TWELVE YEARS' EXPERIENCE OF ANTITHYROID TREATMENT

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SINCE thiouracil was introduced to clinical therapeutics in 1943, antithyroid treatment for thyrotoxicosis has widely increased and proved more and more effective as the years have passed, partly as the result of experience but also through the use of more effective agents, such as carbimazole and methimazole. It is thus possible now to assess their relative value in comparison with surgical treatment, which before 1943 was the only treatment possible and still is the treatment of choice for a proportion of cases sent to the physician in consultation.

Recently Trotter (1961) reviewed his experience over a period of 10 years using thiouracil and methyl thiouracil. He found that it was necessary to abandon treatment in 44% of 70 cases owing to the presence of too large a goitre in some cases and, in others, on account of the necessity for prolongation of courses for more than two years. 45% were satisfactorily maintained euthyroid for 10 years and a smaller number (31%) were given courses of less than two years' duration. Yet for patients successfully treated the inconvenience of hospital admission, the anxieties and fears of operation and the disadvantage of permanent hypothyroidism—sometimes seen following both operation and radioiodine—have been avoided. The present paper illustrates the improved results using carbimazole, and the merit of particular care both in the selection of suitable patients and in dosage control.

In 1948 I commenced the careful selection of suitable cases for medical treatment from those sent for opinions, at the same time referring those to surgical colleagues considered unsuitable for antithyroid therapy. The present study is of the results and potentiality of treatment with methyl thiouracil since 1948 and carbimazole since 1953. The chief value of the study lies in the personal selection of cases and control of therapy by one doctor, with the helpful co-operation of clinical assistants through courses of treatment and follow-up periods. Throughout I have had the co-operation of surgical colleagues who have operated on all cases referred to them and who have themselves referred several cases for antithyroid therapy.

Clinical Material

Since 1948, 271 cases of thyroid disorder have been referred for personal opinions concerning treatment and diagnosis, and in all these, pathological enlargement of the thyroid was apparent. Of 194 cases showing toxic features, 32 cases were referred direct for surgical treatment, which was invariably carried out. The high proportion selected for antithyroid therapy is no doubt attributable, to a certain extent, to preliminary selection of cases by general practitioners and surgical colleagues. Most of these patients were seen at out-patient clinics dealing primarily with general medicine, while about 25% were seen in private practice.

Selection of Cases

Cases selected for medical treatment were those with obvious toxic features in which estimation of the Basal Metabolic Rate (BMR) was not always necessary, where the gland was preferably of soft consistency, without firm nodules; when the diagnosis was one of primary toxic goitre with a small or moderate size goitre without pressure symptoms and adverse effect on the patient's appearance or psychological state. Occasionally medical treatment is given for patients who refuse operation for various reasons. In this series two such cases were encountered of whom one had been operated on 21 years previously and refused surgical treatment in 1948. She was successfully treated and avoided surgery. The other had a goitre of considerable size, repeatedly refused operation, was supervised during a pregnancy and has been under observation over a period of 10 years.

In mild cases, diagnosis from anxiety neurosis (in patients with simple goitres) is often difficult; in such cases the BMR has been estimated or else the patient has been kept under monthly observation for a month or more to assess progress and weight loss. In a few cases a preliminary test course of iodine medication has proved a valuable method of assessment. In this way cases have been selected so that there is no doubt about the accuracy of diagnosis. All cases included in the

series have been under observation for over one year.

