

Observations on the Use of Antithyroid Drugs

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IN THIS REPORT we have summarized twenty years' experience in the treatment of hyperthyroidism with antithyroid drugs. While the primary aim was to determine the long-term effectiveness of this form of therapy, the study provided the opportunity to observe the response in postoperative or recurrent hyperthyroidism, when pregnancy or diabetes complicated the thyrotoxicosis, and in iatrogenic disease. Also described are the unfavorable reactions to the drugs and several instances of unresponsiveness to treatment because of false hyperthyroidism.

Thiouracil, the first drug used, has been replaced by propylthiouracil and methimazole, both drugs of high efficacy and low toxicity. Potassium perchlorate, the most recent addition, while effective, is rendered inactive by iodides, and its safety has not yet been fully established. The initial starting dose of propylthiouracil was 100 to 200 mg every 8 hours; methimazole 10 to 20 mg every 8 hours; and potassium perchlorate 200 mg every 8 hours. While subjective improvement might often be noted in 1 to 3 weeks recognizable remission would generally become evident in 6 to 8 weeks. At this point gradual reduction to a maintenance dose approximately one third the initial amount was instituted and continued for approximately 6 months. Iodine or its compounds were avoided but with euthyroidism established small doses of

desiccated thyroid were started and increased as tolerated. The purpose here was both to meet the peripheral need for thyroxin and to act as a feed-back suppressing the pituitary stimulating action on the thyroid. At the same time the antithyroid dosage was gradually reduced, the ultimate aim being its complete replacement by desiccated thyroid.

Out of 305 ambulatory patients we were able to follow a total of 167 for a time sufficient to draw significant conclusions. Seventy-one of these must be classed as treatment failures who for various reasons were not followed for more than 2 years. The remaining 96 patients have been in permanent remission for 4 years or more and can be classed as having been successfully treated.

TREATMENT FAILURES

This group was made up of 28 patients (10 males and 18 females) with toxic nodular and 43 (14 males and 29 females) with toxic diffuse goiter. In the former, two did not respond to treatment; six elected thyroidectomy while in remission; and 20 relapsed within the year when treatment was stopped after initial remission and were unavailable for further treatment. Most of these patients had large nodular goiters with symptoms prior to treatment lasting an average of 23 months.

Of the 43 with toxic diffuse goiter, 8 failed to respond to treatment; 14 had not achieved euthyroidism when they discontinued treatment; and 21 relapsed after initial treatment. Of the latter, 14 elected thyroidectomy; 4 chose radioactive iodine therapy; and 3 failed to report while on

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TABLE 1. Treatment Failures

Type of Goiter	Number of Patients	No Response	Time Required for Remission	Number Relapsed	Size of Goiter	Duration of Pre-treatment Symptoms
			<i>months</i>			<i>months</i>
Toxic nodular	28	2	4	20	Large	23
Toxic diffuse	43	8	5	21	Not marked	50

combined antithyroid and desiccated thyroid treatment. Symptoms had preceded treatment for 2 or more years.

It is of interest to note that in a number of those who suffered relapse and those who discontinued treatment the psychogenic component was large. In the eight unresponsive patients this factor was especially prominent; the exophthalmos when present appeared more pronounced, the goiters were larger (except in those with postoperative recurrence), the basal metabolic rates were higher, and the toxic symptoms had been in existence for a longer period. Six were females aged 16 to 38; and 2 males, 27 and 30. Two of the females and one of the males had had previous thyroidectomy. These unresponsive patients apparently adapt poorly to any long-range treatment program. Since they generally are poor surgical risks radioactive iodine should be the treatment of choice.

SUCCESSFULLY TREATED PATIENTS

This group of 96 patients ranging in age from 14 to 76 years was characterized by a favorable response to treatment with euthyroidism continuing for the entire period of observation. Thirty-four (25 females, 9 males) had toxic nodular, and 62 (55 females, 7 males) had toxic diffuse goiters.

In the toxic nodular group the goiters were not large, the average duration of pretreatment symptoms was 22 months, and the average time required for stable remission to occur was 8 months.

In 44 of the toxic diffuse group the goi-

ters were small; the average duration of the generally mild pretreatment symptoms was 15 months; and the average time elapsed till stable remission was just under 5 months. Here too, the goiters were small and the symptoms relatively mild.

In the 18 patients with recurrent hyperthyroidism the average duration of pretreatment symptoms was 4 months, and the average time required for remission was just under 7 months.

