longer show interaction; under the same conditions streptomycin and chloramphenicol not only lose their initial antagonism, but with some organisms become synergistic. Unlike some workers (Jawetz *et al.*, 1952; Bliss *et al.*, 1952), we have not found at 18–24 hours that a pair of antibiotics will be synergistic with one organism and antagonistic with another. In our experience any pair of antibiotics will react at this time in the same way, varying only in degree with different organisms. We therefore believe that a limited forecast can be made of the behaviour *in vitro* of a pair of antibiotics when tested against any organism. The value of such a forecast in controlling therapy cannot yet be assessed, since further knowledge of the correlation between laboratory and clinical findings is needed.

Before any prediction can be made of the probable correlation between laboratory and clinical results several difficult questions have to be considered. The first is the problem of the relative importance of bacteriostatic and bactericidal action of antibiotics in the body. The paramount importance of the former mode of action in most forms of infection was not questioned until the combined action of antibiotics was investigated. It then became apparent that the results of testing bacteriostatic activity *in vitro* agreed less well with animal experiments than did the results of tests based on bactericidal action, and the idea has grown up that the lethal activity of antibiotics is the more important *in vivo*. Concentrations used in tests of combined lethal activity have, however, been closer to those attained in the body than the sub-inhibitory levels usually employed in tests based on combined bacteriostatic action, and this may explain some of the divergent results. There can be no doubt that the pattern of interaction alters with time. Jawetz and his colleagues suggest that early readings are of clinical importance, although other workers came to the opposite conclusion (Ahern *et al.*, 1952). Since antibiotic treatment is usually prolonged, we feel that results after 24 hours' contact with the drugs are more likely to be significant. It may even be that results observed after still longer periods are of greatest value. Finally the synergistic lethal action of two antibiotics by allowing fewer survivors may lessen the chance of the emergence of resistant variants. There can be no definite answer to these questions until more work is done to correlate *in vitro* and clinical findings. The method described here may help to serve this purpose.

Summary

There is both experimental and clinical evidence that two antibiotics used simultaneously may be more efficient (synergistic) or less efficient (antagonistic) in their action than either drug used alone.

A simple method suitable for routine diagnostic work is described. It reveals interactions of the bactericidal effect of antibiotics *in vitro*. Sixty-five strains of common pathogens were tested against three pairs of antibiotics. Penicillin with either chloramphenicol or aureomycin generally showed antagonism. Streptomycin with chloramphenicol was synergistic. These results refer to interaction after 18 to 24 hours. The only exceptions to these findings were that no interaction occurred.

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CLINICAL TRIAL OF METHIMAZOLE IN TREATMENT OF THYROTOXICOSIS

BY

LINDSAY A. G. DAVIDSON, M.B., Ch.B.

Medical Registrar, Dundee Royal Infirmary; formerly
 Medical Registrar, Dryburn Hospital, Durham

The history of the drug treatment of thyrotoxicosis dates from Chesney's discovery in 1928 that rabbits fed exclusively on cabbage became myxoedematous and developed goitre.¹ Thiouracil was introduced to clinical medicine in 1943 in a paper by E. B. Astwood,² and in 1949 Stanley and Astwood³ reported that 1-methyl-2-mercaptoimidazole, now known as methimazole, was the most active antithyroid drug they had encountered. Methimazole has a basic ring structure of five atoms. This ring contains two nitrogen atoms connected through a carbon atom to which is attached a sulphur atom. This chemical grouping —N—CS—N—, which is common also to the six-membered ring of the thiouracils, is thought to be responsible for the antithyroid activity of the drug (see Formula).

1-Methyl-2-mercaptoimidazole
 (Methimazole)

2-Thiouracil

Formula of methimazole compared with that of thiouracil.

The normal thyroid gland selectively removes iodine from the blood plasma and converts it into thyroxine. This function is inhibited by antithyroid drugs, which block the formation of di-iodotyrosine within the gland.³⁸ Using the degree of block produced as an index of antithyroid activity, Stanley and Astwood have estimated in man the ability of the different antithyroid drugs to block, in the gland, the conversion into thyroxine of a test dose of radioactive iodine, and thus estimated the clinical potency of each drug.⁴ In experiments of this type they found methimazole one hundred times more effective weight for weight than thiouracil.³ The actual figures published are set out in Table I.

