drug or a similar thiouracil derivative may be the ultimate answer to the problem of the small diffuse goiter with hyperthyroidism.

SUMMARY

1. The development of the anti-thyroid drugs has obviated the necessity of performing thyroidectomy on bad-risk patients at least until the hyperthyroidism is completely controlled.

2. If the bad-risk patients are treated or prepared for operation by thiouracil, the mortality following thyroidectomy performed on the remaining (good-risk) patients is less than that of treatment with thiouracil.

3. The morbidity (injury of recurrent laryngeal nerves, tetany, etc.) associated with thyroidectomy is less than 1 per cent.

4. In view of the low mortality and morbidity of thyroidectomy thiouracil is not recommended for routine treatment or preparation for operation and its use is reserved for those cases presenting unusual risks.

5. Thiouracil accomplishes a physiologic rather than an anatomic thyroidectomy and the mechanism by which it produces a remission is comparable in many respects to that of thyroidectomy.

6. It is hoped that some of the newer anti-thyroid drugs (propyl thiouracil, etc.) now under trial will prove to be non-toxic and will afford a means of effectively controlling hyperthyroidism without recourse to thyroidectomy.

REFERENCES

1. McCullagh, E. P., Dinsmore, R. S., and Keller, F.: Thiouracil in the treatment of complicated hyperthyroidism. Cleveland Clin. Quart. **12**:3-15 (Jan.) 1945.
2. Griesbach, W. E., and Purvis, H. D.: Studies on experimental goitre; thyroid adenomata in rats on Brassica seed diet. Brit. J. Exper. Path. **26**:18-24 (Feb.) 1945.

PRESENT STATUS OF THIOURACIL*

E. PERRY McCULLAGH, M.D.

It is now four years since Kennedy and Purves reported the effects of feeding Brassica seed diets to rats,[1] the goitrogenic effects of which were later shown to be due to their content of allyl thiourea. Their early studies showed that this goiter-producing effect was absent in hypophysectomized animals.[2] Since that time the work of the Mackenzies[3] and Astwood[4] has been followed by a flood of experimental and clinical literature on the subject.

* Presented in part as a lecture at the Post-graduate Course under the Auspices of the American College of Physicians, Chicago, November, 1945.

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

PHYSIOLOGIC EFFECTS

Thiourea has been shown to produce cretinism in rats[5] and to retard metamorphosis in tadpoles.[6] Enlargement of the thyroid occurs in rats in a few days on thiouracil feeding and recedes rapidly when feeding is stopped.[7] Such glands become highly vascular, with tall columnar cells lining their acini and with a marked decrease in colloid. In the pituitary gland thiourea causes a decrease in the number of acidophile cells and an increase in the basophiles, some of which are vacuolated. All of these changes apparently are due to a disappearance of thyroid hormone, since they can be prevented by giving thyroxin.[3]

Astwood found an almost complete disappearance of iodine from the thyroid gland of thiouracil-fed rats as early as five days,[7] and Larson showed that the thyroid glands of thiouracil-fed chicks[8] fail to take up radioactive iodine as well as do normal glands. The adrenal cortex atrophies under the effect of thiouracil,[9] and the plasma proteins change with an increase in β globulin, as after thyroidectomy.[10]

The mechanism by which these actions take place is thought to result from interference with certain enzyme systems necessary for the normal conversion of diiodotyrosine to thyroxin, since thiouracil tends to reduce the action of peroxidase[11] and tyrosinase.[12]

In the human, according to Williams,[11] absorption of thiouracil is very rapid and occurs chiefly from the stomach and duodenum. It is distributed rapidly throughout the body and can be demonstrated in high concentration in the pituitary, thyroid, and adrenal glands, and bone marrow. The white blood cells show a relatively greater concentration than the red cells.

None of the material is excreted in the stool, and about one-third may be excreted in the urine at ordinary dosage levels. The remainder presumably is changed in the body, probably in the liver.

The chief features of the physiologic action of the drug are summarized by Astwood:[13] "Shortly after the drug is administered the organism becomes unable to synthesize thyroid hormone at a normal rate, and the quantity of circulating hormone tends to fall. In response to this deficit an excess of thyrotropin is produced by the pituitary, which stimulates the thyroid to hyperplasia and to the release of the normal thyroid hormone stores therein. Within forty-eight hours of the first administration of the drug these compensatory changes are histologically visible, and for a number of days this mechanism is adequate to maintain the metabolic rate at a normal level. Eventually, however, the store of normal thyroid hormone is exhausted, as evidenced by a complete loss of demonstrable colloid at the end of seven to ten days, and as new

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

hormone can be made only at a reduced rate, the metabolic rate falls even though thyroid hyperplasia is still advancing."