Of the 96 patients 23 have remained in remission 4 years; 4 each, for 5 and 6 years; 6, for 7 years; 4, for 8 years; 5, for 9 years; 4, for 11 years; 5, for 12 years; 3, for 13 years; 4, for 14 years; 4, for 15 years; 10, for 16 years; 13, for 17 years; 6, for 18 years; and 1, for 19 years.

In summary, the patients with toxic nodular goiters who responded favorably to treatment had relatively small goiters, the average duration of pretreatment symptoms was 22 months, and the average time taken to achieve stable remission was 8 months. In those who did not respond favorably the goiters were larger, pretreatment symptoms had existed for 23 months, and the average time required for remission was 4 months. The only significant difference in this group was the size of the goiter.

In the successfully managed patients with toxic diffuse goiter the goiters were not large, symptoms had pre-existed for an average of 15 months, and it took 5 months for remission to occur. In the unsuccessfully treated patients the symptoms had pre-existed for 50 months, while the time required for remission was 5 months. The

TABLE 2. Successfully Treated Patients

Type of Goiter	Number of Patients	Size of Goiter	Time Required for Remission	Duration of Pre-treatment Symptoms
			<i>months</i>	<i>months</i>
Toxic nodular	34	Small	8	22
Toxic diffuse	62*	Small	5	15

* 18 recurrent.

difference in duration of pre-existing symptoms was actually not significant, since the high average of 50 months was due to the inclusion of four patients with symptoms lasting from 16 to 30 years. It is noteworthy that the unresponsive patients with toxic diffuse goiter were hyperkinetic and unstable, their symptoms were more pronounced, goiters larger, exophthalmos more prominent, and basal metabolic rates higher.

Of the total 167 patients treated, 96 or 57 per cent, have remained in remission for more than 4 years.

POSTOPERATIVE HYPERTHYROIDISM

In 1949, one of us (1) described 12 patients with postoperative thyrotoxicosis in remission for 13 months after treatment with antithyroid drugs; 5 others were euthyroid but still under treatment. At this time, 9 of the total are still euthyroid; 2 are of unknown status; 3 died of other diseases within the year after treatment; and 3, dying of myocardial infarction, had remained euthyroid for 12, 14, and 3 years. An additional patient aged 57, with recurrence 3 months after thyroidectomy, has since been treated for 25 months with propylthiouracil and has been euthyroid for the past 9 years.

The duration of treatment in all of these patients averaged 20 months before lasting euthyroidism was achieved. This long ordeal of continuous medication and frequent observation can now be shortened substantially by therapy with radioactive iodine, unless there is objection to its use because of the patient's age.

PREGNANCY AND HYPERTHYROIDISM

Seven thyrotoxic pregnant patients were given antithyroid therapy at the following periods during pregnancy: one had become pregnant while under treatment; one started therapy during the first month; one, during the second month; 2, during the third; and 1 each, during the fourth and fifth months. In each patient treatment was continued through the twenty-eighth week then Lugol's solution was substituted and continued to term. In each instance the delivery was uncomplicated, and the infants were normal. Two of these patients had leukopenia while under treatment, one first from propylthiouracil then from methimazole, and the second from methimazole alone. Potassium perchlorate controlled the hyperthyroidism in each without further reaction. Subsequently, these two patients each had a second uneventful pregnancy, and a third patient later had 2 normal pregnancies without recurrence of hyperthyroidism. The first of these patients relapsed 5 months after delivery, was treated with potassium perchlorate for 6 months, and has since remained euthyroid. Relapse occurred in another one of this group 4 months after delivery, and remission was re-established after 14 months' treatment with propylthiouracil. All of these patients have been taking desiccated thyroid daily since delivery.

One patient, continuously euthyroid since treatment for toxic diffuse goiter at age 12, had been delivered of 2 normal infants 8 and 10 years later and has re-

mained euthyroid. Three others were delivered of normal infants 4 years, 2 years, and 1 year after treatment. The last patient relapsed 5 months after delivery and is presently undergoing treatment. All except this last patient had been taking desiccated thyroid since remission.

We believe that hyperthyroidism in pregnancy should be treated with antithyroid drugs through the twenty-eighth week, then treatment should be replaced by either iodine or desiccated thyroid through delivery. From then on desiccated thyroid, 60 to 120 mg daily should be continued indefinitely.

DIABETES AND HYPERTHYROIDISM

Seventeen patients with combined diabetes mellitus and hyperthyroidism were treated with antithyroid drugs. Seven had toxic nodular goiters (2 males and 5 females ranging in age from 54 to 70 years); and 10, toxic diffuse goiters (4 males and 6 females ranging in age from 27 to 65 years). In the first group 3 patients had diabetes that became difficult to control after the development of thyrotoxicosis. Prompt control of the diabetes was achieved in these after remission was induced by propylthiouracil; the dosage of insulin could be reduced in one and discontinued in the other two. In the remaining four patients with thyrotoxicosis that had preceded the diabetes good control was also achieved with propylthiouracil, insulin being discontinued in two. The diabetes in these patients was mild.

