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PREDICTION OF RELAPSE FOLLOWING ANTITHYROID DRUG TREATMENT OF GRAVES' DISEASE


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Graves' disease with a prevalence of 30/1,000 population in the northeast of England[1] is the most common cause of hyperthyroidism in areas of normal iodine intake. It is likely that the disease is due to antibodies that bind to the thyroid-stimulating hormone (TSH) receptor site (Figure 1).[2] With the introduction of rational therapeutic regimens for the treatment of hyperthyroidism, determination of the natural history of Graves' disease has become difficult. However, it is clear from earlier work that untreated Graves' disease may remit never to return, remit and relapse repeatedly, or progress unabated.

A number of regimens have emerged for the management of hyperthyroid Graves' disease[3]; in particular, partial thyroidectomy, radioiodine, and the thionamide antithyroid drugs all have contributed to controlling hyperthyroidism, and have significantly altered the subsequent outcome of the disease. In treating patients with thionamide drugs for either six months or 12 months, we could find no difference in the subsequent relapse rates in the two groups and therefore chose the shorter time period of drug administration. Our regimen in nonpregnant adults, without cardiac complications, is based primarily on the patient's age at presentation (Figure 2). To patients over age 45 years, we offer an ablative dose (15 mCi) of radioiodine. For younger adults we recommend a six-month course of carbimazole, 45 mg daily, a thionamide widely used in the United Kingdom. This is supplemented with thyroxine, 0.15 mg daily, after the first six weeks. Patients who relapse after a course of carbimazole then are treated by surgery or radioiodine. What is clear from our own study (Figure 2), and from a large number of earlier studies, is that a significant number of patients relapse after a course of antithyroid drugs and that this occurs irrespective of the particular thionamide drug, the dosage, or

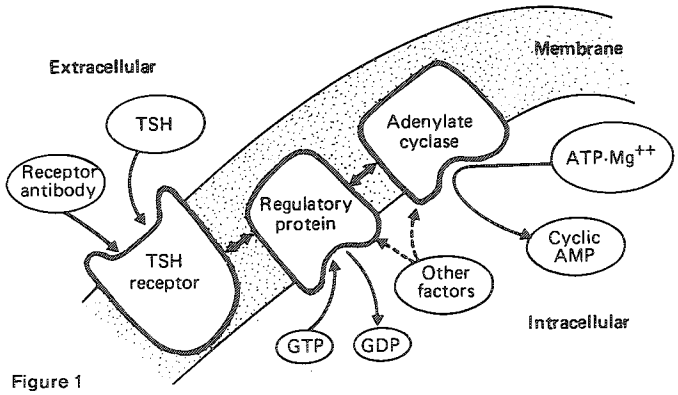

Figure 1
Mechanism of thyroid stimulation by thyrotropin and TSH receptor antibodies. TSH receptor antibodies binding to or in the region of the thyroid follicular cell TSH receptor stimulate thyroid hormone production by acting via the adenylate cyclase—cyclic AMP second messenger system. (Figure modified from Baxter JD, Funder JW: *N Engl J Med* 1980:301:1149, with permission.)

the duration of treatment. Whether early relapse after treatment reflects persistence of unremitting Graves' disease or true recurrence remains uncertain, since no test can distinguish reliably these two situations. It is clear, however, that at least 70% of patients who subsequently relapse do so in the first year after treatment,[4] and that great variations in relapse rates ranging from 30% to 85% have been reported.[5,6,7] The explanation for this variation remains uncertain; however, considerable interest has focused on the effect of dietary iodine on the outcome of the disease,[6,8] particularly since Alexander and colleagues[9] showed that the iodine deficiency induced by long-term treatment with antithyroid drugs protected against early relapse.