In general clinical use methimazole is 20–50 times more effective weight for weight than compounds of thiouracil. In man a single dose of 5 mg. of methimazole almost completely inhibited the accumulation of radioactive iodine by the gland for nearly 24 hours.³ In

TABLE I.—*Relative Activities of Various Antithyroid Drugs Compared in Man*³

2-Thiouracil	1
6-Methylthiouracil	2
6-n-Propylthiouracil	0.75
2-Mercaptoimidazole	10
1-Methyl-2-mercaptoimidazole	100

another investigation in mice, methimazole was found to be seven times more toxic weight for weight than thiouracil.

Clinical Material

This report deals with 44 patients treated with methimazole since January, 1950. Of these, 34 were either untreated cases of thyrotoxicosis or cases which had relapsed after previous drug treatment with methylthiouracil. In the remainder methimazole was used in maintenance dosage following control with methylthiouracil.

The diagnosis of thyrotoxicosis is essentially clinical. In this series the diagnosis was made clinically and confirmed by estimation of the basal metabolic rate. None of the patients had a B.M.R. of less than +15% before treatment. Most of the classical signs of thyrotoxicosis were present in all the cases, and, of the only two who had neither exophthalmos nor goitre, one had a B.M.R. of +88% and the other of +22%. The latter patient had lost 18 lb. (8.2 kg.) in weight, which has been regained with treatment. Estimation of the B.M.R. was found to be a convenient method of following the progress of treatment, and it agreed closely with an independent estimation of the severity of the clinical state in two-thirds of all the tests performed in relation to this series.

In assessing the results of treatment the patients were regarded as euthyroid when all the signs and symptoms of thyroxine intoxication had disappeared and when the B.M.R. was within normal limits. The last sign to disappear was usually tachycardia. The pulse rate was taken to be within normal limits when it was recorded in the out-patient department as under 80 beats a minute without previous rest. In three cases a rate of 84 was accepted as normal. These patients required rest to bring the pulse rate below 80, but were otherwise symptomless.

The patients were treated initially in hospital for two to three weeks, and then either went to the convalescent home for a similar period or were allowed to return home. Thereafter they were seen frequently in the out-patient department.

The 34 cases of thyrotoxicosis comprised 28 women and six men. Their ages varied from 22 to 77 years, with a mean of 45 years 9 months.

The symptoms had been present on the average for eleven months, and the average increase in the B.M.R. was +44.6%. Fourteen cases were classified as mild (average B.M.R. +27%), 14 were classified as of moderate severity (average B.M.R. +48.0%), and six were classified as severe (average B.M.R. +74.5%). This distinction into groups was based on the severity of symptoms, together with the B.M.R. as a secondary consideration, and, although it is difficult to state in words the criteria for inclusion into each group, the clinical distinction will be recognized by all (Table II).

Four cases had had previous treatment with methylthiouracil and had relapsed; these were all mild cases. Five patients had no goitre, eight had a nodular goitre, and the

remaining 21 had a diffuse thyroid enlargement. Twenty-six patients had exophthalmos; it was considered to be severe in six.

Treatment

Methimazole is dispensed as small white tablets slightly larger than a saccharin tablet, each containing 5 or 2 mg. of the drug. The drug is soluble in water at room temperature. The tablets are slightly bitter to the taste, but are not unpleasant to take and were not objected to by the patients. There were no immediate unpleasant side-effects such as nausea or diarrhoea. The drug is excreted in the urine.

The dose adopted was the lower standard dose recommended by the makers. The patients received one 5-mg. tablet three times a day. In two cases an initial dose of 8 to 9 mg. daily resulted in a partial remission of symptoms, but complete control was not obtained until the standard dose of 15 mg. daily was used. Two cases received 20 mg. daily for the short period of two to four weeks, as they were rather slow to respond to the drug. Both were controlled.

As soon as the patient was considered to be euthyroid, a maintenance dose of 5 mg. or less daily was begun. Only one case has required a maintenance dose of greater amount, and this patient received 10 mg. daily.

A complete remission of symptoms was produced in every case save one. This lady was on treatment for two months only, as she failed to attend the follow-up clinic after this. She was initially classified as a severe case (B.M.R. +78%); when last seen she had shown steady and considerable improvement and was classified as a mild case (B.M.R. +23%). She had persistent auricular fibrillation, and died from coronary thrombosis three months after stopping treatment.