In the patients with toxic diffuse goiters the diabetes preceded the hyperthyroid state in four and followed it in the remaining 6. Two of the four were readily controlled with propylthiouracil, but only two of the remaining six were well-controlled. Good control of the diabetes generally depended more on whether the diabetes was stable or unstable than on its appearance before or after the hyperthyroidism.

Thus, in all of the seven patients with

toxic nodular goiters and stable or mild diabetes good control of the diabetes was readily achieved by control of the thyrotoxicosis. In six of ten patients with toxic diffuse goiter and unstable diabetes good control was not achieved. It appears that remission of the hyperthyroidism will not always improve diabetic control especially when the diabetes is unstable.

IATROGENIC HYPERTHYROIDISM

Occasionally hyperthyroidism may be induced by the administration of desiccated thyroid or its congeners, often in sizable doses given empirically.

Three euthyroid patients with hyperthyroidism thus induced and in whom remission did not follow withdrawal of medication were described in a previous report (2). The diagnosis had been established on clinical evidence and elevated basal metabolic rates only. Radioactive iodine (I^{131}) tracer studies had not been done. A fourth patient, a woman aged 34 with a nontoxic enlargement of the thyroid isthmus, had been started abruptly on 180 mg desiccated thyroid daily in an attempt to reduce this enlargement. When seen 3 months later she had developed a full-blown thyrotoxicosis with a serum protein-bound iodine of $9.7 \mu\text{g}/100 \text{ ml}$. No I^{131} tracer was done. Euthyroidism was achieved in 6 months by the use of 600 mg potassium perchlorate daily. This was followed by treatment with 60 mg desiccated thyroid daily, and she has remained euthyroid for the past 6 years. The thyroid enlargement has disappeared. The patients previously reported had responded promptly to treatment with thiouracil after 2 months, 10 months, and 3 months, respectively. While it is unusual for persistent hyperthyroidism to be induced in the euthyroid person such a change could conceivably occur in those with partially developed hyperthyroidism.

In this small group of patients with iatrogenic hyperthyroidism, euthyroidism ap-

pears to have been promptly restored with antithyroid therapy.

ALCOHOLISM MASQUERADING AS THYROTOXICOSIS

Among the patients who have failed to respond to treatment with the antithyroid drugs are a small number in whom the presenting clinical signs, while suggestive of thyrotoxicosis, are actually due to chronic alcoholism. We have seen 6 such patients, 3 men and 3 women, all under 50 whose main complaints were nervousness, palpitation, excessive perspiration, flushed skin, tremor, and weight-loss extending for varying periods of time. Some degree of thyroid enlargement was found in all, and the three women and one man showed mild exophthalmos. All had had iodine previously in some form without improvement. The basal metabolic rate determinations were always elevated principally because these patients did not abstain from stimulants for the required 12 to 14 hours preceding the test.

One patient, a female, age 45, who was scheduled for thyroidectomy was referred for examination because she had been on propylthiouracil for several weeks without improvement. Her face was flushed, there was palpitation, tremor, slight exophthalmos, and the palms were warm and moist. The basal metabolic rate was plus 14 per cent. An enlarged liver and a more detailed history uncovered the cause. The Bromsulphalein retention was 12 per cent in 45 minutes. Improvement followed appropriate therapy.

Although the masquerade may be prolonged in some instances, careful screening by I^{131} tracer study, serum protein-bound iodine or butanol-extractable iodine determination, and the I^{131} trio-iodothyronine erythrocyte uptake test will result in exposure when suspicion is aroused by a history of failure to respond to therapy with a persistently elevated basal metabolic rate.

UNFAVORABLE REACTIONS

DRUG REACTIONS

Ten patients reacted unfavorably to the drugs used; six to thiouracil; one, to propylthiouracil and methimazole; one, to propylthiouracil alone, and two to methimazole. Among patients who reacted to thiouracil, one with toxic diffuse goiter developed chills and urticaria; three with toxic nodular goiters developed chills and fever during the first 2 weeks, and in two of these the reaction recurred when the drug therapy was resumed at a later date; one with toxic diffuse goiter developed chills, nausea, and vomiting; and one with recurrent toxic diffuse goiter developed agranulocytosis 2 months after starting treatment.