THIOURACIL IN HYPERTHYROIDISM

In human hyperthyroidism the use of thiouracil produces a similar sequence of events. The thyroid gland becomes more vascular and hyperplastic and tends to enlarge. The rate of production of thyroid hormone diminishes, and as the stores are depleted the metabolic rate falls. Signs of hyperthyroidism disappear together with amelioration of associated conditions such as fibrillation or diabetes, which may have been caused or aggravated by the excess of thyroid hormone. If the drug is continued, myxedema may supervene. Rawson *et al.*[14] showed that in Graves' disease the thyroid gland treated with thiouracil had a decreased ability to retain iodine and that thyroglobulin prepared from such glands had a decreased physiologic activity when fed to myxedematous patients.

In a fairly large percentage of cases, some toxic effects are evident, the frequency depending to some extent on the dose used.

It is almost certain that over 6000 cases have been treated with thiouracil. My own experience covers 106 patients, almost entirely representing poor risk cases or instances of recurrence of hyperthyroidism after surgery.

THE DOSE

Early in the use of thiouracil the tendency was to use doses as large as 1.0 Gm. per day; more recently workers begin with doses not exceeding 0.6 Gm. and often 0.4 Gm. per day. We have adopted the plan of beginning with 0.6 Gm. per day in severe cases and 0.4 Gm. per day in those less severe. In all instances an attempt is made to reduce the dose to 0.4 Gm. per day or less as soon as definite clinical improvement occurs; when the metabolic rate approaches +15 per cent, we attempt to reduce the dose to 0.3 Gm. per day or less. We have not tried as a rule to discontinue the drug unless the metabolic rate has been maintained at normal range for at least two months. Blood counts are done twice weekly in cases showing any tendency to fall in level of white cells, and in all instances weekly blood counts are continued for at least fourteen weeks, then at less frequent intervals if the dose of thiouracil is reduced. At first the patient is seen weekly and later every two or three weeks. The metabolic rate is usually determined at intervals of two to three weeks until control is established, after which it is tested at less frequent intervals. The danger of agranulocytopenia from this drug is such that

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

we believe it should not be given except in cases where the blood count can be followed frequently.

RESPONSE TO THERAPY

The response to therapy in patients in whom there are no complications, in whom the goiter is not large, and in whom iodine has not been used for more than four weeks, is roughly predictable in most cases but varies widely in a few. The average fall of metabolic rate is about 1 per cent per day. Many cases, however, respond much more slowly. Chart 1 represents a group of patients with moderate hyperthyroidism. The first B.M.R. charted was taken before treatment in each case. The second B.M.R. is the one which first became normal or one representing the first level determined after twelve weeks of therapy. One patient previously untreated failed to show any response until after the dose was increased to 1.4 Gm. per day in the fourth month of treatment. She was

