animal studies, it appears that genes in the HLA-D locus control the immune response.

The defect in suppressor T lymphocytes may be aggravated by stress, which may be either biologic (for example, a viral infection) or emotional (for example, bereavement). Stress may act through the relation between hormones and immunologic status — a relation that is as yet ill defined.

Graves' hyperthyroidism is unique in that the specific defect in suppressor T lymphocytes allows production of an antibody to the thyrotropin receptor, which consequently stimulates production of thyroid hormone. Increasing levels of these hormones appear to cause further decompensation of suppressor-cell function. Conversely, treatment of hyperthyroidism, which decreases thyroid-hormone levels in patients with Graves' disease, seems to improve the defect in suppressor T cells and may hasten recovery.

Discussion

Dr. Sidney H. Ingbar: Would you elaborate on the differences between chronic and silent thyroiditis?

Dr. Volpé: In silent thyroiditis the patient is hyperthyroid but has an uptake of approximately 1 per cent. Usually the gland is enlarged only slightly, if at all, and is not tender. Circulating antibodies may or may not be present. Patients go through phases similar to those in subacute thyroiditis, with a transient hypothyroid phase, and usually recover. Inada and his colleagues[77] have shown complete histologic resolution in the majority of cases studied. The main difference between silent and de Quervain's thyroiditis is that patients with the former have lymphocytic infiltration within the thyroid, whereas patients with the latter have so-called giant cells. Although some people consider silent thyroiditis to be a form of chronic thyroiditis, presumably because of the lymphocytic infiltration, I believe that in patients who have no circulating antibodies and who recover completely within a year, the disorder does not fit the current definition of chronic thyroiditis.[34]

There is another group of patients, however, who are clinically and histologically indistinguishable from patients with silent thyroiditis but who tend to have slightly larger thyroid glands and thyroid antibodies and usually do not fully recover. The syndrome is

probably related to Hashimoto's thyroiditis. Immunologic control in these patients may be precarious, and the disease may emerge under difficult circumstances. Postpartum thyroiditis and postpartum Graves' disease, which are not uncommon, are examples of this disorder.[78] It is unclear why immunologic disease sometimes occurs after delivery. It appears that the fetus supplies suppressor cells or some other suppressor factor to the mother,[79] which may ameliorate autoimmune processes during the third trimester of pregnancy. A rebound then occurs two to six months after delivery.

In summary, I think of silent thyroiditis as being homogeneous clinically but heterogeneous etiologically.

DR. SYED M. AMIR: It seems strange that certain TSAbs can evoke cyclic AMP generation but fail to show any activity in the radioligand assay that measures inhibition of TSH binding to the receptors. Do you have an explanation for this discrepancy?

DR. VOLPÉ: Technical problems with the assays are probably responsible. I am sure that the IgG has to bind in order to stimulate generation of cyclic AMP, and I think it binds to the TSH receptor. Until technical problems with the assays are resolved, it will be difficult to answer that question.

DR. JEFFREY FLIER: I would like to respond to Dr. Amir's question about antibodies to the TSH receptor that stimulate TSH-like action but do not inhibit TSH binding. There are precedents for antireceptor antibodies that are clearly directed against the receptor (as shown by the fact that the antibodies interact with purified solubilized receptors) but do not inhibit binding of the ligand — for example, antibodies to the acetylcholine receptors in myasthenia gravis. If the receptor molecule were sufficiently large and asymmetrical, the ligand binding site would be a relatively small portion of the receptor, and certain inhibitory or stimulatory antireceptor antibodies might not interfere with the binding site.

DR. MARGOT SEGALL-BLANK: Have techniques that employ fluorescent monoclonal antibodies been used to study the association between Graves' or Hashimoto's disease and particular T-cell populations?

DR. VOLPÉ: Simple enumeration by means of monoclonal antibodies has been used, but the results have varied. Studies have shown a small but significant reduction in the number of OKT8-positive cells ($P<0.01$, by the Mann–Whitney U test) — that is, cells that are believed to be suppressor cells.[51] These results are more applicable to patients with active, untreated Graves' disease than to patients who have been treated for some time or who have Hashimoto's disease. Although it is unclear how to interpret these findings, they may represent the effects of the hyperthyroidism itself on suppressor T cells. Other studies do not corroborate these findings.[52] It seems to me that the responsible cell is a single, isolated clone of suppressor T cells that is defective in quality if not in number.