Treatment

Patients were treated throughout as out-patients and in only exceptional cases, for heart failure or for other reasons, were they admitted to hospital. Indeed, with few exceptions, patients were advised to lead a normal life and carry on normal occupations or household duties as before so that periods of rest have not been enforced or advised. In a few cases admission to hospital (for a few days only) for estimation of the BMR was arranged. The routine period of treatment of one year was adopted early on and was adhered to since 1952 as a result of current opinion of those who have made extensive studies of thiouracil up to that time—(Douglas and Kennie 1952, Williams 1950). Moreover, theoretical considerations of the action of antithyroid drugs on the thyroid production of hormone in the gland would support this idea. In this series the aim has been to administer full doses in tablet form for the first two months; thereafter, gradual reduction of dosage in stages to a minimal effective control of toxic symptoms, bearing in mind the resting heart rate and body weight as well as the patient's sense of well-being. Special attention was paid to early symptoms of hypothyroidism and an increasing enlargement of the gland (thiouracil goitre). In such events withdrawal of the drug for a period has resulted in prolongation of the total course beyond one year in some cases. Prolongation of the course, on minimal dosage, was in a few cases rendered necessary by immediate return of symptoms and weight loss soon after completion of a course. Experience has shown the wide variation of sensitivity of individual cases to the drug and dosage requirements from time to time. For this reason patients must be kept under monthly observation for the first year and it is important that they should be seen by the same physician as far as possible or, at any rate, by a doctor conversant with the details of treatment. In this way drug toxicity and overdosage can be easily avoided or corrected. In the majority of cases drug dosage has been on the following lines (Table 1).

TABLE 1

Period	Methyl Thiouracil	Carbimazole
0-2 months	0.2 g. t.d.s.	10 mg. t.d.s.
2-4 "	0.2 " b.d.	10 " b.d.
4-6 "	0.1 " t.d.s.	5 " t.d.s.
6-10 "	0.1 " b.d.	5 " b.d.
10-12 "	0.1 " daily	5 " daily

Thereafter patients are seen at three- or six-monthly intervals.

Assessment of Results

Results have been assessed according to the findings in June 1961, and classified in such a way as to give some indication of the value of antithyroid treatment and its relative success, bearing in mind that medical judgement in selection of cases may occasionally fail. A complete remission is defined as an undoubted success according to the patient's own opinion or his or her ability to lead a normal life in full occupation. The results are given in Table 2.

TABLE 2

Group		Cases	%
A	Complete remission and cessation of treatment without relapse	110	72
B	Complete remission, cessation of treatment, but later relapsing after a period of six months ..	24	16
C	Medical treatment commenced, but patient later required surgical treatment before completing course	18	12
D	Non-toxic goitre referred for surgery	77	
	Toxic goitre referred for surgery, with or without preliminary treatment	32	
E	Thyrotoxicosis associated with pregnancy	10	
		271	

TABLE 3
AGE GROUPS AND SEX GROUPS A, B AND C

Ages	10-19	20-29	30-39	40-49	50-59	60 on-wards	Total
Female	4	21	32	31	23	19	130
Male	0	5	1	5	9	2	22
Total	4	26	33	36	32	21	152

Groups A and B

The figure of 72% (110 cases) who had a complete remission is considerably higher than that of 45% (Douglas and Kennie, 1952) and 48% (Williams, 1950). This improved figure is probably attributable to increasing experience over the last 10 years, the use of carbimazole over the later part of this period in this series, and the very careful selection of cases. In cases which relapsed, the proportion of cases treated with carbimazole is considerably lower than those treated with methyl thiouracil; the same applies to those in which medical treatment failed (Table 4).

In assessing the accuracy of the incidence of relapse cases, consideration must be taken of the

period following courses of treatment when relapses are most likely to occur and it is seen that the majority relapsed in the first two years.

TABLE 4

Group	Methyl Thiouracil	%	Carbimazole	%	Both	Total
A	53	64	55	82	2	110
B	18	22	6	9	—	24
C	12	14	6	9	—	18
Total	83	100	67	100	2	152

TABLE 5

GROUP B CASES. TIME OF RELAPSE FOLLOWING COMPLETED COURSE OF TREATMENT, IN YEARS

Years	0-1	1-2	2-3	4-6	7	8
24 cases	8	8	3	3	1	1

From the following table it is seen that almost 50% of cases in Group A have been under observation at intervals for a period of five years following completion of treatment and those in Group B have all been under observation over two years at the time of writing.