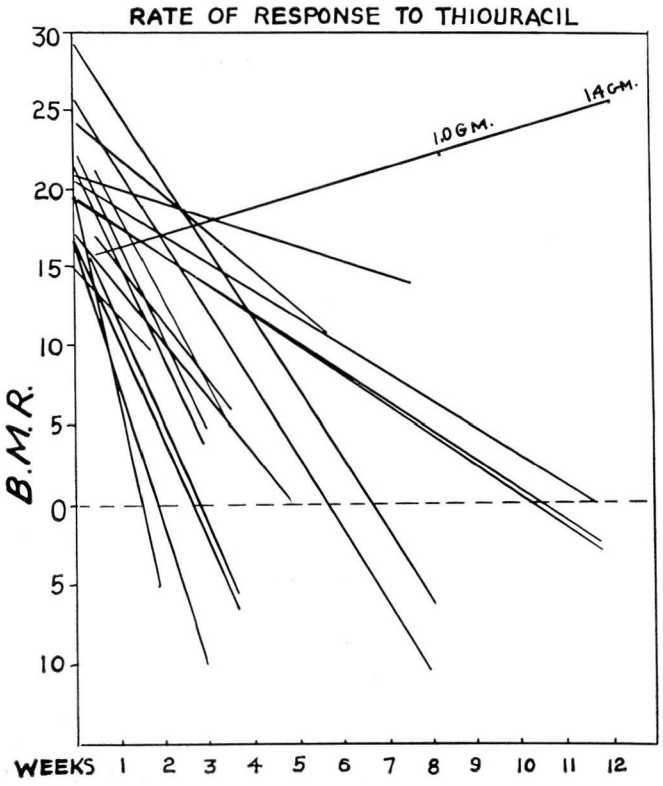

Chart 1

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

33 years of age and had a hyperplastic goiter of moderate size. In more severe cases (chart 2) the response is slower and varies greatly, and in a few, considerable resistance to treatment may be present for many months (chart 3). Such resistance is demonstrated by a woman, aged 55, now under observation. Thiouracil was begun in April, 1944. The metabolic rate decreased from +68 to +8 in four months but rose promptly when the thiouracil dose was reduced to 0.2 Gm. per day. Thyroid lobectomy was performed after one year of treatment. Lugol's solution 1 cc. 3 times per day was given for six weeks preceding operation. Later, following four months of thiouracil therapy, the metabolic rate was not less than +24 per cent in spite of doses of thiouracil as high as 1.2 Gm. per day.

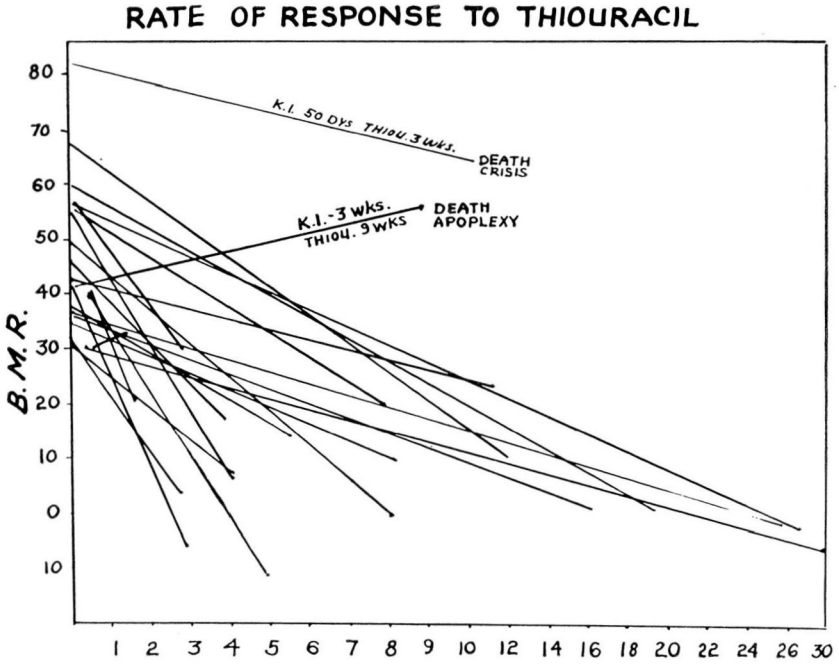

Chart 2

SYMPTOMS

The symptoms of hyperthyroidism disappear at about the same rate as the metabolic rate falls. The subjective symptoms are the first to be affected, disappearing in a few days in those patients who respond rapidly. There is usually a lag in the disappearance of the tachycardia present, and weight gain may not appear until the metabolic rate