One case, following control, was subjected to surgery. This man had moderately severe thyrotoxicosis, a nodular goitre, and angina pectoris. It was felt that a rapid and probably radical cure would be most likely to benefit his cardiac condition. When last seen (February, 1953) he was symptom-free, had no angina, and was back at work as a miner.

Results

Within three or four days of starting treatment with methimazole the patients noted subjective improvement in their condition, and there was obvious clinical improvement within a week in every case; they were feeling more settled and slept better, while their weight had begun to rise and their pulse to fall.

The average time on methimazole until complete control of the symptoms of thyroxine intoxication was achieved was 56 days. The individual figures varied from 15 to 142 days, and it is interesting to note that all the longer times occurred in cases of Graves's disease. The average time taken to control the nodular goitres was 22 days less than that for the cases of Graves's disease. This may be because the average B.M.R. in the nodular goitres with thyrotoxicosis was some 10 points less initially (+36.5%, as against +46.8% for the cases of Graves's disease), or possibly because of the known tendency of thyrotoxicosis with nodular goitre to wax and wane in severity, and so perhaps be the more easily influenced by treatment.

It is also interesting that the four included cases which had relapsed after methylthiouracil treatment were all easily controlled by methimazole. This is not always the case when other drugs are used in the treatment of relapses.

Along with the obvious clinical improvement induced by methimazole, the pulse rate fell (average of 25 beats a minute), the pulse pressure fell (average of 14 mm. Hg), the weight rose (average 14½ lb.—6.5 kg.), and the B.M.R. became normal (average fall of 39.9%). The average B.M.R. after control was +4.7% (see Chart).

All the surviving patients were back doing their full work within four months of starting treatment. The average time for the group was two months.

Eighteen patients have stopped treatment. The average duration of this treatment was 29 weeks 6 days (minimum

TABLE II.—*The Clinical Material*

Character of Disease	No.	Type of Disease		
		Graves's Disease	Nod. Goitre, Thyrotoxicosis	Average B.M.R.
Mild	14	11	3	+27.2%
Moderate	14	10	4	+48.0%
Severe	6	5	1	+74.5%
Total	34	26	8	
Average B.M.R.	+44.6%	+46.8%	36.5%	+44.6%

The average age of the patients was 45.8 years. The average duration of symptoms was 10.9 months. Nodular goitre was present in 8.

Chart showing response to treatment. The individual results of each patient have been combined to give composite curves of a hypothetical "average" patient. A.T.=After treatment.

7 weeks—maximum 93 weeks), and this is probably too short a time. The average observation period of cures, excluding relapses, was 29 weeks 2 days.

Eight (44%) patients have relapsed. Two of these have been cured by further treatment and have been observed since for six and eight months. The remaining six are still on treatment. Three stopped treatment on their own account and failed to attend the follow-up clinic. The maximum treatment time in this group was 13 weeks. Two patients had a gradual recrudescence of symptoms from the day they stopped treatment and must be regarded as having stopped owing to an error of clinical judgment rather than as true relapses. They restarted methimazole treatment in four and six weeks respectively. One patient recently relapsed after 21 months without treatment.

Thus only three out of the eight had a true relapse following what was thought to be adequate treatment. The average length of time between stopping treatment and the onset of symptoms of the relapse was 22 weeks 6 days.

The final cure rate, then, is at present 12 out of 18—that is, 66%—and these cures have been observed for an average period of 29 weeks 2 days.

Of the other cases two are dead—one from coronary thrombosis and one from carcinoma of the pancreas—one has had a thyroidectomy, and the remaining 13 have been on treatment for an average period of four months. Only one of these has been treated for over nine months.

With methimazole treatment only one goitre has increased in size, 14 have definitely decreased in size, and the remainder have remained the same. Only two patients now have severe exophthalmos as against six before treatment, and 15 are now considered to have no exophthalmos as against eight before treatment (Table III).

These observations on the size of the goitre and the persistence of the exophthalmos are purely clinical. Accurate

TABLE III.—*The Change in the Eye Signs and in the Goitre with Treatment*

		Total	Cures	Others
Goitre ..	0 }	12	7	5
Exophthalmos ..	0 }			
Goitre ..	- }	9	3	6
Exophthalmos ..	- }			
Goitre ..	- }	5	3	2
Exophthalmos ..	- }			
Goitre ..	0 }	6	4	2
Exophthalmos ..	- }			
Goitre ..	+	1	1	0
Exophthalmos ..	0 }			
Goitre ..	S }	1	1	0
Exophthalmos ..	- }			

0=No change with treatment. +=Increase with treatment. -=Decrease with treatment. S=Surgical treatment.

objective records of the pretreatment size of goitre and the degree of exophthalmos were unfortunately not available in most cases. The findings were therefore classified according to the answers received to the following questions, together with the clinical impressions of the examiner.

