TABLE II

	Cases	Hallux Valgus	Hallux Rigidus
A. Free of pain and disablement in hallux and foot	28 (58%) (11 bilateral)	25	3
B. Free of pain in hallux, but some occasional or persistent pain elsewhere in foot or disablement	15 (31%) (5 bilateral)	14	1
C. Not free of pain or disablement	5 (11%) (1 bilateral)	2	3
Totals	48 (31 patients —17 bilateral)	41	7

41 cases of hallux valgus and 7 cases of hallux rigidus (Tables I and II). The number of cases of hallux rigidus is smaller because only severe cases were operated upon, most cases being relievably by non-operative means. One case was treated six years ago, and the patient, a man aged 53, has remained free of pain and disablement and is able to lead a life requiring much standing and walking. The other cases were done during the period September, 1950, to September, 1951. The period elapsing since operation in at least some of these cases is too short for a proper assessment of the value of the method, but the results to date seem to be worth recording.

As with other kinds of operation for hallux valgus or rigidus, the result is affected by the association of other states of the feet which may cause pain or disablement or prevent full recovery of function. Such associated states were present in most of the cases, consisting in splaying of the metatarsus, clawing or other deformity of other toes, onychogryposis, pes plano-valgus, dorsal bony prominences, luxation or stiffness of other metatarso-phalangeal joints, osteoarthritis of these joints or of the tarsal or ankle-joints, rheumatoid arthritis, or varicose veins. One case had had a previous Mayo operation. Nevertheless, of the 41 cases of hallux valgus, there is freedom from pain and disablement, and a normal walk, in 25. In 14 cases of hallux valgus no pain is now felt in the hallux (metatarso-phalangeal joint), but still some pain, occasional or persistent in walking, elsewhere in the foot, or some disablement; in two cases pain in the hallux and disablement persist. Of the seven cases of hallux rigidus, three are free from pain and disablement and walk normally; one still has some pain elsewhere in the foot; and three still complain of pain in the hallux and of disablement.

Thus of 48 cases, 28 (58%) may be deemed quite satisfactory. A further 15 (31%) may also be thought satisfactory, allowing for the presence in most cases of other causes of pain or disablement of the foot. Five cases (11%) are failures in that there has been no relief of pain in the hallux. Failure to relieve pain elsewhere in the foot or disablement has been attributable largely to associated states, such as clawing of the toes with stiffness of the metatarso-phalangeal joints, not being fully amenable to treatment carried out at the same time as that for the hallux valgus or rigidus. But failure to relieve pain in the hallux and in some cases elsewhere in the foot has been due to fixation of the metatarso-phalangeal joint during arthrodesis at an angle of less than 30 degrees of dorsiflexion, so that the patient on walking again has not been able to take weight properly and to rise on to the hallux.

Summary

An operation of arthrodesis of the first metatarso-phalangeal joint for hallux valgus and rigidus is described and advocated for use in adults in preference to the other operations at present in vogue for these conditions.

It is considered that in any operation for hallux valgus or rigidus the need is to preserve the function of the

great toe, and that while arthrodesis of the metatarso-phalangeal joint as described observes this principle, other operations (removal of the exostosis, the Mayo, Keller, and Girdlestone) fail to do so and are therefore unsatisfactory.

[Since the above was submitted for publication a year ago 52 more cases have been treated by arthrodesis, making, in 64 patients, 100 cases in all (36 bilateral)—84 of hallux valgus and 16 of hallux rigidus. A survey of all cases treated up to six months ago has given a similar result to that in Table I for the first 48 cases, except that the proportion of cases of hallux rigidus relieved of pain is higher.]

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THIOURACIL IN TOXIC GOITRE

LATE RESULTS IN A PERSONAL SERIES

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Thiouracil and allied substances have been used in this unit since December, 1943, and a preliminary report was published in May, 1945 (Kennie, 1945). It was decided to make a close personal observation of a series of cases of thyrotoxicosis treated by this method for a period of at least five years. This work was undertaken by one of us (A. T. K.), but was interrupted and continued by the other (D. D.) up to the time of writing. The report which follows deals with the results of thiouracil treatment and the conclusions drawn from a personal series observed over a period of approximately seven years.