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

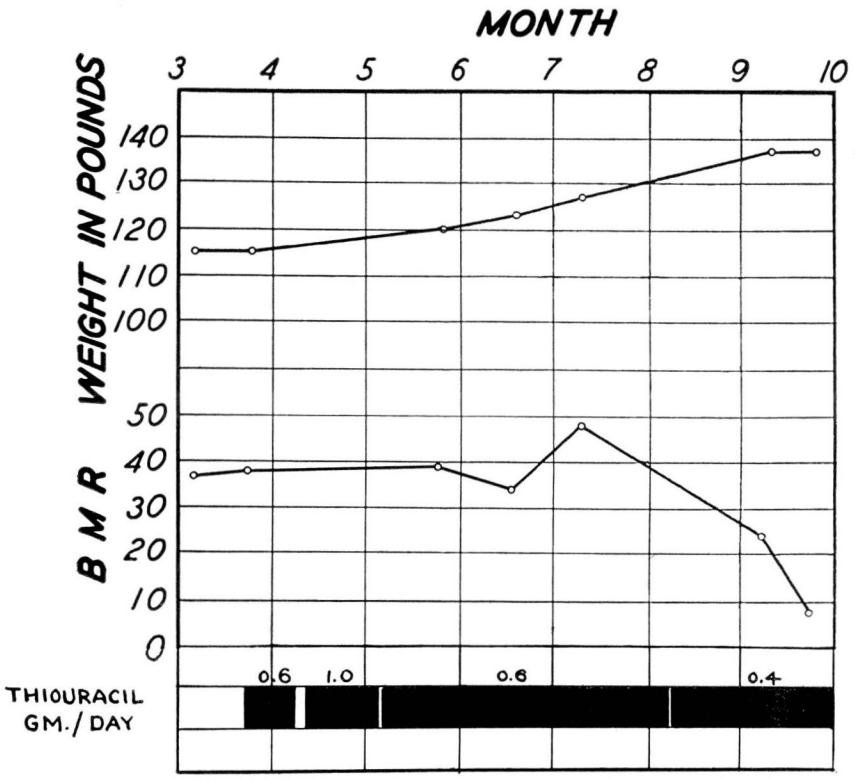

Chart 3

begins to approach normal if the patient is allowed to follow his own inclinations in eating. However, weight gain can be forced from the beginning in almost all patients if the caloric intake is high enough. By giving as much as 4000 calories per day we have seen gains of as much as 20 pounds in weight while the metabolic rate was 40 per cent or more above normal.

Exophthalmos appears to be relatively unaffected by thiouracil therapy. In most cases it does not increase, as might be expected according to existing theories. It may increase and decrease in the same patient during prolonged thiouracil therapy. Until the mechanism of its production is better understood, hypometabolism should be avoided during the use of thiouracil. Williams and Clute[15] have observed the continued increase in malignant exophthalmos and the occurrence of corneal ulcers during thiouracil therapy.

Cardiac decompensation tends to disappear gradually with the control of hyperthyroidism. Five of our patients had auricular fibrillation

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

which disappeared on thiouracil and digitalis in 2 and persisted in 3. McGavack[16] mentions 10 cases of fibrillation, 6 of which reconverted to a normal rhythm on thiouracil alone. Brawny edema is likely to remain, and peripheral edema may occur as a result of the drug.

Diabetes tends to become less severe during thiouracil, just as it does after thyroidectomy. In one of our patients on a constant diet we observed a fall in insulin dosage from 310 units to 60 units per day during therapy. Early in the treatment approximately 310 units were used daily for several weeks.

The size of the thyroid gland often increases after six or eight weeks of therapy. Such an increase was noted in 5 of our analyzed cases. The enlargement is usually mild. The gland tends to be solid at first, and in the diffusely enlarged ones a thrill and bruit can often be heard after a few weeks of therapy. On the basis of experimental findings thyroid feeding has been used to prevent such thyroid enlargement. Good results have been reported. Several small doses of iodine have been much more effective in reducing the vascularity, though we have seen little effect on gland size. In 2 of our patients the goiter increased enormously in size. In 1 of these, desiccated thyroid was given and, in error, the patient took 4 grains per day for a month. No change in size of the goiter was seen and the thrill and bruit remained pronounced. After taking 10 mg. of iodine per day for ten days the thrill and bruit were gone. In some cases after many months of thiouracil treatment the goiter may become quite soft.

At operation, glands of thiouracil-treated patients may be very bloody even after iodine treatment for some weeks preoperatively. Some glands, however, after ten to twenty days of iodine therapy are little, if any, more vascular than after iodine therapy alone. Microscopically they may show marked involution and evident retention of colloid.