DR. DANIEL EINHORN: As one test of your hypothesis, have you been able to demonstrate any changes in the activity or number of suppressor T cells in patients during remission, as compared with the active disease state?

DR. VOLPÉ: We have found a change in function. Of 19 patients who had stopped taking propylthiouracil two years before, almost half were still sensitized to thyroid antigen and still had a suppressor-cell abnormality.[80] The only clinical difference was that patients who were still sensitized had larger and firmer goiters and higher titers of conventional thyroid antibodies than did patients who were normal. The sensitized patients probably had ongoing thyroiditis. Wood and Ingbar[81] showed that several years after patients had stopped taking propylthiouracil, a substantial proportion still had evidence of autoimmune thyroid disease, even though they were not hyperthyroid.

REFERENCES

1. Ehrlich P. On autoimmunity with special references to cell life. Proc R Soc Lond [Biol]. 1900; 66B:424-48.
2. Solomon DH, Kleeman KE. Concepts of pathogenesis of Graves' disease. Adv Intern Med. 1977; 22:273-99.
3. Roitt IM, Doniach D, Campbell PN, Hudson RV. Autoantibodies in Hashimoto's disease (lymphadenoid goitre). Lancet. 1956; 2:820-1.
4. Rose NR, Witebsky E. Studies on organ specificity. V. Changes in the thyroid glands of rabbits following active immunization with rabbit thyroid extracts. J Immunol. 1956; 76:417-27.
5. Adams DD, Purves HD. Abnormal responses in the assay of thyrotrophin. Univ Otago Med School Proc. 1956; 36:11-2.
6. McKenzie JM. The bioassay of thyrotropin in serum. Endocrinology. 1958; 63:372-82.
7. Kriss JP, Pleshakov V, Chien JR. Isolation and identification of the long-acting thyroid stimulator and its relation to hyperthyroidism and circumscribed pre-tibial myxedema. J Clin Endocrinol Metab. 1964; 24:1005-28.
8. Maisey MN. The Ig class and light chain type of the long acting thyroid stimulator. Clin Endocrinol (Oxf). 1972; 1:189-98.
9. Zakarija M, McKenzie JM. Effect of thyrotropin and of LATS on mouse thyroid cyclic AMP. Metabolism. 1973; 22:1185-91.
10. McKenzie JM. Further evidence for a thyroid activator in hyperthyroidism. J Clin Endocrinol Metab. 1960; 20:380-8.
11. Onaya T, Kotani M, Yamada T, Ochi Y. New *in vitro* tests to detect the thyroid stimulator in sera from hyperthyroid patients by measuring colloid droplet formation and cyclic AMP in human thyroid slices. J Clin Endocrinol Metab. 1973; 36:859-66.
12. Burke G. Thyroid stimulators and thyroid stimulation. Acta Endocrinol (Copenh). 1971; 66:558-76.
13. Fenzi GF, Pinchera A, Bartalena L, et al. Thyroid plasma membrane antigens and TSH receptor. In: Stockigt JR, Nagataki S, eds. Thyroid research VIII: proceedings of the eighth International Thyroid Congress, Sydney, Australia, 3-8 February, 1980. Oxford: Pergamon Press, 1980:703-6.
14. Solomon DH, Chopra IJ. Is TSH a LATS-protector?: evidence suggesting different sites of binding of TSH and thyroid-stimulating immunoglobulins (TSI's) in thyroid tissue. In: Stockigt JR, Nagataki S, eds. Thyroid research VIII: proceedings of the eighth International Thyroid Congress, Sydney, Australia, 3-8 February, 1980. Oxford: Pergamon Press, 1980:717-20.
15. Manley SW, Bourke JR, Hawker RW. The thyrotrophin receptor in guinea-pig thyroid homogenate: interaction with the long-acting thyroid stimulator. J Endocrinol. 1974; 61:437-45.
16. Smith BR, Hall R. The interaction of Graves' immunoglobulins with the TSH receptor. In: Stockigt JR, Nagataki S, eds. Thyroid research VIII: proceedings of the eighth International Thyroid Congress, Sydney, Australia, 3-8 February, 1980. Oxford: Pergamon Press, 1980:715-6.
17. Endo K, Amir SM, Ingbar SH. Development and evaluation of a method for the partial purification of immunoglobulins specific for Graves' disease. J Clin Endocrinol Metab. 1981; 52:1113-23.
18. Wenzel B, Wenzel KW, Kotulla P, Schleusener H. Binding of solubilized human TSH-receptor protein by peripheral blood lymphocytes of patients with Graves' disease. J Endocrinol Invest. 1981; 4:161-6.