Clinical Material

During the period under review 222 cases were accepted for treatment. All the patients referred to the unit as cases of toxic goitre and in whom the diagnosis was considered to be correct were treated by this method. In mild cases the differentiation between anxiety states and thyrotoxicosis is often difficult. Many cases of anxiety neurosis were referred from other sources as toxic goitre, but were rejected for thiouracil treatment at the clinic. Even so, 13 cases included in the series were later thought to be anxiety states. Eleven cases have been excluded because the follow-up period has been less than one year, which is regarded as too short for reliable assessment of the outcome of treatment. In a further 11 cases trace of the patient has been lost. There are thus left for study 187 cases. An assessment of initial severity was made on clinical grounds, the B.M.R. being found less reliable. The numbers in each group were as follows: severe 55, moderate 84, mild 48.

The series comprised 21 men and 166 women, a proportion of males to females of 1 to 8. Their ages ranged from 14 to 68 years. One hundred and eleven were treated entirely as out-patients and were seen at a special weekly clinic. The remaining 76 were in hospital at some stage in their illness. The early cases were all admitted, but, later, out-patient treatment was customary and patients were admitted

only when seriously ill, for operation, or for the control of complications such as auricular fibrillation or congestive heart failure.

Treatment

Management.—The management of cases has been described previously (Kennie, 1945), and can be stated briefly. All patients were told to rest during the first two weeks of treatment and in-patients were given a high-carbohydrate diet. The importance of a large fluid intake was emphasized. Sodium phenobarbitone was given to those who did not sleep well. Patients were warned to report at once such toxic phenomena as inflamed eyes, sore throat, or rash. The dose of thiouracil was divided over the day and the tablets were crushed and given in solution. These few rules were followed strictly in the wards and stressed to out-patients, both orally and by written instruction. To them we ascribe the low incidence of serious toxic phenomena.

Thiouracil.—Thiouracil was used for the early cases and methylthiouracil for the later ones. In the earliest cases the dose used was 1 g. daily, and sometimes more in unresponsive cases, but it was soon found that an increased dosage did not mean better results. Later the dose was reduced to 0.6 g. daily. The reduction in the daily dose was made first at the end of two to three weeks, and again after a further two to four weeks, depending on the patient's progress. A maintenance dose of 0.1 to 0.2 g. daily was given when symptoms were well controlled. In most cases this was achieved by the fifth to the seventh week. In the earliest cases treatment was discontinued when evidence of thyrotoxicosis had been in abeyance for a few months. In common with other observers, it was soon found that prolonged control was necessary to prevent early relapse, and latterly the course has been less than one year only in exceptional cases. Usually it has been a few months more.

Results

The results of treatment have been assessed at the end of the seven-year period. As in most diseases which are not usually fatal and which run a prolonged course with natural remissions, the assessment of results of treatment is difficult in thyrotoxicosis. Between the case which is a complete success and the one which is a complete failure an infinite variety of results is possible. In the scheme that has been adopted cases classified as "complete remissions" are those which have been relieved of all symptoms and in which weight has returned to normal, tremor and sweating have gone, the patient's manner has become calm, and normal employment has been resumed. Tachycardia is known to be one of the last signs to disappear under this treatment, and some of our patients had a labile cardiac rate. Those with "satisfactory remissions" have been relieved of most of their symptoms, have gained weight, and have resumed employment, but still have some residual evidence of thyrotoxicosis, such as tremor, tachycardia, or nervousness.

The results are presented in Table I. The figure of 45% of patients who had a complete remission is in general

TABLE I.—Results

Complete remission and cessation of treatment, without relapse	84 (45%)
Complete remission and cessation of treatment, later relapsing	46 (25%)
Satisfactory remission, requiring continued maintenance, not relapsing	23 (12%)
*Satisfactory remission but relapsing while still on maintenance	12 (6%)
*Failure of thiouracil to achieve a remission	18 (10%)
Thyroidectomy chosen because of large goitres	4 (2%)

* Five deaths occurred among the patients in these two groups, mostly from unrelated causes. These cases are described later.

agreement with other reported series. Himsworth *et al.* (1947) and Eaton (1947) record 40% of cases remaining "apparently cured" two years after the beginning of treatment. Williams (1950) claims 48% of cases with a sustained remission.