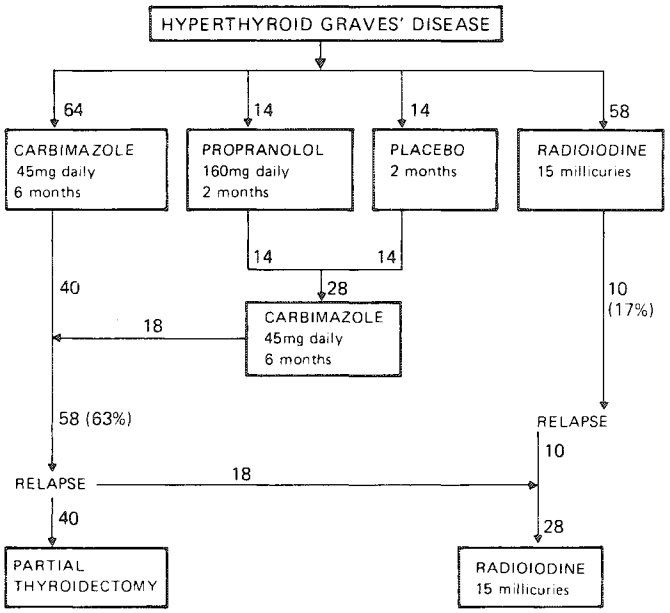

Figure 2
The treatment regimens used in 150 patients with Graves' disease and their responses to therapy during the 12 months after treatment.

Clearly, the uncertainty of trying to predict the subsequent outcome of Graves' disease in response to a course of antithyroid drugs makes management of the disease difficult. If one could predict those patients likely to relapse, there would be little point in treating them with a substantive course of antithyroid drugs; they could be treated primarily by surgery or radioiodine. A number of parameters of Graves' disease have been investigated as predictors of disease outcome, including the immune system and the role that a variety of immunogenetic parameters may have in influencing disease course. This is hardly surprising since the hyperthyroidism of Graves' disease is an organ-specific autoimmune disease linked to the antigens of the major histocompatibility system (HLA) of man[10] that is almost certainly due to thyroid stimulation by TSH receptor antibodies.[2] A further impetus to the investigation of the influence of the immune system on the outcome of the disease has emerged from the recognition that antithyroid drugs not only lower thyroid autoantibody levels, independent of their influence on thyroid hormone metabolism,[11] but, in fact, are capable of inhibiting autoantibody production *in vitro* (Figure 3) and *in vivo*. Astwood's comments of 1967 have become even more pertinent: "Why does any patient remain well indefinitely after treatment? If the long-acting thyroid stimulator is etiologically related to Graves' disease, why should it diminish during therapy, must it do so for a remission to ensue, and by what possible means could the drug interfere with the formation of what is said to be an antibody?"[12]

Predictors of Relapse

Clinical. A number of studies, reviewed by Solomon and associates,[5] have investigated the prognostic value of clinical parameters as predictors of relapse. None of these, including the patient's age and sex, the nature and size of the goiter, or the duration and severity of the disease proved sufficiently reliable. In Solomon's own study of 101 hyperthyroid patients, while patients treated previously were more likely to relapse when re-treated, the only clinical feature