REMISSIONS

It is evident that if a lasting remission cannot be brought about by thiouracil, and if the risk of surgery is not greater than the risk of using the drug, thiouracil is of no advantage to the patient. No one to date has been able to define any criteria by which to judge when the drug may be stopped, in what cases a remission may be expected, or how long the remission will last. Remissions have been reported where treatment has been carried on for periods varying from two to sixteen months. In many patients it appears that an increase in thyroid activity occurs in a few days to a few weeks after discontinuing the drug. Astwood has mentioned 9 cases with remission lasting up to sixteen months. In Fishberg and Verzimer's 96 cases, remissions lasting as long as fifteen months

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

have been obtained in 16 per cent of the cases.[17] In our analyzed group remissions have occurred in 10 cases after one to twenty-five months of treatment and have lasted as long as fifty-two weeks. In 9 other cases an attempt was made to stop the drug, but it became necessary to resume it. After fifteen months of therapy a sharp increase in metabolic rate and symptoms was seen in 1 patient when she reduced the dose below 0.4 Gm. per day. In another patient a similar recurrence was seen after five months' treatment when the dose was reduced to 0.2 Gm. Williams,[18] in a series of 247 cases treated, has attempted to withdraw therapy and to maintain a remission in 100. In half of these it was found necessary to resume the treatment. It is generally agreed that thiouracil produces a more complete remission than any other previous form of medical therapy, but the total advantage is reduced greatly by its toxic effects.

TOXIC EFFECTS

Toxic effects appear in 14 to 20 per cent of cases treated. Various estimates place the frequency of toxic effects at about 15 per cent and agranulocytosis at about 1 to 2 per cent. In many the toxic effects are mild. In most the drug can be used in decreased dosage without a return of symptoms. Toxic reactions apparently are more apt to occur (a) with large daily doses, (b) in severely ill patients, and (c) when the drug has been stopped for intervals and repeated.

TOXIC EFFECTS OF THIOURACIL

Mild	**Moderate**	**Severe**
Headache	Nausea	**Agranulocytosis**
Malaise	Vomiting	Thrombocytopenia
Chilliness	Diarrhea	Purpura
Itching	Jaundice	Hematuria
Sweating	**Fever**	Psychosis
Myalgia	Urticaria	
Anorexia	Rash	
Aphthous ulcers	Painful joints	
Conjunctivitis	Edema legs-eyes	
	Leukopenia	
	Dental abscesses	

The table shows some of the toxic effects noted in the literature. Toxic reactions were seen in 20 of our first 100 patients. In only 1 of these was it impossible to continue either thiouracil or thiobarbital. In 1, which has shown the most brilliant result, severe diabetes, severe hyperthyroidism, and cardiac decompensation were present. On 0.6 Gm. of thiouracil the white blood count promptly dropped to 2000, and

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

neutrophiles to 20 per cent. After beginning with 0.1 Gm. the dose was gradually increased and a good result obtained. In another chronic glomerulonephritis was present before therapy. After 17 weeks of treatment the white count fell to 2350, and neutrophiles to 19 per cent. Subsequently she took the drug, and it controlled her hyperthyroidism moderately well, while the white blood count rose to 4300. She later died of uremia and what appeared clinically to be thyroid crisis.

Of more than 5700 cases known to have been treated with thiouracil there have been 21 deaths from agranulocytosis, about one-third of 1 per cent, and granulopenia has occurred in approximately 3 per cent. It is worth remembering that granulopenia is a typical feature of hyperthyroidism, accounting for the relative lymphocytosis which is so frequently seen. Agranulocytosis is most apt to occur early in the course of therapy, but it has been reported after three months and one week. In one case it appeared 1 month after stopping the drug.

When severe agranulocytosis appears, the treatment of choice is (1) discontinuance of thiouracil, (2) transfusions, and (3) generous use of penicillin, 300,000 to 500,000 units daily.

In mild or uncomplicated cases of hyperthyroidism the risk of surgery in good hands is little, if any, greater than the risk of thiouracil alone. There is, therefore, no need to add to the total risk of these patients by giving thiouracil. In severely ill or complicated cases, however, the situation is quite different. In them the good to be obtained from the complete control of all hyperthyroidism is so great in comparison to a risk of one-third of 1 per cent that no question remains as to the advisability of giving the drug.