Doubtless further relapses will occur among these 84 cases at present completely well, but many of them have been under observation for a long time (Table II), the earliest cases having had remissions of almost seven years, and it is reasonable to expect that the number of fresh relapses will be small.

TABLE II.—Duration of Remissions at End of Seven-year Period (Calculated from Cessation of Treatment)

Duration	No. of Cases
Over 5 years	15
" 4 "	10
" 3 "	13
" 2 "	12
" 1 year	15
Less than 1 year	19
	84

Relapses

Of the 130 patients who were able to discontinue treatment 46 (35%) had a relapse, and a further 12 relapsed while still on a maintenance dose of thiouracil. It is now generally recognized that at least a year's treatment is necessary to give the greatest chance of prolonged remission (Himsworth, 1948; Dunlop, 1948; Means, 1948; Williams, 1950). Our experience is in complete agreement, as Table III shows. From this it follows that the optimum length

TABLE III.—Relation of Length of Treatment to Rate and Rapidity of Relapse

Length of Course of Treatment	No. of Cases	No. of Relapses	Average Time Off Treatment Before Relapse
Less than 6 months	11	8	15.4 months
6 months to 1 year	50	19	20.2 "
1 to 1½ years	37	9	9.7 "
1½ to 2 "	16	7	6.6 "
2 to 2½ "	11	5	
More than 2½ years	17	10	

for thiouracil treatment is about one year, and that if a patient has not attained a completely euthyroid state by that time the chance of doing so without subsequent relapse becomes rapidly and progressively less. Not only does the resistant case have less chance of a remission free of relapse but the remission itself is likely to be much shorter than that of a patient who has responded quickly.

Factors Associated with Relapse

Table IV emphasizes the importance of social problems. We had the enthusiastic co-operation of the hospital almoner and her staff, and with their assistance an attempt has been made to investigate the social background of each patient. The almoner was present at each clinic, interviewing all new cases and such of the return cases as were

TABLE IV.—Incidence of Adverse Factors

	Relapse-free Cases (Total 107)			Relapses (Total 58)		
	Off Treatment (84)	On Maintenance (23)		While Off Treatment (46)	On Maintenance (12)	
Social problems:						
A. Marital unhappiness	1	3	10.3%	4	2	29.3%
B. Illness or death of close relative ..	5	2		8	3	
C. Bad housing ..	4	1	15.9%	3	0	15.5%
D. Financial strain ..	7	0		2	0	
E. Unsuitable work ..	3	2		3	0	
F. Delinquency in patient ..	0	0		1	0	
Infections ..	15	0	14.0%	6	4	17.2%
Complicating disease ..	9	1	9.3%	6	1	12.0%
Premature cessation of treatment by default ..	0	0		0	2	3.4%
Total ..	44	9	49.5%	33	12	77.4%

necessary. She also often visited in their homes those who for some reason were prevented from reporting.

To us the type of social problem present seems to be of the utmost importance. Marital unhappiness or the serious illness or death of a close relative was directly responsible for 17 relapses (29%). The marital unhappiness was mostly of very serious nature: desertion, unfaithfulness, or drunkenness. Among the illnesses of relatives were tuberculosis, carcinoma, insanity, rheumatoid arthritis, and disseminated sclerosis. When the invalid was a husband financial strain was often added—as instance a family who were compelled to sell a house which had been purchased through a building society and on which the instalments could not be continued. There is also frequently a call for heavy nursing in such cases, in addition to normal household duties and sometimes the care of young children. Such problems not only affect the individual in the most intimate way, but are often those which the almoner can do little to remove.

By contrast, serious marital disharmony was present in only four of the cases which did not relapse, and serious illness or death in a near relative occurred in a further seven cases, making a total of 10%. In one of the four cases of marital unhappiness the problem was solved by the almoner. The change in the patient was dramatic, and there is no doubt that her recovery owed as much to relief from her unhappiness as to medicinal treatment. It is to be noted that the remaining three cases have required continued maintenance therapy.

