hyperthyroid patients for surgery, to discontinue the thiouracil two to three weeks before operation and to administer iodine alone for the remaining period (Rundle, 1951; Lange, 1953). However, Maxwell *et al.* (1946) and Williams (1946) reported satisfactory results with the concurrent administration of thiouracil and iodine. Rawson *et al.* (1945) believed that the iodinating and involuting actions of iodine are separate, and that, although the administration of the iodine does not result in the synthesis of thyroid hormone when iodine and thiouracil are given together, it does cause involution of the gland.

Conclusion

Although the number of cases observed in the present series is small we believe that the use of concurrent thiouracil and iodine (whether given as iodothiouracil or as methylthiouracil with potassium iodide) is a most satisfactory method of preparing for operation patients with moderate or severe hyperthyroidism. Those patients with mild hyperthyroidism who require operation are adequately prepared with iodine alone. Preparation with concurrent thiouracil and iodine is more rapid and produces a more satisfactory surgical field than does preparation with thiouracil followed by iodine. In cases of moderate severity the relatively slight increase in the duration of pre-operative treatment, compared with the duration of pre-operative treatment with iodine alone, is fully justified by the increased degree of safety obtained.

Summary

The literature concerning iodothiouracil, an organic combination of iodine with thiouracil, is reviewed, and a further clinical trial of this drug is reported.

Twenty-three patients suffering from hyperthyroidism, 18 of whom had subsequent thyroidectomies, were treated with iodothiouracil in doses of 200 to 300 mg. daily for periods of 12 days to 7 months.

The reduction in hyperthyroidism and the involution produced in the thyroid gland of patients prepared for surgery were most satisfactory; the results of prolonged medical treatment with iodothiouracil were variable.

It is doubtful whether the pharmacological properties of iodothiouracil differ from those of the constituent iodine and thiouracil fractions when the latter are administered at the same time.

Our thanks are due to Ciba Laboratories, Ltd., for the generous supplies of iturmil and to the Pathological Department of St. Bartholomew's Hospital for the preparation of the microscopical sections.

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The National Gastroenterological Association announces that the name of its official publication, established in 1934, has been changed from *The Review of Gastroenterology* to *The American Journal of Gastroenterology*. There has been no change in the editorship. An earlier journal of this name was published from 1911 to 1914 by the American Hospital for Diseases of the Stomach, Philadelphia.

LONG-TERM THERAPY OF THYROTOXICOSIS WITH THIOURACIL COMPOUNDS

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Now that the treatment of thyrotoxicosis by thiouracil compounds has been in use for a number of years, it is becoming possible to determine its long-term effects and, in particular, the conditions under which this therapy is likely to be most successful. Most of the earlier contributions to this aspect of the subject have been reviewed by Astwood (1949), and accounts of more recent investigations have been published by Himsworth (1948), Williams (1949), Dunlop and Rolland (1950), Trotter (1950), Poate (1950), Wing and Asper (1952), and Douglas and Kennie (1952).

The present report is a summary of observations which began in 1944 at the Sheffield Royal Infirmary on the effects of treating thyrotoxicosis by means of thiouracil compounds. The inquiry was planned with a view to throwing light on three main questions which are of special interest to the medical practitioner: (a) How successful are these drugs in initially controlling the signs and symptoms of this disease? (b) To what extent can control be maintained over long periods by continuous administration of maintenance doses of the drug? (c) What are the chances of relapse after maintenance treatment is withdrawn? In particular, is length of remission after withdrawal related to such factors as the age of the patient, length of his illness, and the duration of his treatment before withdrawal?

Procedure

A total of 126 patients with typical signs and symptoms of thyrotoxicosis were treated for varying periods of up to six years with thiouracil, methylthiouracil, or propylthiouracil, according to the scheme already described in previous communications (Wilson, 1946; Wilson and Goodwin, 1947). As was pointed out previously, we have found that, though propylthiouracil was not superior to methylthiouracil, both compounds were less apt than thiouracil to produce toxic effects, and that the therapeutic response was favourable in either type of thyrotoxicosis. For the purpose of the present analysis no attempt is made to distinguish patients with primary from those with secondary thyrotoxicosis, or to differentiate between them according to severity of the disease, presence or absence of specific symptoms, the particular thiouracil compound and dose used, and the length of treatment needed before initial control was achieved. "Initial control" was assessed by the criteria previously described (Wilson, 1946). All patients who were controlled initially were given maintenance treatment, and from 94 of these it was subsequently withdrawn

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after varying periods of treatment. The decision to withdraw it from individual patients who were satisfactorily controlled was made arbitrarily and without regard to their age and previous history.

Results and Discussion

Initial Control.—Fig. 1 shows that of the 126 patients treated with thiouracil compounds 113, or 90%, were initially controlled, usually after three to six weeks of treatment.