One patient with recurrent toxic diffuse goiter developed agranulocytosis while on propylthiouracil; and one developed leukopenia, then had a similar experience when transferred from propylthiouracil to methimazole. One patient developed agranulocytosis and toxic hepatitis (3); and one, leukopenia while on methimazole. All patients recovered after withdrawal of the drug and appropriate supportive care.

The over-all incidence of drug reactions in 305 patients was 3 per cent.

THYROID ENLARGEMENT

Five patients developed thyroid enlargement during treatment: one while taking thiouracil; and four while taking propylthiouracil. Three had highly toxic diffuse goiters, one had a mild toxic nodular goiter, and one was being treated for intractable angina pectoris. All of these patients had been taking antithyroid drugs alone without additional iodine in any form. When antithyroid treatment was either discontinued or the dosage reduced, the enlargement receded.

EXOPHTHALMOS

Although it was the last sign to remiss or disappear, the exophthalmos generally

lessened when it was related directly to the hyperthyroidism. In those with ophthalmic ophthalmoplegia there was little or no improvement. Increase in exophthalmos was not observed during treatment.

COMMENT

Although the antithyroid drugs have not fulfilled all of the early expectations, they have earned a respected place in both the clinical and investigative fields. Clinically their usefulness is now firmly established in the preoperative preparation of the thyrotoxic patient. Differences exist as to their value in prolonged therapy either in hyperthyroidism alone or when this is combined with other disorders. These will only be resolved after much additional experience has been acquired.

In a study to determine the long-term outcome of hyperthyroidism treated with antithyroid drugs, Hershman, Givens, Cassidy, and Astwood (4) found that 54 per cent of 176 patients were well and required no further treatment for from 6 to 19 years. In 70 per cent of those who relapsed, the disease returned within 1 year. No significant difference was noted between those who stayed in remission and those who relapsed.

At present, the documented evidence (5-7) including that presented here tends to show that permanent remission may be expected in a little more than half the patients treated with the antithyroid drugs; that over-all reactions occur in less than 3 per cent; that those most likely to respond favorably are younger, have relatively small goiters with mild degrees of toxicity, and have had the disturbance for less than 2 years.

The necessarily prolonged treatment and close observation may not appeal to those who seek fast action and prompt relief. But there remains a sizable number who, having attained the euthyroid state are content to continue treatment aimed toward extended or permanent remission. For these

a minimal period of treatment for at least one year, first with the antithyroids alone, then with desiccated thyroid added, and finally with desiccated thyroid alone seems to be a practical plan (8). If sustained remission is not achieved there is then ample opportunity to turn either toward thyroidectomy or radioactive iodine therapy.

In our patients with recurrent hyperthyroidism the duration of treatment with the antithyroid drugs averaged 20 months, as good results may be had with radioactive iodine in a shorter time at lesser cost to the patient. Barring valid objections to its use, the latter treatment would seem preferable in such patients.

Opinions vary as to whether the pregnant patient with hyperthyroidism is best treated surgically or with antithyroid drugs. This difference is exemplified in the opinion of Howe and Francis (9) who favor thyroidectomy because it is "safe, efficient, maternal complications are rare and the subsequent course of the pregnancy is virtually normal," against that of Herbst and Selenkow (10) who find that "combined therapy with an antithyroid drug and full thyroid hormone replacement provides physiological control of the disorder with minimal risk to the welfare of the mother, continuation of the pregnancy and development of the fetus." Astwood (11) claims that antithyroid drugs provide a satisfactory treatment during pregnancy if excessive doses are avoided. Asper, Jr. (6) holds a similar opinion. We fully agree with these views.

The present increase in suspicion as to the possible teratogenic effect of all drugs given during pregnancy may however further limit the acceptance of antithyroid therapy.

When diabetes and hyperthyroidism coexist the diabetes may not be more effectively controlled when the hyperthyroidism is subdued. At one time one of us (11) was impressed with the better control achieved in instances where the diabetes preceded the hyperthyroidism than when it devel-

oped afterward. This is not borne out in the group of patients described here. Here it was noted that when the diabetes and hyperthyroidism are both mild a good result is readily achieved. But when one is dealing with the more fulminant form of hyperthyroidism, as in toxic diffuse goiter combined with a brittle or unstable diabetes, satisfactory control of the former will have only small influence on the fluctuations characteristic of a brittle diabetes.

Iatrogenic hyperthyroidism is no longer as prevalent as it was when weight-reducing nostrums containing desiccated thyroid were available to the public over-the-counter. Now the occasional patient with this disturbance is usually one who is exceptionally sensitive to desiccated thyroid or has occult hyperthyroidism. If the hyperthyroidism fails to subside after discontinuing the desiccated thyroid therapy, the antithyroid drugs appear to be well-suited for treatment of this disturbance.