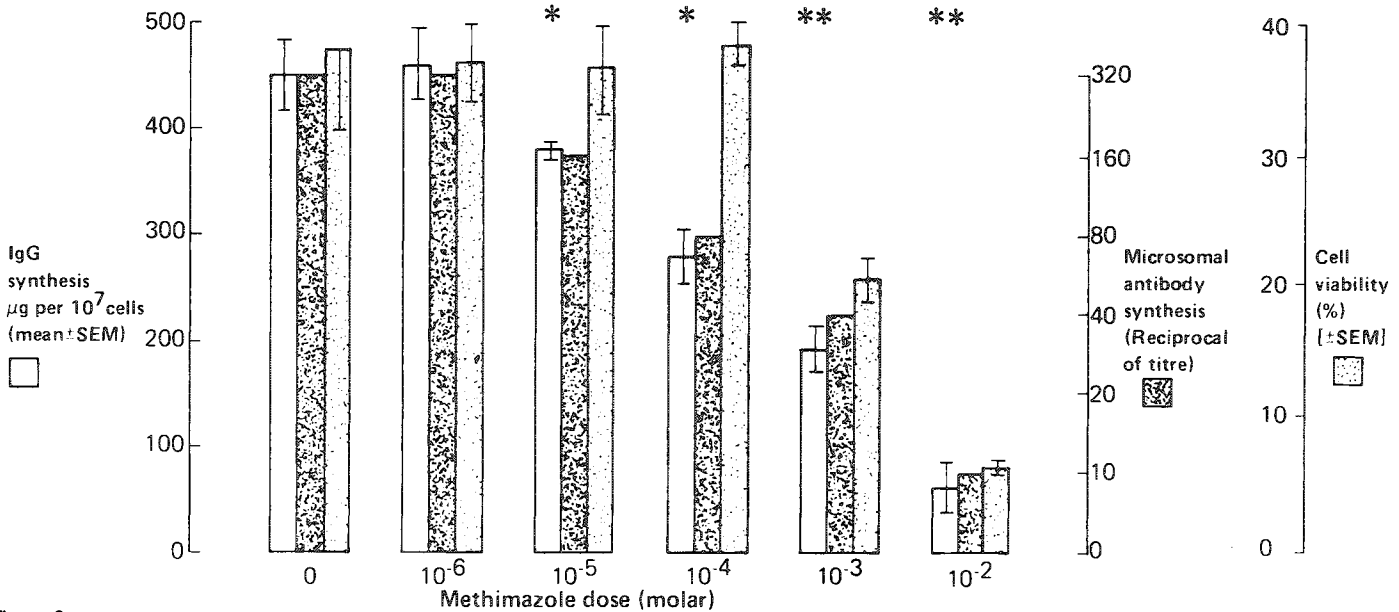

Figure 3
Influence of methimazole on immunoglobulin and autoantibody synthesis *in vitro* by lymphocytes from a patient with Hashimoto's thyroiditis. The thyroid, by selectively concentrating methimazole, achieves intrathyroidal levels of the drug in the range 10^{-4} to 10^{-5} molar; at these levels the drug suppresses autoantibody production. *p<.01 **p<.001

of significant predictive value was a decrease in goiter size among those patients whose disease was controlled.

Thyroid Function. Whereas in earlier studies[5] the severity of the hyperthyroidism did not seem to influence the outcome of the disease, Uller and van Herle, in a small series of 19 patients, showed significantly higher pretreatment serum triiodothyronine (T3) levels in those patients who subsequently relapsed.[13] More importantly, using a specific radioimmunoassay for human thyroglobulin (HTg), they were able to show that patients who subsequently relapsed had a higher mean pretreatment HTg level that failed to fall to lower levels during the course of treatment. While these observations on the value of HTg estimations subsequently have been confirmed in a number of centers, the predictive value of HTg is by no means absolute and a prospective study is needed to define the true value of either the initial HTg value, or the pattern of HTg in response to antithyroid drugs, or both. In addition, interference by anti-HTg antibody in the assay system makes the assay of less value in those patients in whom such antibodies are present, although methods are now available for measuring HTg levels in the presence of HTg antibodies.

Hypothalamus-Pituitary-Thyroid Axis. Since the initial observation by Werner and associates[14] that administration of thyroid hormone does not suppress thyroidal radioisotope uptake in patients with hyperthyroidism, and the recognition that patients rendered euthyroid have return of thyroid function suppression when exogenously administered thyroid hormone, a number of studies, in confirming these observations, have sought to use thyroid function suppression (or the lack of it) as a means of predicting disease outcome.[15] The initial hopes that serial studies of thyroid function suppression by T3 would lead to a clear division of suppressed and nonsuppressed individuals, with the latter relapsing and the former remitting, has not been borne out.[16]

Similarly, since the serum TSH response to thyrotropin-releasing hormone (TRH) is so sensitive to minor changes in circulating thyroid hormone levels, it was hoped that a subnormal or absent TSH response to TRH, indicating that thyroid function was not under TSH control, might help to predict those patients who were likely to relapse. No such relationship was demonstrated.[17] Gardner and Utiger, in assessing multiple predictors of disease course in 20 patients studied over several years, found that whereas serum HTg levels and a measure of TSH receptor antibody activity were of no value, a combination of abnormal thyroid hormone suppression and a subnormal TSH response to TRH made recurrence of hyperthyroidism more likely.[18]

Immunological and Genetic Markers. (1) *Antibody Activity.* In our patients with Graves' disease, approximately 20% have antithyroglobulin antibodies and 70% have antimicrosomal antibodies as assessed by tanned red cell hemagglutination. The relevance of these antibodies to the pathogenesis of Graves' disease remains uncertain, although a link has been noted between the persistence of antimicrosomal antibodies in HLA-B8 positive patients treated with antithyroid drugs and their likelihood of remaining in remission.[19]