FIG. 1.—Results of treating 126 patients with thyrotoxicosis by thiouracil compounds. White columns=Satisfactory. Cross-hatched columns=Relapsed. I.C.=Initial control. M.T.=Maintenance therapy. W.M.T.=Withdrawal of maintenance therapy.

From the remaining 13 patients (10%) the drug was withdrawn without initial control having been established: 6 of these showed no signs of responding to the drug, 3 developed leucopenia, and 4 developed drug fever and nausea.

Maintenance Therapy.—Of the 113 patients who had been controlled initially, 105 were treated with maintenance doses for periods ranging from 3 to 62 months (mean=18.0, S.D.=12.9). Treatment of the remaining eight patients had eventually to be discontinued because two developed leucopenia five and fifteen months respectively after beginning treatment, one became drug resistant after two years, and five were referred for thyroidectomy on account of increasing thyroid enlargement.

Withdrawal of Maintenance Therapy.—Treatment was withdrawn from 94 of the 105 patients who had been on satisfactory maintenance for periods ranging from 2 to 55 months (mean=17.1, S.D.=12.2). Of these, 55 eventually relapsed at various times after withdrawal (relapsed group), while 39, at the time of the last interview, were still in remission after periods which ranged from 3 to 47 months since withdrawal of therapy (satisfactory group).

Factors Influencing the Incidence and Onset of Relapse

In an attempt to determine what factors might influence a patient's response to withdrawal of maintenance therapy, the two groups (satisfactory and relapsed) were compared with respect to four characteristics which a survey of the literature had suggested as relevant. These were: (1) age at first interview; (2) length of illness; (3) length of treatment before drug withdrawal; and (4) length of remission after withdrawal. It will be appreciated, however, that our satisfactory group includes patients who have been observed for only short periods and therefore may yet relapse.

In Table I it will be seen that the two groups were equally matched in respect of the patient's age and length of treatment before withdrawal of the drug. The mean length of

previous illness in the relapsed group, however, was approximately double that of the satisfactory group, but the scatter is very wide and the difference between the means is not statistically significant.* It is of interest to note that the standard deviation of length of illness in the relapsed group is also double that in the satisfactory group, indicating that the relapsed group has included a greater proportion of patients with illness of very short and of very long duration. The mean length of remission—that is, relief from signs and symptoms after withdrawal of maintenance therapy—is much less in the relapsed group (8.7 months) than in the satisfactory group (24.5 months). The difference between these two means is highly significant ($P<0.001$). This suggests that if relapse is to occur it tends to do so fairly soon after treatment is withheld. This is confirmed by Fig. 2, which shows the distribution of

FIG. 2.—Distributions of relapsed and satisfactory patients in relation to time after withdrawal of maintenance therapy.

length of remission following withdrawal of treatment. It will be seen that 49 out of 55 relapses occurred within the first fifteen months after withdrawal and, further, that of 33 patients with remissions of between 15 and 48 months only 6 have so far relapsed.

The liability to relapse after the withdrawal of treatment can be determined more precisely by arranging the data in the form of a life-table and calculating the probability of an individual relapsing within any given period after withdrawal (Fig. 3). It will be seen that the risk of relapsing is greater within 15 months or so from withdrawal of treatment, and thereafter does not increase greatly. The shape of the curve suggests that not many more relapses are likely to occur after the end of the 36th month following withdrawal. On the basis of our data, the overall probability of relapsing within 48 months after withdrawal of treatment (the maximum time that any of these subjects have been observed) is about 0.66; in other words, the odds are 2 to 1 that a patient will relapse within this period. These results are similar to those of Trotter (1950), except that he found the overall chances of relapse to be about 0.5—rather lower than ours. As he has pointed out, however, since the number of patients studied becomes progressively less, the later parts of this kind of probability curve are less reliable than the earlier. In view of this and the relatively small number of cases involved in each investigation (about 100), the difference between his figure and ours is probably to be attributed to sampling fluctuations.

*In view of the non-normality of the distributions and the discrepancy between the standard deviations, the proportions of satisfactory and relapsed patients above and below the median were compared by a χ^2 test. The results were in agreement with the tests on means.