False hyperthyroidism in the alcoholic can deceive the unwary particularly when facilities for thorough diagnostic studies are not available. When such patients fail to respond to treatment, carefully performed screening tests and a diligent search for signs of alcoholism may be rewarding.

Unfavorable reactions rarely attain proportions significant enough to deter one from using antithyroid medication. Agranulocytosis, the only serious reaction, occurred in about 1.0 per cent of the patients we treated. With the other annoying disturbances such as skin rashes, urticaria, chills and fever, nausea and vomiting, the total incidence of reactions was about 3 per cent.

SUMMARY AND CONCLUSIONS

Of 167 patients treated for hyperthyroidism with antithyroid drugs 96, or 57 per cent, achieved permanent remission and have maintained their euthyroidism for from 4 to 19 years. Patients with toxic nodular goiters who responded to treatment favorably, generally had smaller goiters.

Those with toxic diffuse goiters not only had smaller goiters, but their symptoms had existed for shorter periods and the toxicity was not marked.

In those with postoperative hyperthyroidism, the response to antithyroid therapy, while favorable, required an average 20 months of treatment to achieve euthyroidism. As good results may be achieved in a shorter time with radioactive iodine, we believe this to be the treatment of choice for this condition.

There is considerable difference of opinion as to whether the patient with hyperthyroidism during pregnancy should be treated surgically or with the goitrogens. We favor the latter method and feel that the risk is minimal if hypothyroidism in the mother is prevented and iodine or desiccated thyroid replace the goitrogen from the twenty-eighth week to delivery. Continued postpartum administration of desiccated thyroid indefinitely is a helpful preventive measure.

Diabetes and hyperthyroidism when combined can create a marked metabolic upheaval. When control of the hyperthyroidism has been achieved with the antithyroid drugs the diabetes will be more easily managed unless it is brittle or unstable when it will continue its unruly course at a lower level of activity.

When iatrogenic hyperthyroidism persists after abstinence from the desiccated thyroid, sedation and rest, antithyroid therapy can subdue the toxic state and restore the patient to euthyroidism.

False hyperthyroidism in the alcoholic should not go unrecognized for long, since it can be unmasked by thorough diagnostic screening.

Unfavorable reactions of all kinds rarely exceed 3 per cent in those treated. The incidence of agranulocytosis in this study was 1 per cent which is higher than that generally reported. Occurrence of exophthalmos and thyroid enlargement were insignificant.

If elected, long-term therapy with anti-thyroid drugs should consist first of treatment with antithyroids alone until remission is achieved. This is then followed by adding small doses of desiccated thyroid and increasing these while gradually reducing the dosage of the antithyroid drug. Finally, the antithyroid drug therapy is stopped and only desiccated thyroid treatment is continued. If sustained remission is not achieved at the end of a year, there is then ample opportunity to resort either to thyroidectomy or radioactive iodine therapy.

SUMMARIO IN INTERLINGUA

Cinquanta-septe pro cento de 167 patientes tractate pro hyperthyroidismo con pharmacos antithyroidee attingeva euthyroidismo que poteva esser mantenite durante periodos de inter 4 e 19 annos. Un satisfacente remission occurreva plus frequentemente in subjectos con micre strumas, leve grados de toxicitate, e symptomias de relativamente curte durata. Adverse reactiones de omne le varie generes non excedeva 3 pro cento.

In hyperthyroidismo post chirurgia o recurrente, le responsa—ben que favorable—requireva un tractamento medie de 20 menses. Isto es plus longe que le intervallo requirite quando iodo radioactive es usate.

In casos in que pregnantia e hyperthyroidismo coexisteva, le pregnantia continuava usque a su termino con parturition de un infante normal quando le medication antithyroidee esseva suspendite al vinti-octave septimana e esseva reimplaciate per iodo o dissiccate extracto thyroidee. Le responsa al therapia antithyroidee in le diabetico con hyperthyroidismo esseva variabile. Meliorate stabilisation del diabete esseva notate quando le diabete esseva leve o stabile.

Hyperthyroidismo de origine iatrogene ha

essite reprimita con pharmacos antithyroidee in un certe numero de patients.

False hyperthyroidismo in alcoholicos pote esser dismaskate per un meticulose discrimination.

Quando perdurative therapia antithyroidee pro hyperthyroidismo es elegite, un tractamento de un anno de duration es a recomendar: primo, usque al remission, con agentes antithyroidee sol; postea con le addition de crescente doses de dissiccate extracto thyroidee e le reduction gradual del agentes antithyroidee; e finalmente con dissiccate extracto thyroidee sol.

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