19. Smith BR, Hall R. Binding of thyroid stimulators to thyroid membranes. FEBS Lett. 1974; 42:301-4.
20. Hinds WE, Takai N, Rapoport B, Filetti S, Clark OH. Thyroid-stimulating immunoglobulin bioassay using cultured human thyroid cells. J Clin Endocrinol Metab. 1981; 52:1204-10.
21. Atkinson S, Kendall-Taylor P. The stimulation of thyroid hormone secretion *in vitro* by thyroid-stimulating antibodies. J Clin Endocrinol Metab. 1981; 53:1263-6.
22. Strakosch CR, Joyner D, Wall JR. Thyroid-stimulating antibodies in patients with autoimmune disorders. J Clin Endocrinol Metab. 1978; 47:361-5.
23. Sugenoya A, Kidd A, Row VV, Volpé R. Correlation between thyrotropin-displacing activity and human thyroid-stimulating activity by immunoglobulins from patients with Graves' disease and other thyroid disorders. J Clin Endocrinol Metab. 1979; 48:398-402.
24. Endo K, Kasagi K, Konishi J, et al. Detection and properties of TSH-binding inhibitor immunoglobulins in patients with Graves' disease and Hashimoto's thyroiditis. J Clin Endocrinol Metab. 1978; 46:734-9.
25. Studer H, Hunziker HR, Ruchti C. Morphologic and functional substrate of thyrotoxicosis caused by nodular goiters. Am J Med. 1978; 65:227-34.
26. Schleusener H, Joseph K, Mahlstedt J, et al. Differences between immunogenic toxic diffuse goiter (Graves' disease) and goiter with disseminated autonomy: preliminary results. J Mol Med. 1980; 4:129-34.
27. Smyth PPA, Neylan D, O'Donovan DK. The prevalence of thyroid-stimulating antibodies in goitrous disease assessed by cytochemical section bioassay. J Clin Endocrinol Metab. 1982; 54:357-61.
28. Davies TF, Yeo PPB, Evered DC, Clark F, Smith BR, Hall R. Value of thyroid-stimulating-antibody determinations in predicting short-term thyrotoxic relapse in Graves' disease. Lancet. 1977; 1:1181-2.
29. O'Donnell J, Trokoudes K, Silverberg J, Row V, Volpé R. Thyrotropin displacement activity of serum immunoglobulins from patients with Graves' disease. J Clin Endocrinol Metab. 1978; 46:770-7.
30. Teng CS, Yeung RTT. Changes in thyroid-stimulating antibody activity in Graves' disease treated with antithyroid drugs and its relationship to relapse: a prospective study. J Clin Endocrinol Metab. 1980; 50:144-7.
31. Finke R, Schleusener H, Kotulla P, Sörje H, Kim C-H, Wenzel KW. The radioligand receptor assay for Graves' disease: immunoglobulins — a prognostic test? Acta Endocrinol [Suppl] (Copenh). 1977; 208:7-8. abstract.
32. Docter R, Bos G, Visser TJ, Hennemann G. Thyrotrophin binding inhibiting immunoglobulins in Graves' disease before, during and after antithyroid therapy, and its relation to long-acting thyroid stimulator. Clin Endocrinol (Oxf). 1980; 12:143-53.
33. Drexhage HA, Bottazzo GF, Doniach D, Bitensky L, Chayen J. Evidence for thyroid-growth-stimulating immunoglobulins in some goitrous thyroid diseases. Lancet. 1980; 2:287-92.
34. Volpé R. Auto-immunity in the endocrine system. Monogr Endocrinol. 1981; 20:19-111.
35. Venter JC, Fraser CM, Harrison LC. Autoantibodies to β_2-adrenergic receptors: a possible cause of adrenergic hyporesponsiveness in allergic rhinitis and asthma. Science. 1980; 207:1361-3.
36. Pinchera A, Fenzi GF, Bartalena L, Chiovato L, Marcocci C, Pacini F. Thyroid antigens involved in autoimmune thyroid disorders. In: Klein E, Horster FA, eds. Autoimmunity in thyroid diseases. Stuttgart: Schattauer, 1979:49-67.
37. Lamki L, Row VV, Volpé R. Cell-mediated immunity in Graves' disease and in Hashimoto's thyroiditis as shown by the demonstration of migration inhibition factor (MIF). J Clin Endocrinol Metab. 1973; 36:358-64.
38. Kowalczyk D, Zembala M. Migration inhibition of T lymphocytes from human peripheral blood by specific antigen and lymphokines. Clin Exp Immunol. 1978; 32:333-8.
39. Okita N, Kidd A, Row VV, Volpé R. Sensitization of T-lymphocytes in Graves' and Hashimoto's diseases. J Clin Endocrinol Metab. 1980; 51:316-20.
40. Okita N, Topliss D, Lewis M, Row VV, Volpé R. T-lymphocyte sensitization in Graves' and Hashimoto's diseases confirmed by an indirect migration inhibition factor test. J Clin Endocrinol Metab. 1981; 52:523-7.
41. Mäkinen T, Wägar G, Apter L, Von Willebrand E, Pekonen F. Evidence that the TSH receptor acts as a mitogenic antigen in Graves' disease. Nature. 1978; 275:314-5.
42. Wall JR, Trewin A, Joyner DM. Peripheral blood lymphocyte transformation in response to human thyroid fractions in patients with Graves' hyperthyroidism and ophthalmopathy. Acta Endocrinol (Copenh). 1980; 93:419-23.
43. Wenzel B, Kotulla P, Wenzel KW, Finke R, Schleusener H. Mitogenic response of peripheral blood lymphocytes from patients with Graves' disease incubated with solubilized thyroid cell membranes containing TSH receptor and with thyroglobulin. Immunobiology. 1981; 160:302-10.
44. Rose NR, Kong YM, Okayasu I, Giraldo AA, Beisel K, Sundick RS. T-cell regulation in autoimmune thyroiditis. Immunol Rev. 1981; 55:299-314.
45. Burnet FM. The clonal selection theory of acquired immunity. Cambridge: Cambridge University Press, 1959.