Poor housing conditions, financial strain, and unsuitable work are problems which can be viewed by the patient more dispassionately, and they are also more easily alleviated by the almoner. They formed the bulk of the problems found in those who remained well on treatment. The almoner's note, "No settled home since marriage," occurred several times, and many patients were living in a room in the house of "in-laws" with the almost unavoidable sense of lack of freedom and privacy, or with actual friction. For such a patient the acquiring of a house of her own often initiated recovery. In comparison, financial strain and unsuitable work were straightforward problems to the almoner.

In 10 cases an intercurrent infection was thought by the patient to be directly responsible for the relapse. Such infections are common and unavoidable. They occurred with roughly equal frequency among those who did not relapse. Yet it is our clinical impression that the patients were right in attributing to them responsibility for their relapse. It may be that the infection was only the final precipitating factor. Respiratory and upper-respiratory-tract infections, as might be expected, were the most numerous, but there was a slight difference in severity and type of infection in the two groups, which may be significant, although the numbers are not large enough for reliable judgment.

Subsequent Treatment of Patients Relapsing

When a patient relapsed the treatment best applicable to the case had to be reconsidered. In four of the 58 relapsed cases operation was advised and carried out instead of a further trial of thiouracil: two of them have made a full recovery and two have had recurrence of symptoms. Forty-two patients responded to a second course of thiouracil, but so far only 16 have obtained a second complete remission and have been able to discontinue treatment for the second time. The remaining 26 still require maintenance therapy. Several second relapses have occurred, and most of the remissions in this group are of short duration as yet, so that more relapses are to be expected. Four patients in the group died, three from an unrelated cause, and one in a thyroid crisis when treatment was prematurely stopped elsewhere. They are referred to later. Six defaulted, and in the remaining two cases other forms of medical treatment were given.

The results in the relapsed cases are therefore far from satisfactory. One may say that these patients have themselves demonstrated their unsuitability for further thiouracil treatment, and, provided there are no serious contraindications, operation should be carefully considered. It is instructive to find that of the original 187 patients 49 still have to continue treatment.

Failures

In 18 cases (10%) thiouracil failed to produce an adequate remission of symptoms. In four the cause was intolerance to the drug. In the remaining 14 there was no response or it was inadequate. Of these 18 patients, 14 came to operation, but only 7 obtained a complete remission of symptoms. There was one post-operative death.

This experience confirms that of others, that the patient who does not respond to thiouracil often fails to respond well to thyroidectomy. Nevertheless, of these 14 cases, 7 have obtained from operation a remission which thiouracil could not give them. There were no outstanding social problems or intercurrent illnesses in this group, which would suggest that failure to respond to thiouracil is not due to the same factors as relapse.

Operation

The purpose of the investigation being the evaluation of thiouracil therapy, thiouracil was used whenever there was a legitimate choice of treatment. Operation was advised only when thiouracil was contraindicated. In all, 23 thyroidectomies were performed. Reference has already been made to 18 operations following relapse, or intolerance to or failure of thiouracil. There were, in addition, four cases of very large goitre, all having a complete remission after operation. The reason for operation in the remaining case was suspected malignancy. The patient had responded very well to thiouracil and had been off treatment for more than four years, when she was noted to have developed a very hard nodule in the thyroid. The fear of neoplastic change was not confirmed histologically. It is of interest to note that although the thyroid hyperplasia induced by thiouracil might, in time, be expected to lead to malignancy, and has done so in animal experiments (Williams, 1950), no established human case has yet been reported.

Toxic Reactions

Toxic phenomena encountered were those of common experience—painful eyes, skin eruptions, sore throat, leucopenia, agranulocytosis, nausea and vomiting, diarrhoea, and jaundice. Agranulocytosis occurred in only one patient, who had ulcers in the mouth, sickness, and diarrhoea, but no sore throat. No further thiouracil was given, and the blood condition improved rapidly. She was later found sensitive to a number of other drugs. No patient was rendered seriously ill and there were no deaths from toxic reactions.

Auricular Fibrillation

Fibrillation was found in a total of 23 patients. Eleven of these were over 50 years of age. One also had mitral stenosis. There is general agreement that auricular fibrillation of thyrotoxic origin will often cease when thyrotoxicosis is brought under control, whatever the treatment employed.