TABLE I.—Summary of Age, Length of Illness, of Treatment, and of Remission of 94 Patients from Whom Maintenance Therapy had been Withdrawn

	Satisfactory (39)			Relapsed (55)		
	Range	Mean	S.D.	Range	Mean	S.D.
Age at interview (years)	13-73	45.48	14.31	19-69	44.02	11.58
Length of illness (months)	1-44	23.41	29.96	1-240	42.22	58.15
Length of treatment (months)	2-55	16.13	10.97	2-54	17.75	12.97
Length of remission after withdrawal of treatment (months)	3-47	25.54	13.56	1-35	8.67	7.54

FIG. 3.—The probability of relapsing in relation to time after withdrawal of maintenance therapy. In calculating the probabilities, allowance has been made for the fact that the satisfactory patients who had been in remission for only a limited period when the observations ended could subsequently be expected to relapse. To fail to make an allowance of this kind would bias the table. It has, furthermore, been assumed that all satisfactory cases were "at risk" for half the three-months period in which they ceased to be observed.

In order to examine further whether length of remission was related to the age of the patient, length of his illness, or length of treatment, correlations were calculated between these four variables for the relapsed group (Table II).

TABLE II.—Correlations Between Age, Length of Illness, of Treatment, and of Remission for 55 Patients who Relapsed After Withdrawal of Maintenance Therapy

	Length of Illness	Length of Treatment	Length of Remission
Age of patient	+0.064	-0.040	-0.208
Length of illness ..		-0.144	-0.058
" " treatment ..			-0.264

There was no point in calculating similar correlations for the satisfactory group, because for them the length of remission could not be finally determined. As a result, information concerning a number of patients with long and possibly permanent remissions, who from the practitioner's point of view are perhaps the most interesting of all, could not be taken into account. For this reason the correlations we have calculated, using data from the relapsed group only, do not give a complete picture.

It will be seen from Table II that the correlations are all very small. The only one which approaches statistical significance at the 5% level is between length of treatment and length of remission. The correlation is negative, suggesting a possible tendency for longer treatments to be associated with shorter remissions. This is contrary to what might be expected on the basis of previous reports that, if treatment was maintained for longer periods, the patient tended to take correspondingly longer to relapse (Himsworth, Morgans, and Trotter, 1947; Himsworth, 1948; Dunlop and Rolland, 1950). Douglas and Kennie (1952) have shown that the proportion of patients who relapse is much greater among those who have had treatments of less than one year before withdrawal than among patients who have been treated for one to two and a half years or more. However, inspection of their figures also suggests that, of the patients who do relapse, those who have had treatments of one year or longer tend to relapse sooner—in half the time, on an average—than those who have been treated for periods of less than one year. Our own observations provide some striking examples of patients with long remissions following

short treatments; seven patients, for instance, whose treatments were nine months or less were still in remission more than three years after treatment had been withdrawn. Furthermore, out of 12 patients treated for two and a half years or longer, only 2 have not yet relapsed, and in every case the relapse occurred well under twelve months after withdrawal of treatment.

Himsworth (1948) found that in patients with remissions of over two years after withdrawal of the drug the average duration of treatment had been 15 months (S.D.=6.3). This agrees well with our own figures, where the corresponding average for 23 patients with remissions of over two years is 17.6 months (S.D.=8.8). But since this figure is almost identical with the average length of treatment for the whole of our relapsed group (17.8 months, S.D.=13), length of treatment in our sample of patients, at any rate, clearly cannot be used to discriminate between short and long remissions.

The correlation between age of patient and length of remission, though not statistically significant, is negative—suggesting a possible tendency for longer remissions to be more common in younger patients—which is probably what one would expect.

The length of the patient's illness before treatment does not seem to be significantly associated with the length of his remission after withdrawal of treatment. This, however, may not be the case with thyrotoxicosis of several years' standing; for example, out of 13 of our patients who had been ill for more than four years only one had not relapsed at the time of the last recorded interview, and 10 of the 12 who relapsed have done so after remissions lasting only a few months. This high relapse rate among the patients with very long illnesses seems to be the main reason for the discrepancy between the mean length of illness of the relapsed and that of the satisfactory group (Table I).

That there should be no correlation in our sample of patients between length of treatment and age or length of illness is, of course, what might be expected, since length of treatment for each patient was determined at random.

In view of the relative lack of association between length of remission and the three factors which we have examined above, it seems reasonable to conclude that other influences, such as intercurrent infection and social maladjustment (Douglas and Kennie, 1952), may be more relevant in determining a patient's response to withdrawal of maintenance therapy with thiouracil compounds.

Summary

Of 126 patients with thyrotoxicosis who were treated by thiouracil compounds 90% were initially controlled.

Of 113 patients who were continued on maintenance therapy for periods from three to sixty-two months, 105 remained in remission during such treatment.

Maintenance therapy was withdrawn from 94 of the patients after periods of treatment ranging from 2 to 55 months, and 55 relapsed. It has been shown that the probability of relapsing is greatest within about 15 months after withdrawal of treatment. After 36 months the chances of relapsing are slight. On the basis of these figures it has been calculated that approximately two out of every three patients will eventually relapse after withdrawal of treatment.