Goitre: What has happened to the swelling in your neck since you started treatment?

Exophthalmos: What has happened to your eyes since you started treatment?

Where any doubt existed in the examiner's mind about the accuracy of the answers, the result was recorded as "no change." This method is admittedly inaccurate, but the patient is probably as sound a judge of the state of his or her personal appearance as the doctor, and none seemed to be in doubt about the answers to be given to these questions.

Apart from other diseases coinciding with treatment in 20% of cases, the only complications were in the cardiovascular system. Nine patients had complicating cardiovascular disease. In five cases, of whom two had mild cardiac failure, this was the result of the disease and is now cured. In two further cases the diastolic blood pressure has risen with treatment to over 100 mm. Hg, and these two patients must be regarded as cases of essential hypertension masked by thyrotoxicosis. The remaining two patients showed auricular fibrillation. One of these has died of coronary thrombosis, and when last seen after two months' methimazole treatment she was still fibrillating. The other, who when first seen had sinus rhythm, lately presented as a relapse, with auricular fibrillation as the main symptom. He has been under treatment again for eight weeks, and is still fibrillating.

In the 44 people so far treated with methimazole, three unexplained reactions have occurred, but only two of these can properly be attributed to methimazole.

A woman developed a maculo-papular rash on the sixtieth day of treatment. This disappeared within seven days without change in the dosage of the drug or giving specific treatment.

A woman developed a transient papular erythema which came on about half an hour after each dose of methimazole and lasted for about one hour. She was having at this time 20 mg. of methimazole daily in four doses. The rash has not recurred on smaller doses of the drug.

A woman had fever up to 99.8° F. (37.7° C.) with an eosinophilia during the first ten days of treatment, but as this fever started two days before the initial dose of methimazole it cannot be attributed to the drug.

No serious toxic effects have occurred, and in those cases examined there is and has been no evidence of granulocytopenia. The rate of toxic reactions observed in this series was 4.5%.

Comment

At the present time it is generally accepted that the thyroid gland in thyrotoxicosis is producing excess thyroxine in response to stimulation by excess pituitary thyrotrophic hormone.^{5, 38} The basic lesion which produces the increased secretion of thyrotrophic hormone has not been defined, but may lie in the pituitary itself, in the hypothalamus, or conceivably in an abnormal reaction of the thyroid gland to the hormone. This last is unlikely, because the hyperplastic tissue of toxic thyroid glands has been found capable of inactivating five to ten times the amount of thyrotrophic hormone that can be inactivated by normal thyroid tissue.⁶ Further, in those cases in which exophthalmos is progressing, excess active thyrotrophic hormone can usually be demonstrated in the blood, as well as excess inactive thyrotrophic hormone in the urine, indicating that the stimulus to thyroid gland hyperplasia and hyperfunction comes initially from outside the gland,⁷ and, finally, the whole picture can be reversed by destruction of the pituitary.³⁸

Clinically the disease seems to be eventually self-limiting in most cases, and from the practical point of view a cure will result provided the body can be protected from the evil effects of excessive stimulation by thyroxine long enough for the basic hormonal upset to subside.

All the modern methods of treatment are attacks on the thyroid gland itself, and are probably basically unsound.

Except in cases in which operation is obligatory, the antithyroid drugs, with their finely graded and only temporary effect, seem to be as good a method of protecting the body from thyroxine excess as any method that has yet been devised,⁸ especially as the incidence of carcinoma in Graves's disease is only 0.5% and in toxic nodular goitre less than 1%.⁹

Each antithyroid drug which has been used in the treatment of thyrotoxicosis has been discarded in favour of another as the newcomer has been shown to be more potent in its clinical effect and less noxious to the human body. The aims of treatment are to produce permanent remission of symptoms by means which are at the same time rapid, uniformly successful, and safe.