46. Wenzel BE, Strakosch CR, Row VV, Volpé R. In vitro induction of antithyroglobulin antibody secretion by peripheral blood lymphocytes. Ann Endocrinol (Paris). 1982; T43:64a.
47. Okita N, Row VV, Volpé R. Suppressor T-lymphocyte deficiency in Graves' disease and Hashimoto's thyroiditis. J Clin Endocrinol Metab. 1981; 52:528-33.
48. Topliss DJ, Okita N, Lewis M, Row VV, Volpé R. Allosuppressor T lymphocytes abolish migration inhibition factor production in autoimmune thyroid disease: evidence from radiosensitivity experiments. Clin Endocrinol (Oxf). 1981; 15:335-41.
49. Topliss DJ, How J, Strakosch CR, Lewis M, Row VV, Volpé R. Graves' disease (GD) and insulin dependent diabetes mellitus (IDDM) are each associated with separate specific defects in suppressor T lymphocyte function. In: Proceedings of the 64th meeting of the Endocrine Society, San Francisco, California, 1982:132. abstract 209.
50. Thielemans C, Vanhaelst L, de Waele M, Jonckheer M, Van Camp B. Autoimmune thyroiditis: a condition related to a decrease in T-suppressor cells. Clin Endocrinol (Oxf). 1981; 15:259-63.
51. Sridama V, Pacini F, DeGroot LJ. Decreased suppressor T-lymphocytes in autoimmune thyroid diseases detected by monoclonal antibodies. J Clin Endocrinol Metab. 1982; 54:316-9.
52. Canonica GW, Bagnasco M, Moretta L, Cocco R, Ferrini O, Giordano G. Human T-lymphocyte subpopulations in Hashimoto's disease. J Clin Endocrinol Metab. 1981; 52:553-6.
53. MacLean DB, Miller KB, Brown R, Reichlin S. Normal immunoregulation of *in vitro* antibody secretion in autoimmune thyroid disease. J Clin Endocrinol Metab. 1981; 53:801-5.
54. Aoki N, Pinnamaneni KM, DeGroot L. Studies of suppressor-cell function in thyroid diseases. J Clin Endocrinol Metab. 1979; 48:803-18.
55. Balázs C, Leövey A, Bordan L. Decrease of concanavalin-A activated and short lived suppressor T cell function in thyrotoxicosis. Biomedicine. 1979; 30:143-7.
56. Beall GN. Production of human antithyroglobulin *in vitro*. IV. Specific stimulation by antigen. J Clin Endocrinol Metab. 1982; 54:1-5.
57. McLachlan SM, Wee SL, McGregor AM, Smith BR, Hall R. *In vitro* studies on the control of thyroid autoantibody synthesis. J Clin Lab Immunol. 1980; 3:15-21.
58. Robinson RG, Guttler RB, Rhea TH, Nicoloff JT. Delayed hypersensitivity in Graves' disease. J Clin Endocrinol Metab. 1974; 38:322-4.
59. Cahill GF Jr, McDevitt HO. Insulin-dependent diabetes mellitus: the initial lesion. N Engl J Med. 1981; 304:1454-65.
60. Volpé R, Row VV, Ezrin C. Circulating viral and thyroid antibodies in subacute thyroiditis. J Clin Endocrinol Metab. 1967; 27:1275-84.
61. Wall JR, Fang S-L, Ingbar SH, Braverman LE. Lymphocyte transformation in response to human thyroid extract in patients with subacute thyroiditis. J Clin Endocrinol Metab. 1976; 43:587-90.
62. Strakosch CR, Joyner D, Wall JR. Thyroid stimulating antibodies in patients with subacute thyroiditis. J Clin Endocrinol Metab. 1978; 46:345-8.
63. Volpé R. Acute and subacute thyroiditis. Pharmacol Ther. 1976; 1C:171-81.
64. McDevitt HO. Regulation of immune response by the major histocompatibility system. N Engl J Med. 1980; 303:1514-7.
65. Farid NR, Bear JC. The human major histocompatibility complex and endocrine disease. Endocr Rev. 1981; 2:50-86.
66. Volpé R, Edmonds M, Lamki L, Clarke PV, Row VV. The pathogenesis of Graves' disease: a disorder of delayed hypersensitivity? Mayo Clin Proc. 1972; 47:824-34.
67. Bartrop RW, Luckhurst E, Lazarus L, Kiloh LG, Penny R. Depressed lymphocyte function after bereavement. Lancet. 1977; 1:834-6.
68. Monjan AA, Collector MI. Stress-induced modulation of the immune response. Science. 1977; 196:307-8.
69. Claman HN. Corticosteroids and lymphoid cells. N Engl J Med. 1972; 287:388-97.
70. Balázs C, Leövey A, Szabó M, Bakó G. Stimulating effect of triiodothyronine on cell-mediated immunity. Eur J Clin Pharmacol. 1980; 17:19-23.
71. Aoki N, Pinnamaneni KM, DeGroot LJ. Studies on suppressor cell function in thyroid diseases. J Clin Endocrinol Metab. 1979; 48:803-10.
72. Wall JR, Manwar GL, Greenwood DM, Walters BA. The in vitro suppression of lectin induced ^{3}H-thymidine incorporation into DNA of peripheral blood lymphocytes after the addition of propylthiouracil. J Clin Endocrinol Metab. 1976; 43:1406-9.
73. Weiss I, Davies TF. Inhibition of immunoglobulin-secreting cells by antithyroid drugs. J Clin Endocrinol Metab. 1981; 53:1223-8.
74. McGregor AM, McLachlan SM, Rooke P, Smith BR, Hall R. The influence of methimazole on the thyroidal autoimmune response in vitro. In: Stockigt JR, Nagataki S, eds. Thyroid research VIII: proceedings of the eighth International Thyroid Congress, Sydney, Australia, 3-8 February, 1980. Oxford: Pergamon Press, 1980:629-32.
75. Wenzel KW, Wunderlich H, Wenzel BE. Thyroid-stimulating immunoglobulins (TSI) in Graves' disease during treatment with thionamide drugs or perchlorate. Acta Endocrinol [Suppl] (Copenh). 1982; 246:64-5.