TABLE V.—*Auricular Fibrillation (Total Cases, 23)*

Treatment Employed	Normal Rhythm Restored	Fibrillation Unaffected	Later Relapse to Fibrillation
Course of thiouracil alone ..	9	5	—
Course of thiouracil followed by quinidine ..	8	—	4
Thiouracil premedication and operation	1	—	—

In nine cases normal rhythm returned spontaneously during the course of thiouracil. When this result had not occurred by the time thyrotoxicosis was believed to be fully controlled, one or more courses of quinidine were given, provided there were no contraindications to its use. Normal rhythm was restored by this means in a further eight cases. Quinidine was contraindicated in five cases, and these remain in fibrillation. In one case normal rhythm returned after thiouracil premedication and thyroidectomy.

Relapse to auricular fibrillation occurred in four cases in association with relapse of thyrotoxicosis. All four had originally required the use of quinidine after effective control of thyrotoxicosis. Two were again corrected with quinidine, but one has relapsed to fibrillation for the second time. This was the patient with mitral stenosis. She had a thyroidectomy performed, but fibrillation remains.

Pregnancy

Pregnancy has not proved a serious difficulty, and this is an important merit in thiouracil treatment. Joll (1932) regards the ability to bear children successfully without relapse as indication of successful treatment. Miscarriage is still apt to occur if the pregnancy precedes the beginning of treatment or the effective control of the thyrotoxicosis, but has not occurred in this series after effective control has been established.

In all, 14 pregnancies have been observed. Two patients became pregnant for the second time during the period under review. Five patients became pregnant either before or immediately upon the beginning of treatment; three of them miscarried, and two went on to a successful confinement. In nine cases pregnancy occurred after control of thyrotoxicosis, and all, including two who had had earlier miscarriages, went successfully to term. The only relapse occurred in the case of the patient who developed puerperal sepsis. Thyrotoxic symptoms recurred while she was in an isolation hospital, but no special treatment was given, and nothing was heard of her at the clinic until she reported two months later looking very ill and with a recurrence of all her signs and symptoms. She has since made a good recovery after operation.

Goitre and cretinism have been reported in the infants of mothers receiving thiouracil (Eaton, 1945; Ball and Morrison, 1948) but were not encountered in this series. It is our custom to discontinue thiouracil, if it is still being given, about a month before term and to replace it with iodine.

Deaths

Five deaths occurred during the period under review. Three of these patients had responded well to thiouracil and had been able to discontinue treatment for some time. The causes of death were diphtheria, mitral stenosis with congestive failure, and cerebral haemorrhage respectively. Reference has already been made to the one post-operative death, that of a man aged 61 who also had bronchiectasis, who was acutely ill, and in whom thiouracil had failed. Operation, in spite of the risk entailed, was regarded as his only hope of recovery. The fifth fatal case was that of a woman who was well and on a maintenance dose when she was admitted to hospital with suspected appendicitis. She was not operated upon, but one month later, during which time she was undergoing investigation and had been given no thiouracil, she developed a thyroid crisis for which treatment was unavailing.

Of these deaths only that of the last-mentioned patient can be attributed to the choice of thiouracil therapy.

Discussion

The majority of those reporting their experience with thiouracil have given it their rather guarded blessing. There is general agreement that drugs of this group have a valuable part to play. They control the effects of thyrotoxicosis more completely than does iodine. They are ideal for patients in whom operation is contraindicated. They are excellent in

the preparation of a case for operation. On the other hand, while one-third to one-half of all cases of thyrotoxicosis given thiouracil as the principal line of treatment may expect a long and probably permanent remission, the greater number will relapse after responding in varying degree or will fail to respond.

Primary thyrotoxicosis, at least, is regarded as a disease which runs a natural course and ultimately subsides, and the hope in the mind of the physician using thiouracil is that he can suppress the symptoms of the disease and protect his patient from its effect until such time as the natural remission occurs. Our experience seems to suggest that in more than half the cases this hope will not be realized. If the cause of the disease is the impact of unfavourable environment on a susceptible constitution, as is generally believed, the failure of thiouracil is understandable. It cannot alter the constitution. It has no permanent inhibitory effect on the thyroid gland. If the natural remission, as seems likely, is most often due to the aggravating circumstance ceasing to act for a time, and not to the disease "burning itself out" by exhaustion of the thyroid gland or in some other way, then all the factors necessary to produce the disease remain present and capable of reacting to the next suitable stimulus. Thus the high relapse rate is easily understood.