A variety of assay systems have been used to detect TSH receptor antibody activity.[2] Of these systems, the most readily applicable to large scale analysis of antibody activity is the radioreceptor assay of Rees Smith and associates,[2] which measures the ability of these antibodies to inhibit the binding of radiolabelled TSH to human membranes. In our laboratory, detectable activity, expressed as significant inhibition of TSH binding, is present prior to treatment in about 75% of patients with hyperthyroid Graves' disease. As originally described by Davies et al,[20] the persistence of this activity at cessation of antithyroid drug treatment (Figure 4) increases the likelihood of subsequent relapse; although, since 25% of patients have no detectable receptor antibody activity prior to treatment and so much overlap exists between relapsing and remitting groups, an isolated receptor antibody value at the end of treatment is of limited value.

(2) *HLA Status.* While it has long been recognized that genetic factors are involved in the development of Graves' disease[21] it is only recently that methods for the analysis of markers (HLA) of the genetic susceptibility of disease have become available. On the basis of HLA typing in white patients it is clear that an increased frequency of HLA-B8 and HLA-DR3 exists in patients with Graves' disease as compared with controls.[10] The association between B8, DR3, and Graves' disease is by no means absolute, with the frequency of both being around 50% in patients with the disease compared with 25% in controls. Using either B8[19] or B8 and Dw3,[22] it was possible to show that patients who relapsed were more likely to be B8 or Dw3 positive as compared with those who remained in remission; again, the association was not absolute.

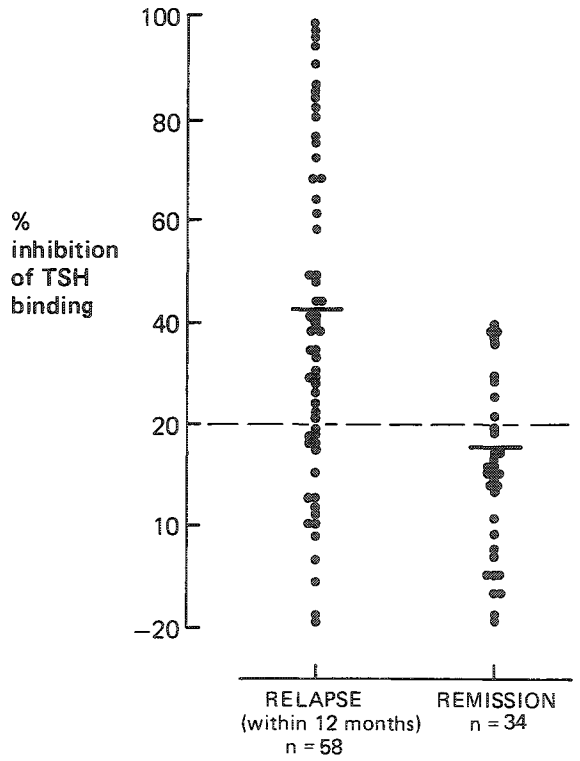

Figure 4
TSH receptor antibody levels on completion of a six-month course of carbimazole as a predictor of the subsequent outcome of the disease in 92 patients with Graves' disease.

(3) *Combined Receptor Antibody and HLA Status.* In trying to improve the ability to predict the subsequent outcome of treated Graves' disease we combined the two parameters: HLA status and TSH receptor antibody activity.[23] Each parameter considered in isolation confirmed the previous predictive value reported by others.[19,20,22] When the data from a study of 65 patients were combined, prediction of the subsequent outcome of the disease (at least over the first 12 months after therapy) was possible in 62 of the patients (Figure 5). Patients who were DRw3 positive relapsed, almost without exception, irrespective of their immediate posttreatment receptor antibody level. In contrast, patients who were DRw3 negative were more likely to relapse if antibody activity was still detectable at the time of cessation of therapy.