Methimazole cannot be expected to produce a cure rate higher than any other antithyroid drug, as its antihormonal effect is produced in the same way, at the same point of action, as is the effect of these other antithyroid drugs. The crude cure rate depends upon the length of treatment, the length of time the basic hormonal upset persists, and the length of observation of the cures. The figure of 50 to 60% long-term cures with antithyroid drugs is widely quoted,¹⁰ and it is likely that the final figures in this series will be similar. Methimazole has, however, been shown to act more rapidly than any other drug in common use. It produced a fall in the B.M.R. of 0.8% a day. The average time taken to achieve complete control of symptoms with methimazole is only 60% of the time taken in this clinic with a similar series using methylthiouracil. This has been the general experience of all those who have conducted clinical trials with the drug, and applies also to comparison with propylthiouracil.

Methimazole not only acts more quickly but has a smaller failure rate than methylthiouracil. No case treated here failed to respond to methimazole, nor did any case escape from control once this was established. One out of each 15 cases (7%) treated in this clinic with methylthiouracil was not controlled, and this figure is not abnormal.¹¹ Propylthiouracil fails in almost twice as many cases as methylthiouracil.¹²⁻¹³ The failure rate of methimazole in over 1,300 cases treated with the drug is less than 1%.¹⁴ The incidence of toxic effects with methimazole in this series was 4.5%, and none of these effects were serious.

As the usefulness of this drug may well be assessed not so much by its effectiveness as by the incidence of toxic reactions, all the published reports on methimazole in the literature, have been studied,¹⁵⁻³⁶ and, in addition, the makers of the drug have supplied to me all the information they have collected about its clinical use in 1,350 cases.¹⁴

The following facts came to light: (1) The toxic effects of methimazole are similar to those of the other antithyroid drugs. (2) The commonest are skin reactions occurring in about 3% of cases. These comprise in the main maculopapular rashes and urticaria. (3) The serious toxic effects described are agranulocytosis, two cases (one fatal),³⁵⁻³⁶ a few cases of granulocytopenia, and one case of thrombocytopenic purpura.³² (4) The reactions have been of such severity as to merit stopping the treatment in 1.5% of cases treated with the drug. The overall incidence of toxic reactions is 4.6%, and that of agranulocytosis 0.15%.¹⁴

It should be noted that the incidence of reactions is definitely related to dosage. Only a few mild skin reactions have occurred with a dose of less than 20 mg. daily; all the severe reactions have followed doses of more than 30 mg. daily.

It has been shown that 5 mg. of methimazole is effective for nearly 24 hours,³ and so it is to be expected that 5 mg. eight-hourly will certainly be effective, and there would seem to be little point in raising the dose beyond this, as the rate of response will not be affected and the incidence of toxic reactions will definitely increase. It will be remembered that in the early series reported, using methylthiouracil, the dose was higher than that now normally used, and the incidence of toxic reactions was correspondingly higher than that now expected.¹¹⁻¹⁵

The development, maintenance, and progression of the exophthalmos of thyrotoxicosis seem to depend in some way upon the relative balance between production and inactivation of pituitary thyrotrophic hormone, the presence of excess of active hormone in the body producing exophthalmos.⁷ Presumably in this series the glands were all able to strike a balance with the hormone production or inactivate more hormone than was produced, and so the exophthalmos did not progress and in many cases has subsided. This is probably a chance finding.

There is no doubt that the lack of enlargement and regression of the goitres in this series is a very real thing. The reason for this finding is unknown. Several tentative hypotheses could be advanced in explanation, but in the absence of any confirmatory evidence these would be valueless. Suffice it to say that the histological picture of glands treated with methimazole and methimazole and iodine does not differ qualitatively from that produced by other antithyroid drugs,²⁵⁻²⁷⁻³⁷ but that in the case reports of other authors those in which the dose used in treatment was of the same magnitude as in our own series tended to confirm our findings, while some of those using larger doses reported occasional enlargements. The majority did not consider the question, as most of their cases were eventually treated by surgery or radioactive iodine therapy.

Conclusions

Methimazole is a potent antithyroid drug.

It is more effective than the other antithyroid drugs in common use, as regards both the rate of response and the paucity of failures.

It is definitely less toxic than methylthiouracil, and, although slightly more toxic than propylthiouracil, the incidence of severe toxic reactions is of the same order of magnitude as with this latter drug.

Methimazole seems to be the best available preparation for the drug treatment of thyrotoxicosis.

I would like to thank Dr. Robert Mowbray for permission to use his cases for the purposes of this report, and for his interest and help in preparing this paper. Eli Lilly and Company, who supplied the drug for clinical trial under the trade name "tapazole," have been extremely helpful throughout the period of this investigation.

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