TABLE 6

COMPLETED YEARS OF OBSERVATION OF CASES IN GROUPS A AND B

Completed Years	12	11	10	9	8	7	6	5	4	3	2	1-2	Total
Group A	11	11	3	7	5	7	9	11	9	7	12	18	110
Group B	3	2	1	3	6	1	1	3	3	1	—	—	24
Total	14	13	4	10	11	8	10	14	12	8	12	18	134

Only three patients in Group B had two relapses.

TABLE 7

TIME OF ONSET OF RELAPSES SINCE TREATMENT FIRST COMMENCED IN PATIENTS WHO RELAPSED TWICE, IN YEARS

Case	First Relapse	Second Relapse
1	1½	6
2	1½	4
3	¾	3½

It might be expected that the incidence of relapse would be higher in those cases treated for less than one year but Table 8 does not bear this out.

Relapses were usually found to be associated with chronic mental or physical strain which was occupational or domestic. These patients were not investigated specially from this point of view but

TABLE 8
DURATION OF PRIMARY COURSE OF THERAPY IN GROUPS A AND B

Length of Course	Group A Cases	%	Group B Cases	%
Less than 1 year	33	30	8	33
1 year	62	56.4	8	33
1 to 1½ years ..	9	8.2	4	17
1½ to 2½ years ..	6	5.4	4	17
Total	110	100	24	100
Minimum ..	3 months		5 months	
Maximum ..	2½ years		2 years in 3 cases	

in the 24 cases in Group B such factors were obvious in all except three cases (87%) compared with 47 of 110 cases in Group A (43%) and 15 of 18 in Group C (83%). It would seem that in cases which relapse, chronic mental strain over a long period of time continues to stimulate the gland after drug withdrawal whereas in those patients who never relapse (Group A) the precipitating causative factor is an acute mental episode, such as a bereavement, accident or acute illness from which recovery and adjustment occurs in the course of a year or so. Illness and deaths of near relatives, marital disharmony, occupational and financial anxiety, emotional stress, childbirth, operations, injury and acute physical illness, such as influenza, were common factors in causation. In one case a relapse occurred five years after the original treatment was commenced, the relapse being associated with the onset of diabetes which was investigated in hospital. In two cases the patients' husbands were air pilots, one patient had been previously treated for depression in a mental hospital and another had been under observation for an anxiety neurosis.

It has sometimes been said that relapse of thyrotoxicosis, following a course of treatment, is a serious indictment of antithyroid treatment. That this is by no means true is seen in the fact that in all 24 cases relapses have been easily and satisfactorily overcome by a further course or two of treatment and, indeed, in some cases, the subsequent course can be given in lower dosage over a similar or longer period than the original one. There has been no difficulty in controlling relapses in any case recorded in this series.

Group C

This group consists of 18 cases commenced on antithyroid therapy which later failed to achieve the response hoped for. Enlargement of the thyroid which continues, in spite of drug withdrawal or drastic reduction, is the commonest reason. For these and other reasons treatment was

immediately withdrawn and surgical treatment was sought.

Carbimazole (6 Cases). In four cases treatment failed within the first three months; in one case there was no remission of toxic symptoms, the size of the thyroid remaining unchanged. In three cases the gland enlarged markedly, one of these patients provided the only death of the whole series of cases studied. A woman, aged 27, had been treated for 11 weeks on a dosage of only 20 mg. daily, followed by an interval of seven weeks before operation during which oral iodine was given for three weeks. No remission was seen with carbimazole treatment while the size of the gland increased. Though operation presented no difficulties or technical complications, post-operative cardiac arrest occurred within an hour of completion. At post-mortem no abnormality was found save some enlargement of the thymus gland.

In the other two cases thyrotoxicosis could not be adequately controlled within periods of 18 and 28 months respectively. In both these patients chronic mental stress was seen, one having an alcoholic husband and the other being beset with emotional problems.