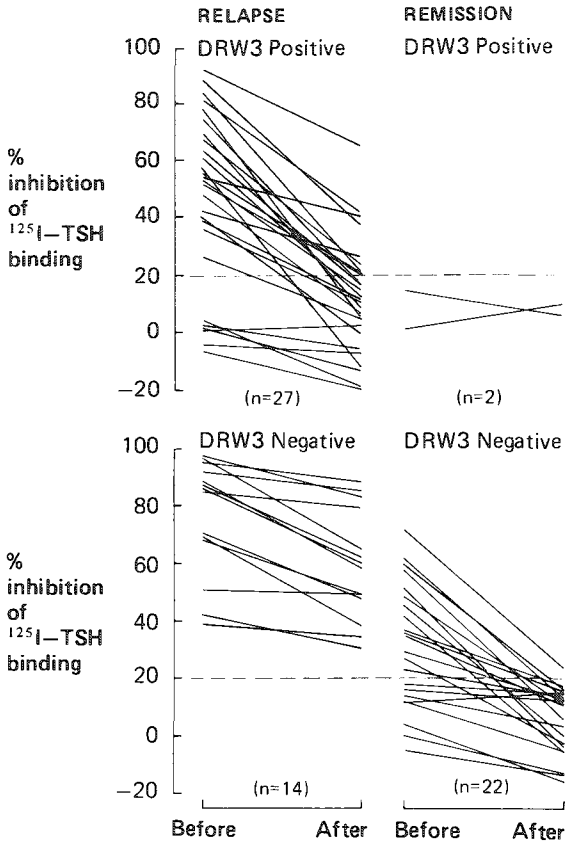

Figure 5
Prediction of relapse in 65 patients with Graves' disease on the basis of their TSH receptor antibody levels and HLA-DRw3 status. Within 12 months of finishing their course of antithyroid drugs, 41 (63%) of the patients relapsed. Of the 29 patients with HLA-DRw3, all but two relapsed. Of the 36 patients without HLA-DRw3, 14 relapsed and all had readily detectable TSH receptor antibody levels immediately after drug withdrawal. (McGregor AM, et al: *Lancet* 1980;1:1101, with permission.)

Conclusions

Graves' disease, an organ-specific autoimmune disease almost certainly due to TSH receptor antibodies that stimulate thyroid function, is surprisingly common. Therapeutic regimens for its treatment primarily focus on inhibiting or irreversibly destroying thyroid function. To date, little attention has focused on trying to treat the disease by manipulation of the aberrant autoimmune response, even though such selective therapy is of potentially considerable value. Until such time as one can influence the immune response directly it is helpful to predict the likely outcome of the disease following conventional antithyroid drug therapy. The majority of patients with Graves' disease in the United Kingdom are treated initially with one of the thionamide agents. The wide variety of dosage and duration regimens, and, the population differences (not only genetically, but also in terms of environmental influences such as iodine intake), make prediction of response to treatment by any single marker of disease unlikely.

A large number of markers have been investigated as possible indicators of outcome. While all have some predictive value, initial enthusiasm for their use has not been borne out by subsequent studies. In trying to improve prediction of the outcome of treatment for Graves' disease, we have used a combination of HLA status and TSH receptor antibody activity as markers.[23] Since immunogenetic abnormalities are likely to play a fundamental role in the pathogenesis of the disease, it seemed appropriate to investigate such markers as predictors. Preliminary studies from other groups have now confirmed this observation.[24] It is too early to suggest the association between these markers and disease outcome is absolute; however, it is clear that once a means is possible for reliably predicting relapse, a more rational approach to therapy will be possible. On the basis of our own observations we feel it is justified at present to offer destructive therapy to any patient who is DR3 positive, and to those patients who are DR3 negative with persisting detectable receptor antibody after a six-month course of antithyroid drugs.

Clearly, in trying to predict subsequent disease relapse after antithyroid drug treatment, a major limitation for most practicing physicians will be in their access to the laboratory investigations suggested, particularly the analysis of HLA and TSH receptor antibody status. Improved methodology and the development of commercial kits for such techniques will undoubtedly improve their accessibility in the next few years. In the meantime, we see little benefit in treating patients for any longer than six months with antithyroid drugs. Our blocking and replacement regimen with carbimazole and thyroxine is simpler to manage and requires fewer hospital visits for the patient than trying to titrate the dose of antithyroid drug against the patient's clinical and biochemical response; and we would not advocate re-treatment with such a regimen in patients who, while previously controlled on this regimen, subsequently relapse.

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