No consistent relation has been found between the length of the patients' remission and their age, the

duration of their illness, and the duration of treatment. It is concluded that other factors may determine a patient's response to withdrawal of maintenance therapy with these drugs.

We wish to thank Professor E. J. Wayne for the opportunities of studying the cases under his care and the physicians of Sheffield Royal Infirmary for their valuable co-operation. We also wish to thank Dr. A. G. MacGregor for his help and for supplying data on the follow-up of some of the patients, and Mr. Arthur Summerfield for helpful advice on the statistical analysis. Part of the expenses of this research were defrayed by a grant from the Medical Research Council to one of us (A. W.) and to another (H. S.) who is in receipt of a whole-time personal grant.

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MILK, *p*-AMINOBENZOATE, AND MALARIA OF RATS AND MONKEYS

BY

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This paper describes investigations concerning the effect of milk diets upon the course of malarial infections, and the supplementation of such diets by *p*-aminobenzoate, which is a growth factor for many species of plasmodia.

In 1952 Maegraith, Deegan, and Jones reported that infections of *Plasmodium berghei* do not develop properly if the hosts (rats) are maintained on a milk diet. A preliminary communication from this laboratory (Hawking, 1953) pointed out that a milk diet was deficient in *p*-aminobenzoate, which is apparently needed by many plasmodia. It was shown that if *p*-aminobenzoate was added to the milk diet the infection of *P. berghei* developed normally, and it was concluded that *p*-aminobenzoate (or some derivative) is a growth factor for *P. berghei*. According to our conception the body fluids of animals usually contain very little *p*-aminobenzoate (otherwise sulphonamides would not be therapeutically effective against so many bacteria); *p*-aminobenzoate is present in many diets; when ingested in the food it raises the blood concentration sufficiently for malaria parasites to grow; and it is rapidly excreted or destroyed, so that constant renewal is necessary. The interrelationship of growth factors and malarial infections raises so many questions, both practical and academic, that several years will be needed to investigate them adequately. As, however, the subject is of interest to other workers, the results obtained to date are presented here.

Plasmodium berghei in Rats

The animals employed were obtained from the strain of piebald rats maintained at this institute. After preliminary experiments it was found that rats weighing 200 g. were

preferable to those of 100 g. or 50 g., because with the smaller weights suppression of the infection by milk diet was more difficult to demonstrate. The normal diet of these rats is a stock laboratory one which has been described by Bruce and Parkes (1949). Briefly, it contains wholemeal flour 46%, Sussex ground oats 40%, white fish meal 8%, dried skimmed milk 3%, dried yeast 1%, cod-liver oil 1%, and salts 1%. The milk employed was obtained from the ordinary dairy, and had been pasteurized. One sample of it was found by bioassay (kindly performed by Dr. A. T. Fuller) to contain 3.1 mμg. free and 19 mμg. total *p*-aminobenzoate per ml. The rats were housed three in a cage over a grid to allow escape of faeces. They were supplied with milk from a bottle. The bottles were changed morning and evening, and they were autoclaved in between each change. The quantity of milk was limited to the amount which the rats would probably consume in four to five hours, and all other possible steps were taken to prevent the milk going sour. The rats were placed on the diets for two to four days before inoculation. The strain of *P. berghei* was the RSVP strain obtained from Professor P. C. C. Garnham. The inoculum usually contained about 2 million parasitized cells per rat, and it was injected intraperitoneally. The degree of infection was expressed as the number of parasitized red blood corpuscles in a thin stained film per microscope field; this usually contained about 200 corpuscles.

The result of a typical experiment is shown in Fig. 1, in which the intensity of infection in each cage of three rats is shown as the mean of the logarithms of the number of

FIG. 1.—The development of *P. berghei* in rats on milk diet, milk plus *p*-aminobenzoate (P.A.B.) 1/40,000, and stock diet. Each line represents the mean of the logarithms of three rats, the infections being expressed as the number of parasitized cells per 20,000 erythrocytes. Inoculation intraperitoneally on Day 0 with 100,000 parasitized cells per rat. Weight of rats, 190–220 g.

parasitized erythrocytes per 20,000 cells in a thin blood film. (For this calculation, animals which showed no parasites were deemed to have 1 per 20,000 cells; animals dying of the infection towards the end of the experiment were deemed to have 8,000 parasites per 20,000.) This figure shows that the infection of *P. berghei* does not develop in rats on a milk diet (confirming the report of Maegraith *et al.*), but that if *p*-aminobenzoate is added to the milk the infection develops as well as in the control rats on the complete laboratory diet.

In order to obtain suppression of the infection on milk diet various precautions are necessary. Thus the rats employed should be fully adult—that is, weighing 200 g.—in younger rats the suppression is more difficult to obtain. The