Methyl Thiouracil (12 Cases). Eleven of these cases were advised surgery during the first year, the other at 16 months. In seven cases the thyroid became larger; in two of these pressure symptoms also ensued; while another developed auricular fibrillation. Drug toxicity (two cases), pressure effects only (one case), congestive heart failure (one case) and exophthalmic ophthalmoplegia (one case) were other reasons for surgery in the remaining cases.

It is interesting that in all 18 cases in Group C, with the exception of three, mental stress was a striking feature of the aetiology.

Toxic Effects

In only five cases in the whole series was drug toxicity seen and in no case was carbimazole the drug responsible. No undue anxiety was aroused and in only two cases was surgical treatment resorted to for this reason; in one case recurrent keratitis and conjunctivitis occurred and cleared up on withdrawal and in the other case an erythematous rash with leucopenia occurred. In one case in Group A leucopenia and some sore throat at six months in the course necessitated premature termination of therapy. In one case after two weeks therapy in 1947, propylthiouracil was successfully used as a substitute for thiouracil which caused nausea and vomiting during the first two weeks. In one case a short course was terminated owing to a drug rash, abdominal pain and diarrhoea. No case of agranulocytosis was

seen. It is, therefore, safe to say that, at any rate when using carbimazole, routine blood counts are quite unnecessary except when toxic symptoms appear—nausea, vomiting, diarrhoea, rashes or ulceration of the throat. It is common practice to recommend omission of the drug if such symptoms persist for more than two days and in any case of sore throat.

Deaths

As already mentioned, one surgical death occurred from cardiac arrest among 50 successful surgical results; some of these patients had had preliminary short courses of antithyroid therapy prior to operation, at the request of the surgeon, while 18 had been unsuccessfully treated medically (Group C).

No patient treated medically during this period of 12 years has died of causes attributable to treatment though four patients have died at the ages of 76, 68, 64 and 50. The first was an old diabetic with hypertension and congestive heart failure, who died three years after treatment; the second had a cerebral hæmorrhage and was hypertensive; the remaining two died of congestive heart failure three years and five years respectively after completion of treatment.

Associated Diseases

Three patients are known cases of Addisonian anaemia of several years' duration; two patients have insulin treatment for diabetes; one has extensive ocular involvement and the other developed diabetes at the same time as her relapse of thyrotoxicosis and was referred for surgery for that reason. One patient developed evidence of early disseminated sclerosis one-and-a-half-years after therapy was completed. One patient became acutely depressed and attempted suicide unsuccessfully while under a course of carbimazole, but she has shown an excellent response to psychiatric treatment, has completed antithyroid treatment and is perfectly fit.

Thyrotoxicosis Associated with Pregnancy

Treatment in pregnancy provides no particular difficulties. Four patients conceived during the course of treatment so that a full course was possible before childbirth. In five cases conception occurred before treatment was commenced, thus necessitating an interrupted course, the drug being omitted for a month before and after childbirth. All the babies were healthy and robust from birth onwards. One case, a woman of 46 in her seventh pregnancy, was advised termination owing to a large, severe, toxic goitre causing pressure symptoms.

The most interesting case in the series was that of Mrs. R., who was 30 when first seen in 1951 with a large, smooth and firm toxic goitre, for which she was advised surgical treatment. This advice has been persistently refused up to the present time. During 1951 she was given six months' thiouracil treatment in less than the usual dosage. She was well until October 1953, when she was again treated from the second month of pregnancy, resulting in the normal delivery of a healthy baby in June 1954. She has had subsequently intermittent courses of carbimazole since 1956, lasting four, eight and nine months respectively, with a long intermission without treatment from November 1958 to August 1960. During 10 years she has felt fit and led an active life in spite of a large goitre.

This case is a good example of the remarkable potentiality of antithyroid treatment, in patients persistently refusing surgical treatment, when carried out with careful regard to dosage and duration of treatment. The same principles apply to all thyrotoxicosis patients treated in pregnancy, there being no danger from medical treatment to mother or child though it is wise to omit antithyroid drugs for at least three weeks before delivery owing to possible secretion of drugs in human milk (Illingworth, 1953).