76. McGregor AM, Smith BR, Hall R, Petersen MM, Miller M, Dewar PJ. Prediction of relapse in hyperthyroid Graves' disease. Lancet. 1980; 1:1101-3.
77. Inada M, Nishikawa M, Naito K, Ishii H, Tanaka K, Imura H. Correlation of the histological abnormalities of the thyroid with the stage of transient thyrotoxicosis associated with painless thyroiditis. In: Stockigt JR, Nagataki S, eds. Thyroid research VIII: proceedings of the eighth International Thyroid Congress, Sydney, Australia, 3-8 February, 1980. Oxford: Pergamon Press, 1980:563-6.
78. Amino N, Mori H, Iwatani Y, et al. High prevalence of transient post-partum thyrotoxicosis and hypothyroidism. N Engl J Med. 1982; 306:849-52.
79. Froelich CJ, Goodwin JS, Bankhurst AD, Williams RC Jr. Pregnancy, a temporary fetal graft of suppressor cells in autoimmune disease? Am J Med. 1980; 69:329-31.
80. How J, Topliss DJ, Lewis M, Row VV, Volpé R. Persistence of T lymphocyte sensitization and suppressor T lymphocyte defect long after treatment for Graves' disease. Clin Endocrinol. (in press).
81. Wood LC, Ingbar SH. Hypothyroidism as a late sequela in patients with Graves' disease treated with antithyroid agents. J Clin Invest. 1979; 64:1429-36.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