PREOPERATIVE USE OF THIOURACIL

We have chosen, therefore, for the present to reserve thiouracil for those patients whose safety is to be distinctly increased by using thiouracil, or for those who refuse surgery. Patients for whom we recommend thiouracil include those who are poor risks because of (1) old age and severe hyperthyroidism, (2) poor general health and severe weight loss, especially in elderly people, (3) cardiac decompensation or cardiac status in which mild degrees of hyperthyroidism may add distinctly to the surgical risk, (4) hyperthyroidism with deep intrathoracic extension of the goiter, severe tracheal compression or asthma, (5) hyperthyroidism with a history of one or more previous operations, and (6) patients who have been treated over long periods with iodine and who cannot obtain further improvement by its use. As improvement occurs each patient's problem must be judged on an individual basis. Some will remain in remission and require no therapy; in others the risk of surgery may still

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

be great, and continued use of thiouracil will be the treatment of choice. In others, operative surgery may be desirable, and the risk may be reduced by thiouracil to the point where this is feasible. When thyroidectomy is anticipated after thiouracil has been used, Lugol's solution may be given for three weeks before the day of operation, and thiouracil discontinued completely for at least one week preoperatively, as recommended by Lahey and Bartels.[19,20] Later, if distinctly safer drugs are obtainable, the question of choice of treatment will depend chiefly on the consistency with which lasting remissions can be obtained.

OTHER RELATED DRUGS

It is obvious that a safer drug is needed to replace thiouracil. Thiobarbital[21] has already been used in several hundred cases over periods up to several months. Unfortunately, its toxic effects are similar to those seen from thiouracil. Three cases of agranulocytosis have been seen with one death. We have 10 cases in which thiobarbital has been tried, and these were patients in whom toxic effects from thiouracil appeared. One developed fever and nausea with thiouracil and also with thiobarbital. In 1, aphthous ulcers recurred repeatedly on thiouracil but did not on thiobarbital. In the others thiobarbital was well borne and was effective in doses of 150 mg. per day or less. Other related drugs that are under investigation at present include normal ethyl thiouracil, propyl thiouracil, and butyl thiouracil. Astwood and VanderLaan have recently reported the use of ethyl and propyl thiouracil. The former was used in 14 patients, the latter[22] in 29. One uritarial reaction was encountered with the ethyl derivative and no side effects were noted with the propyl. The recommended doses were 25 mg. every eight to twelve hours to control hyperthyroidism and 25 to 50 mg. per day to maintain such control. No untoward side effects have been seen in the first 20 cases treated by propyl thiouracil in this Clinic in spite of the fact that one of these patients had disturbing symptoms following the administration of both thiouracil and barbital. If these drugs proved effective in non-toxic doses, lasting remissions will probably be frequent enough to increase the usefulness of the method greatly. Para-aminobenzoic acid has been tried with some promise.[23] So far the reported cases have responded slowly and corroboration is needed.

THIOURACIL IN OTHER CONDITIONS

The use of thiouracil in certain cases of arterial hypertension and in angina pectoris is a natural development following the use of total thyroidectomy for these diseases. A few good results have been reported,

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

but on the whole they are not impressive. Some promising results have been reported in thyroiditis.[24]

SUMMARY

In general it can be stated that the chief value of thiouracil and related substances is that complete control of all types of hyperthyroidism can be obtained by their use, and the patient can remain ambulatory except for complications. Their chief disadvantage is that they cause granulopenia in about 3 per cent of the cases and death in perhaps one-third to one-half of 1 per cent. For this reason patients must be kept under the most careful prolonged observation. Whether the use of thiouracil or related substances will bring about a large enough proportion of lasting remissions of hyperthyroidism to supersede surgery as treatment is not known. Until this knowledge is established, thiouracil should be reserved for those patients who can be treated more safely with the help of the drug than by the established methods.