Conclusion

Early experience with thiouracil and similar drugs showed their value in the control of primary thyrotoxicosis in particular, in patients in whom the risk of operation was high, the preoperative control of toxic features in severe cases and in those patients who refused operation, this group including those cases who have relapsed at some period after partial thyroidectomy. In earlier years the expectation of permanent remission after thiouracil courses lasting one year were between 30% and 50% though experience recorded here showed 64% permanent remission. This figure has been markedly improved upon since carbimazole and methimazole have come into use so that 80% of permanent remission should be attained in carefully selected cases; of the remaining cases approximately an equal proportion relapse or, failing to respond, require surgery. This study shows the improved expectation of success using carbimazole compared with methyl thiouracil though it should be admitted that the increasing experience of a single observer in handling dosage control may be a factor in this improvement.

Many reports stress the seriousness of relapses but this study shows that they are easily treated often in lower dosage than that previously given; that they occur in less than 10% of carbimazole-treated cases and that they are usually associated with chronic mental strain—a factor noted in earlier reports (Douglas and Kennie, 1952) to be the cause both of the primary illness and the

relapse. It would seem that the aim of prolonged treatment is the control of thyroid hormone activity under the stimulus of over-production until such a time as natural remission occurs or the excessive stimulus to the thyroid passes away. Antithyroid therapy should thus extend over a considerable period; the physician should always personally control treatment and interest himself in its details once his decision has been made to commence. Its management provides him with excellent opportunities of rational therapeutics in that he must exercise clinical judgment in adjustment of dose control from time to time, in the early recognition of excess dosage and in avoiding an increase of the size of the thyroid gland. It is sometimes said that the long period of treatment and the repeated attendances of the patient are distinct drawbacks of medical treatment. Yet each consultation can be carried out in five minutes and provides an excellent opportunity for the physician to explore the patient's individual problems and to provide the same type of simple psychotherapy that is practised in any doctor's surgery. There are few disorders treated by the general physician today which provide such excellent opportunities for helping the patient's sense of good health and for earning her gratitude.

Moreover, the dangers and toxic effects of carbimazole can be entirely discounted and avoided with reasonable care. In this series no undue anxiety arose from the use of either drug. Nor is there need to fear the consequences of overdosage or delayed hypothyroidism sometimes seen after radio-iodine therapy.

Summary

Since 1948, 194 cases of thyrotoxicosis have been referred for consultation by general practitioners and surgical colleagues. Thirty-two cases were advised surgical treatment in the first place; nine cases were treated during pregnancy with antithyroid drugs and 150 were given courses of methyl thiouracil (83 cases) or carbimazole (67 cases) in courses lasting in the majority for one year though in some cases the courses required to be prolonged. In all, 72% of patients obtained complete remission without relapse at the present time, carbimazole in this respect being more effective (82%), than methyl thiouracil (64%). A relapse is defined as a return of toxic features after a period of six months from termination of a course. The relapse rate was 22% for methyl thiouracil and 9% for carbimazole cases.

The factors contributing to relapse are considered. Chronic mental strain and physical illness were the usual causes of relapses and also of failure of medical treatment in 18 cases which

required surgery, either during or after courses of treatment, in 12 cases using methyl thiouracil and six cases using carbimazole.

No deaths were attributable to therapy though five cases later died from other causes. Drug toxicity was encountered in five cases using thiouracil and none using carbimazole. None of these reactions caused anxiety.

Nine women were successfully controlled through pregnancy and no anxiety arose for mother or child. Thyrotoxicosis should not be regarded as a contra-indication to pregnancy unless serious complications are present.

Carbimazole has been shown to be the more effective drug and completely non-toxic though

perhaps in this series greater skill has been achieved in control of treatment and selection of cases since carbimazole has been mainly used in recent years.

It is emphasized that the physician who decides on the initiation of treatment should himself be responsible for therapy throughout and for subsequent follow-up attendances of patients. Only in this way can careful adjustment of the necessary dosage be achieved.

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