We feel, therefore, that treatment with the thiouracil type of drug is far from ideal. Psychic trauma and infection are the common experience of everyone, and cannot be avoided. The patient whose thyrotoxicosis is being suppressed by thiouracil or who has achieved a remission with its aid is constantly at risk of a relapse, even after long intervals. Nine of our cases relapsed after more than two years of perfect health, and one case after more than three years. If the suppression has been incomplete insidious damage has quite probably occurred, particularly in the cardiovascular system, which may also be showing the effects of age. In this way the patient may finally be advised operation when less fit.

There are other risks to be faced. Fortunately, toxic reactions are usually mild. Thiouracil treatment extends over long periods, and regular medical supervision is essential. Some patients will inevitably, by removal or otherwise, leave the care of the physician who initiated treatment. There are innumerable ways in which treatment may be stopped prematurely. Our patient who died in thyroid crisis after treatment was discontinued elsewhere is a good example. Prolonged treatment is in itself apt to produce some degree of neurosis in the patient, especially in a group whose mental constitution is often already unstable. Even the special clinic, while very convenient for the doctor, is not ideal for the patient in this respect.

As stressed by Dunlop (1948), the physician has a natural reluctance to interfere radically with the endocrine system of a young person with primary thyrotoxicosis, but thyroidectomy has at least a theoretical advantage over medical treatment. While both act by breaking the sequence of events producing the disease at the same point—namely, the thyroid gland—thyroidectomy does so in a permanent manner by actual removal of functioning thyroid tissue, while medical treatment leaves the functional capacity of the gland intact. Relapse after thyroidectomy, therefore, can occur only when enough gland has not been removed, but the decision on exactly how much to remove in any individual case can usually be made after careful assessment and consideration. Thyroidectomy has the added advantage that when relapse does occur it is usually relatively mild, whereas with thiouracil and a fully functioning thyroid gland the relapse may be, and often is, more serious than the original illness.

The test of the matter lies in the results to be obtained from the two treatments, but it is widely recognized that comparison is difficult. As many writers point out, the substantive results of thyroidectomy, both here and in America, are not known. We can only quote the figures for such institutions as university centres and special thyroid clinics,

and there is no doubt that their results are much superior to those obtained over the country generally. The best comparative series is that of Himsworth *et al.* (1947), who studied 65 cases treated medically and 93 cases treated surgically. The groups were in every way comparable, and the authors found little to choose between the results obtained. At 30 months after beginning treatment, approximately 40% in each series were "apparently cured." The criteria of "apparent cure" employed were very stringent.

Many writers have commented on the fact that symptoms may remain after thyroidectomy, but that they do not vitiate the benefit of the operation. Joll (1932) stated that "if complete and permanent disappearance of all signs and symptoms of the disease is to be the necessary criterion for success, comparatively few patients would pass the test." Martin (1948) came to the conclusion that eye signs were the only true residua of thyrotoxicosis. Other features, such as nervousness, palpitation, sweating, tremor, and labile pulse rate, he attributed to constitutional factors, to the emotional effect of the disease and operation, or to unrelated causes. Rundle (1941) suggested that the disease permanently canalized the responsible nervous pathway.

The value of any form of treatment is probably better indicated by the relapse rate than by persistence of symptoms. Most will agree that a large proportion of patients with thyrotoxicosis receive permanent relapse-free benefit from thyroidectomy. Williams (1950) records only 15 recurrences in 195 thyroidectomies, Robertson (1948) only 2 unsatisfactory cases in 250. Joll (1932) had 90% cured and another 7.2% classed as improved in a total of 795 cases: 35 (4.3%) required a second removal, the figures quoted being the final outcome. It is against such favourable results that thiouracil must be judged. Himsworth (1948), speaking of the comparison in a later article, states that the "majority receive lasting benefit" from operation, but that only two-thirds of thiouracil-treated cases can expect a probably permanent remission after their first course of treatment.