ROBERT E. SCULLY, M.D., *Editor*
EUGENE J. MARK, M.D., *Associate Editor*
BETTY U. MCNEELY, *Assistant Editor*

CASE 49-1982

PRESENTATION OF CASE

First admission. A 62-year-old man was admitted to the hospital because of a question of subarachnoid hemorrhage.

He was in excellent health until the evening of admission, when he experienced the sudden onset of a frontal headache that radiated to the nuchal area and was accompanied by vomiting. He was taken to another hospital, where he was observed to be somnolent but periodically agitated. The blood pressure was 170/100 mm Hg. The neck was supple. The optic fundi appeared normal. He moved the left extremities less well than the right, and there was a questionable right Babinski sign. The urine was normal. The hematocrit was 38 per cent, and the white-cell count 13,700. The urea nitrogen was 15 mg per 100 ml (5.4 mmol per liter), the glucose 173 mg per 100 ml (9.60 mmol per liter), the cholesterol 203 mg per 100 ml (5.25 mmol per liter), and the protein 7.2 g (the albumin 4.4 g and the globulin 2.8 g) per 100 ml. Mannitol, furosemide, trimethobenzamide hydrochloride, and hydroxyzine pamoate were given, and reserpine was administered intramuscularly. The blood pressure fell to 130/90 mm Hg. Nuchal rigidity developed, and the patient was transferred to this hospital.

The patient was known to have kidney stones. He smoked one package of cigarettes daily and drank alcohol occasionally. There was no history of hypertension, diabetes mellitus, hemorrhagic diathesis, or stroke.

The temperature was 37.2°C, the pulse 50, and the respirations 16. The blood pressure was 160/60 mm Hg.

On examination the patient was somnolent but arousable. The neck was stiff. The carotid pulses were normal, and no bruit was heard. The lungs were clear, and the heart, abdomen, and extremities were normal. Neurologic examination disclosed that the patient knew his name but was 32 months in error on the date. He counted forward to 10 and backward only from 20 to 10. Coordination and gait were not tested. The pupils were 4 mm, equal, and reactive, and no gaze preference was noted. Simultaneous visual stimulation was ignored on the left side. The optic fundi were poorly seen; the disks appeared flat, and no subhyaloid hemorrhages were observed; extraocular movements were full, and corneal reflexes were intact. There was a mild left central facial weakness. Pinprick sensation was intact on the right side but not clearly so on the left. He moved all the extremities; there was drift of the extended left arm. The deep tendon reflexes were ++ and equal, and bilateral Babinski signs were present.

The urine was normal. The hematocrit was 36 per cent; the white-cell count was 16,800, with 94 per cent neutrophils. The platelet count was 300,000. The prothrombin time and the partial thromboplastin time were normal. An electrocardiogram demonstrated sinus bradycardia at a rate of 57, with normal intervals; there was evidence of probable old myocardial infarction. X-ray films of the chest revealed a normal appearance of the heart and lungs. A computed tomographic (CT) scan of the brain (Fig. 1), performed without injection of contrast material, showed a large mass with elevated absorptive values in the right temporal lobe and a midline shift to the left; no evidence of subarachnoid hemorrhage was observed. A bilateral internal carotid angiographic examination (Fig. 2) disclosed a large, avascular right-temporal-lobe mass and was otherwise negative.

Mannitol, phenytoin sodium, and methylprednisolone sodium succinate were administered. On the sec-