REFERENCES

1. Kennedy, T. H., and Purves, H. D.: Studies on experimental goitre; effect of Brassica seed diets on rats. Brit. J. Exper. Path. **22**:241-244 (Oct.) 1941.
2. Griesbach, W. E., Kennedy, T. H., and Purves, H. D.: Studies on experimental goitre; effect of goitrogenic diet on hypophysectomized rats. Brit. J. Exper. Path. **22**: 249-254 (Oct.) 1941.
3. Mackenzie, C. G., and Mackenzie, J. B.: Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism. Endocrinology **32**:185-209 (Feb.) 1943.
4. Astwood, E. B.: Chemical nature of compounds which inhibit function of thyroid gland. J. Pharmacol. and Exper. Therap. **78**:79-89 (May) 1943.
5. Hughes, A. M.: Cretinism in rats induced by thiouracil. Endocrinology **34**:69-76 (Jan.) 1944.
6. Hughes, A. M., and Astwood, E. B.: Inhibition of metamorphosis in tadpoles by thiouracil. Endocrinology **34**:138-139 (Feb.) 1944.
7. Astwood, E. B., and Bissell, A.: Effect of thiouracil on the iodine content of the thyroid gland. Endocrinology **34**:282-297 (April) 1944.
8. Larson, R. A., Keating, F. R., Jr., Peacock, W., and Rawson, R. W.: Comparison of effect of thiouracil and of injected thyrotropic hormone on collection of radioactive iodine and anatomic changes induced in thyroid of chick. Endocrinology **36**:149-159 (Feb.) 1945.
9. Baumann, E. J., and Marine, D.: Involution of adrenal cortex in rats fed with thiouracil. Endocrinology **36**:400-405 (June) 1945.
10. Leathem, J. H.: Influence of thiourea on plasma proteins and organ weights in rat. Endocrinology **36**:98-103 (Feb.) 1945.
11. Williams, R. H.: Antithyroid drugs, with particular reference to thiouracil. Arch. Int. Med. **74**:479-487 (Dec.) 1944.
12. Paschkis, K.: Read at the meeting of the Association for the Study of Internal Secretions, Chicago, June 12, 1944.
13. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil. J.A.M.A. **122**:78-81 (May 8) 1943.
14. Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. C., Herman, J., and Cortell, R. E.: Action of thiouracil upon thyroid gland in Graves disease. J. Clin. Endoc. **4**:1-12 (Jan.) 1944.

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.

15. Williams, R. H., and Clute, H. M.: Thiouracil in treatment of thyrotoxicosis: a report of 72 cases. New England J. Med. **230**:657-667 (June 1) 1944.
16. McGavack, T. H., Gerl, A. J., Morton, J. H., Vogel, M., and Schwimmer, D.: Observations on 78 thyrotoxic patients treated with thiouracil. J. Clin. Endoc. **6**:259-272 (July-Aug.) 1945.
17. Fishberg, E. H., and Verzimer, J.: Extrathyroid effects of thiouracil therapy. J.A.M.A. **128**:915-921 (July 28) 1945.
18. Williams, R. H.: Personal communication to the author.
19. Bartels, E. C.: Use of thiouracil in the preoperative preparation of patients with severe hyperthyroidism. Ann. of Int. Med. **22**:367-373 (Mar.) 1945.
20. Lahey, F. H., Bartels, E. C., Warren, S., and Meissner, W. A.: Thiouracil—use in the preoperative treatment of severe hyperthyroidism. Surg., Gynec., and Obst. **81**:425-439 (Oct.) 1945.
21. Astwood, E. B., Bissell, A., and Hughes, A. M.: Antithyroid activity of thiobarbital (5, 5-diethyl-2-thiobarbituric acid). Endocrinology **36**:72-74 (Jan.) 1945.
22. Astwood, E. B., and VanderLaan, W. P.: Thiouracil derivatives of greater activity for the treatment of hyperthyroidism. J. Clin. Endoc. **5**:424-430 (Dec.) 1945.
23. Berman, L.: Human thyrotoxicosis; response to para-aminobenzoic acid. Proc. Soc. Exper. Biol. and Med. **59**:70-72. 1945.
24. King, B. T., and Roselline, L. J.: Treatment of acute thyroiditis with thiouracil. J.A.M.A. **129**:267-272 (Sept.) 1945.

TYPHOID SHOCK THERAPY

Results of Fifteen Years' Experience

JOHN TUCKER, M.D.

A survey of the medical literature for the past five years reveals that the use of typhoid shock therapy is less popular than during the preceding decade. This is probably due to lessened need for non-specific protein in treatment of infections and inflammatory processes. This is indicative of medical progress and reflects better understanding of the cause and treatment of disease. Yet in spite of the amazing bactericidal and bacteriostatic effects of the sulfa drugs and penicillin, we are confronted still with many medical conditions which are refractory to ordinary therapy. It is among these that nonspecific protein shock therapy has a useful place in clinical medicine.

In some instances typhoid vaccine given subcutaneously or intravenously merely relieves painful symptons, but in many cases it shortens the course of disease and contributes to recovery. Experience with its use in several thousand patients during a fifteen-year period has determined the course of administration and indications and contraindications for its use.

We know relatively little about chemical and biological changes that take place in the body during this type of shock therapy. However, it can be rightfully assumed that fever produced by proteins injected intra-

Downloaded from www.ccjm.org on August 20, 2025. For personal use only. All other uses require permission.