There is no doubt that operation carries a slightly higher mortality rate (probably not more than 2% against 0.5% for thiouracil). There is also a risk of complications such as myxoedema, hypoparathyroidism, and vocal-cord paralysis, which do not arise with thiouracil; their incidence, however, is very low. Williams (1950), in the series already quoted, had four cases of myxoedema, two of hypoparathyroidism, and two of cord palsy in 195 cases. In Joll's (1932) much bigger series there were only four cases of partial myxoedema, none of tetany, and six (0.75%) of unilateral cord palsy. We feel that these disadvantages of operation are outweighed by the uncertainty of the final outcome in thiouracil-treated cases. We suspect that, although the employment of thiouracil in itself does not involve a significant mortality rate, there is probably a hidden mortality among the unsatisfactory cases and the defaulters, when some subsequent illness is complicated by incompletely controlled thyrotoxicosis.

Obviously there are certain cases in which operation is the treatment of choice, such as those with a very large goitre, those with pressure symptoms, and those regarded as too unreliable to embark on medical treatment. On other occasions one has to accept operation because the patient has proved resistant to thiouracil or has had toxic reactions. There are times when the economic factor requires that the illness should be as short as possible. This need not always exclude the use of thiouracil, since patients are fit for work as soon as they are on a maintenance dose, and mild cases may even be allowed to remain at work from the start. On the other hand, severity of illness, the presence of serious complicating disease, or the preference of the patient may suggest the employment of thiouracil. There remain a majority of cases for which the two forms of treatment must be judged on their own merits. Himsworth (1948) has suggested that all such cases should have a full trial of thiouracil at first. If relapse occurs after cessation

of treatment the patient may have either a further course of thiouracil or an operation.

As a result of our investigation we now feel a bias towards surgery and would suggest that a patient coming under treatment for the first time should not be advised against operation if that is his wish, and that a patient who has relapsed after adequate treatment with thiouracil should be strongly advised to have operation unless he himself is definitely averse to it. In saying this we are influenced not only by the facts presented but by a firm clinical impression that the patient who has had a successful thyroidectomy is in some indefinable way better in mental and physical health than the patient successfully treated with thiouracil. We feel, like Dunlop (1948), that "the ultimate beneficial effect of operation may be superior."

Summary

The results of thiouracil treatment of thyrotoxicosis are reported in a series of 187 cases observed for periods of from one to seven years. A complete remission was obtained in 130 cases and an incomplete remission in a further 35 cases, but 58 have relapsed. The factors contributing to relapse are considered, and the importance of social problems and intercurrent infections is stressed. Thiouracil is effective in the control of auricular fibrillation of thyrotoxic origin and of thyrotoxicosis complicating pregnancy.

A comparison is attempted with the results of operative treatment, and a preference for surgery is expressed.

We wish to thank Dr. David Smith for permission to make this investigation and for much invaluable help and encouragement throughout. We also acknowledge our indebtedness to Miss Alison Keen, the hospital almoner, and her staff for their whole-hearted co-operation.

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An experiment by which carcinoma of the lung in mice was induced by cigarette smoke is described in *Science* (November 21). Dr. J. M. Essenberg, of the Department of Anatomy, Chicago Medical School, used an apparatus with two chambers, air being drawn through one, and air and smoke through the other. Thirty-six mice were put into each chamber and kept there for a year. They were from a strain that had a hereditary tendency to lung tumours. At the end of the experiment 23 in the smoked chamber and 32 in the control chamber were well preserved. They were then killed, and their lungs were sectioned serially. Of the 23 smoked mice 21 showed primary neoplasms of the lung, while of the 32 control mice only 19 showed primary neoplasms of the lung. These are 91.3% and 59.4% respectively, and the difference was found to be statistically significant. The smoked mice grew more slowly than the controls, and no young were obtained from them, though the controls reproduced freely. There was considerable variation in the size of the tumours. In some mice the entire lobe of the lung was a mass of tumour tissue, while in others the tumour was small. In some it started from a single focus, in others it was multifocal. Papillary adenocarcinoma was the commonest type of tumour, but adenomas were also found. Morbid changes were also noted in the reproductive organs, endocrine glands, kidney, and liver.